الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية 2

د.رامز ونوس

المحاضرة العاشرة

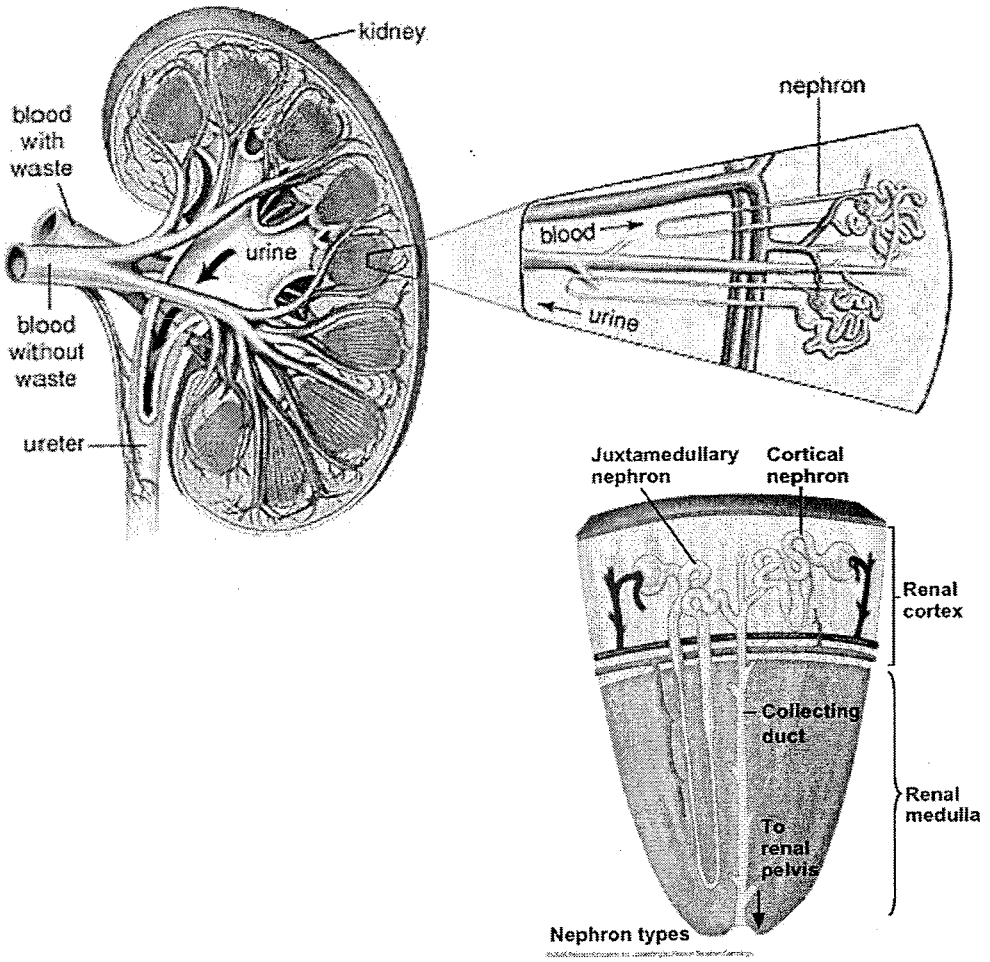
175

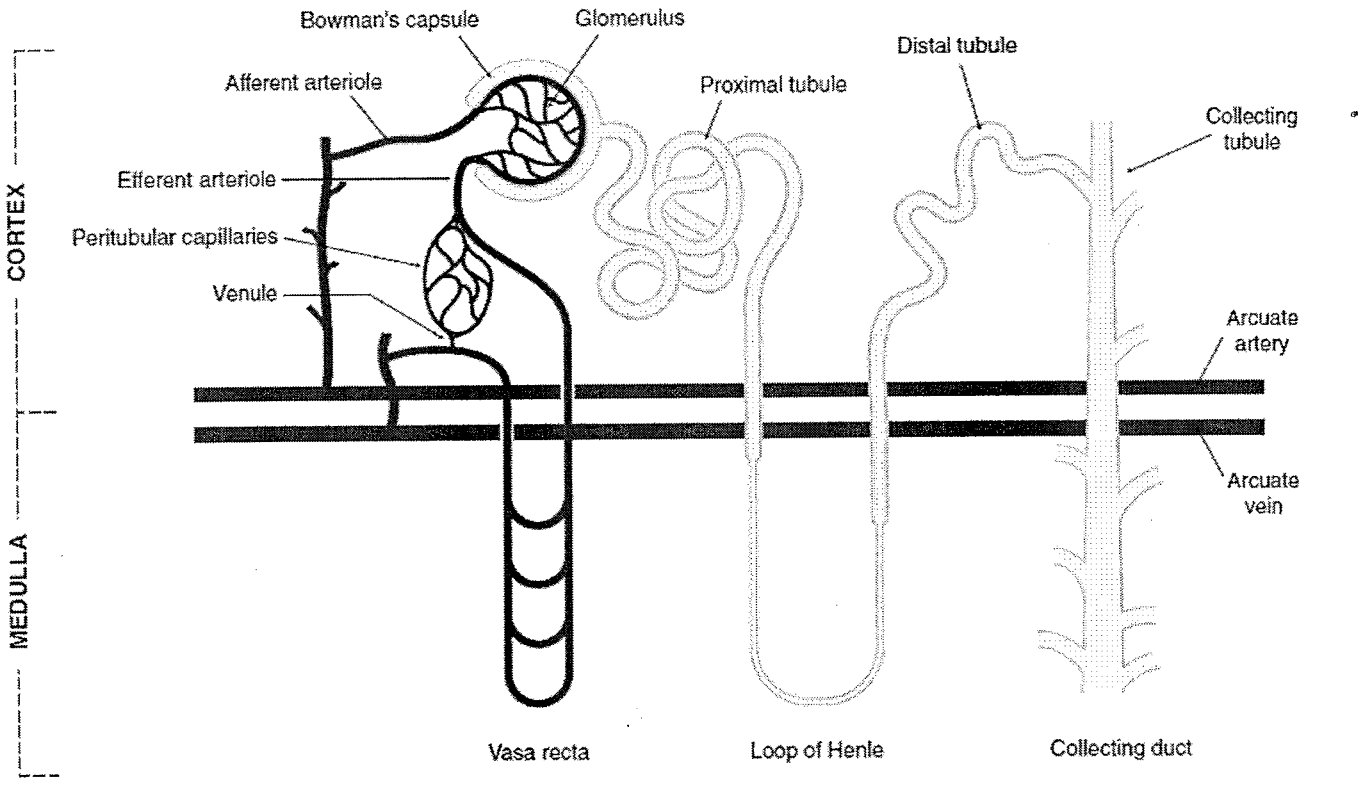
Diuretics

Pharmacology II
Dr. Ramez WANNOUS
2017

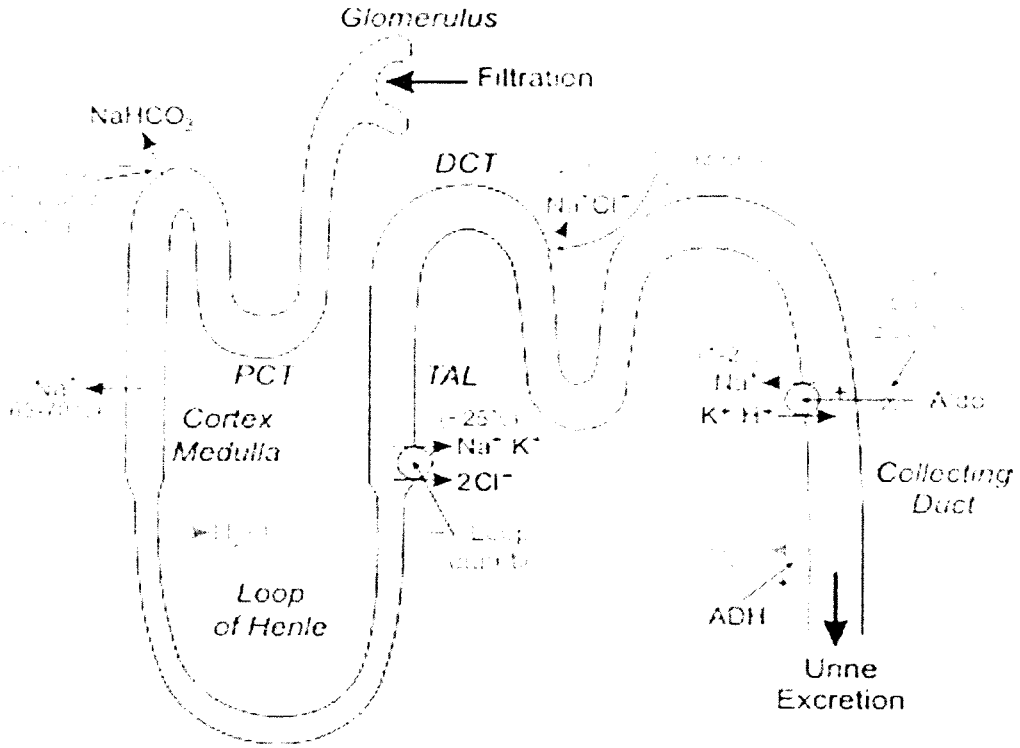
Major Classes of Antihypertensive Medications

- Diuretics
- Vasodilators
- Sympatholytics
- Renin Angiotensin System (RAS) blockers


kidney
blood with waste
urine
blood without waste
ureter
nephron
blood
urine
Juxtamedullary nephron
Cortical nephron
Renal cortex
Collecting duct
Renal medulla
To renal pelvis
Nephron types


CORTEX
MEDULLA
Bowman's capsule
Glomerulus
Afferent arteriole
Efferent arteriole
Peritubular capillaries
Venule
Proximal tubule
Distal tubule
Collecting tubule
Arcuate artery
Arcuate vein
Vasa recta
Loop of Henle
Collecting duct

Renal handling of sodium and water



Sodium and water regulation by the nephron

- Blood flows through the glomerular capillaries which are highly permeable to water and electrolytes
- Hydrostatic pressure of the blood produces the ultrafiltrate that forms in Bowman's space and flow into the proximal convoluted tubule (PCT)
- 65-70% of the filtered sodium, water and bicarbonate is reabsorbed from the PCT

Proximal tubular sodium reabsorption

- Sodium reabsorbed in the form of sodium bicarbonate and sodium chloride
- Na^+/H^+ exchanger in the luminal membrane of the proximal tubule epithelial cell pulls Na^+ in, H^+ out
- The H^+ secreted into the lumen combines with bicarbonate to form carbonic acid which is rapidly dehydrated to CO_2 and H_2O by carbonic anhydrase

Proximal tubular sodium reabsorption

- The CO_2 diffuses into the proximal tubule cell and rehydrated to H_2CO_3 by intracellular carbonic anhydrase
- The H_2CO_3 dissociates and the bicarbonate is transported out of the cell by a basolateral membrane transporter
- The proton is exchanged back out into the lumen by the Na^+/H^+ exchanger

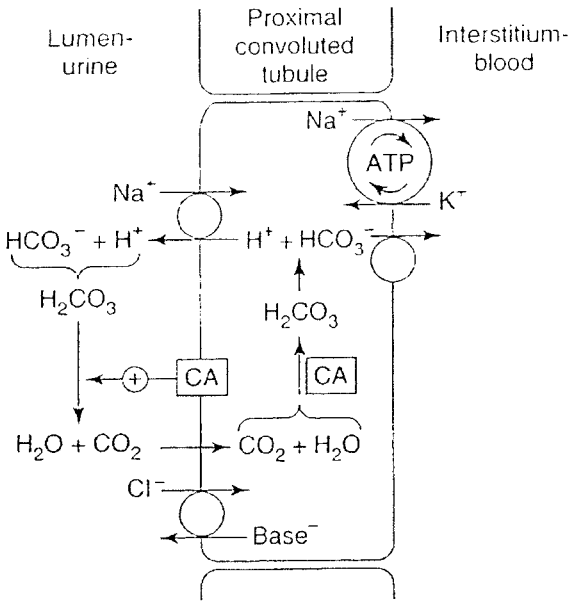


Figure 15–2. Mechanism of sodium bicarbonate reabsorption in the proximal tubule cell. CA, carbonic anhydrase. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

Diuretic agents

- Carbonic anhydrase inhibitor
- Osmotic agents
- Loop agents
- Thiazides
- Aldosterone antagonists
- ADH antagonists

Carbonic Anhydrase Inhibitors

- Sulfanilamide—unsubstituted sulfonamide moiety
- Diuretic properties discovered when sulfanamide antibiotics caused alkaline diuresis
- Mechanism of action: Inhibition of membrane bound and cytoplasmic carbonic anhydrase
- Pharmacokinetics: Well absorbed orally. Urine pH increases within 30 minutes and lasts for 12 hours after single dose. Secreted in the proximal tubule

Carbonic Anhydrase Inhibitors: Pharmacodynamics and Toxicity

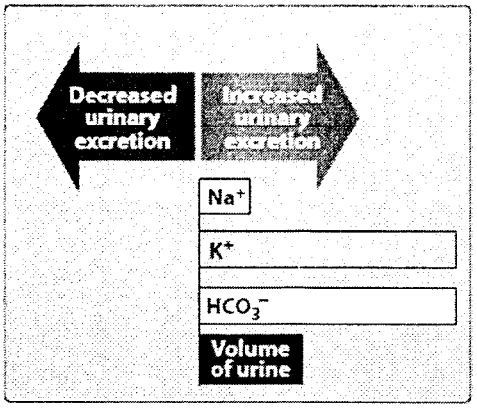
- 85% of PCT bicarbonate reabsorption inhibited
- Renal potassium wasting
- Contraindicated in Na^+ and K^+ depletion
- Causes hyperchloremic metabolic acidosis and limits the diuretic efficacy to 2-3 days. Renal stones may occur due to hypercalciuria and phosphaturia and calcium salts being insoluble at alkaline pH

Carbonic Anhydrase Inhibitors: Clinical Indications

- Open-angle glaucoma: Reduces aqueous humor formation decreases the intraocular pressure (carbonic anhydrase inhibitor in the ciliary body)
- Urinary Alkalinizaton: Enhanced urinary excretion of uric acid, cystine and other weak acids which can also be achieved by bicarbonate administration
- Metabolic Alkalosis
- Acute Mountain Sickness: Decreases the pH of cerebrospinal fluid and brain, ventilation is increased which reduces symptoms

Carbonic Anhydrase Inhibitors:

- Acetazolamide 250 mg 1-4 times daily
- Dichlorphenamide 50 mg 1-3 times daily
- Methazolamide 50-100 mg 2-3 times daily
- Not used for hypertension or heart failure



Diuretic agents

- Carbonic anhydrase inhibitor
- Osmotic agents
- Loop agents
- Thiazides
- Aldosterone antagonists
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Osmotic diuretics

- Relatively inert pharmacologically
- Freely filtered at the glomerulus with limited reabsorption by the renal tubule
- Causes water retention in the proximal tubule and descending limb of Henle's loop which are freely permeable to water
- Increases the osmolality of the plasma and tubular fluid
- Mannitol (IV) is the prototype, Urea , Glycerin

Osmotic diuretics: Clinical Indications

- Increase urine volume where water excretion is preferred over sodium excretion
- To prevent anuria (⟶ acute renal failure) that may arise when large pigment load comes to the kidney (hemolysis or rhabdomyolysis)
- Reduction of intracranial and intraocular pressure (glycerin) by inducing water to leave cells and reduce intracellular volume. Cerebral edema, Glaucoma (increase plasma osmolarity by solutes that do not entre theses tissues)

Diuretic agents

- Carbonic anhydrase inhibitor
- Osmotic agents
- Loop agents
- Thiazides
- Aldosterone antagonists
- ADH antagonists

Sodium and water regulation by the nephron: Loop of Henle

- Water is reabsorbed into the interstitium across the loop of Henle which is more permeable to water and moves across a concentration gradient
- The urine becomes more concentrated as it reaches the thick ascending limb (TAL) of the loop of Henle
- The sodium potassium chloride co-transporter at the TAL reabsorbs 25% of the original sodium load of the urine

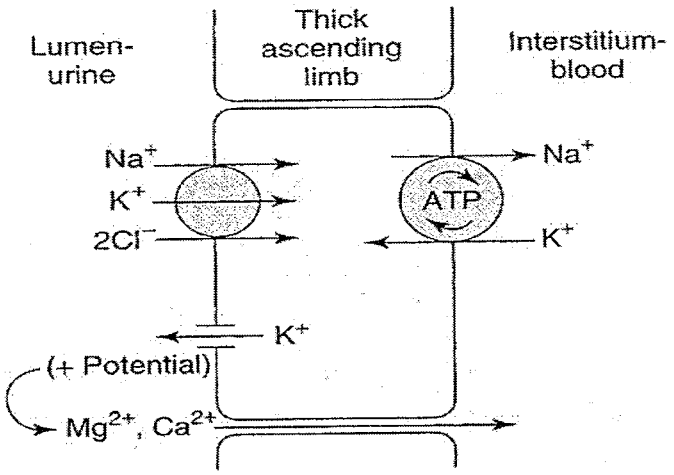
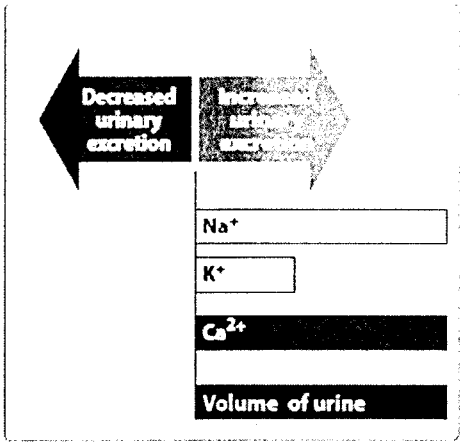


Figure 15–3. Mechanism of sodium, potassium, and chloride reabsorption in the thick ascending limb of the loop of Henle. Note that pumping of potassium into the cell from both the lumen and the interstitium would result in unphysiologically high intracellular K^+ concentration. This is avoided by movement of K^+ down its concentration gradient back into the lumen, carrying with it excess positive charge. This positive charge drives the reabsorption of calcium and magnesium. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

Loop Diuretics

- Selectively inhibits NaCl reabsorption in the thick ascending loop by blocking the $Na^+/K^+/2\ Cl^-$ co-transporter
- Furosemide, bumetanide and torsemide are sulfonamides
- Ethacrynic acid is not a sulfonamide
- Similar efficacy



Loop diuretics: Pharmacokinetics

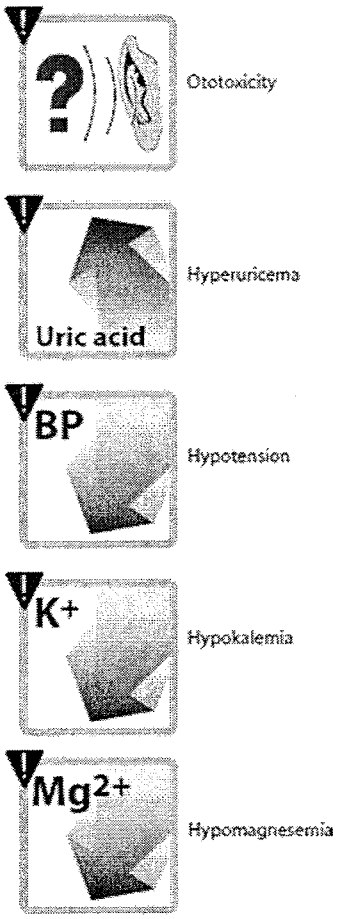
- Rapidly absorbed and bound to plasma proteins
- Loop agents are secreted in the proximal tubule as weak acid by secretion by the organic acid (anionic) transport system, there may be reduction in secretion when NSAIDs or probenecid compete for the same site
- Loop agents act on the luminal side of the tubule
- Torsemide oral absorption rapid and similar to IV
- Furosemide duration 2-3 h, torsemide 4-6 h

Loop diuretics: Clinical Uses

- Acute pulmonary edema (emergency, rapid onset)
- Edema of nephrotic syndrome
- Edema and ascites of cirrhosis
- Congestive heart failure
- Drug overdose to force more excretion of certain drugs
- Hypercalcemia

Loop diuretics: Toxicity

- Ototoxicity due to alteration in the electrolyte composition of endolymph: tinnitus, deafness, vertigo
- Hypokalemia
- Hyperuricemia precipitating acute gout attack (Furosemide, Ethacrynic acid)
- ⦿ Hypomagnesemia
- ⦿ Allergic reactions: Skin rash, eosinophilia
- ⦿ Contraindicated if allergic to sulfonamides: Use ethacrynic acid instead



Loop diuretics: Dosage

- Bumetanide 0.5 – 2 mg/day
- Ethacrynic acid 50-200 mg/day
- Furosemide 20-80 mg/day
- Torsemide 5-20 mg/day

Diuretic agents

- Carbonic anhydrase inhibitor
- Osmotic agents
- Loop agents
- Thiazides
- Aldosterone antagonists
- ADH antagonists

Sodium and water regulation by the nephron: distal convoluted tubule

- The urine flows into the distal convoluted tubule (DCT) where another 5% of the sodium is reabsorbed by the sodium chloride co-transporter
- Thiazide diuretics (hydrochorothiazide) inhibit this co-transporter

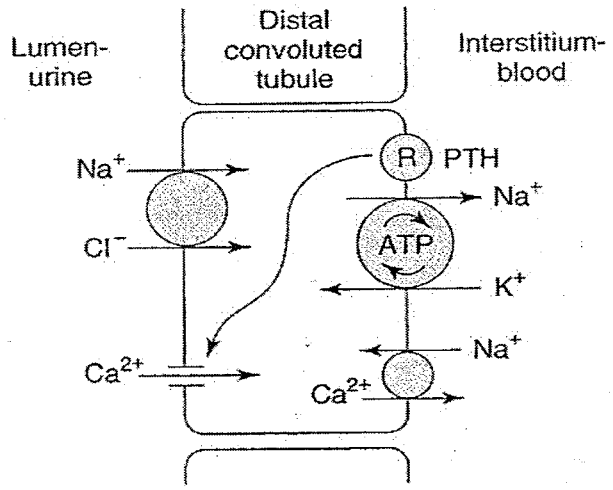


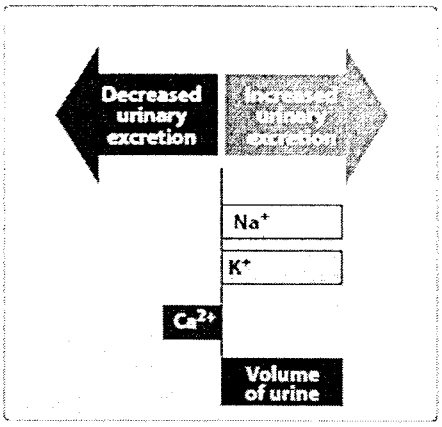
Figure 15–4. Mechanism of sodium and chloride reabsorption in the distal convoluted tubule. A separate reabsorptive mechanism, modulated by parathyroid hormone, is present for movement of calcium into the cell from the urine. This calcium must be transported via the sodium-calcium exchanger back into the blood. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

Thiazide Diuretics

- Developed to be more potent carbonic anhydrase inhibitor
- Contain unsubstituted sulfonamide group
- Orally absorbed well. Chlorothiazide is the only parenteral form. Indapamide is excreted mainly by the biliary system (less accumulated so more useful in the treatment of advanced renal failure)
- Secreted by the organic acid secretory system in the proximal tubule and competes with uric acid secretion
- Enhances Ca^{2+} reabsorption at both the PCT and DCT
- Inhibits NaCl symport at the DCT

Thiazide diuretics: Toxicity

- Decreased glucose tolerance (hyperglycemia)
- Hypercalcemia
- Allergic reactions, Skin rash. Sulfonamide sensitivity
- Hyperuricemia
- Hypokalemia



Thiazide diuretics: Uses

- Edema
- Ineffective when GFR less than 30-40 ml/min except metolazone
- Hypertension, CHF (1st choice, effect in 3-7 days)
- Osteoporosis, hypercalciuria (beneficial in calcium oxalate stones)
- Nephrogenic diabetes insipidus

Thiazide diuretics: Dosage

- Hydrochlorothiazide 12.5-50 mg daily\
  - Prototypical
- Chlorthalidone 25-50 mg daily
- Metolazone 2.5-10 mg daily
  - Thiazide-like in action, not structure
- Indapamide 2.5-10 mg daily
  - Thiazide-like in action, not structure

Diuretic agents

- Carbonic anhydrase inhibitor
- Osmotic agents
- Loop agents
- Thiazides
- Aldosterone antagonists
- ADH antagonists

Sodium and water regulation by the nephron: distal nephron

- The distal segment of the DCT and the upper collecting duct has a sodium potassium hydrogen antiporter which reabsorbs 1-2 % of the sodium
- The activity of this transporter is dependent on the tubular concentration of sodium. The more sodium delivered to this segment of the nephron, the more sodium absorbed
- Aldosterone stimulates the reabsorption of sodium with increase in urinary losses of potassium and hydrogen ions through this transporter

Sodium and water regulation by the nephron: distal nephron

- Water is reabsorbed in the collecting duct through pores regulated by antidiuretic hormone (ADH) or vasopressin released by the posterior pituitary
- This leads to a more concentrated urine and reduced urine outflow (anti diuresis)
- In the final urine, less than 1% of the original filtered sodium remains

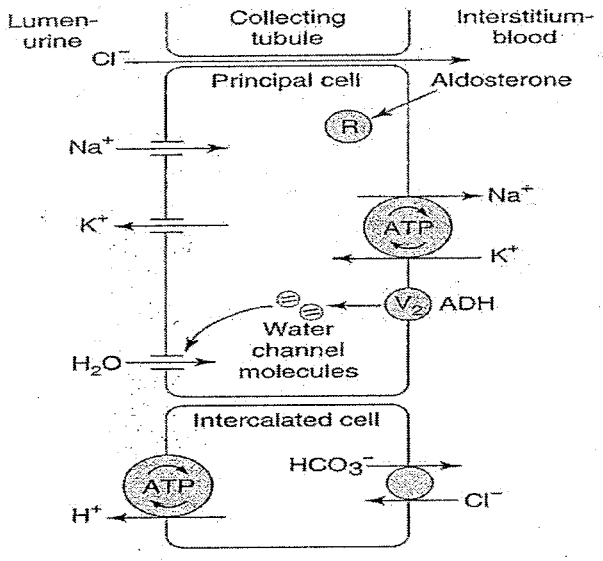


Figure 15–5. Mechanism of sodium, potassium, and hydrogen ion movement and water reabsorption in the collecting tubule cells. Synthesis of Na^+/K^+ ATPase and sodium and potassium channels is under the control of aldosterone, which combines with an intracellular receptor, *R*, before entering the nucleus. ADH acts on its receptor, V_2, to facilitate the insertion of water channels from storage vesicles into the luminal membrane. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 9th ed. McGraw-Hill, 2004.)

Potassium Sparing Diuretics

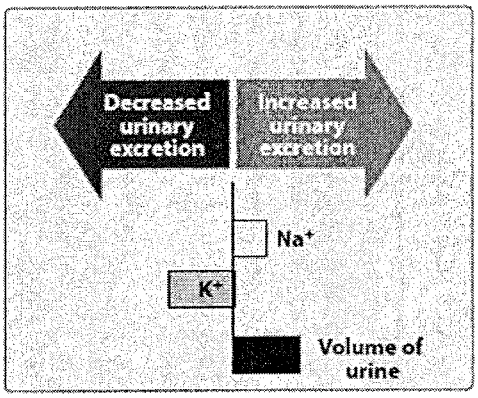
- Reduces Na absorption in the collecting tubules and ducts
- This site is regulated by aldosterone
- Spironolactone and eplerenone are aldosterone receptor antagonists which reduce the intracellular expression of Na^+/K^+ ATPase pump
- Amiloride and Triamterene interfere with Na^+ entry through the epithelial sodium ion channels in the apical membrane of the collecting tubule

Potassium Sparing Diuretics

- Amiloride and triamterene are both organic bases and transported by the organic base secretory mechanism in the proximal tubule
- NaCl excretion is modestly increased
- May be contraindicated if renal failure present, hyperkalemia, or in combination with other K sparing diuretics, angiotensin converting enzyme inhibitors
- Must be cautious if K supplements taken

Potassium Sparing Diuretics: Uses

- Combined with other diuretics to prevent hypokalemia, in particular thiazide diuretics
- Spironolactone the diuretic of choice for hepatic cirrhosis
- Spironolactone is used in secondary hyperaldosteronism



Aldosterone Antagonists: Toxicity

- Eplerenone less toxicity
- Life threatening hyperkalemia
- May induce metabolic acidosis in cirrhotic patients
- Gynecomastia, impotence, decreased libido, hirsutism, deepening of voice, and menstrual irregularities
- Peptic ulcers

Potassium Sparing Diuretics: Combinations/Dosage

- Maxzide (Triamterene 75 mg/HCTZ 50 mg)
- Midamor (Amiloride 5 mg)
- Moduretic (Amiloride 5 mg/HCTZ 50 mg)
- Dyazide (Triamterene 37.5 mg/HCTZ 25 mg)
- Aldactone (Spironolactone 25, 50, 100 mg
- Aldactazide (Spironolactone 25 mg/HCTZ 50 mg)

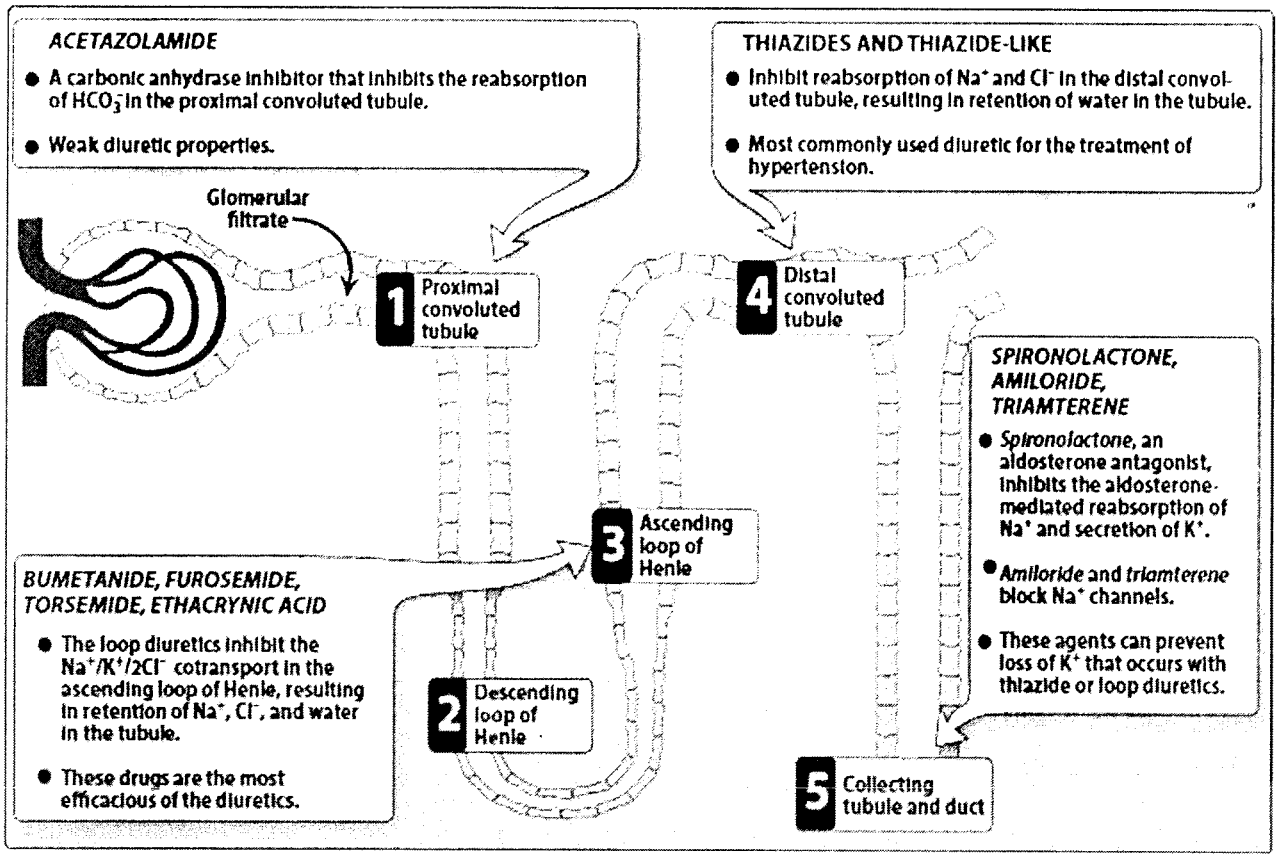


Figure 18.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.