Ann. Rev. Pharmacol. Toxicol. 1986. 26:293–309

CONTROL BY DRUGS OF RENAL POTASSIUM HANDLING[1]

Heino Velázquez and Fred S. Wright

Departments of Medicine and Physiology, Yale University School of Medicine, New Haven, Connecticut, and Veterans Administration Medical Center, West Haven, Connecticut

INTRODUCTION

The kidney plays a major role in maintaining potassium homeostasis. Investigations during the past thirty years have provided a great deal of information about renal mechanisms involved in the regulation of potassium excretion. Much of this information is summarized in several recent reviews (1–3). Potassium undergoes both glomerular filtration and reabsorptive and secretory transport. Potassium is filtered freely in the large volumes of plasma that are filtered by the glomeruli and that course through the proximal portions of the nephron. Water, organic substances, and electrolytes are extensively reabsorbed from this ultrafiltrate of plasma so that 10% or less of the filtered volume emerges from the loop of Henle. Nearly all of the filtered potassium has been reabsorbed before the luminal fluid reaches the distal tubule. Potassium is added to the luminal fluid by cells of the distal tubule. As a consequence, the concentration of potassium in luminal fluid increases to levels that can exceed the plasma concentration by several fold. The potassium secreted from blood to luminal fluid by the distal cells accounts for most of the potassium that appears in the urine. The gradient for potassium generated in the distal tubule is maintained by the collecting duct system as fluid continues to flow downstream and more water is absorbed. Further secretion of potassium by collecting duct cells contributes to the final regulation of excretion of potassium by the kidney. The distal tubule, strategically located in the distal nephron downstream from the thick ascending limb of Henle's loop and upstream from the collecting duct system, makes a key contribution to the sensitive regulation of the rate at which potassium leaves the body via the kidneys. Under some circumstances, howev-

[1]The US Government has the right to retain a nonexclusive, royalty-free license in and to any copyright covering this paper.

er, this distal location of the potassium secretory mechanism between a segment responsible for diluting luminal fluid and a segment responsible for concentrating luminal fluid can lead to disturbances in the potassium balance of the organism.

In this chapter we review interactions between diuretic drugs and the mechanisms controlling renal potassium excretion. First we summarize briefly some of the ways in which net potassium transport by the kidney can be modified. Determinants of distal potassium transport can exert their influence by acting on distal cells from either the blood side or the lumen side of the epithelium. We then focus on six diuretic drugs and discuss their effects on renal potassium handling and what is known about their mechanism of action. Finally, we consider briefly how changes in plasma levels of aldosterone and vasopressin that occur during changes in volume status can affect distal potassium secretion. These physiologic influences modify the impact of certain diuretic drugs.

DETERMINANTS OF DISTAL POTASSIUM TRANSPORT

The distal tubule is the primary site for potassium secretion from blood to lumen. For the present discussion we define the distal tubule as the portion of the nephron located between the macula densa region and the junction of that tubule with another distal tubule to form the collecting duct. This structure is heterogeneous and contains at least four cell types. Sodium and chloride absorption occurs throughout the distal tubule. Potassium secretion, however, occurs predominantly in the downstream portion, the late distal tubule.

Potassium is transported from plasma and interstitial fluid into distal cells across the basolateral membrane by an ATP driven Na-K exchange pump. Potassium is able to diffuse out of distal cells via conductive pathways in both the basolateral membrane and the luminal membrane. More potassium diffuses across the luminal membrane partly because the electrochemical driving force for potassium is greater: the luminal membrane voltage is less than the basolateral membrane voltage because sodium conductance permits an inward flow of sodium ions that depolarizes the luminal membrane. Thus, net transcellular movement of potassium normally occurs from blood to lumen. This mechanism of active uptake across the basolateral membrane and passive diffusion across the luminal membrane can account for a large part of the potassium secreted, although other mechanisms also influence net potassium transport by distal cells. These include a mechanism for active potassium uptake from lumen to cell (4) and a coupled mechanism for potassium and chloride movement from cell to lumen (5, 6). The rate of net potassium secretion by the distal tubule is regulated by several factors that modify these transport mechanisms.

Factors Acting From the Systemic Circulation

1. A rise in the acidity of plasma causes a decrease in the rate of renal potassium excretion and a decrease in potassium secretion by the distal tubule (7–11). It has been suggested that this decrease in secretion occurs as a result of a shift of hydrogen ions into the cell and potassium ions out of the cell (8, 12). Some evidence also indicates that a decline in the pH of luminal fluid lowers the potassium conductance of the apical cell membrane, which results in decreased potassium secretion (13, 14). If systemic acidosis is prolonged, rates of potassium excretion increase (15, 16). This change appears to be a secondary effect related to increased urine flow rate (11, 16) (see below).

A decrease in acidity of plasma increases the rate of renal potassium excretion and potassium secretion by the distal tubule (8–11, 15). This effect has been attributed to a shift of hydrogen ions out of the cell and of potassium into the cell (8). Metabolic alkalosis is usually associated with an increase in nonchloride anions in plasma, a change that may contribute to an increase in distal potassium secretion (11).

2. States in which plasma aldosterone levels are elevated are sometimes associated with increased rates of potassium excretion and distal potassium secretion (17–20). Aldosterone appears to act first by increasing the permeability of the luminal membrane to sodium, thus depolarizing the luminal membrane and increasing the electrochemical driving force for potassium movement from cell to lumen (21). Later, aldosterone stimulates potassium secretion further by increasing Na-K, ATPase activity in the basolateral membrane and potassium conductance in the luminal membrane (21–23). If a normal or high sodium intake is maintained, potassium wasting will occur (24–26).

3. Antidiuretic hormone (ADH) has been found to increase potassium secretion by the distal tubule under controlled experimental conditions (27). A reciprocal relationship between ADH levels and distal flow rate may serve to keep potassium excretion constant during normal fluctuations of ADH levels (27, 93; see section on influence of volume status on drug action).

4. The rate of distal potassium secretion correlates directly with changes in the plasma potassium concentration (28–30). Systemic events that raise plasma potassium concentration stimulate distal potassium secretion. Potassium secretion continues, but at lower rates when plasma potassium concentration is decreased.

Factors Acting From the Tubule Lumen

1. The rate of flow of luminal fluid is an extremely important determinant of renal potassium excretion and distal potassium secretion (31–34). Increases in fluid flow rate stimulate distal potassium secretion. This effect does not require

a change in sodium transport, sodium concentration, or an increase in the transepithelial voltage (lumen is negative with respect to the interstitium) (31).

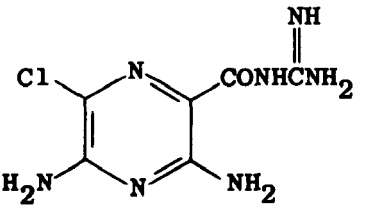
2. Net distal potassium secretion depends on the luminal potassium concentration. Decreases in lumen potassium concentration stimulate potassium secretion (31). Increases in lumen potassium concentration reduce net potassium secretion (31).

3. When chloride concentration in lumen fluid is reduced to low levels, distal potassium secretion is stimulated (5, 35). This effect does not appear to depend on the transepithelial voltage or on the particular nonchloride anions that are present when chloride concentration is low (5, 6, 36). It is thought that this increase in potassium secretion is mediated by a mechanism in the luminal membrane of cells of the distal tubule that couples the movement of both potassium and chloride from cell to lumen.

4. An increase or a decrease in the transepithelial voltage (lumen negative) reflects an increased or a decreased electrical driving force for potassium secretion. It sometimes, but not always, correlates with a change in the rate of distal potassium secretion (6, 37–40). It always correlates with a change in the potassium concentration in luminal fluid.

ACTIONS OF DIURETIC DRUGS

Amiloride



Amiloride (*N*-amidino-3,5-diamino-6-chloropyrazine carboxamide)

Amiloride decreases renal potassium excretion. Because it can counteract influences that tend to produce potassium wasting by the kidney, amiloride has been termed "potassium sparing" (41). Triamterene (2,4,7-triamino-6-phenylpteridine) (42–44) acts in a manner similar to that of amiloride.

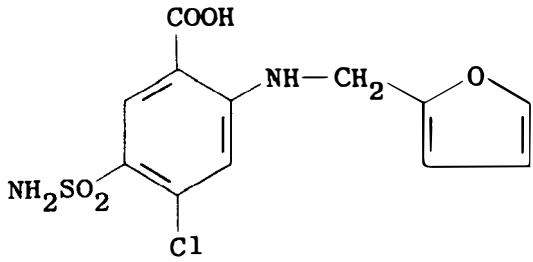
Clearance and micropuncture experiments in rats demonstrated a decrease in the renal excretion of potassium when amiloride was administered systemically (37, 44). Sodium excretion increased in some studies (37) but not in others (45, 46). Experiments employing in vivo microperfusion to study the distal tubule of rats showed that amiloride in concentrations of less than 0.1 mM decreases potassium secretion (45, 47), sodium absorption (45, 47), and the transepithelial voltage (39, 40, 48), and increases the rate of calcium absorption (45). The

effects on potassium and sodium transport are also present in cortical collecting ducts that are isolated from the kidney and perfused in vitro (49, 50). Amiloride is without effect in the thick ascending limb of Henle's loop (49, 59).

In the distal tubule and the cortical collecting duct, amiloride decreases distal potassium secretion and renal excretion indirectly; it does not act on a potassium transport mechanism directly. Amiloride blocks pathways for sodium ion diffusion in the luminal membrane of cells of the cortical collecting duct. The mechanism of action in distal tubule cells appears to be similar (14, 51). In the absence of amiloride this sodium-conductive pathway partially depolarizes the luminal membrane relative to the basolateral membrane and establishes a favorable electrochemical gradient for potassium movement from cell to lumen. Amiloride decreases distal potassium secretion by hyperpolarizing the luminal membrane and thus decreasing the electrochemical gradient for potassium movement into the lumen. We are not aware of any other setting encountered clinically in which a primary change in the apical membrane voltage (and transepithelial voltage) is the likely explanation for a subsequent change in the rate of potassium secretion by the distal tubule.

Furosemide

Furosemide (4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid)



Furosemide increases renal potassium excretion. It is used to promote renal sodium and water excretion, and the loss of increased amounts of potassium is not generally a desired effect. Other examples of this class of so-called "high ceiling" diuretics or loop diuretics are bumetanide (3-*N*-butylamino-4-phenoxy-5-sulfamoylbenzoic acid) (52–54), ethacrynic acid ([2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid) (55, 56), and muzolimine or BAY g 2821 [3-amino-1-(3,4-dichloro-α-methylbenzyl)-2-pyrazolin-5-one] (57–59, 97).

Potassium, sodium, chloride, and water excretion rates increase when furosemide is administered to rats (33, 37). Results of recent microperfusion experiments in rats show that furosemide does not increase the rate of potassium secretion by the distal tubule (60). Bumetanide appears to stimulate net distal potassium secretion by a small amount (61). Results from in vivo micropunc-

ture experiments show that both the potassium concentration and the volume flow rate out of the loop of Henle are increased after furosemide is administered intravenously (37). It is apparent that the rate of potassium absorption by the loop of Henle is greatly decreased. This could contribute directly to the increased rate of renal potassium excretion that is observed (62). As noted earlier, an increase in the concentration of potassium in the lumen of the downstream distal tubule, however, would be expected to decrease the rate of net potassium secretion by this segment. In contrast, the increase in volume flow through the distal tubule would be expected to stimulate net potassium secretion. Thus, the action of furosemide on net potassium transport is complex: a primary inhibition of potassium absorption in the loop of Henle and a secondary stimulation of potassium secretion by the distal tubule are the main factors responsible for the increased urinary potassium loss. This diuretic does not appear to affect potassium transport by the collecting duct (63).

The predominant specific renal effect of furosemide is to inhibit a mechanism mediating the movement of 1 Na, 1 K, and 2 Cl from lumen to cell in the thick ascending limb of Henle's loop (64, 65). The lumen positive voltage decreases towards zero and thus lowers the electrical driving force for passive potassium absorption. Inhibition of potassium absorption via this three-ion cotransporter causes luminal potassium concentration to rise and contributes directly to the increased renal potassium loss (62). Inhibition of sodium and chloride absorption via the cotransporter causes luminal sodium and chloride concentrations to increase and prevents the normal dilution of luminal fluid by this segment. Although furosemide does not affect potassium transport in the distal tubule, it does decrease sodium and chloride transport by this segment (60). The mechanism for sodium and chloride absorption in the distal tubule appears to be different from the mechanism that is found in the thick ascending limb of Henle's loop (47).

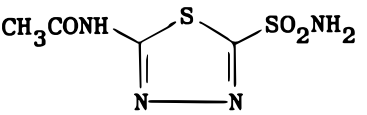
Furosemide can also stimulate renal potassium loss by increasing the renal blood flow and filtration rate and thus increasing the flow rate in the distal tubule. This contribution, however, appears to be of minor significance (66–68).

When furosemide is in systemic circulation it binds extensively to plasma proteins. It is effective only from the lumen compartment and reaches its site of action not by filtration at the glomerulus but by secretion by cells of the proximal tubule (63, 69). Probenecid [*p*-(dipropylsulfamyl)benzoic acid] and indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] affect the renal response to furosemide. Probenecid interferes with the organic acid transport mechanism in proximal tubules that also mediates the transport of a wide variety of organic anions, including furosemide and other diuretics, from plasma into luminal fluid (70, 71). The administration of furosemide,

together with probenecid, decreases the rate at which furosemide reaches its site of action and prolongs the time course of the effect. However, the magnitude of the diuresis for a given dose of furosemide is not decreased (72). Indomethacin has been reported to decrease the diuretic response to furosemide by a mechanism not related to inhibition of the cyclooxygenase pathway for prostaglandin synthesis or to inhibition of secretory transport of furosemide (73, 98). It may influence the action of furosemide on cells of the thick ascending limb (68, 73).

Acetazolamide

Acetazolamide (5-acetamido-1,3,4-thiadiazole-2-sulfonamide)



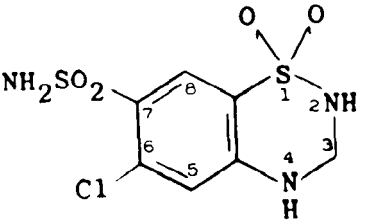
Acetazolamide increases renal potassium excretion. It is a diuretic drug that inhibits carbonic anhydrase activity and promotes sodium bicarbonate and fluid excretion. Other examples of this class of diuretics are benzolamide (benzolsulfonamido-5-thia-1-diazol-3,4-sulfonamide) (74, 75) and ethoxolamide (6-ethoxy-2-benzothiazolesulfonamide) (75).

When acetazolamide is administered to rats or dogs, renal potassium loss is stimulated (60, 74, 76, 77). A direct effect of acetazolamide on potassium secretion by the distal tubule has not been demonstrated. This class of diuretic decreases bicarbonate, sodium, and volume absorption in the proximal tubule (74, 77). Thus, more bicarbonate and less chloride is delivered into the loop of Henle. Increased flow rates in the distal tubule result in increased rates of distal potassium secretion and increased renal loss of potassium.

These diuretics act by inhibiting the enzyme carbonic anhydrase of proximal tubule cells (75, 78). The absorption of bicarbonate is thus impaired, and the fluid that is delivered into the loop of Henle and the distal tubule after administering the diuretic has a reduced chloride concentration and increased concentrations of nonchloride anions. It was suggested that distal potassium secretion is stimulated because the increased load of bicarbonate led to an increase in the lumen negative voltage under these conditions (3, 25). In view of more recent evidence, it is unlikely that a rise in luminal bicarbonate increases the lumen negative voltage (5, 36). It is possible but not certain that systemic administration of carbonic anhydrase inhibitors causes lumen chloride concentration in distal tubules to decline sufficiently to stimulate potassium secretion (74). Current evidence supports the conclusion that an increase in lumen flow rate is primarily responsible for the enhanced renal potassium loss after acetazolamide administration.

Hydrochlorothiazide

Hydrochlorothiazide (6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide)



Hydrochlorothiazide increases renal potassium excretion. This diuretic also increases water and sodium chloride losses but decreases the rate of calcium excretion. Another example is chlorthalidone [2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinlyl)benzenesulfonamide] (99).

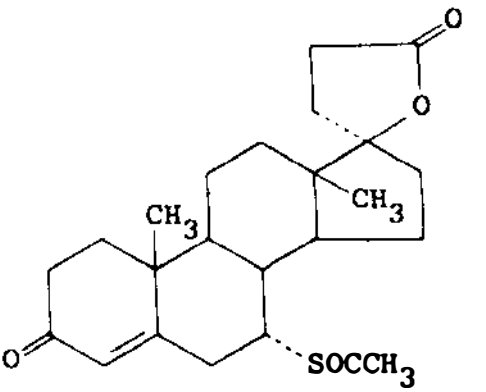
The increased rate of potassium loss after hydrochlorothiazide administration does not appear to result from a direct effect on the distal tubule. When thiazide-containing solutions are perfused directly into distal tubules of rats, rates of potassium secretion do not increase (47). However, rates of net sodium, chloride, and water absorption are decreased dramatically after thiazides (46, 47, 79). This effect appears to occur predominantly in the early distal tubule or in distal convoluted tubule cells. In experiments in rats, results from in vivo perfusion of the first part of the distal tubule showed that hydrochlorothiazide decreased net water absorption and net sodium absorption and increased net calcium absorption (46). The diuretic was without effect in the later portion of the distal tubule.

The mechanism by which hydrochlorothiazide increases potassium loss is indirect. It decreases salt and water absorption upstream from the potassium secretory site. Increases in flow rate through the late distal tubule and the collecting duct stimulate rates of potassium secretion. The potassium loss with chlorthalidone appears to be larger than that with hydrochlorothiazide (99). Thiazides can also have a small effect on proximal salt and water absorption because they can inhibit the enzyme carbonic anhydrase (75, 79) (see acetazolamide above).

Spironolactone

Spironolactone decreases potassium excretion when aldosterone is present and is stimulating potassium secretion.

Spironolactone is a competitive antagonist of aldosterone and blocks the stimulating effect of aldosterone on potassium secretion and sodium absorption (58, 80–82). In isolated perfused cortical collecting tubules, spironolactone reduces the ability of aldosterone to stimulate the lumen negative transepithelial

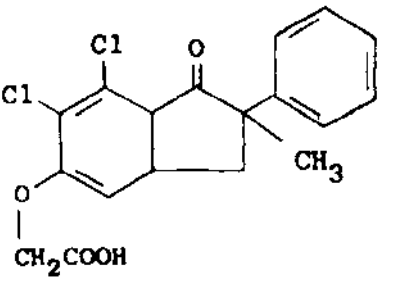


Spironolactone (17-hydroxy-7-mercapto-3-oxo-17αpregn-4-ene-21-carboxylic acidγ-lactone, 7-acetate)

voltage (42). Although spironolactone has not always been found to have an effect on the distal tubule of rats (82) or rabbits (42), it is likely that the late portions of the distal tubule are sensitive to this agent. The late portion of the distal tubule, the initial collecting tubule, responds to aldosterone by increasing sodium absorption and potassium secretion, by increasing the lumen negative transepithelial voltage, and by increasing the basolateral membrane area of the principal cells (23, 28, 83). We are not aware of any study that has directly determined the effect of spironolactone on potassium transport by the distal tubule.

Aldosterone binding to specific receptors (19, 81) in the cytoplasm of target cells in the distal nephron leads initially (within hours) to an increase in sodium permeability of the apical membrane followed by an increase (within days) in the potassium conductance of the luminal membrane and in the ATPase activity of the basolateral membrane (21–23). The increase in sodium permeability would be expected to depolarize the apical membrane. This reduction in the cell-negative voltage across the luminal membrane increases the electrochemical driving force for potassium movement from cell to lumen and leads to an increase in net potassium secretion. Continued exposure to aldosterone increases luminal potassium conductance and basolateral ATPase activity, which results in a further increase in net potassium secretion. It appears that a continued high rate of sodium entry into the cell from the luminal compartment is necessary to establish and maintain the higher ATPase levels of cortical collecting tubules (21). Depending on the physiological circumstances, then, the secondary effect on potassium secretion may not always be present. For example, amiloride treatment prevents sodium entry into late distal cells and blocks aldosterone's effect on the ATPase and potassium conductance. Spironolactone prevents aldosterone binding and thus blocks both the initial and delayed aldosterone-stimulated increases in distal potassium secretion.

Indacrinone (Mk 196)



Indacrinone (MK 196) [(6,7-dichloro-2-methyl-1-oxo-2-phenyl-5-indanyl)oxy] acetic acid

Indacrinone increases renal potassium excretion. Systemic administration of indacrinone causes diuresis and promotes renal sodium and potassium loss (84, 85). Results from in vivo micropuncture and microperfusion experiments in the rat (84, 86) show that this agent decreases sodium and potassium absorption by the loop of Henle. Sodium absorption, but not potassium secretion, was inhibited in the perfused distal tubule (86). Sodium absorption by the collecting duct also appears to be decreased (84). When indacrinone was applied to segments of the rat medullary thick ascending limb of Henle's loop, which were isolated and perfused in vitro, both the transepithelial voltage (lumen positive) (59, 87) and net chloride absorption were decreased (87).

This diuretic appears to have a complex renal mechanism of action. Its ability to decrease potassium, sodium, and chloride absorption in the loop of Henle and to inhibit the lumen positive voltage suggests that it is inhibiting the furosemide sensitive Na-K-2Cl cotransport mechanism that is known to be present in this segment. The related drug ethacrynic acid (88) also inhibits this cotransport mechanism. In the distal tubule, it is possible that indacrinone affects a mechanism for sodium chloride cotransport (60). Although rates of chloride transport and the transepithelial voltage were not measured, sodium absorption in the distal tubule was reduced without an effect on net potassium secretion (86). We have found that in the distal tubule both furosemide and hydrochlorothiazide also inhibit sodium and chloride absorption without affecting potassium secretion (47, 60). The possibility that sodium chloride cotransport in the distal tubule is inhibited by indacrinone needs to be investigated further.

Finally, indacrinone appears to reduce sodium absorption by the collecting duct (84). Its mechanism of action in this segment is not clear and requires further investigation. A recent report of experiments in toad and frog skin (89) suggests that this agent can block conductive channels for chloride movement. However, at the same time that it blocked chloride conductance in this tissue, it also increased the sodium conductance of the apical membrane. Thus, it

stimulated the transepithelial voltage and the short circuit current while decreasing the transepithelial electrical conductance.

Indacrinone enhances renal potassium loss via two mechanisms. First, by inhibiting potassium absorption in the thick ascending limb of Henle's loop it contributes directly to a kaliuresis. Second, because of the decreased solute and water absorption in both the diluting segment and in the distal tubule, potassium secretion is stimulated because of an enhanced fluid flow rate through the distal tubule.

INFLUENCE OF VOLUME STATUS ON DRUG ACTION

We have discussed the mechanisms of action of several drugs and how they affect renal potassium excretion. Most of this information has come from experiments in which a control or a normal state of the organism prevailed. In practice, however, these drugs are used to treat a variety of clinical disorders including hypertension, congestive heart failure, cirrhosis of the liver, idiopathic edema, and the nephrotic syndrome. Diuretic drugs do not generally induce excessive potassium loss when given acutely, and the maintenance of an adequate dietary potassium intake can prevent an imbalance between potassium excretion and intake. In contrast, when diuretics are given chronically, it is sometimes necessary to give potassium supplements to prevent hypokalemia and severe potassium depletion. The etiology of the conditions mentioned above and the treatment regimens applied are beyond the scope of this review and are not discussed.

The effects of diuretic drugs on the renal handling of potassium, however, can be altered dramatically depending on the physiologic state of the organism. Several components of the systems involved in the regulation of body fluid balance are related and interdependent: volume status, aldosterone levels, antidiuretic hormone levels, and rates of potassium secretion by the distal tubule.

Despite the generally accepted view that aldosterone stimulates renal potassium excretion, a number of studies have shown that aldosterone administration is without effect on renal potassium excretion (90–92). Recent results, however, suggest that other variables influencing distal potassium transport are also changed when aldosterone levels are elevated and thus provide a possible explanation for the apparently negative results associated with aldosterone administration. It is well established that flow rate of lumen fluid is an important determinant of distal potassium secretion (31). When aldosterone was infused into rats it was noted that urine flow rates were reduced (28). A decrease in distal flow rate occurring at the same time that aldosterone is promoting distal potassium secretion could result in no net effect on potassium transport (26,

85). Thus, it may be that under normal circumstances fluctuations of aldosterone levels have little effect on renal potassium excretion because of reciprocal changes in tubule flow rate. Disease states in which this counter regulatory system is disturbed could establish conditions in which aldosterone does stimulate distal potassium secretion. If flow rate increases or remains high at a time when the cells of the distal tubule are stimulated by the hormone, the rate of potassium secretion will be enhanced above the control levels. Thus, the use of diuretic drugs under these conditions would greatly stimulate the renal loss of potassium (93). The additional administration of a potassium-sparing diuretic would reduce the overall potassium loss. Spironolactone would prevent the expression of aldosterone's effect on the cells of the distal tubule and would thus decrease the rate of potassium secretion by the distal tubule and the cortical collecting duct.

The volume status of the organism correlates not only with levels of plasma aldosterone but also with levels of vasopressin circulating in plasma. Under conditions of volume contraction, plasma ADH levels are high, water reabsorption by the kidney is maximal, and fluid flow rates are low. To maintain potassium homeostasis during fluctuations of volume status the rates of renal potassium excretion must remain constant. Recent evidence suggests that plasma levels of ADH may influence potassium transport cells of the distal tubule directly and thus contribute to potassium homeostasis (27, 94). In experiments employing Brattleboro rats, which are deficient in ADH, Field and co-workers (27) noted that interruption of the diuresis by administration of ADH did not decrease distal potassium secretion. These results were obtained using free-flow micropuncture techniques in which ion concentrations and fluid flow rates in the distal tubule were permitted to vary. Tubule flow rates and lumen potassium concentrations were not the same in both states. When in vivo microperfusion techniques were employed to maintain constant lumen flow rates, the rate of distal potassium secretion was increased by ADH administration. Thus, it appears that this hormone can have a direct effect on cells of the distal tubule. Under in vivo circumstances the effect is masked because the stimulation of distal potassium secretion by ADH and the reduction of luminal flow rate in the volume-contracted state oppose each other. If ADH levels are high at a time when the organism is not volume contracted, higher rates of potassium secretion are expected because the effect of ADH on potassium-secreting cells is not mitigated by low luminal flow rates. In this setting of inappropriately high ADH (95, 96), the administration of diuretic drugs to correct the water balance would lead to an increased renal potassium loss.

The volume status of the organism, plasma aldosterone levels, and plasma ADH levels all help to determine the magnitude of the renal potassium loss that occurs when diuretics are administered.

SUMMARY

This review has focused on the influence of several diuretic drugs on potassium handling by the kidney. One class of drugs (loop diuretics) acts by directly inhibiting a potassium absorptive mechanism in the luminal membrane of cells of the thick ascending limb of Henle's loop. Two other groups of diuretics affect potassium transport indirectly by inhibiting salt and water absorption upstream from the potassium secretory site in the late distal tubule: carbonic anhydrase inhibitors act in the proximal tubule; thiazides act in the early distal tubule. The subsequent increase in lumen flow rate then stimulates net potassium secretion by the distal tubule. A fourth class of drugs (spironolactone) acts by antagonizing the response of the distal tubule to aldosterone. These drugs decrease the ability of aldosterone to stimulate distal potassium secretion. Finally, a fifth group of drugs (potassium-sparing diuretics) decreases potassium secretion by increasing the luminal membrane voltage and thus decreasing the electrochemical gradient for potassium exit from the cell.

Literature Cited

1. Wright, F. S., Giebisch, G. 1985. Regulation of potassium excretion. In *The Kidney: Physiology and Pathophysiology*, ed. D. W. Seldin, G. Giebisch, pp. 1223–50. New York: Raven
2. Wright, F. S. 1977. Sites and mechanisms of potassium transport along the renal tubule. *Kidney Int.* 11:415–32
3. Giebisch, G., Malnic, G., Berliner, R. W. 1981. Renal transport and control of potassium excretion. In *The Kidney*, ed. B. M. Brenner, F. C. Rector, pp. 408–39. Philadelphia: W. B. Saunders. 2nd ed.
4. Giebisch, G. 1975. Some reflections on the mechanism of renal tubular potassium transport. *Yale J. Biol. Med.* 48:315–36
5. Velázquez, H., Wright, F. S., Good, D. W. 1982. Luminal influences on potassium secretion: chloride replacement with sulfate. *Am. J. Physiol.* 242:F46–55
6. Ellison, D., Velázquez, H. E., Wright, F. S. 1985. Stimulation of distal potassium secretion by low lumen chloride in presence of barium. *Am. J. Physiol.* 248:F638–49
7. Gennari, F. J., Cohen, J. J. 1975. Role of the kidney in potassium homeostasis: lessons from acid-base disturbances. *Kidney Int.* 8:1–5
8. Malnic, G., de Mello-Aires, M., Giebisch, G. 1971. Potassium transport across renal distal tubules during acid-base disturbances. *Am. J. Physiol.* 221:1192–1207
9. Toussaint, C., Vereerstraeten, P. 1962. Effects of blood pH changes on potassium excretion in the dog. *Am. J. Physiol.* 202:768–72
10. Schwartz, W. B., Cohen, J. J. 1978. The nature of the renal response to chronic disorders of acid-base equilibrium. *Am. J. Med.* 64:417–28
11. Stanton, B. A., Giebisch, G. 1982. Effects of pH on potassium transport by renal distal tubule. *Am. J. Physiol.* 242:F544–51
12. Roberts, K. E., Magida, M. G., Pitts, R. F. 1953. Relationship between potassium and bicarbonate in blood and urine. *Am. J. Physiol.* 172:47–54
13. Boudry, J. F., Stoner, L. C., Burg, M. B. 1976. The effect of lumen pH on potassium transport in renal cortical collecting tubules. *Am. J. Physiol.* 230:239–44
14. O'Neil, R. G., Sansom, S. C. 1984. Characterization of apical cell membrane Na^+ and K^+ conductances of cortical collecting duct using microelectrode techniques. *Am. J. Physiol.* 247:F14–24
15. Scott, D., McIntosh, G. H. 1975. Changes in blood composition and in urinary mineral acid excretion in the pig in response to acute acid-base disturbances. *Q. J. Exp. Physiol.* 60:131–40
16. DeSousa, R. C., Harrington, T. J., Ricanate, E. S., Shelkrot, J. W., Schwartz, W. B. 1974. Renal regulation

of acid-base equilibrium during chronic administration of mineral acid. *J. Clin. Invest.* 53:465–76
17. Young, D. B., Jackson, T. E. 1982. Effects of aldosterone on potassium distribution. *Am. J. Physiol.* 243:R526–30
18. Rabinowitz, L. 1979-80. Aldosterone and renal potassium excretion. *Renal Physiol. Basel* 2:229–43
19. Marver, D., Kokko, J. P. 1983. Renal target sites and the mechanism of action of aldosterone. *Miner. Electrolyte Metab* 9:1–18
20. Kassirer, J. P., London, A. M., Goldman, D. M., Schwartz, W. B. 1970. On the pathogenesis of metabolic alkalosis in hyperaldosteronism. *Am. J. Med.* 49:306
21. O'Neil, R. G., Hayhurst, R. A. 1985. Sodium-dependent modulation of the renal Na-K-ATPase: Influence of mineralocorticoids on the cortical collecting duct. *J. Membr. Biol.* 85:169–79
22. Sansom, S. C., O'Neil, R. G. 1985. Mineralocorticoid regulation of apical cell membrane Na^+ and K^+ transport of the cortical collecting duct. *Am. J. Physiol.* 248:F858–68
23. Stanton, B., Giebisch, G., Klein-Robbenhaar, G., Wade, J., DeFronzo, R. A. 1985. Effects of adrenalectomy and chronic adrenal corticosteroid replacement of potassium transport in rat kidney. *J. Clin. Invest.* 75:1317–26
24. George, J. M., Wright, L., Bell, N. H. 1970. The syndrome of primary aldosteronism. *Am. J. Med.* 48:343
25. Cohen, J. J., Gennari, F. J., Harrington, J. T. 1981. Disorders of potassium balance. See Ref. 3, pp. 908–39
26. Seldin, D. W. 1982. Diuretic-induced potassium loss. In *Recent Advances in Diuretic Therapy,* pp. 9–20. Amsterdam: Excerpta Med.
27. Field, M. J., Stanton, B. A., Giebisch, G. H. 1984. Influence of ADH on renal potassium handling: a micropuncture and microperfusion study. *Kidney Int.* 25: 502–11
28. Field, M. J., Stanton, B. A., Giebisch, G. H. 1984. Differential acute effects of aldosterone, dexamethasone, and hyperkalemia on distal tubular potassium secretion in the rat kidney. *J. Clin. Invest.* 74:1792–1802
29. Young, D. B. 1982. Relationship between plasma potassium concentration and renal potassium excretion. *Am. J. Physiol.* 242:F599–F603
30. Stanton, B. A., Giebisch, G. H. 1982. Potassium transport by the renal distal tubule: effects of potassium loading. *Am. J. Physiol.* 243:F487–93
31. Good, D. W., Wright, F. S. 1979. Luminal influences of potassium secretion: Sodium concentration and fluid flow rate. *Am. J. Physiol.* 236:F192–F205
32. Kunau, R. T., Webb, M. L., Borman, S. C. 1974. Characteristics of the relationship between the flow rate of tubular fluid and potassium transport in the distal tubule of the rat. *J. Clin. Invest.* 54:1488–95
33. Dirks, J. H., Seely, J. F. 1970. Effect of saline infusions and furosemide on the dog distal nephron. *Am. J. Physiol.* 219:114–21
34. Khuri, R. N., Wiederholt, M., Strieder, N., Giebisch, G. 1975. Effects of flow rate and potassium intake on distal tubular potassium transfer. *Am. J. Physiol.* 228:1249–61
35. Good, D. H., Velázquez, H., Wright, F. S. 1984. Luminal influences on potassium secretion: low sodium concentration. *Am. J. Physiol.* 246:F609–19
36. Velázquez, H., W. 1980. Effects of luminal anion composition and acidity on potassium secretion by renal distal tubule. *Fed. Proc.* 39:1079
37. Duarte, C. G., Chomety, F., Giebisch, G. 1971. Effect of amiloride, ouabain and furosemide on distal tubular function in the rat. *Am. J. Physiol.* 221:632–39
38. Good, D. W., Wright, F. S. 1980. Luminal influences on potassium secretion: transepithelial voltage. *Am. J. Physiol.* 239:F289–98
39. Garcia-Filho, E., Malnic, G., Giebisch, G. 1980. Effects of changes in electrical potential difference on tubular potassium transport. *Am. J. Physiol.* 238:F235–46
40. Barratt, L. J. 1976. The effect of amiloride on the transepithelial potential difference of the distal tubule of the rat kidney. *Pfluegers Arch.* 361:251–54
41. Baer, J. E., Jones, C. B., Spitzer, S. A., Russo, H. F. 1967. The potassium sparing and natriuretic activity of N-amidino - 3,4 - diamino - 6 - chloropyrazinecarboxamide hydrochloride dihydrate (amiloride hydrochloride). *J. Pharmacol. Exp. Ther.* 157:472–85
42. Gross, J. B., Kokko, J. P. 1977. Effects of aldosterone and potassium-sparing diuretics on electrical potential differences across the distal nephron. *J. Clin. Invest.* 59:82–89
43. Crabbé, J. 1968. A hypothesis concerning the mode of action of amiloride and triamterene. *Arch. Int. Pharmacodyn. Ther.* 173:474
44. Guignard, J. P., Peters, G. 1970. Effects

of triamterene and amiloride on urinary acidification and potassium excretion in the rat. *Eur. J. Pharmacol.* 10:255–67
45. Constanzo, L. S. 1984. Comparison of calcium and sodium transport in early and late rat distal tubules: effect of amiloride. *Am. J. Physiol.* 246:F937–45
46. Costanzo, L. S. 1985. Localization of diuretic action in microperfused rat distal tubules: Ca and Na transport. *Am. J. Physiol.* 248:F527–35
47. Velázquez, H., Wright, F. S. 1983. Distal tubule pathways for sodium, chloride and potassium transport assessed by diuretics. *Kidney Int.* 23:269
48. Wright, F. S., Velázquez, H. 1983. Enhancement of amiloride action by calcium in rat renal distal tubule. *28th Congr. Int. Union Physiol. Sci., Australia* (Abstr.)
49. Stoner, L. C., Burg, M. B., Orloff, J. 1974. Ion transport in cortical collecting tubule; effect of amiloride. *Am. J. Physiol.* 227:453–59
50. Stokes, J. B. 1982. Ion transport by the cortical and outer medullary collecting tubule. *Kidney Int.* 22:473–84
51. Koeppen, B. M., Biagi, B. A., Giebisch, G. H. 1983. Intracellular microelectrode characterization of the rabbit cortical collecting duct. *Am. J. Physiol.* 244:F35–47
52. Gutsche, H. U., Müller-Ott, K., Brunkhorst, R., Niedermayer, W. 1983. Dose related effects of furosemide, bumetanide and piretanide on the thick ascending limb function in the rat. *Can. J. Physiol. Pharmacol.* 61:159–65
53. Imai, M. 1977. Effect of bumetanide and furosemide on the thick ascending limb of Henle's loop of rabbits and rats perfused in vitro. *Eur. J. Pharmacol.* 41: 409–16
54. Ostergaard, E. H., Magnussen, M. P., Nielsen, C. K., Eilertsen, E., Frey, H.-H. 1972. Pharmacological properties of 3-N-butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide), a new potent diuretic. *Drug. Res.* 22:66–72
55. Goldberg, M., McCurdy, K. K., Flotz, E. L., Bluemle, L. W. 1964. Effect of ethacrynic acid (a new saliuretic agent) on renal diluting and concentrating mechanisms: Evidence for site of action in loop of Henle. *J. Clin. Invest.* 43:201
56. Earley, L. E., Friedler, R. M. 1964. Renal tubular effects of ethacrynic acid. *J. Clin. Invest.* 43:1495
57. Moeller, E., Horstmann, H., Meng, K., Loew, D. 1977. 3-amino-1-(3,4-dichloro-α-methyl-benzyl)-2-pyrazolin-5-one (Bay g 2821), a potent diuretic from a new substance class. *Experientia* 33:382–83
58. Campen, T. J., Vaughn, D. A., Fanestil, D. D. 1983. Mineralo- and glucocorticoid effects on renal excretion of electrolytes. *Pfluegers Arch.* 399:93–101
59. Schlatter, E., Greger, R., Weidtke, C. 1983. Effect of "high ceiling" diuretics on active salt transport in the cortical thick ascending limb of Henle's loop of rabbit kidney. Correlation of chemical structure and inhibitory potency. *Pfluegers Arch.* 396:210–217
60. Velázquez, H., Good, D. W., Wright, F. S. 1984. Mutual dependence of sodium and chloride absorption by renal distal tubule. *Am. J. Physiol.* 247:F904–11
61. Velázquez, H., Wright, F. S. 1984. Sodium, chloride, and potassium transport by the distal nephron: effect of bumetanide and chlorothiazide. *Kidney Int.* 25:319
62. Burg, M., Green, N. 1973. Effect of ethacrynic acid on the thick ascending limb of Henle's loop. *Kidney Int.* 4:301–8
63. Burg, M. B., Stoner, L., Cardinal, J., Green, N. 1973. Furosemide effect on isolated perfused tubules. *Am. J. Physiol.* 225:119–24
64. Greger, R., Schlatter, E. 1981. Presence of luminal K, a prerequisite for active NaCl transport in the cortical thick ascending limb of Henle's loop of rabbit kidney. *Pfluegers Arch.* 392:92–94
65. Eveloff, J., Kinne, R. K.-H. 1981. Sodium-chloride cotransport in plasma membranes isolated from thick ascending limb of Henle's loop. *Fed. Proc.* 40:356
66. Gerber, J. G., Nies, A. S. 1981. Interaction between furosemide-induced renal vasodilation and the prostaglandin system. *Prostaglandins Med.* 6:135–45
67. Birtch, A. G., Zakheim, R. M., Jones, L. G., Barger, A. C. 1967. Redistribution of renal blood flow produced by furosemide and ethacrynic acid. *Circ. Res.* 21:869–78
68. Brater, D. C. 1983. Pharmacodynamic considerations in the use of diuretics. *Ann. Rev. Pharmacol. Toxicol.* 23:45–62
69. Deetjen, P. 1966. Micropuncture studies on site and mode of diuretic action of furosemide. *Ann. NY Acad. Sci.* 139: 408–15
70. Hook, J. B., Williamson, H. E. 1965. Influence of probenecid and alterations in acid-base balance of the saluretic activity of furosemide. *J. Pharmacol. Exp. Ther.* 149:404
71. Honari, J., Blair, A. D., Cutler, R. E. 1977. Effects of probenecid on furose-

mide kinetics and natriuresis in man. *Clin. Pharmacol. Ther.* 22:395
72. Homeida, M., Roberts, C., Branch, R. A. 1977. Influence of probenecid and spironolactone on furosemide kinetics and dynamics in man. *Clin. Pharmacol. Ther.* 22:402–9
73. Chennavasin, P., Seiwell, R., Brater, D. C. 1980. Pharmacokinetic-dynamic analysis of the indomethacin-furosemide interaction in man. *J. Pharmacol. Exp. Ther.* 215:77–81
74. Kunau, R. T. 1972. The influence of the carbonic anhydrase inhibitor, benzolamide (CL-11,366), on the reabsorption of chloride, sodium and bicarbonate in the proximal tubule of the rat. *J. Clin. Invest.* 51:294–306
75. Maren, T. H. 1976. Relations between structure and biological activity of sulfonamides. *Ann. Rev. Pharmacol. Toxicol.* 16:309–27
76. Malnic, G., Klose, R. M., Giebisch, G. 1966. Micropuncture study of distal tubular potassium and sodium transport in rat nephron. *Am. J. Physiol.* 211:529–47
77. Malnic, G., Giebisch, G. 1972. Mechanism of renal hydrogen ion secretion. *Kidney Int.* 1:280
78. Rector, F. C. Jr., Carter, N. W., Seldin, D. W. 1965. The mechanism of bicarbonate reabsorption in the proximal and distal tubules of the kidney. *J. Clin. Invest.* 44:278–90
79. Kunau, R. T., Weller, D. R., Webb, H. L. 1975. Clarification of the site of action of chlorothiazide in the rat nephron. *J. Clin. Invest.* 56:401–7
80. Liddle, G. W. 1966. Aldosterone antagonists and triamterene. *Ann. NY Acad. Sci.* 134:466
81. Edelman, I., Fimognari, G. 1968. On the biochemical mechanisms of action of aldosterone. In *Recent Progress in Hormone Research,* p. 1. New York: Academic
82. Bengele, H. H., McNamara, E. R., Alexander, E. A. 1977. Natriuresis after adrenal enucleation: effect of spironolactone and dexamethasone. *Am. J. Physiol.* 233:F8–12
83. Allen, G. G., Barratt, L. J. 1981. Effect of aldosterone on the transepithelial potential difference of the rat distal tubule. *Kidney Int.* 19:678–86
84. Kauker, M. L. 1977. Clearance and micropuncture studies of the effects of a new indanyloxyacetic acid diuretic on segmental nephron function in rats. *J. Pharmacol. Exp. Ther.* 200:81–87
85. Field, M. J., Giebisch, G. H. 1985. Hormonal control of renal potassium excretion. *Kidney Int.* 27:379–87
86. Field, M. J., Fowler, N., Giebisch, G. H. 1984. Effects of enantiomers of indacrinone (MK-196) on cation transport by the loop of Henle and distal tubule studied by microperfusion in vivo. *J. Pharmacol. Exp. Ther.* 230:62–68
87. Stoner, L. C., Trimble, M. E. 1982. Effects of MK-196 and furosemide on rat medullary thick ascending limbs of Henle in vitro. *J. Pharmacol. Exp. Ther.* 221:715–20
88. Solms, S. J. De, Woltersdorf, O. W. Jr., Cragoe, E. J. Jr., Watson, L. S., Fanelli, G. M. Jr. 1978. (Acylaryloxy)acetic acid diuretics. 2. (2-Alkyl-2-aryl-1-oxo-5-indanyloxy)acetic acids. *J. Med. Chem.* 21:437–43
89. Nagel, W., Beauwens, R., Crabbé, J. 1985. Opposite effects of indacrinone (MK-196) on sodium and chloride conductance of amphibian skin. *Pfluegers Arch.* 403:337–43
90. Cortney, M. A. 1969. Renal tubular transfer of water and electrolytes in adrenalectomized rats. *Am. J. Physiol.* 216: 589–98
91. Davis, J. O. 1961. Mechanisms regulating the secretion and metabolism of aldosterone in experimental secondary hyperaldosteronism. *Recent Prog. Horm. Res.* 17:293–352
92. Hierholzer, K., Wiederholt, M., Holzgreve, H., Giebisch, G., Klose, R. M., Windhager, E. E. 1965. Micropuncture study of renal transtubular concentration gradients of sodium and potassium in adrenalectomized rats. *Pfluegers Arch. Gesamte Physiol.* 285:193–210
93. Kelly, R. A., Wilcox, C. S., Souney, P., Mitch, W. E. 1984. Effects of aldosterone and ADH on potassium excretion with furosemide. *Kidney Int.* 25:169
94. Kelly, R. A., Wilcox, C. S., Mitch, W. E., Meyer, T. W., Souney, P. F., et al. 1983. Response of the kidney to furosemide. 2. Effect of captopril on sodium balance. *Kidney Int.* 24:233–39
95. Hantman, B., Rossier, B., Zohlman, R., Schrier, R. 1973. Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone: An alternative treatment to hypertonic saline. *Ann. Intern. Med.* 78: 870
96. Reineck, H. J., Stein, J. H. 1981. Mechanisms of action and clinical uses of diuretics. See Ref. 3, pp. 1097–1131

97. Loew, D., Ritter, W., Dycka, J. 1977. Comparison of the pharmacodynamic effects of furosemide and BAY g 2821 and correlation of the pharmacodynamics and pharmacokinetics of BAY g 2821 (Muzolimine). *Eur. J. Clin. Pharmacol.* 12:341–44
98. Smith, D. E., Brater, D. C., Lin, E. T., Benet, L. Z. 1979. Attenuation of furosemide's diuretic effect by indomethacin: Pharmacokinetic evaluation. *J. Pharmacokinet. Biopharm.* 7:265–74
99. Ram, C. V. S., Garret, B. N., Kaplan, N. M. 1981. Moderate sodium restriction and various diuretics in the treatment of hypertension. *Arch. Intern. Med.* 141: 1015–19