

A REVIEW ON “HOW EXACTLY DIURETIC DRUGS ARE WORKING IN OUR BODY”

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ABSTRACT

Diuretics are among the most commonly used drugs. They act by diminishing sodium reabsorption at different sites in the nephron, thereby increasing urinary sodium and water losses. The ability to induce negative fluid balance has made diuretics useful in the treatment of a variety of conditions, particularly edematous states and hypertension. A review on physiology of kidney, nephron, urine formation, diuretic drugs with their classification and the mechanism of various diuretics are discussed here with neatly described schematic diagrams.

Key words Diuretics, Kidney, Nephron, Physiology of urine formation, Mechanism of action of various diuretic drugs.

INTRODUCTION

Kidney

The kidneys are reddish-brown, bean-shaped organs situated *retroperitoneal* on the posterior abdominal wall. There are two, one on each side of the spine. The asymmetry within the abdominal cavity caused by the liver typically results in the right kidney being slightly lower than the left, and left kidney being located slightly more medial than the right. The left kidney is approximately at the vertebral level T12 to L3, and the right slightly lower. Each adult kidney weighs between 125 and 170 grams in males and between 115 and 155 grams in females.¹ The left kidney is typically slightly larger than the right kidney.² Each kidney is about 4 or 5 inches long - about the size of a fist. The kidneys' participates in whole-body homeostasis, regulating acid-base balance, electrolyte concentrations, extracellular fluid volume, and regulation of blood pressure. Many of the kidney's functions are accomplished by relatively simple mechanisms of filtration, reabsorption, and secretion,

which take place in the nephron. Filtration, which takes place at the renal corpuscle, is the process by which cells and large proteins are filtered from the blood to make an ultrafiltrate that eventually becomes urine. The kidney generates 180 liters of filtrate a day, while reabsorbing a large percentage, allowing for the generation of only approximately 2 liters of urine. Reabsorption is the transport of molecules from this ultrafiltrate and into the blood. Secretion is the reverse process, in which molecules are transported in the opposite direction, from the blood into the urine. All the blood in our bodies passes through the kidneys several times a day. The kidneys remove wastes, control the body's fluid balance, and regulate the balance of electrolytes. As the kidneys filter blood, they create urine, which collects in the kidneys' pelvis - funnel-shaped structures that drain down tubes called ureters to the bladder. Each kidney contains around a million units called nephrons, each of which is a microscopic filter for blood.³

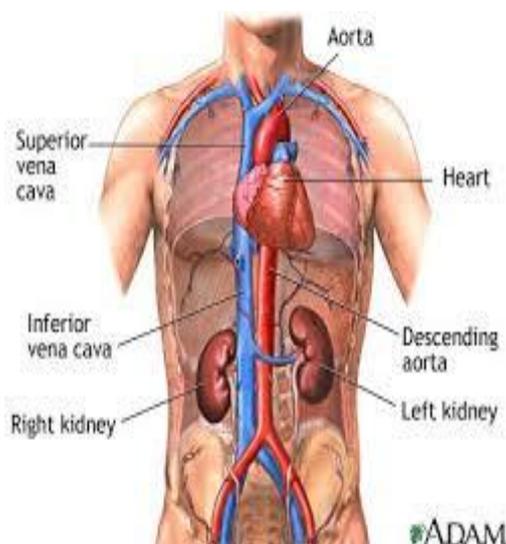


Figure 1: Location of kidney in human body

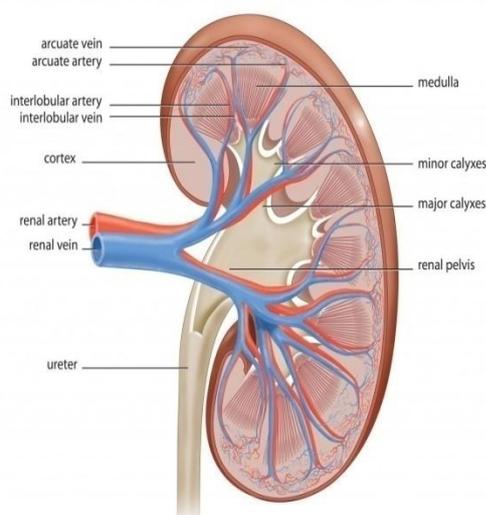


Figure 2: Anatomy of kidney

Nephron

(From Greek νεφρός - nephros, meaning "kidney") is the basic structural and functional unit of the kidney. Its chief function is to regulate the concentration of water and soluble substances like sodium salts by filtering the blood reabsorbing what is needed and excreting the rest as urine. A nephron eliminates wastes from the body,

regulates blood volume and blood pressure, controls levels of electrolytes and metabolites, and regulates blood pH. Its functions are vital to life and are regulated by the endocrine system by hormones such as antidiuretic hormone, aldosterone, and parathyroid hormone.⁴ In humans, a normal kidney contains 800,000 to 1.5 million nephrons.⁵

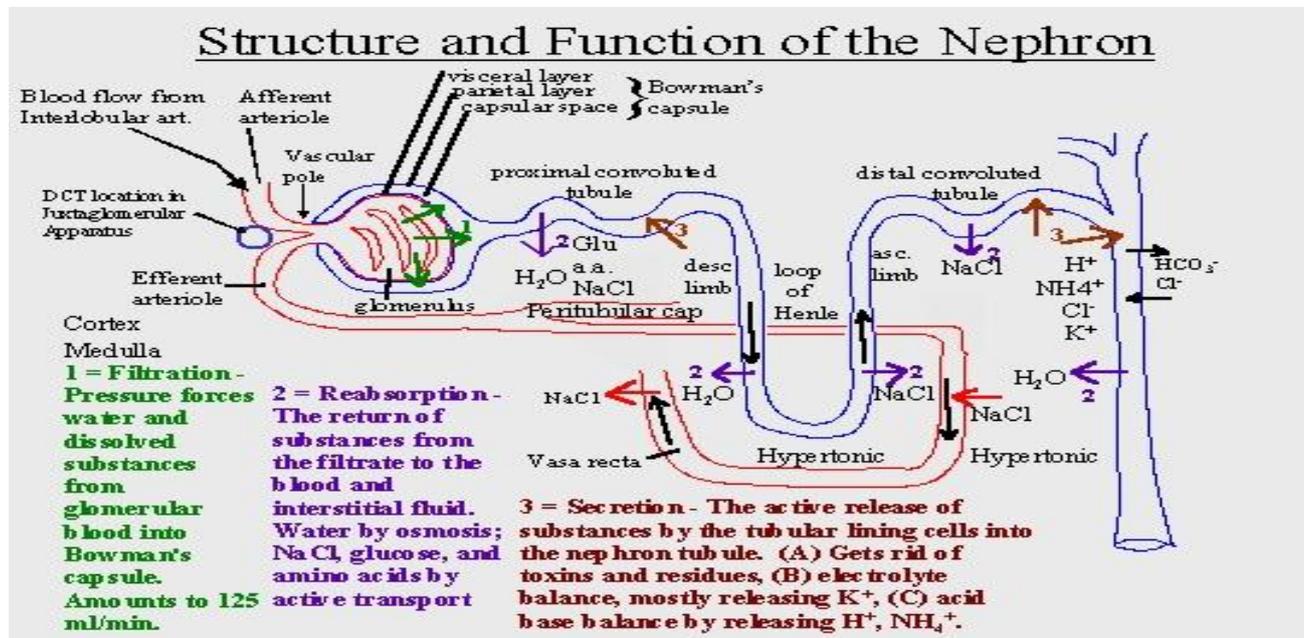


Figure 3: structure and function of nephron

Renal Pharmacology

Each nephron is composed of an initial filtering component (the "renal corpuscle") and a tubule specialized for reabsorption and secretion (the "renal tubule"). The renal corpuscle filters out solutes from the blood, delivering water and small solutes to the renal tubule for modification.

The glomerulus is a capillary tuft that receives its blood supply from an afferent arteriole of the renal circulation. The glomerular blood pressure provides the driving force for water and solutes to be filtered out of the blood and into the space made by Bowman's capsule. The remainder of the blood (only approximately 1/5 of all plasma passing through the kidney is filtered through the glomerular wall into the Bowman's capsule) passes into the efferent arteriole. The Bowman's capsule, also called the glomerular capsule, surrounds the glomerulus. It is composed of a visceral inner layer formed by specialized cells called podocytes.

The renal tubule is the portion of the nephron containing the tubular fluid filtered through the glomerulus.⁶ After passing through the renal tubule, the filtrate continues to

the collecting duct system, which is not part of the nephron. The components of the renal tubule are:

- Proximal convoluted tubule (lies in cortex and lined by simple cuboidal epithelium with brushed borders which help to increase the area of absorption greatly.)
- Loop of Henle (hair-pin like i.e. U-shaped and lies in medulla)
 - Descending limb of loop of Henle
 - Ascending limb of loop of Henle
 - The ascending limb of loop of Henle is divided into 2 segments: Lower end of ascending limb is very thin and is lined by simple squamous epithelium. The distal portion of ascending limb is thick and is lined by simple cuboidal epithelium.
 - Thin ascending limb of loop of Henle
 - Thick ascending limb of loop of Henle (enters cortex and becomes DCT-distal convoluted tubule.)
- Distal convoluted tubule

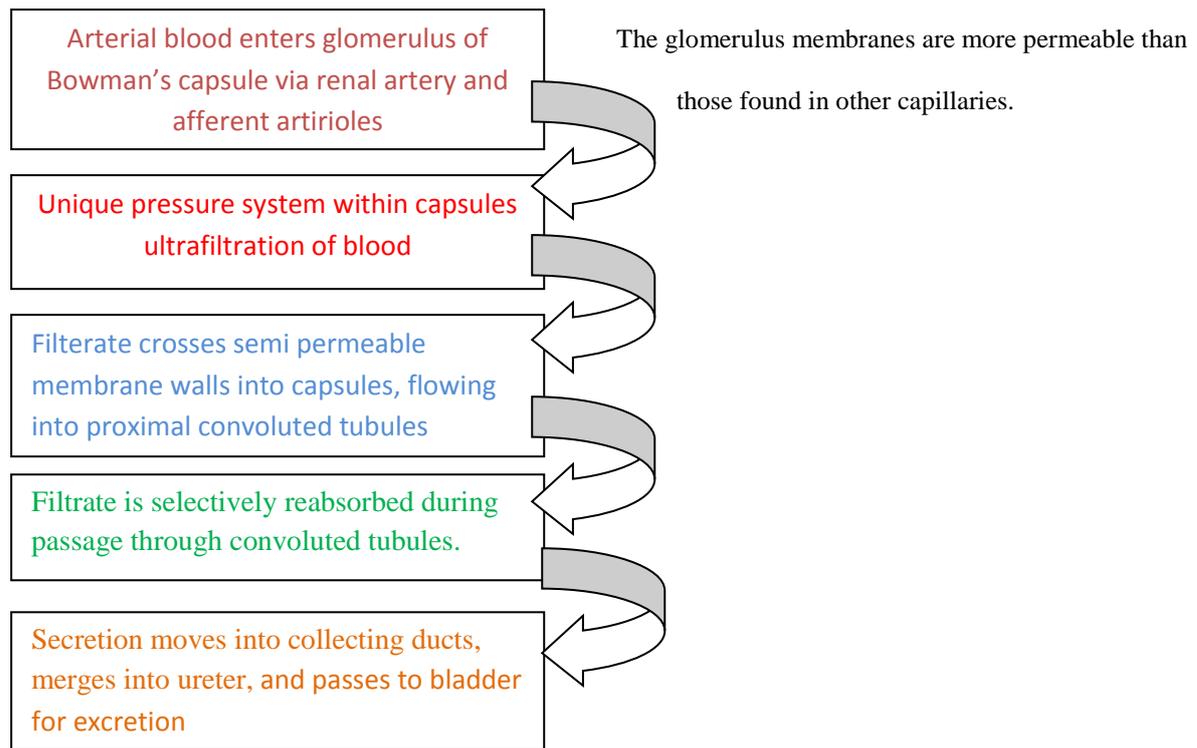


Fig.4 Schematic flow chart of urine production

Urine production In regards to urine production, the most important hormone is Antidiuretic hormone, or ADH. ADH makes the collecting duct more permeable to water. Thus, secretion of ADH causes the retention of water in the body, and more concentrated urine. (ADH is usually secreted in response to environmental situations that require the retention of water.)

Diuretics

A diuretic will have opposite effect: decreases permeability of collecting tubule, so body loses lots of water (copious, dilute urine). Examples of diuretics: caffeine, alcohol etc. Diuretic agents are drugs that increase renal excretion of water and solutes (mainly sodium excretion). Major purposes of diuretic therapy are to decrease fluid volume of the body, and to adjust the

water and electrolyte balance. Diuretics are often used in the management of pathological conditions such as edema (e.g. in congestive heart failure and certain renal diseases), hypertension⁷, cirrhosis⁸, autism⁹, toxemia¹⁰, poisoning¹¹.

Most diuretics exert their effects by inhibiting tubular sodium and water reabsorption by epithelial cells lining the renal tubule system. Certain diuretics (such as carbonic anhydrase inhibitors, loop diuretics, thiazide-like diuretics and potassium-sparing diuretics) suppress sodium and water reabsorption by inhibiting the function of specific proteins that are responsible for (or participate in) the transportation of electrolytes across the epithelial membrane; osmotic diuretics inhibit water and sodium reabsorption by increasing intratubular osmotic pressure. Different types of diuretics may inhibit different transporters in different segments of the tubular system.⁷

Table 1: DTL descending thin limb, TAL Thick ascending limb

Type	Example	Site of action	Mechanism
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	inhibition of Carbonic anhydrase
Osmotic	Mannitol	Loop of Henle (DTL)	Osmotic action Proximal tubule
Loop diuretics	Furosemide	Loop of Henle (TAL) Proximal tubule	inhibition of Na ⁺ -K ⁺ -2Cl ⁻ symport
Thiazides	Hydrochlorothiazide	Distal convoluted	inhibition of Na ⁺ -Cl ⁻ tubule symport
Potassium-sparing diuretics	Na ⁺ channel inhibitor Triamterene, Amilorides	Cortical collecting tubule	inhibition of Na ⁺ channels
	Aldosterone antagonist Spironolactone	Cortical collecting tubule	inhibition of aldosterone receptor

Carbonic anhydrase inhibitor: (acetazolamide)
 Acetazolamide acts by interfering with bicarbonate (HCO_3^-) reabsorption in the kidneys, thereby reacidifying the blood – hence alkalyzing the urine. There is an enzyme called carbonic anhydrase which catalyzes the reaction reversibly. $\text{CO}_2 + \text{H}_2\text{O} \xrightleftharpoons{\text{CA}} \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$

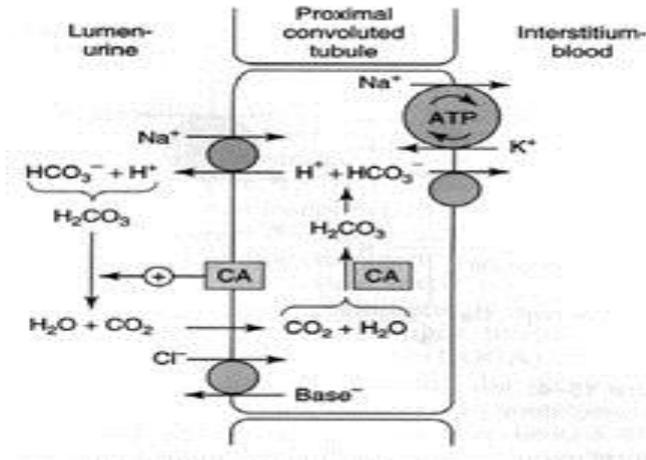


Fig. 5 Mechanism of action of acetazolamide

In the kidney tubules, locally secreted hydrogen ions normally combine with filtered bicarbonate (HCO_3^-) to form carbonic acid (H_2CO_3). Carbonic acid in turn is normally acted upon by carbonic anhydrase, leading to formation of CO_2 . As CO_2 rapidly leaves the tubules by diffusing across cell membranes, the above reaction

normally runs shifted strongly to the left (i.e. reversed), and more bicarbonate can be continuously reabsorbed from the preurine. However, in the presence of acetazolamide, carbonic anhydrase is inhibited and carbonic acid levels build up. The inhibition of carbonic anhydrase in turn leads to a slowing of the reverse reaction and a decrease in the body's ability to reabsorb serum bicarbonate, resulting in urinary bicarbonate wasting. This leads to a decreased ability to exchange Na^+ for H^+ in the presence of acetazolamide (in proximal convoluted tubules of kidney) resulting in a mild diuresis¹².

In short we can say inhibition of H^+ secretion and reabsorption of HCO_3^- takes place which results in reduction of Na^+ reabsorption in proximal tubules by inhibiting the enzyme carbonic anhydrase¹³.

Osmotic diuretic Osmotic diuretics are freely filterable but not reabsorbed and prevent H_2O reabsorption in the proximal tubule. Osmotic diuretics also extract H_2O from systemic body compartments. This expands extracellular fluid volume and increases renal blood flow. This increase in blood flow removes NaCl and urea from the renal medulla¹⁴. Loss of these solutes decreases the medullary toxicity and hence the ability to generate a concentrated urine. Compounds such as mannitol are filtered in the glomerulus, but cannot be reabsorbed. Their presence leads to an increase in the osmolarity of the filtrate. To maintain osmotic balance, water is retained in the urine¹⁵.

Osmotic Diuretics

Normal Osmotic pressure within the kidney is determined by concentrations of Na , other electrolytes, and urea. In conditions that do not require water conservation, the luminal, cellular, and interstitial osmotic pressures are fairly equal. OSMOTIC DIURETICS (which are filtered but NOT reabsorbed) remain in the lumen, creating an osmotic pressure that pulls water from the cell and interstitium into the lumen, hence a diuretic effect.

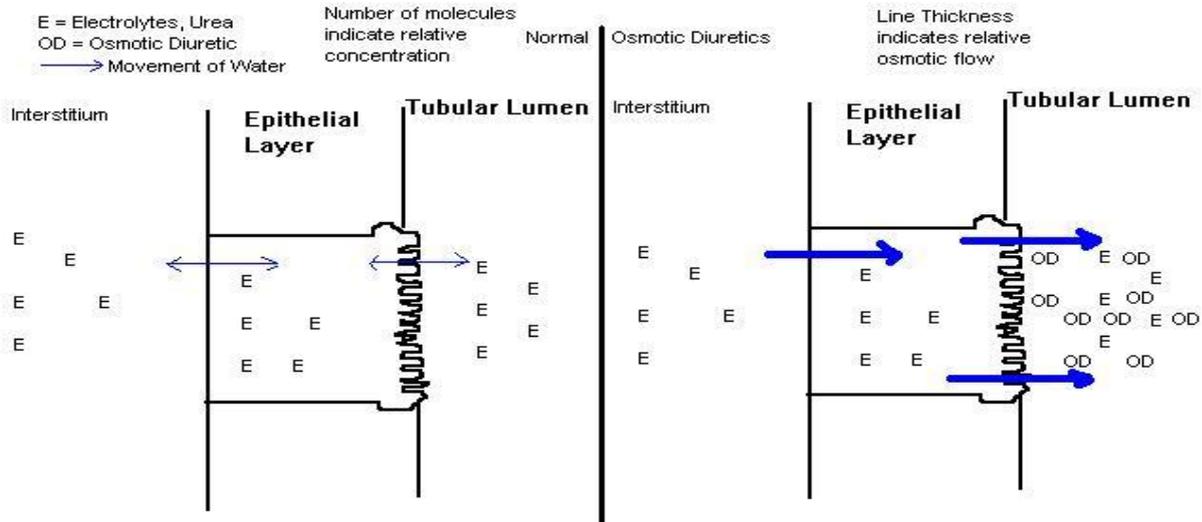


Figure 6: Showing mechanism of action of osmotic diuretic

Loop diuretics: These diuretics act on the ascending loop of Henle in the kidney. Loop diuretics act on the $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ symporter (cotransporter) in the thick ascending limb

of the loop of Henle to inhibit sodium and chloride reabsorption. This is achieved by competing for the Cl^- binding site.

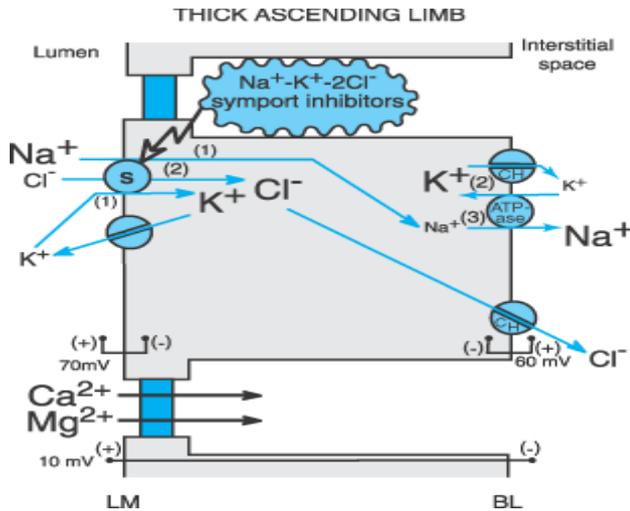


Figure 7: Mechanism of action of loop diuretics

Therefore, reabsorption of these ions is decreased. The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25 to 30 percent of filtered NaCl, and downstream sites are not able to compensate for this increased Na⁺ load.

Changes in the composition of the urine induced by loop diuretics. Loop diuretics increase the Ca²⁺ content of urine, whereas thiazide diuretics decrease the Ca²⁺ concentration of the urine. In patients with normal serum Ca²⁺ concentrations, hypocalcemia does not result, because Ca²⁺ is reabsorbed in the distal convoluted tubule. However, hypomagnesemia can occur due to loss of Mg²⁺.¹² The reabsorption of calcium in the loop of Henle is primarily passive, being driven by the gradient created by NaCl transport and occurring through the paracellular pathway^{16, 17}. As a result, inhibiting the reabsorption of NaCl leads to a parallel reduction in that of calcium, thereby increasing calcium excretion. This effect is clinically important, because enhancing urinary calcium losses with saline and a loop diuretic is a mainstay of therapy in patients with hypercalcemia¹⁸.

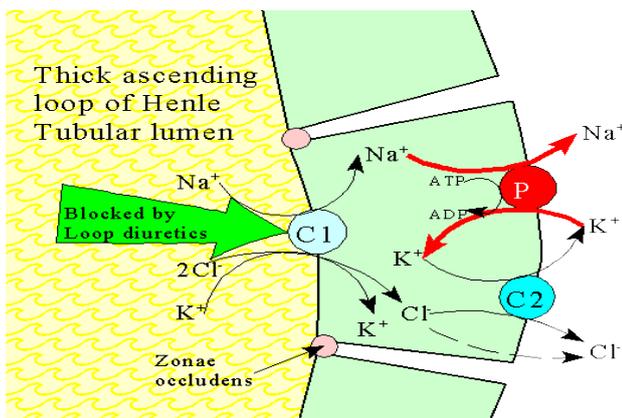


Figure 8: Mechanism of action of thiazide diuretics

Thiazide: The thiazide diuretics primarily inhibit sodium transport in the distal tubule^{19, 20}, the connecting segment at the end of the distal tubule²¹, and possibly the early cortical collecting tubule (although this finding is controversial)²². Thiazide-sensitive sodium entry in the

distal nephron is mediated by neutral Na-Cl cotransport. Both a Na-Cl cotransporter and, to a lesser degree, parallel Na-H and Cl-HCO₃ exchangers are responsible for NaCl reabsorption at these sites²³. The thiazides inhibit NaCl reabsorption in these segments by competing for the chloride site on the transporters²⁴. Some of these drugs (such as chlorothiazide) also modestly impair sodium transport in the proximal tubule, due in part to partial inhibition of carbonic anhydrase²⁵.

Potassium sparing diuretics: The three potassium-sparing diuretics, amiloride, spironolactone, and triamterene, act in the principal cells in the cortical collecting tubule (and possibly in the papillary or inner medullary collecting duct)¹⁹. Sodium entry in these segments occurs through aldosterone-sensitive sodium channels, rather than being carrier-mediated^{26, 27}. The reabsorption of cationic sodium without an anion creates a lumen-negative electrical gradient that then favors the secretion of potassium (through selective potassium channels) and hydrogen ions. Thus, inhibition of sodium reabsorption at this site can lead to hyperkalemia and metabolic acidosis due to the concurrent reductions in potassium and hydrogen ion excretion^{19, 20}.

Amiloride, triamterene, and spironolactone decrease the number of open sodium channels; the first two are cations and act directly on the channels and spironolactone competitively inhibits the effect of aldosterone^{28, 29}. Spironolactone also may inhibit the effect of aldosterone in the distal tubule, diminishing the number of Na-Cl cotransporters³⁰. The potassium-sparing diuretics have relatively weak natriuretic activity, leading to the maximum excretion of only 1 to 2 percent of the filtered sodium¹⁹. Thus, they are primarily used in combination with a loop or thiazide diuretic, either to diminish the degree of potassium loss or to increase the net diuresis in patients with refractory edema.

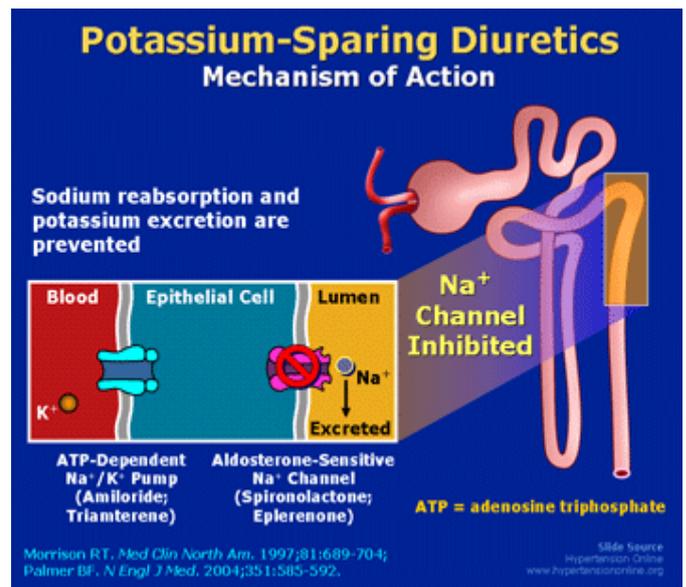


Figure 9: Mechanism of action of potassium sparing diuretics

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