DIURETICS

REFERENCES

- BRODY'S HUMAN PHARMACOLOGY, 4TH EDITION
- GUYTON HUMAN PHYSIOLOGY

OUTLINE

1. SITES OF DRUG ACTION

2. OSMOTIC DIURETICS

3. CARBONIC ANHYDRASE INHIBITORS

4. THIAZIDE DIURETICS

5. LOOP DIURETICS

6. POTASSIUM-SPARING DIURETICS

DEFINITIONS

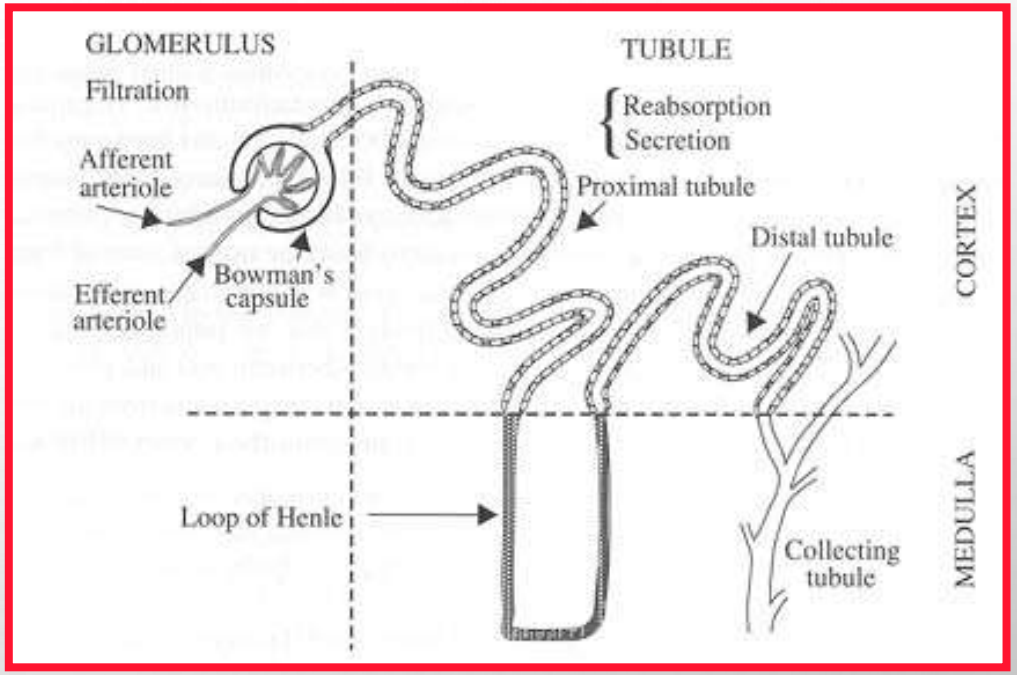
Diuretic: substance that promotes the excretion of urine

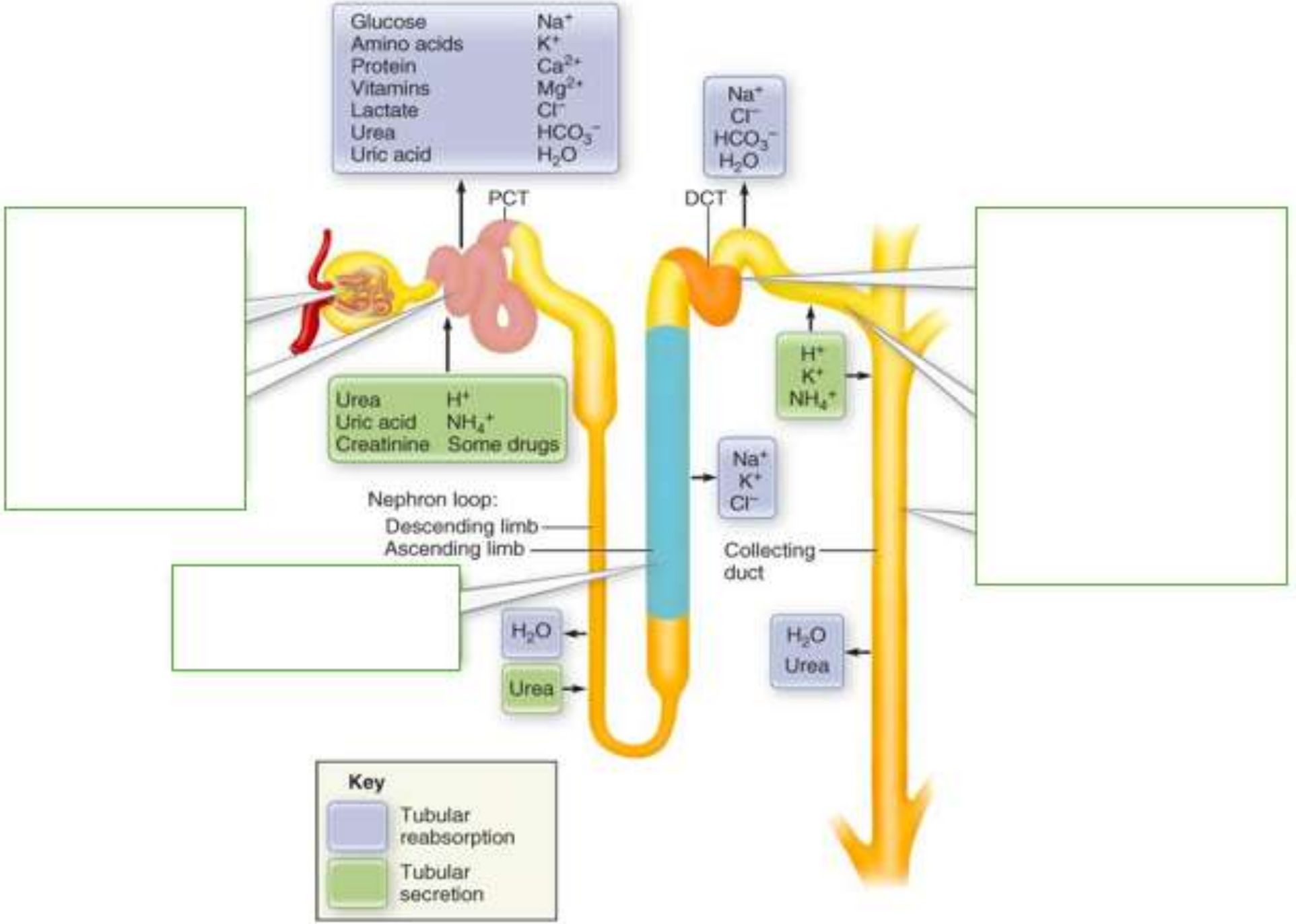
- **caffeine, yerba mate, nettles, cranberry juice, alcohol**

- **Natriuretic: substance that promotes the renal excretion of Na+**

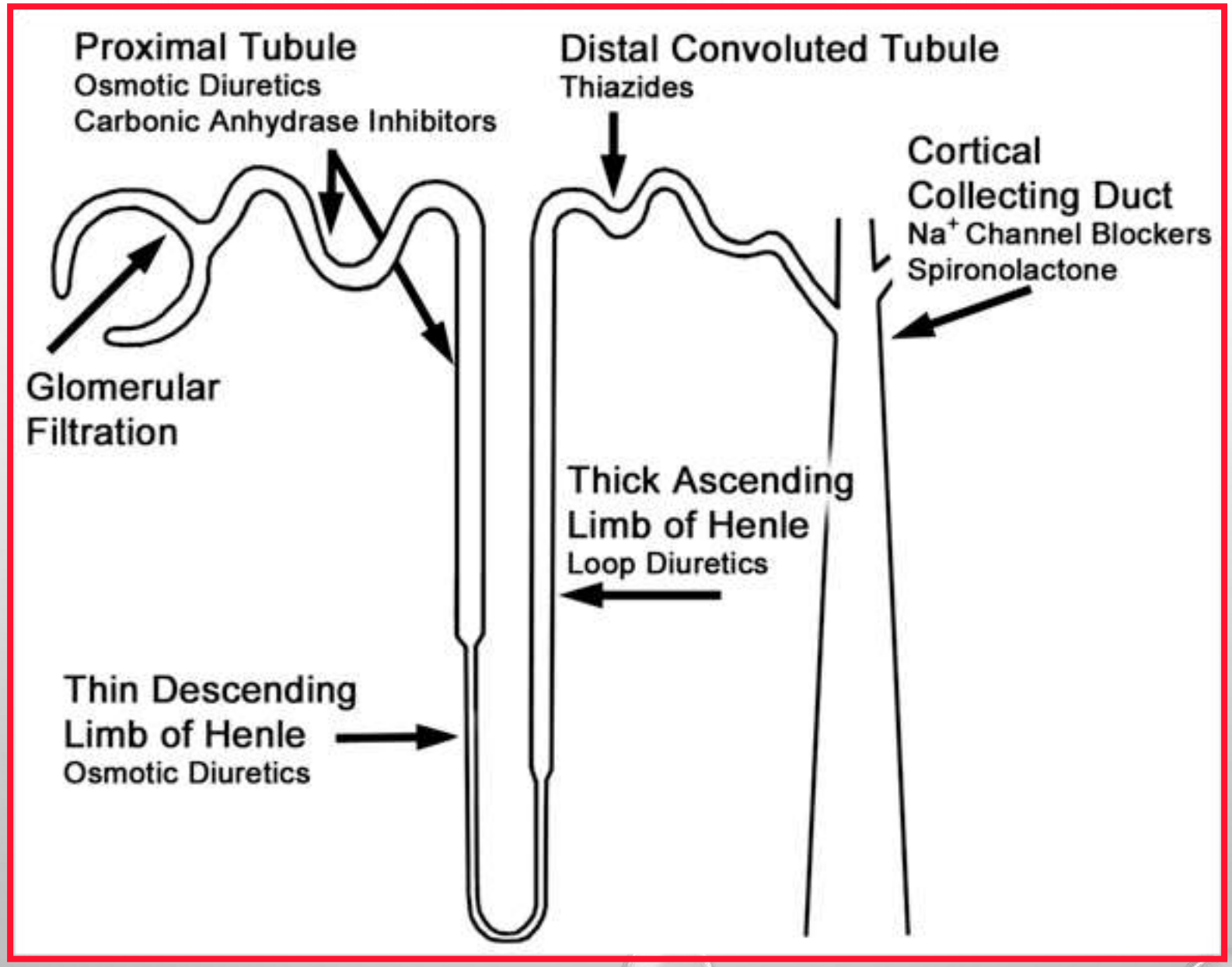
RENAL PHYSIOLOGY

- renal epithelial transport
- tubular reabsorption
- proximal tubule
- loop of Henle
- thick ascending limb
- distal convoluted tubule
- collecting tubule
- tubular secretion
- collecting tubules




Glucose
Amino acids
Protein
Vitamins
Lactate
Urea
Uric acid
Na+
K+
Ca2+
Mg2+
Cl−
HCO3−
H2O
PCT
DCT
Na+
Cl−
HCO3−
H2O
Urea
Uric acid
Creatinine
H+
NH4+
Some drugs
H+
K+
NH4+
Na+
K+
Cl−
Nephron loop:
Descending limb
Ascending limb
Collecting duct
H2O
Urea
H2O
Urea
Key
Tubular reabsorption
Tubular secretion

SUMMARY: SITES OF ACTION

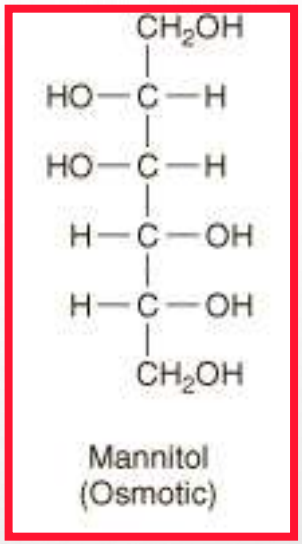


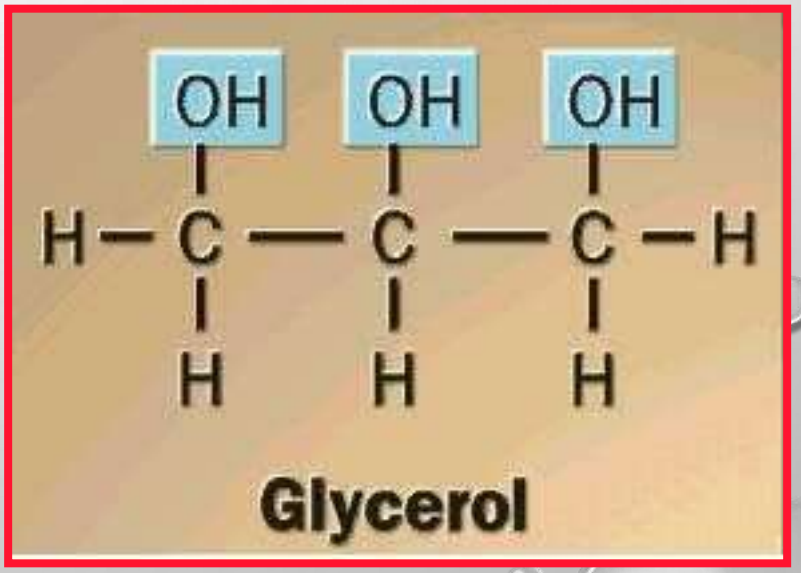
OSMOTIC DIURETICS

do not interact with receptors or directly block renal transport

- activity dependent on development of osmotic pressure

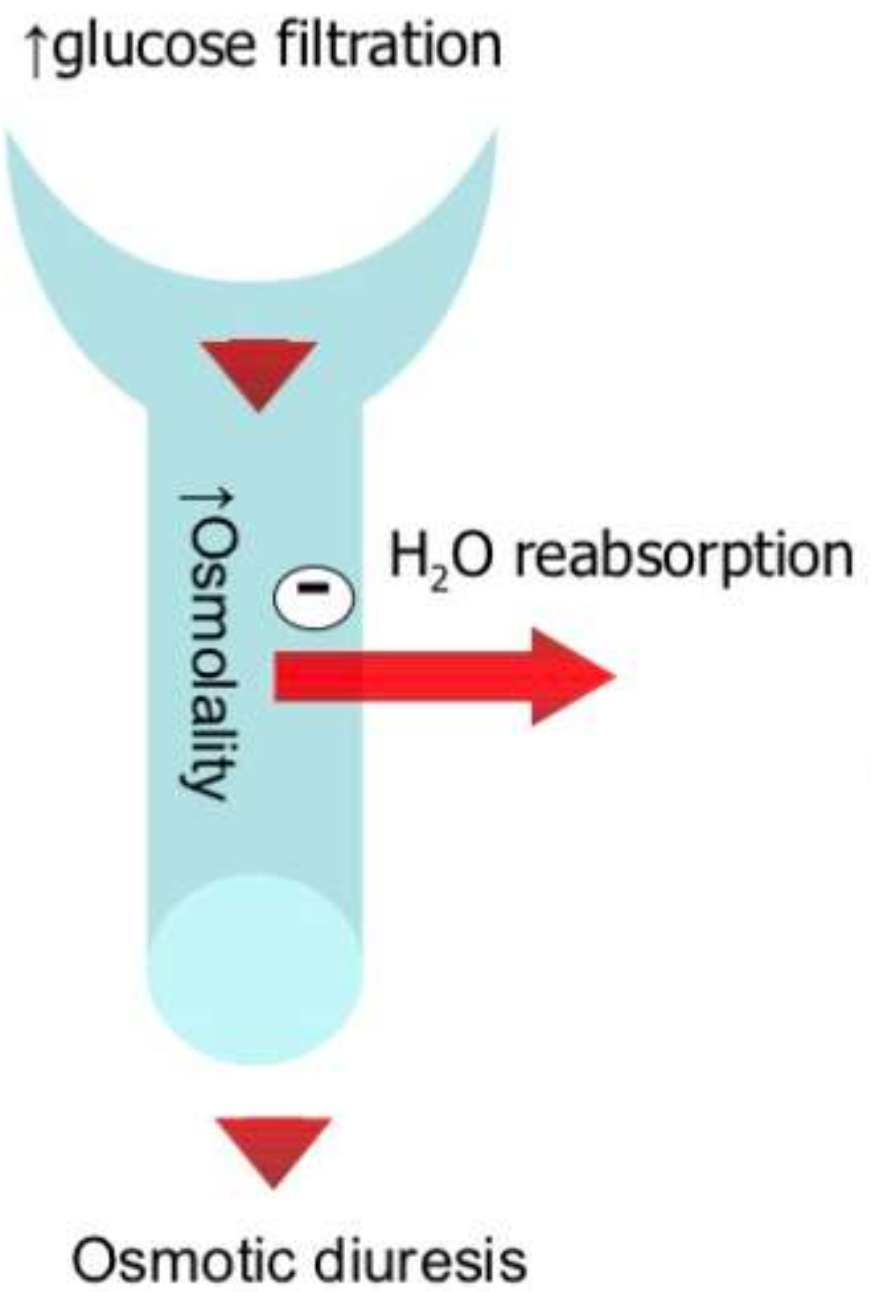
- Mannitol (prototype)
- Urea
- Glycerol
- Isosorbide





MECHANISM OF ACTION

- osmotic diuretics are not reabsorbed
- increases osmotic pressure specifically in the proximal tubule and loop of Henle
- prevents passive reabsorption of H_2O
- osmotic force solute in lumen > osmotic force of reabsorbed Na^+
- increased H_2O and Na^+ excretion



Osmotic diuresis

Increased blood glucose

↓

↑Glomerular filtration of glucose

↓

↑Osmotic pressure of renal tubular fluid

↓

↓Water reabsorption

↓

Osmotic diuresis

THERAPEUTIC USES

Mannitol

- drug of choice: non-toxic, freely filtered, non-reabsorbable and non-metabolized
- administered prophylatically for acute renal failure secondary to trauma, CVS disease, surgery or nephrotoxic drugs
- short-term treatment of acute glaucoma
- infused to lower intracranial pressure
- Urea, glycerol and isosorbide are less efficient
- can penetrate cell membranes

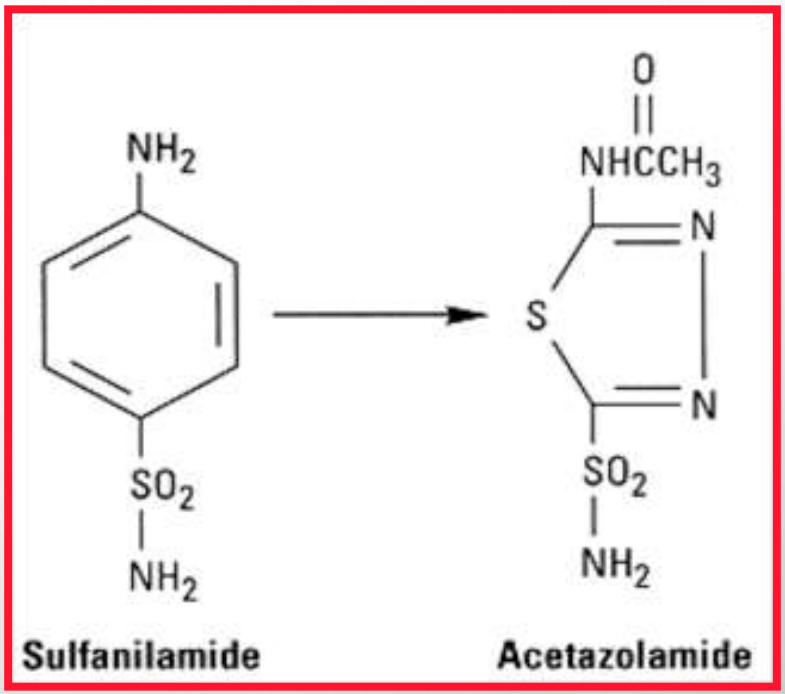
SIDE EFFECTS

- increased extracellular fluid volume
- cardiac failure
- pulmonary edema
- hypernatremia
- hyperkalemia secondary to diabetes or impaired renal function
- headache, nausea, vomiting

CARBONIC ANHYDRASE INHIBITORS

- limited uses as diuretics

- Acetazolamide

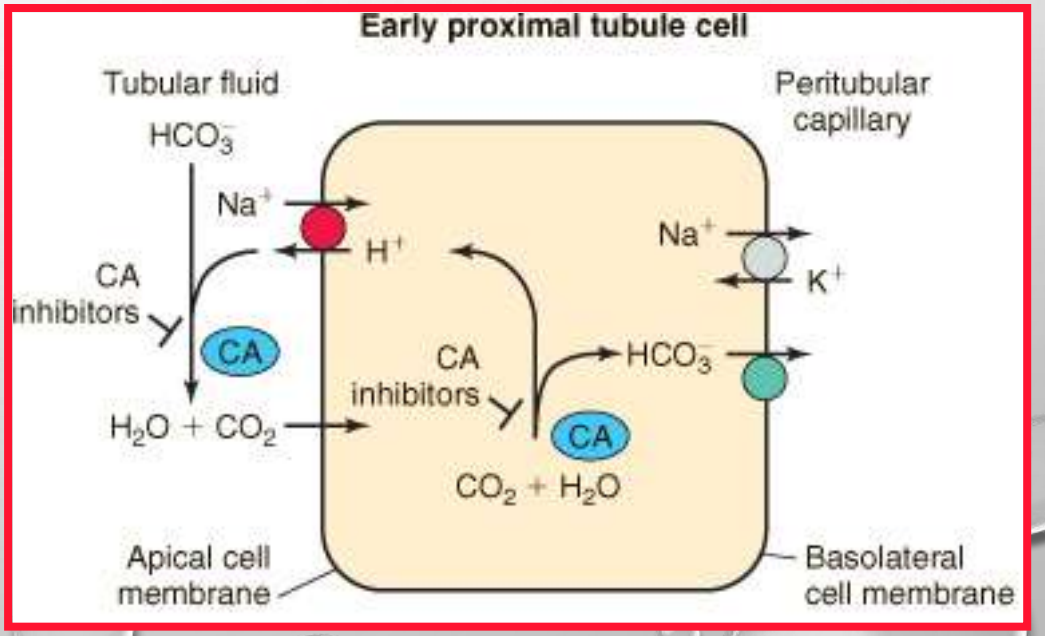


- prototype carbonic anhydrase inhibitor

- developed from sulfanilamide (caused metabolic acidosis and alkaline urine)

MECHANISM OF ACTION

- inhibits carbonic anhydrase in renal proximal tubule cells
- carbonic anhydrase catalyzes formation of HCO3- and H+ from H2O and CO2
- inhibition of carbonic anhydrase decreases [H+] in tubule lumen
- less H+ for for Na+/H+ exchange
- increased lumen Na+, increased H2O retention



THERAPEUTIC USES

- used to treat chronic open-angle glaucoma
- aqueous humor has high [HCO_3^-]
- acute mountain sickness
- prevention and treatment
- metabolic alkalosis
- sometimes epilepsy
- mostly used in combination with other diuretics in resistant patients

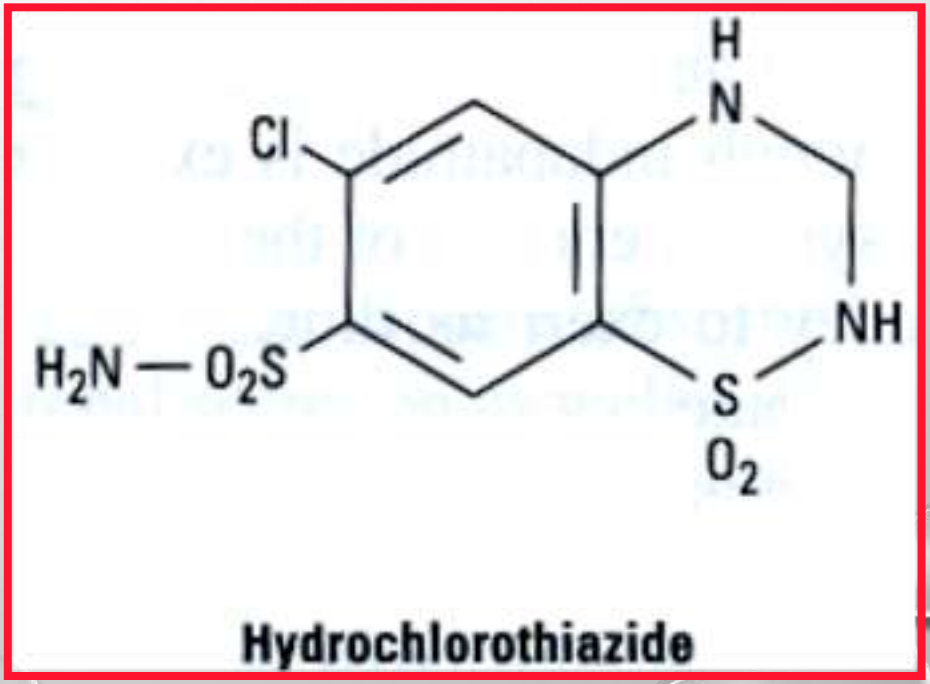
SIDE EFFECTS

- rapid tolerance
- increased HCO3- excretion causes metabolic acidosis
- drowsiness
- fatigue
- CNS depression
- paresthesia (pins and needles under skin)
- nephrolithiasis (renal stones)
- K+ wasting

THIAZIDE DIURETICS

active in distal convoluted tubule

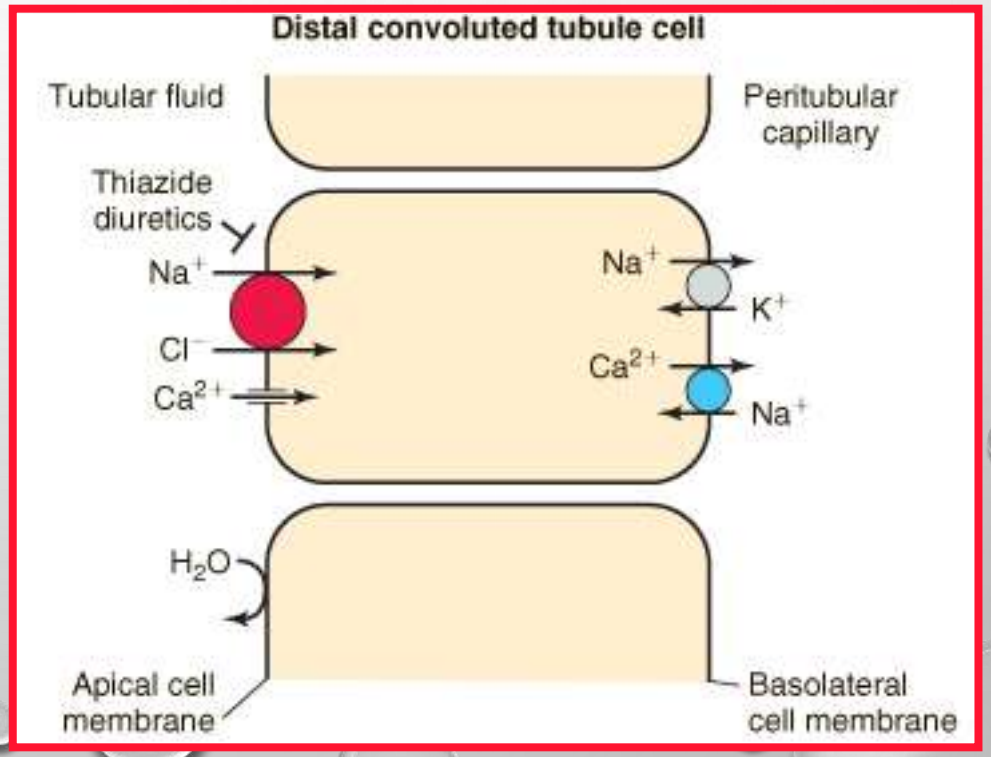
- **Chlorothiazide (prototype)**
- **Hydrochlorothiazide**
- **Chlorthalidone**
- **Metolazone**



Hydrochlorothiazide

MECHANISM OF ACTION

- inhibit Na+ and Cl- transporter in distal convoluted tubules
- increased Na+ and Cl- excretion
- weak inhibitors of carbonic anhydrase, increased HCO3- excretion
- increased K+/Mg2+ excretion
- decrease Ca2+ excretion



THERAPEUTIC USES

- hypertension
- congestive heart failure
- hypercalciuria: prevent excess Ca2+ excretion to form stones in ducts
- osteoperosis
- nephrogenic diabetes insipidus
- treatment of Li+ toxicity

PHARMACOKINETICS

- orally administered
- poor absorption
- onset of action in ~ 1 hour
- wide range of T 1/2 amongst different thiazides, longer then loop diuretics
- free drug enters tubules by filtration and by organic acid secretion

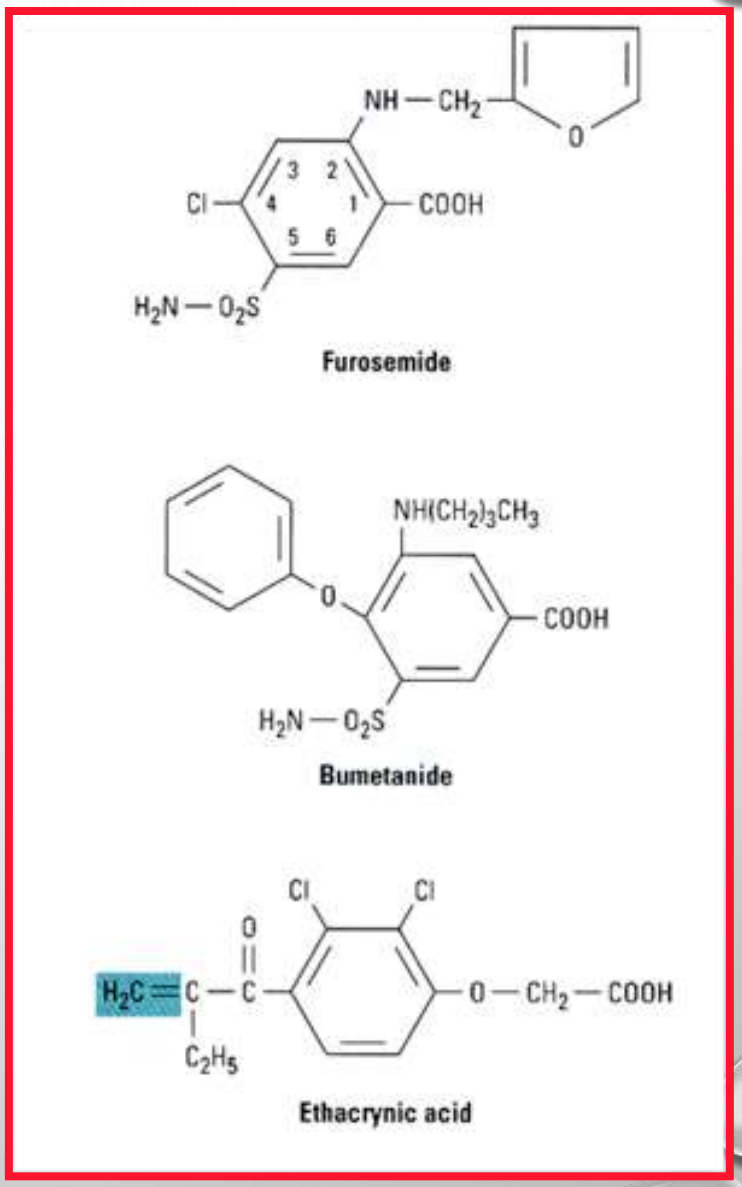
SIDE EFFECTS

- hypokalemia
- increased Na+ exchange in CCD
- volume-contraction induced aldosterone release
- hyponatremia
- hyperglycemia
- diminished insulin secretion
- elevated plasma lipids
- hyperuricemia
- hypercalcemia

LOOP DIURETICS

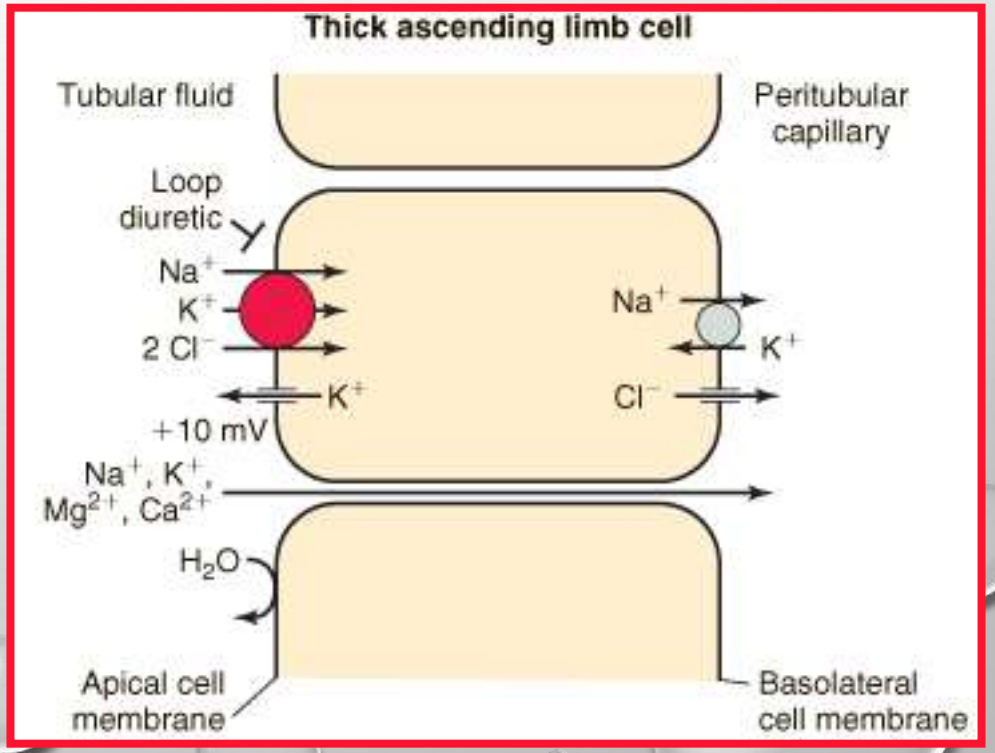
active in “loop” of Henle

- Furosemide (prototype)
- Bumetanide
- Torsemide
- Ethacrynic acid



MECHANISM OF ACTION

- enter proximal tubule via organic acid transporter
- inhibits apical Na-K-2Cl transporter in thick ascending loop of henle
- competes with Cl- binding site
- enhances passive Mg2+ and Ca2+ excretion
- increased K+ and H+ excretion in CCD
- inhibits reabsorption of ~25% of glomerular filtrate



THERAPEUTIC USES

- edema: cardiac, pulmonary or renal
- chronic renal failure or nephrosis
- hypertension
- hypercalcemia
- acute and chronic hyperkalemia

PHARMACOKINETICS

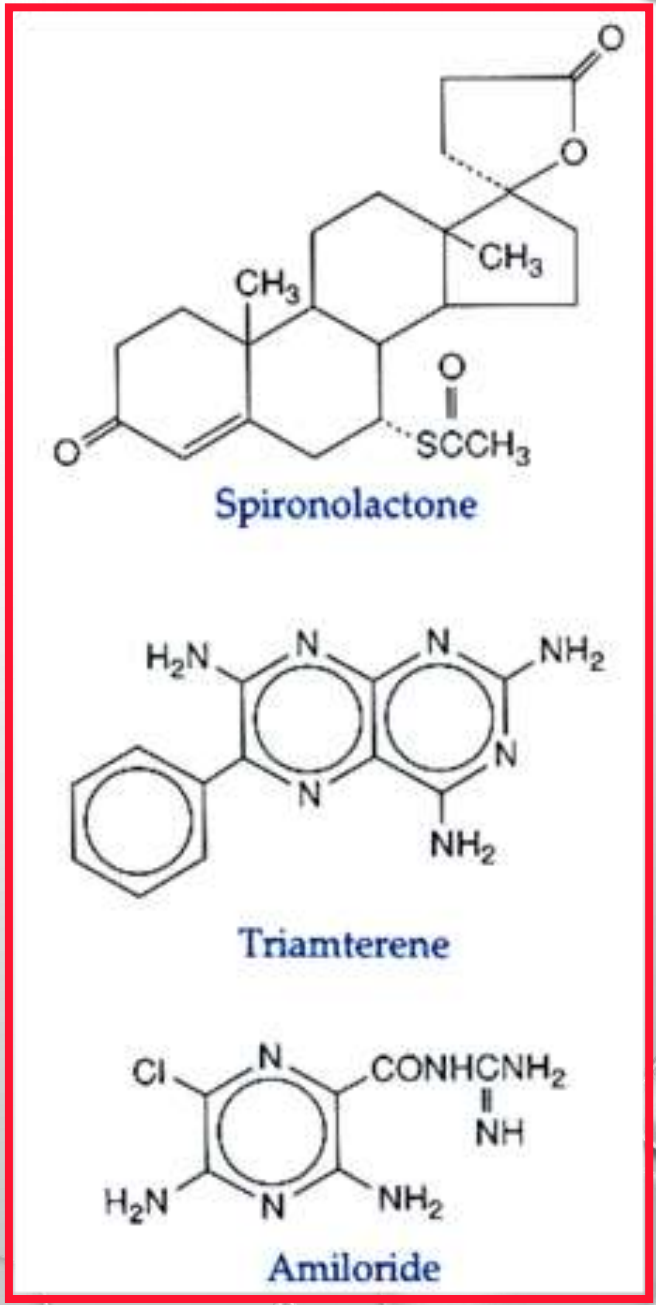
- orally administered, rapid absorption
- rapid onset of action
- bound to plasma proteins: displaced by warfarin, and clofibrate
- increase toxicity of cephalosporin antibiotics and lithium
- additive toxicity with other ototoxic drugs
- inhibitors of organic acid ion transport decrease potency (i.e. probenecid, NSAID's)

SIDE EFFECTS

- hypokalemia
- hyperuricemia
- metabolic alkalosis
- hyponatremia
- ototoxicity
- Mg2+ depletion

K+ SPARING DIURETICS

- three groups
- steroid aldosterone antagonists
- spironolactone, eplerenone
- Pteridines
- triamterene
- Pyrazinoylguanidines
- amiloride



MECHANISM OF ACTION

K+ sparing diuretics function in CCD

decrease Na+ transport in collecting tubule

Spironolactone

competitive antagonist for mineralocorticoid receptor

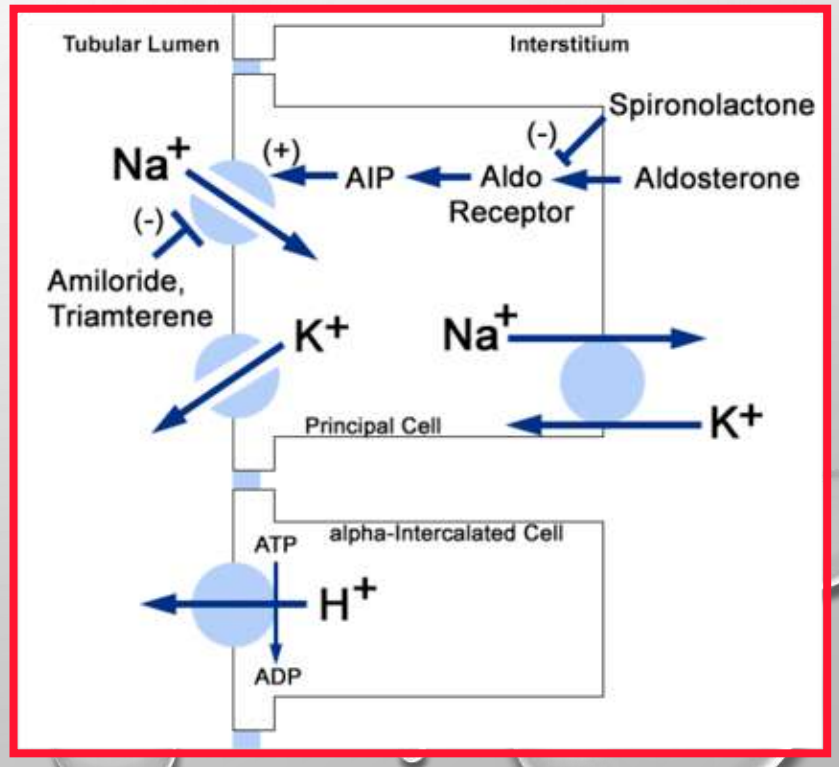
prevents aldosterone stimulated increases in Na+ transporter expression

Triamterene/Amiloride

organic bases

secreted into lumen by proximal tubule cells

inhibit apical Na+ channel



THERAPEUTIC USES

primary hyperaldosteronism (adrenal adenoma, bilateral adrenal hyperplasia)

- **congestive heart failure**
- **cirrhosis**
- **nephrotic syndrome**
- **in conjunction with K+ wasting diuretics**

PHARMACOKINETICS

- **Spironolactone**

orally administered

aldactazide: spironolactone/thiazide combo

- **Amiloride**

- **oral administration, 50% effective**
- **not metabolized**
- **not bound to plasma proteins**

- **Triamterine**

- **oral administration, 50% effective**
- **60% bound to plasma proteins**
- **liver metabolism, active metabolites**

SIDE EFFECTS

- **hyperkalemia: monitor plasma [K+]**
- **spironolactone: gynecomastia**
- **triamterene: megaloblastic anemia in cirrhosis patients**
- **amiloride: increase in blood urea nitrogen, glucose intolerance in diabetes mellitus**