DIURETICS: SITES AND MECHANISMS OF ACTION

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INTRODUCTION

One of the most powerful and frequently used clinical tools in the physician's pharmaceutical armamentarium is the class of diuretic drugs. The list of available and currently investigated agents is quite long. This review examines the renal pharmacology of these drugs with respect to their sites and mechanisms of action. First we outline normal renal physiology with respect to the major locations and mechanisms of salt and water transport along the nephron as determined largely by micropuncture and in vitro microperfusion. Then we examine each class of diuretic agents with respect to what is presently known about their specific alteration of the normal renal physiology that results in their beneficial and, at times, adverse effects.

NORMAL TRANSPORT PHENOMENA

The mechanisms and sites of action of the various diuretics have been studied with multiple experimental techniques: clearance studies, stop-flow technique, in vitro enzyme analysis, toad bladder studies, micropuncture, and most recently in vitro microperfusion of isolated tubules. These techniques have also contributed in a major way to our understanding of normal renal physiology.

In Figure 1 is depicted a schematic representation of salt and water transport along the nephron. Under normal circumstances 50–60% of salt and water reabsorption occurs in the proximal tubule. The early segment of the proximal convoluted tubule actively and electrogenically reabsorbs sodium coupled to organic solute transport (1). This segment also reabsorbs most of the bicarbonate resulting in a commensurate increase in luminal chloride concentration (2–4). Bicarbonate reabsorption is dependent on intracellular and brush border carbonic anhydrase (3, 5, 6). This alteration in luminal fluid constituents by the early proximal convolution establishes several potential passive driving forces for further salt and water reabsorption in the latter proximal tubule: chloride diffusion gradient, chloride diffusion

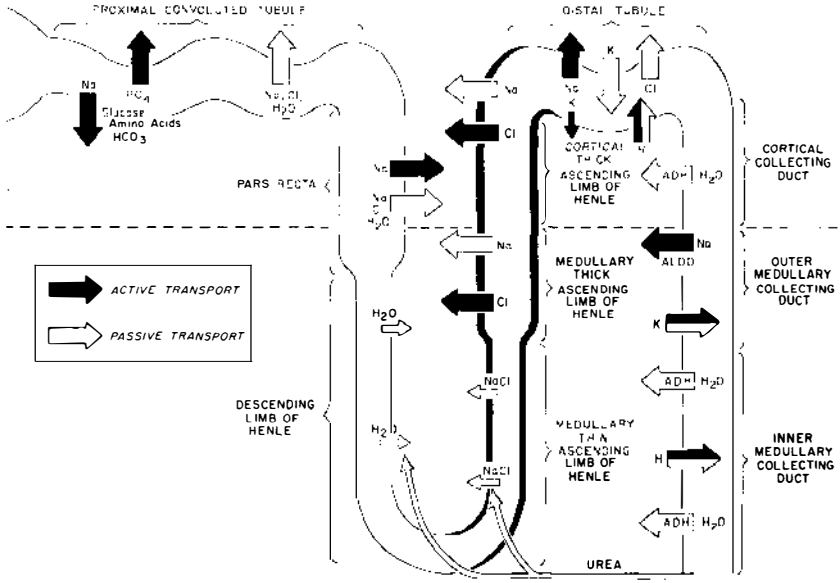

Figure 1 Schematic representation of the major transport processes in the nephron that may be affected by diuretics.

potential (lumen positive), and osmotic effects of higher peritubular concentrations of bicarbonate, glucose, acetate, and amino acids (7, 8). The majority of phosphate reabsorption also occurs in the proximal convolution and appears to be partially mediated by the effects of intraluminal pH on the relative concentrations of the mono- and dihydrogen phosphates (9–18). The presence of phosphate in the urine has been classically used as a marker for proximal tubular inhibition (10). Although its significance with respect to the diuretic agents is unknown, the pars recta of the proximal tubule has recently been shown to exhibit active electrogenic transport of sodium independent of organic solute transport (19). Thus, under normal circumstances approximately 40% of the glomerular filtrate, isosmotic to plasma but with major changes in composition, enters the thin descending limb of Henle's loop.

The thin descending limb of Henle has been shown to lack active sodium chloride transport and to have a low permeability to sodium and a high osmotic water permeability (20). These characteristics enable it to play an important passive role in the countercurrent system by allowing water abstraction and osmotic equilibration with the hypertonic interstitium (21). Hypertonic (mostly due to sodium chloride) fluid thus enters the thin ascending limb of Henle.

The thin ascending limb is relatively impermeable to water, highly permeable to sodium and chloride, and less permeable to urea (22). This segment appears to passively reabsorb sodium chloride along its concentration gradient from lumen to interstitium (21, 22) although this issue is still controversial (23, 24). Both the

absolute quantity and concentration of sodium chloride thus gradually decreases as the fluid enters the thick ascending limb.

It now appears that the thick ascending limb of Henle actively reabsorbs sodium chloride by active electrogenic chloride reabsorption (25, 26). This segment has been shown to develop a lumen positive transepithelial potential difference secondary to active chloride transport and to be relatively impermeable to water even in the presence of antidiuretic hormone (25–27). These characteristics, active chloride reabsorption with subsequent passive sodium reabsorption and water impermeability enable the thick limb to complete two most important functions: generate hypotonic luminal fluid that moves into the distal convoluted tubule, and add osmotically active sodium chloride to the medullary interstitium (21). It must be remembered that the thick ascending limb is a long segment with a medullary and cortical component. The medullary segment is the active force behind the generation of the sodium chloride component of the hypertonic medullary interstitium. The cortical segment, by virtue of its water impermeability and active transport of sodium chloride into an interstitium isosmotic to normal plasma, is the major diluting portion of the nephron (21).

The distal convoluted tubule exhibits active electrogenic sodium reabsorption (28, 29). Potassium secretion in this segment is basically passive and dependent on the transepithelial potential difference, luminal membrane permeability, tubular fluid flow rate and sodium content, intracellular potassium stores, and intracellular pH (28, 30, 35). Although potassium secretion is the usual circumstance in mammalian distal tubules, this segment appears to be capable of active potassium reabsorption under conditions of potassium depletion (36). Although previous micropuncture studies have shown that the distal convoluted tubule has a small amount of net volume reabsorptive capacity (37–39) recent evidence from in vitro microperfusion suggests that this segment is impermeable to water even in the presence of antidiuretic hormone (29). It has been recently shown that the microscopic morphology of surface tubules that have been micropunctured as distal tubules have included segments from both cortical thick ascending limb and cortical collecting duct (40).

Fluid leaves the distal convoluted tubule and enters the collecting duct system including the cortical, medullary, and papillary collecting duct. The collecting duct also exhibits active electrogenic sodium reabsorption (29, 41, 42) that appears to depend on the presence of mineralocorticoid (29). Potassium secretion in this segment appears to be secondary to the same passive driving forces as in the distal convoluted tubule (34, 43) although active secretion has been postulated (41). This segment is impermeable to water in the absence of antidiuretic hormone, but in its presence is the important segment responsible for free water reabsorption and final concentration of the urine (29, 44–46). The papillary portion of the collecting duct is also important with respect to recirculation of urea. It appears to be the only segment distal to the thin ascending limb with any degree of urea permeability (27). Under hydropenia this property enables urea to diffuse out of the papillary duct and into the interstitium and thin ascending limb (27). Urea is thus recirculated and kept in the papillary interstitium where it can exert its osmotic effect.

Although this brief discussion of salt and water transport does not touch upon possible differences between superficial and juxtamedullary nephrons or address itself to the transport characteristics for the other major ions, it serves as a useful foundation for discussion of the renal pharmacology of the various diuretics. However, before discussing diuretics, two important concepts about clearance studies require definition. Free water clearance, or C_{H_2O}, is that solute free water that can be removed from the final urine and leave the remaining urinary solutes isosmotic to plasma. Free water clearance will be positive if final urine is hypoosmotic and negative if it is hyperosmotic to plasma. Since free water is formed in those nephron segments that reabsorb sodium chloride but not water, it can be seen that the medullary and cortical thick ascending limbs and, to a small degree, the distal convoluted tubule are the segments responsible for free water formation or clearance. Free water reabsorption, $T^{C}_{H_2O}$, is the amount of water that needs to be added to hyperosmotic urine to make the solute concentration isosmotic to plasma. Thus, with urine hyperosmotic to plasma, free water reabsorption is positive and with hypoosmotic urine it is negative. For any given delivery of fluid out of the distal convoluted tubule, the collecting duct, depending on the presence or absence of antidiuretic hormone and the degree of hypertonicity of the medullary interstitium, is responsible for changes in free water reabsorption.

For the purpose of convenience, the diuretic compounds are divided into six groups: (*a*) osmotic diuretics, (*b*) carbonic anhydrase inhibitors, (*c*) organomercurials, (*d*) sulfonamide diuretics including both thiazide and nonthiazide sulfonamides, (*e*) high ceiling or loop diuretics, and (*f*) potassium sparing diuretics. These agents can exert their diuretic effect via several different mechanisms. They can specifically inhibit an active transport process, alter the epithelial permeability to various ions, inhibit energy-producing processes within cells and thus indirectly effect active transport, alter intrarenal hemodynamics and peritubular physical forces, and antagonize the effects of endogenous hormones. Keeping these mechanisms in mind and using the previously outlined model of the nephron and the concepts of free water reabsorption and clearance, we discuss the six groups of diuretic agents.

OSMOTIC DIURETICS

Mannitol is the prototype of the osmotic diuretics. Although previous explanations for its action have centered around a pure osmotic effect in the proximal convoluted tubule (47), it is clear that there are several important mechanisms of action. Mannitol has been found to increase renal plasma flow and glomerular hydrostatic pressure secondary to vasodilatation of the afferent arteriole (48, 49).

There is also suggestive evidence that mannitol affects renin release in hypoperfused kidneys and thus may decrease local angiotensin effects in the afferent arteriole (50–52). Mannitol diuresis also has a profound effect on the composition of the renal medulla. Goldberg & Ramirez (53) found that mannitol diuresis in hydropenic dogs caused a significant decrease in medullary and papillary sodium and urea concentration and an increase in water content of the medulla. Goodman & Levitan (54) have

similarly found a decrease in sodium content of the medulla and papilla in osmotic diuresis. Seely & Dirks (55), using micropuncture in dogs, found a significant effect of hypertonic mannitol infusion on net fluid reabsorption in the proximal tubule but an even greater effect in the loop of Henle, which was attributed to both the osmotic effect of mannitol and to the dissipation of the medullary osmotic gradient. In a recent micropuncture study Blantz (56) using the hydropenic rat found an increase in renal plasma flow, an increase in superficial single nephron glomerular filtration rate, an increase in glomerular hydrostatic pressure that was offset by an increase in intratubular pressure of the proximal tubule so that net transglomerular hydrostatic pressure was unchanged, and a significant decrease in afferent arteriolar oncotic pressure. This last effect, a decrease in afferent arteriolar oncotic pressure due to dilution of plasma proteins, appeared to play the largest role in increasing the effective filtration pressure and thus glomerular filtration rate.

It thus appears that mannitol and similar osmotic agents have multiple sites and mechanisms of action; their major component probably is a decrease in medullary solute content resulting in less water reabsorption from the thin descending limb of Henle and collecting duct and less sodium chloride reabsorption in the ascending limb of Henle.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide is the major representative of this class of diuretics. Inhibition of carbonic anhydrase has been shown to decrease bicarbonate reabsorption in the proximal convoluted tubule (57–59). However, direct proof of an effect on salt and water reabsorption in the proximal tubule was provided by Kunau (60) who demonstrated, via micropuncture in rats, decreased sodium chloride and volume reabsorption with the carbonic anhydrase inhibitor benzolamide. Low doses of this agent did not affect glomerular filtration rate whereas high doses produced a significant decrease (6). A similar effect on sodium and water reabsorption in the proximal tubule of the rat was observed by Radtke et al (61). These investigators also postulated that acetazolamide directly inhibited hydrogen ion secretion when glycodiazine instead of bicarbonate was used as a buffer.

Two major questions about the mechanism of action of the carbonic anhydrase inhibitors have recently been partially answered. Through what mechanisms do carbonic anhydrase inhibitors inhibit the enzyme and how is this translated into the diuretic effect? Several investigators have shown that parathyroid hormone increases renal excretion of bicarbonate, phosphate, sodium, and water (16, 62–64). Rodriguez et al (65) recognized the similarity in urinary excretion patterns of parathyroid hormone and carbonic anhydrase inhibitor administration. These investigators showed that acetazolamide increased the urinary excretion of cAMP in normal and parathyroidectomized rats, and that in vitro acetazolamide stimulated renal cortical adenyl cyclase activity (65). This observation, along with recent studies by Beck et al (66) that demonstrated in vitro inhibition of carbonic anhydrase in rat renal cortex by parathyroid hormone and cAMP, led to the conclusion that

carbonic anhydrase inhibitors inhibit the enzyme via the intermediary step of adenyl cyclase stimulation.

With respect to the resultant diuretic effect of these agents, recent evidence from in vitro microperfusion suggests that in addition to the small amount of sodium reabsorption that directly accompanies bicarbonate reabsorption in the proximal convolution, the inhibition of bicarbonate reabsorption might negate the osmotic effect of having an increased peritubular bicarbonate concentration (8) and might prevent the development of a chloride concentration gradient in the later proximal convolution, thus decreasing the passive forces for net reabsorption (7). Although carbonic anhydrase inhibitors have been shown to affect distal tubule and collecting duct hydrogen ion secretion (42, 67) there have been no studies demonstrating a direct distal diuretic effect. Rosin et al (68) have shown in clearance studies on dogs that for a given delivery of salt and water out of the proximal tubule, C_{H_2O} increases less with acetazolamide than hypotonic saline volume expansion. This discrepancy, which may well represent the major diuretic expression of carbonic anhydrase inhibitors, was attributed to the greater amount of nonreabsorbable anion presented to the diluting segment with acetazolamide diuresis. This principle of increased distal delivery of nonreabsorbable anion has recently been reemphasized by Seldin, Rosin & Rector (69). Carbonic anhydrase inhibitors cause a significant kaliuresis, which can be attributed to passive forces in the distal nephron—increased lumen negativity and increased flow rate of luminal fluid (28, 30–35).

In summary, carbonic anhydrase inhibitors decrease bicarbonate reabsorption in the proximal convolution via the intermediate step of adenyl cyclase stimulation. However, they also inhibit net volume reabsorption in the proximal tubule possibly through indirect inhibition of passive forces favoring sodium chloride reabsorption. Their major effect on electrolyte and water excretion may be explained by increased delivery of nonreabsorbable sodium bicarbonate to the cortical thick ascending limb and distal tubule.

ORGANOMERCURIALS

Before the development of the loop diuretics, the organomercurials were the most potent diuretic available. However, investigative efforts aimed at defining their renal pharmacology have not been extensive. Early clearance studies have shown conflicting results partially due to the use of different agents and the presence of theophylline in some of the preparations (70–75). A stop-flow study by Schmitt & Sullivan (76) disclosed a distal site of action on sodium transport. These investigators also found that organomercurials decrease potassium secretion in the chronic potassium-loaded animal and increase secretion in potassium depletion. Giebisch (77) found that mercurials decrease the transepithelial potential difference in the proximal tubule of the necturus. However, the mercurial concentration used was 10^{-3} M which has been shown by Burg & Green to have an irreversible, probably toxic, effect in the thick ascending limb of Henle (78).

More recent studies have consistently found that the major effect of organomercurials appears to be in the ascending limb of Henle and specifically, the thick

ascending limb. Initially Berliner, Dirks & Cirksena (79) found no proximal effect of the mercurials. Clapp & Robinson (80) found, utilizing micropuncture in dogs, an increase in early distal tubular fluid osmolality with chlormerodrin diuresis. Evanson, Lockhart & Dirks (81) later confirmed the absence of a proximal effect and the increased delivery of sodium chloride out of the ascending limb to the distal tubule. These investigators also confirmed that chlormerodrin decreased distal tubular potassium secretion in chronic potassium loaded dogs given an acute potassium load. A recent in vitro microperfusion study by Burg & Green (78) has shown that mersalyl inhibits active chloride transport in the cortical thick ascending limb of Henle. These authors found a reversible decrease in net chloride flux and transepithelial potential difference (lumen positive) when the thick limb was perfused with a solution containing mersalyl. In this study *p*-chloromercuribenzoate, which in vivo antagonizes the diuretic effect of mercurials, reversed the potential difference effect of mersalyl.

Although the site of action of organomercurials is reasonably well established, the mechanism of action has generated some controversy. Early experience suggested that the diuretic effect of organomercurials was in part dependent on intraluminal pH and its effect on either the binding of the intact organomercurial to its receptor, or on making available the free mercuric ion (82–85). However, the recent study of Burg & Green (78) found no difference in the effect of mersalyl from pH 6.0 to 7.4. They also discovered significant differences between the effect of mercuric chloride and mersalyl. The mercuric chloride took longer to have an effect which was then not reversed by *p*-chloromercuribenzoate. It thus still needs to be established specifically how pH affects the response to organomercurials and whether the diuretic response requires in vivo release of mercuric ion.

Another unresolved controversy with respect to these agents is whether the diuresis is dependent on in vivo inhibition of Na-K-dependent ATPase. Jones, Lockett & Landon (86) found that organomercurials inhibit the activity of Na-K-dependent ATPase in kidney membranes and the ability of the membrane-bound enzyme to stimulate glycolysis in the cytoplasm. Similarly, Tulloch, Gibson & Harris (87) found inhibition of the enzyme by high concentrations of mercaptomerin. However, Nechay et al (88) failed to find a correlation between diuretic effect and Na-K ATPase activity. As discussed subsequently, a similar problem exists with respect to the molecular mechanism of other diuretic agents.

In summary then, the organomercurials inhibit active chloride reabsorption in the thick ascending limb of Henle and under appropriate circumstances inhibit or enhance distal potassium secretion. The molecular basis of this effect and the precise role of pH on the degree of diuretic response are unresolved.

SULFONAMIDE DIURETICS

In contrast to the organomercurials, studies on the sulfonamide diuretics, including the thiazides and nonthiazides such as chlorthalidone and the newer agent metholazone, have generally been in agreement about sites and mechanisms of action.

Early clearance studies in animals showed a decrease in C_{H_2O} with no effect on renal concentrating ability (89–91). Clearance studies in man have found an effect both in the cortical diluting segment (thick ascending limb) and a proximal effect (92–94) based on changes in C_{H_2O}.

Subsequent micropuncture studies have demonstrated both decreased proximal reabsorption and increased osmolality and sodium content of early distal tubular fluid (80, 95–98). To date there have been no published studies on this class of diuretics using in vitro microperfusion.

With respect to mechanism of action, most of the sulfonamide diuretics are capable of inhibiting carbonic anhydrase (99, 100). If one can extrapolate from acetazolamide, then the acute phosphaturia and increased bicarbonate excretion seen with the sulfonamides is probably secondary to their capacity to inhibit carbonic anhydrase. The kaliuresis seen with these agents is most likely a passive phenomenon similar to that discussed previously with the other diuretics. Since it is generally considered that these agents must exert their major action on the cortical thick ascending limb, the sulfonamides must be included with the organomercurials and as we see later, the loop diuretics as inhibitors of active chloride reabsorption in this segment. The specific means by which chloride transport is inhibited is unknown. However, although conclusive studies are lacking, inhibition of Na-K ATPase and inhibition of glycolysis and energy supply for transport have been suggested (87, 101, 102).

In summary, the sulfonamides have as their major site of action the cortical thick ascending limb of Henle where they inhibit active chloride transport. Proximal tubular effects are probably secondary to their ability to inhibit carbonic anhydrase. The kaliuresis seen with these agents is secondary to passive phenomena in the distal nephron. Although beyond the scope of the present review, the major impact of the sulfonamides on decreasing calcium excretion with chronic administration and their utility in diabetes insipidus are well documented (103–109).

LOOP DIURETICS

The "high-ceiling" or loop diuretics currently are the most potent available agents and include furosemide, ethacrynic acid, and two newer agents triflocin and bumetanide. Although differences exist between these agents, they are alike in the most important aspect underlying their potency, in their site of action in the medullary and cortical thick ascending limb of Henle.

Initial clearance studies have shown that these agents decrease C_{H_2O} during water diuresis (ethacrynic acid more so than furosemide) and $T^{C}_{H_2O}$ during hydropenia (91, 110–113). These two properties would localize their site of action to the medullary and cortical thick ascending limb. However, because of greater phosphate and bicarbonate loss in the urine as well as lesser degrees of inhibition of C_{H_2O}, furosemide and bumetanide are thought to have proximal tubular effects also (113–118).

Although no distal tubule micropuncture studies of ethacrynic acid diuresis have been published, micropuncture studies of its proximal tubular action are available

but conflicting. Wilczewski, Olson & Carrasquer (124) as well as Berliner, Dirks & Cirksena (79) have found no effect in rats and dogs, while Clapp, Nottebohm & Robinson (125) and Meng & O'Dea (97) have found a decrease in proximal reabsorption in the same species. A recent micropuncture study of triflocin has confirmed an ascending limb site for its action (126).

As with the organomercurials, in vitro microperfusion of rabbit nephrons has confirmed the principal site of action of both furosemide and ethacrynic acid (25, 127). Burg & Green found no effect of furosemide on proximal convoluted tubules and collecting ducts. However, 10^{-5} M furosemide in the lumen of the thick ascending limb reversibly inhibited the lumen positive potential difference and the active transport of chloride out of the lumen. An identical result was obtained with ethacrynic acid (127), although a higher concentration was required. When an ethacrynic acid cysteine adduct (as occurs in vivo) was used, a much lower concentration was required. In addition to the thick ascending limb effect, ethacrynic acid was found to be an antagonist to vasopressin at the level of the receptor site of the hormone in the isolated perfused rabbit collecting tubule by Abramow (128).

These observations of the effects of furosemide and ethacrynic acid were not without precedent since similar effects on active chloride transport have been found in frog cornea, frog skin, and frog gastric mucosa (129–131).

Although the major site of action of loop diuretics is in the medullary and cortical thick ascending limb via inhibition of active chloride reabsorption, several investigators have attributed significant diurectic effects to the alteration of intrarenal hemodynamics that these agents produce (132–134). In spite of reasonable evidence for redistribution of renal blood flow, it has, as of yet, been difficult to translate these changes directly into the diuresis observed with these agents. However, washout of medullary solute as with the osmotic diurectic may be a factor.

A molecular basis of action of these diuretics has been actively sought. This search has centered about three basic process: (*a*) inhibition of Na-K ATPase; (*b*) inhibition or displacement of cAMP; (*c*) inhibition of glycolysis (87, 135–146). Although the majority of these studies did not find a correlation of diuretic action with Na-K ATPase inhibition (135–139, 143), a definitive answer awaits indentification of what role this enzyme actually plays in baseline salt and water reabsorption. Similarly, although profound degrees of inhibition of glycolysis would be expected to affect transport nonspecifically, the degree of inhibition of glycolysis with these agents does not appear to affect transport (145). With respect to inhibition of cAMP genesis or displacement of cAMP from its receptor, further studies are required before any conclusion can be reached.

In summary, loop diuretics inhibit active chloride transport over the entire length of the thick ascending limb of Henle. Whereas, furosemide, bumetanide, and possibly ethacrynic acid have a proximal effect, the clinical importance of this is probably minimal because of the known capacity of the loop to increase reabsorption as delivery increases. The kaliuresis seen with these agents can again be explained by increased distal delivery of fluid and sodium. Although intrarenal hemodynamic changes occur, and multiple studies suggest possible molecular mechanisms of action, the exact significance of these findings requires further study.

POTASSIUM SPARING DIURETICS

The final family of diuretics to be considered are the potassium sparing agents represented by spironolactone, triamterene, and amiloride. The effects on urinary electrolyte composition with these agents are similar in that they cause a mild natriuresis and decrease potassium and hydrogen ion excretion (147–153). In spite of this similarity, these agents actually compose two groups with respect to mechanism of action.

Spironolactone has been adequately shown to be a specific competitive inhibitor of aldosterone at the receptor site level and to have an effect only when aldosterone is present (148, 154–156). Aldosterone has been shown to bind initially to a specific receptor protein in the cytoplasm (157–159). The aldosterone antagonists have been shown to inhibit competitively the initial binding step (160–161). The other two potassium sparing diuretics, triamterene and amiloride, exert their effect independent of the presence or absence of mineralocorticoid (147, 149, 162).

Recently Gross, Imai & Kokko (29) using in vitro microperfusion have localized the site of action of aldosterone to the collecting duct. These investigators have found that the lumen negative potential difference in the cortical collecting duct is dependent on mineralocorticoid activity while the negative potential difference in the distal convoluted tubule appears to be independent of mineralocorticoid. They have also shown that triamterene, on the peritubular side, inhibits the potential in the collecting duct and not the distal tubule while amiloride in the lumen inhibits the potential in both segments (163). Another in vitro microperfusion study of the cortical collecting tubule (41) shows that amiloride significantly decreased the net sodium reabsorption and potential difference as well as the secretion of potassium. These investigators found no effect of amiloride on the lumen positive potential or active chloride transport in the thick ascending limb. The collecting duct thus appears to be the principal site of action of the aldosterone agonists and antagonists as well as of triamterene. Amiloride, however, in addition to its collecting duct site, appears to have an effect in the distal convoluted tubule as shown by Gross & Kokko (163) and a previous micropuncture study (122). In addition, two recent micropuncture studies have shown that amiloride decreases sodium transport in the proximal tubule (124, 164). Although the clinical significance of this finding is probably not significant because of the previously discussed capacity of more distal sites to reabsorb proximally rejected sodium, both of these studies provided insight into the probable mechanism of action of amiloride—alteration of the luminal membrane permeability to sodium. Previous studies on toad bladder and frog skin have suggested that amiloride decreases cell membrane permeability to sodium and thus decreases the amount of sodium available to any active sodium pump (165, 166).

With respect to the decreased potassium and hydrogen secretion seen with these agents, their ability to decrease the negativity of the lumen negative potential difference would decrease the passive force influencing potassium and hydrogen secretion. However, a direct effect on possible active potassium and hydrogen secretion is conceivable but has not been directly examined.

To summarize this last group of diuretic agents, the potassium sparing diuretics are only moderately potent and cause similar electrolyte excretion patterns whether

or not they antagonize endogenous mineralocorticoids. Their site of action is in the collecting duct with the exception of amiloride, which decreases sodium reabsorption in the proximal and distal convoluted tubules. Their effect on potassium and hydrogen secretion is, as with the majority of the previously discussed diuretics, basically due to alteration of passive forces controlling the movement of these ions.

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