Diuretic Drugs

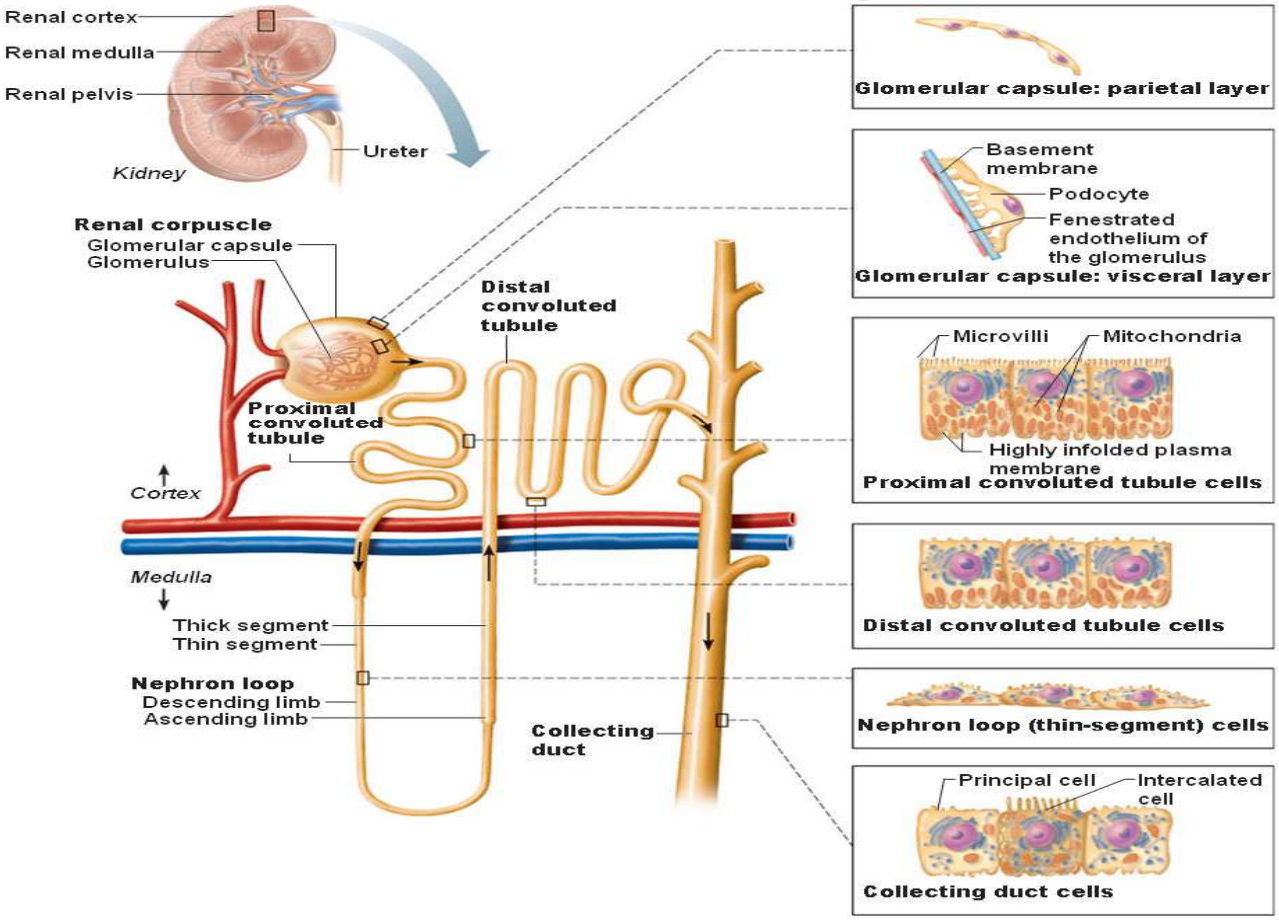
Dr. Shadi HOMSI

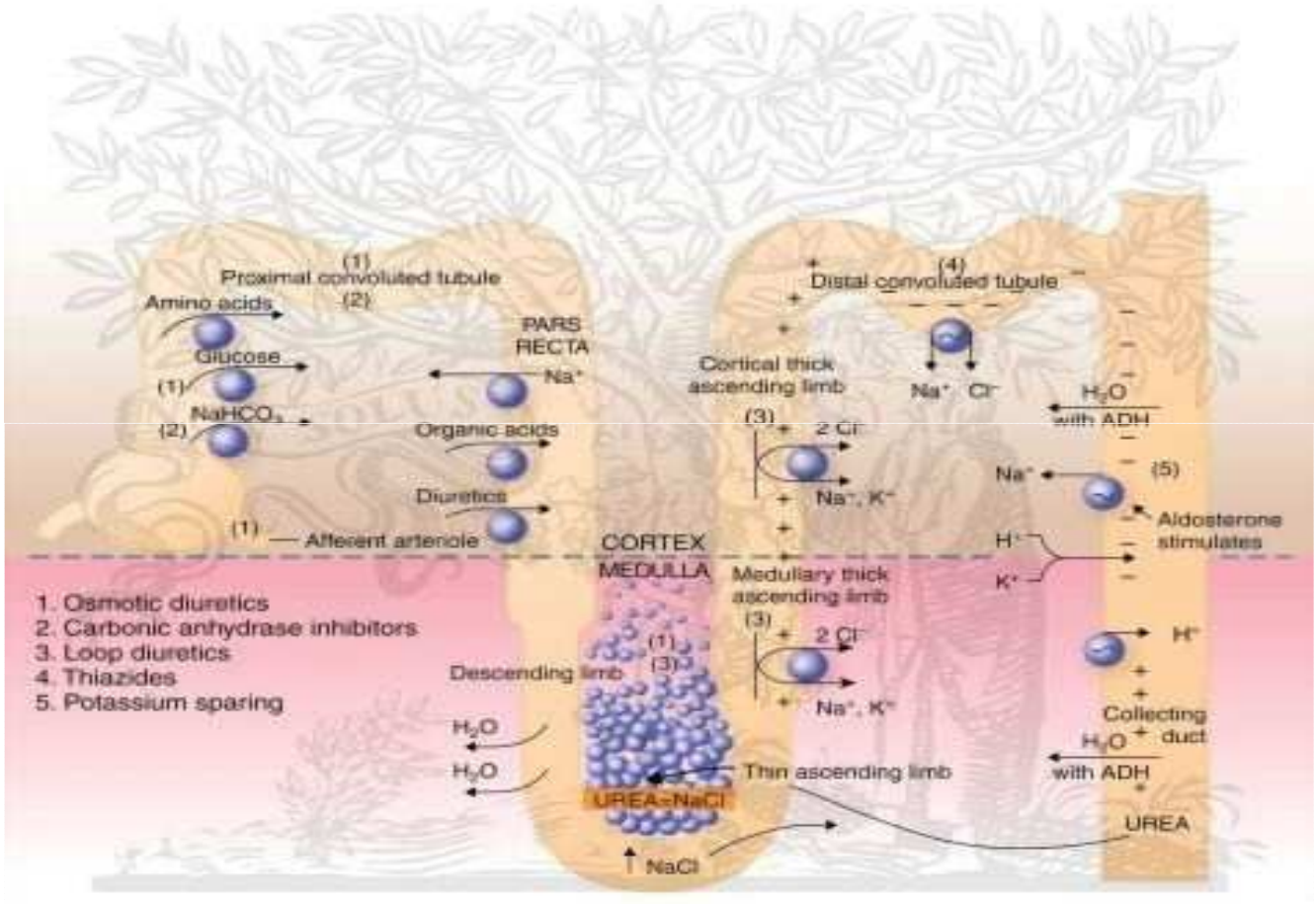
24-8-2016

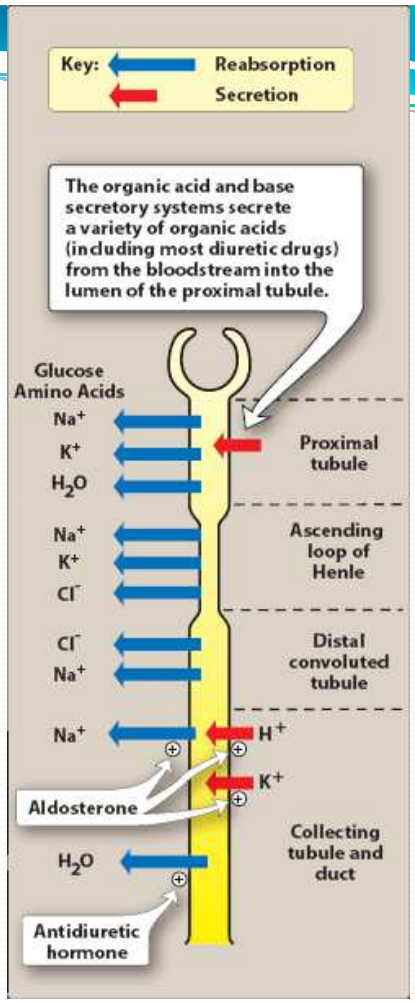
Diuretics

- Drugs that increase the volume of urine excreted.
- Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of Na+ at different sites in the nephron.
- Most commonly used for management of abnormal fluid retention (edema) or treatment of hypertension.

Renal Tubule







THIAZIDE DIURETICS

Chlorothiazide DIURIL, SODIUM DIURIL
Chlorthalidone THALITONE
Hydrochlorothiazide (HCTZ) MICROZIDE
Indapamide
Metolazone ZAROXOLYN

LOOP DIURETICS

Bumetanide
Ethacrynic acid EDECRIN
Furosemide LASIX
Torsemide DEMADEX

POTASSIUM-SPARING DIURETICS

Amiloride MIDAMOR
Eplerenone INSPRA
Spironolactone ALDACTONE
Triamterene DYRENIUM

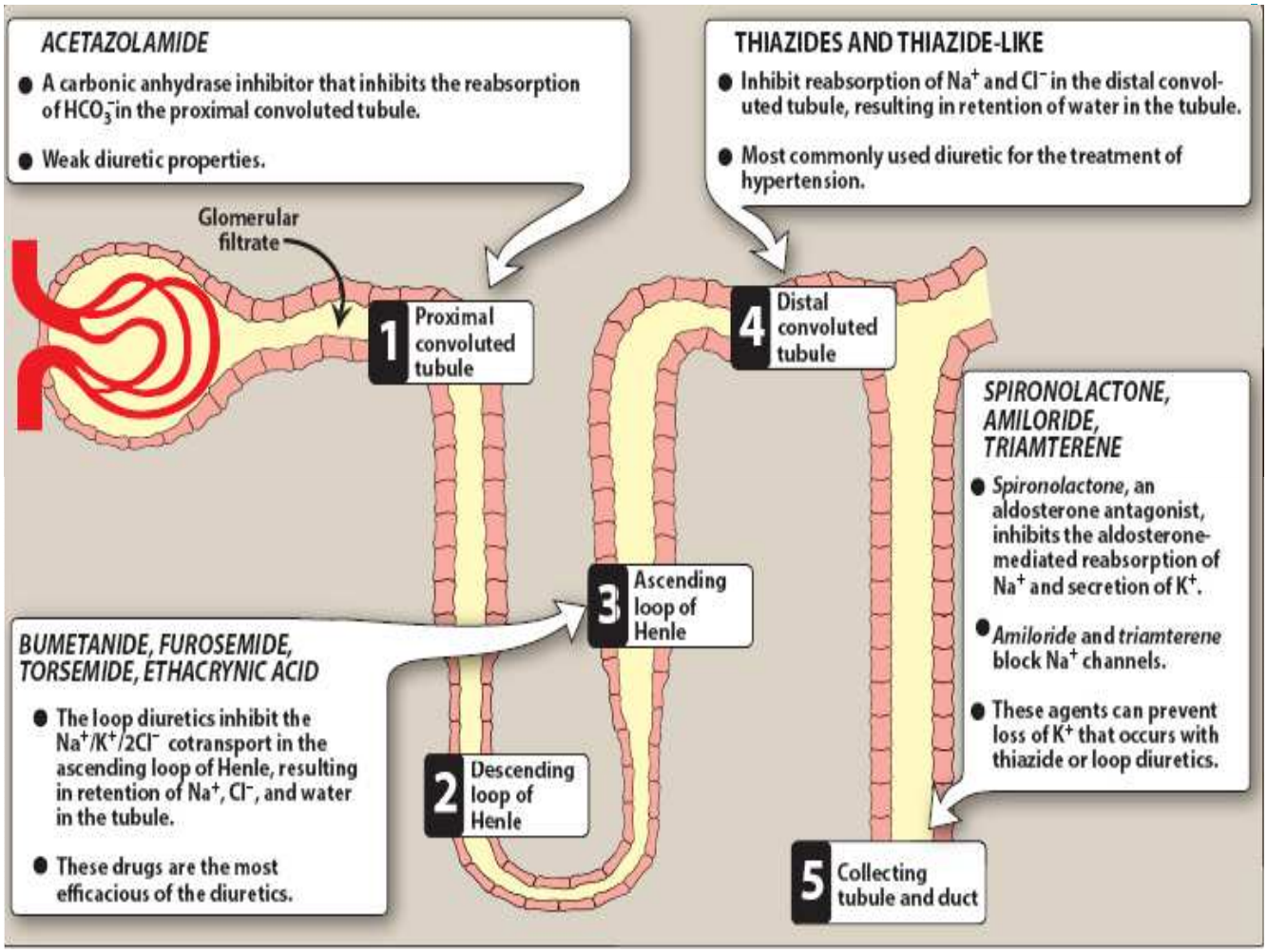
CARBONIC ANHYDRASE INHIBITORS

Acetazolamide DIAMOX

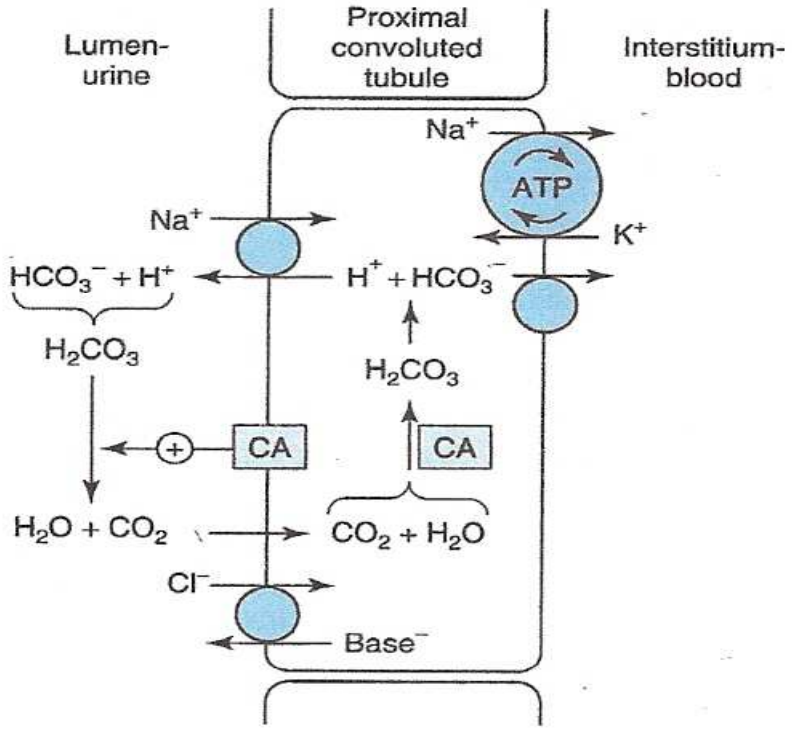
OSMOTIC DIURETICS

Mannitol OSMITROL
Urea

Figure 18.1
Summary of diuretic drugs.



Proximal convoluted tubule



1. CARBONIC ANHYDRASE INHIBITOR

- They are much less efficacious than the thiazide or loop diuretics.

Mechanism of action:

- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- The decreased ability to exchange Na+ for H+ in the presence of acetazolamide results in a mild diuresis.
- Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH.
- The loss of HCO_3^- causes a hyperchloremic metabolic acidosis.
- Phosphate excretion is increased by an unknown mechanism.

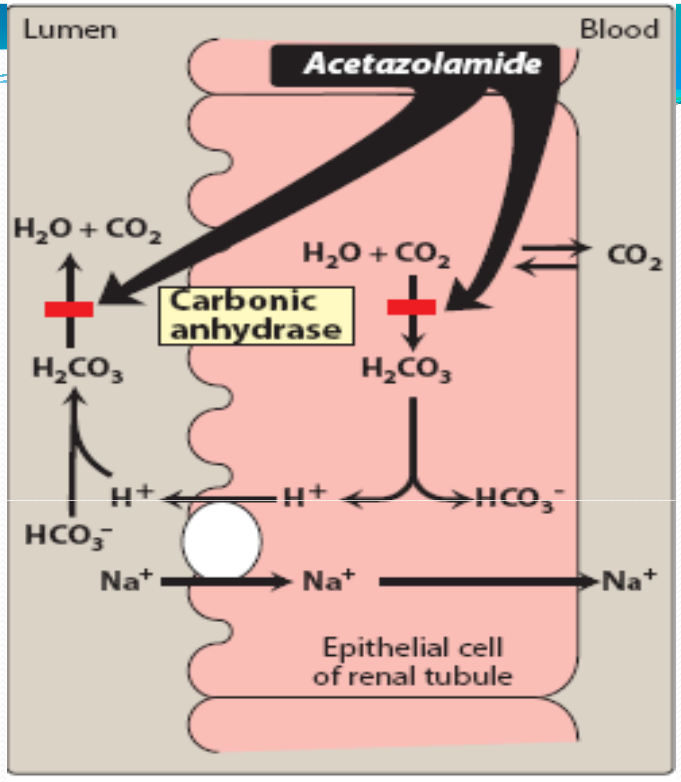


Figure 18.9
Role of carbonic anhydrase in sodium retention by epithelial cells of the renal tubule.

Pharmacokinetics:

- Acetazolamide can be administered orally or intravenously.
- It is approximately 90% protein bound
- eliminated renally.

Adverse effects:

- Metabolic acidosis (mild),
- Potassium depletion,
- Renal stone formation, drowsiness.

2. Therapeutic uses:

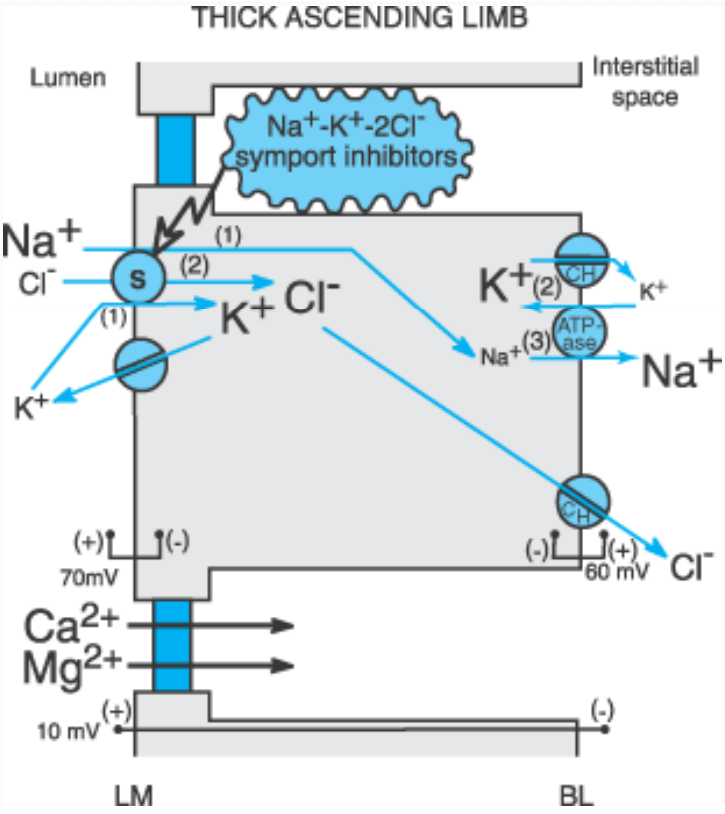
a. Glaucoma:

- Acetazolamide decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma.

b. Mountain sickness:

- Prophylaxis use of Acetazolamide prevents weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

Ascending Limb of Loop of Henle

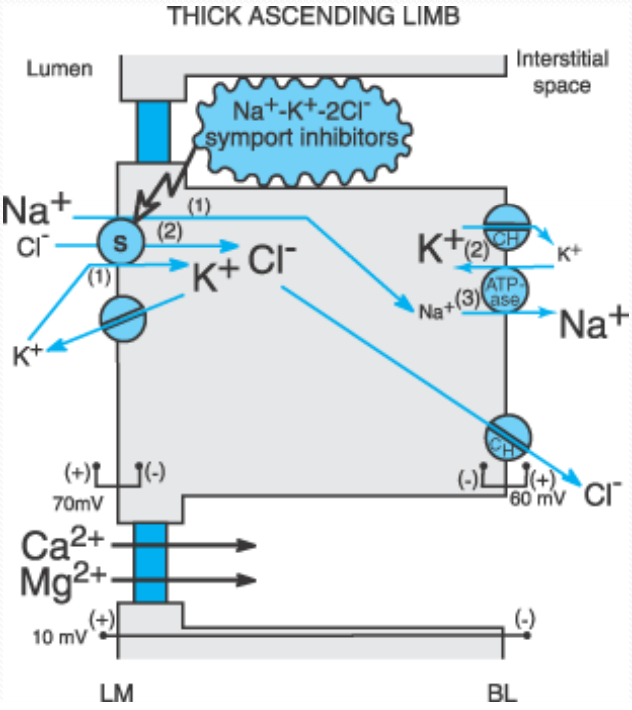


LOOP OR HIGH-CEILING DIURETICS

- Have their major diuretic action on the ascending limb of the loop of Henle.
- These agents have the greatest diuretic effect of all the diuretic drugs.
- Have the highest efficacy in mobilizing Na+ and Cl– from the body.
- Furosemide is the most commonly used of these drugs.
- Bumetanide and torsemide are much more potent than furosemide, and the use of these agents is increasing.
- Ethacrynic acid is used infrequently due to its adverse effect profile.
- Rarely used alone to treat hypertension.

1. Mechanism of action:

- Loop diuretics inhibit the cotransport of Na+/K+/2Cl– in the ascending limb of the loop of Henle → ↓ reabsorption of these ions.



2. Actions:

- Increase the Ca2+ content of urine.
- Increase renal blood flow, possibly by enhancing prostaglandin synthesis.
- NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics.

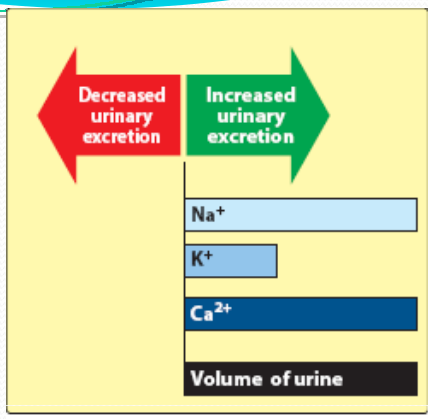


Figure 18.6
Relative changes in the composition of urine induced by loop diuretics.

Pharmacokinetics:

- Loop diuretics are administered orally or parenterally.
- Their duration of action is relatively brief (2 to 4 hours),
- They are secreted into urine.

Therapeutic uses:

- **Heart failure or renal impairment**: drugs of choice .
  - Diuretics are useful in the HF in :

1) relieve pulmonary congestion and peripheral edema.
2) decrease plasma volume and, subsequently, decrease venous return to the heart (preload) which decreases cardiac workload and oxygen demand.

  - Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency.

- **Emergency situations** (iv, rapid onset of action)
- **Hypercalcemia.**
- **Hyperkalemia.**

5. Adverse effects:

a. Ototoxicity:

b. Hyperuricemia:

c. Acute hypovolemia:

d. Potassium depletion:

e. Hypomagnesemia.

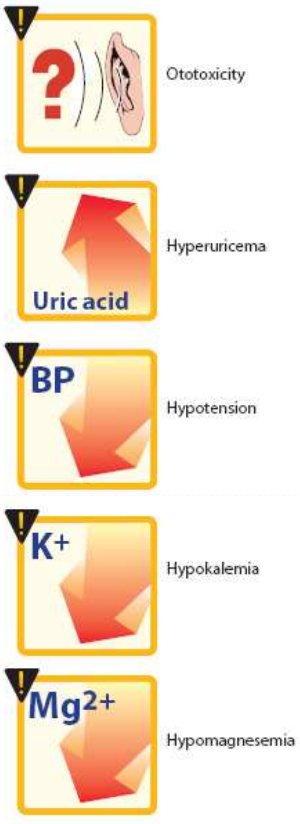
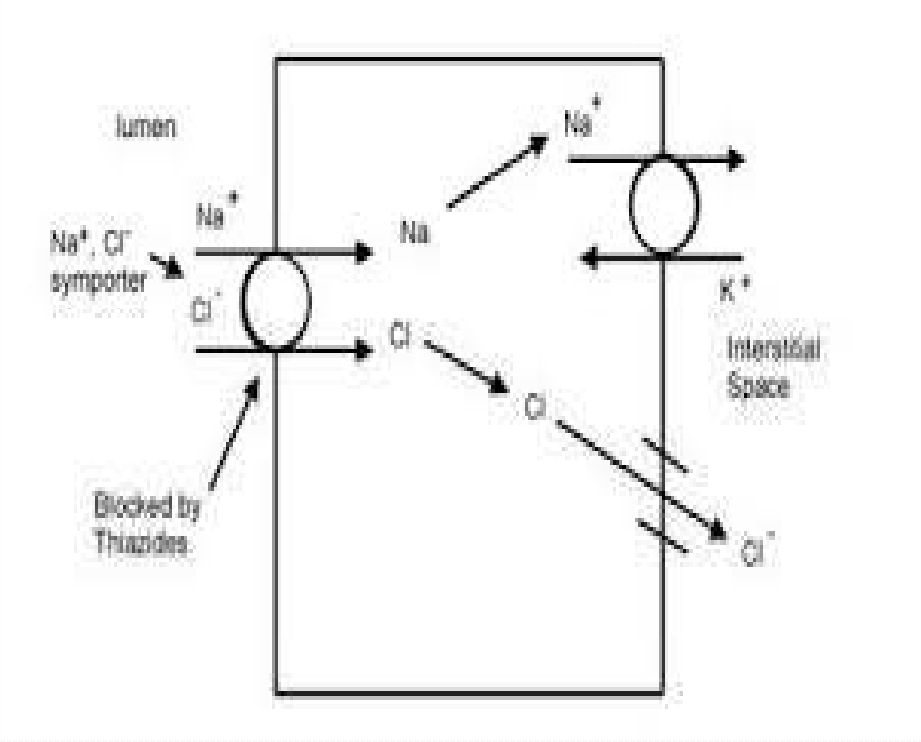
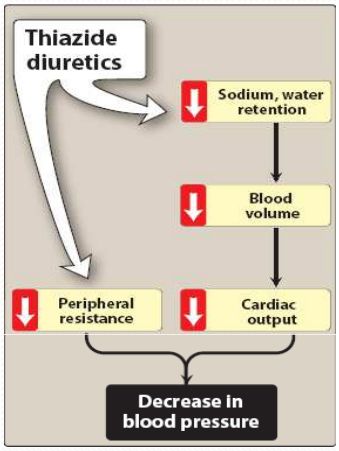


Figure 18.7
Summary of some adverse effects commonly observed with loop diuretics. BP = blood pressure.

Distal convoluted tubule



THIAZIDES AND RELATED AGENTS



- The most widely used diuretics (Sulfonamide derivatives)
- All thiazides affect the distal convoluted tubule
- All have equal maximum diuretic effects, differing only in potency.
- Called "low ceiling diuretics"
- Thiazide diuretics can be used as initial drug therapy for hypertension (unless there are compelling reasons to choose another agent).
- Useful in combination therapy (with β-blockers, ACE inhibitors, ARBs, and K-sparing diuretics).
- Not effective in patients with inadequate kidney function. (SOLUTION= Loop diuretics).

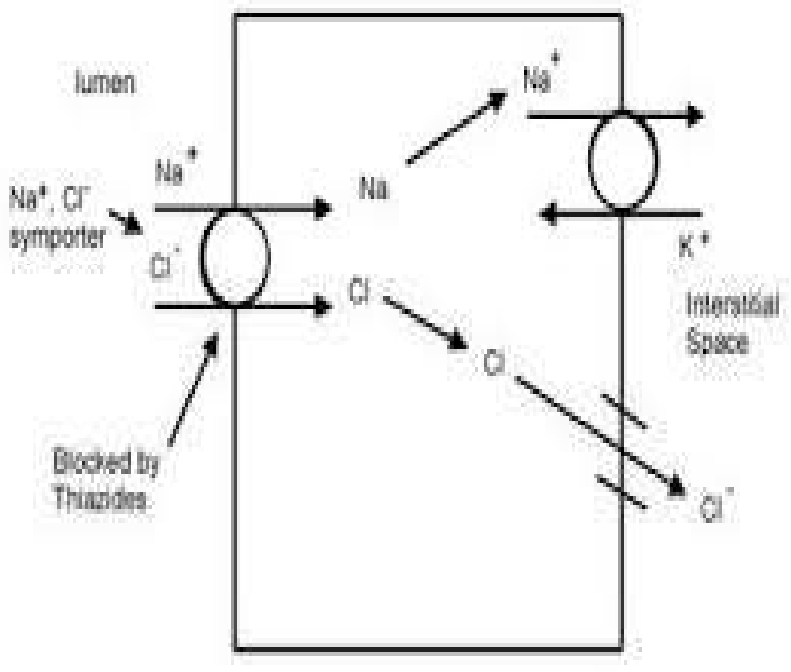
A. Thiazides

- Chlorothiazide : first orally active diuretic
- Hydrochlorothiazide is more potent but the efficacy is comparable to that of the parent drug.

1. Mechanism of action:

- Act mainly in the cortical region of the ascending limb of the loop of Henle and the distal convoluted tubule.
- Inhibition of a Na+/Cl– cotransporter on the luminal membrane of the tubules → ↓ the reabsorption of Na+.
- ↑ Na+ and Cl– in the tubular fluid.

Distal convoluted tubule



2. Actions:

a. Increased excretion of Na+ and Cl–

b. Loss of K+.

c. Loss of Mg2+

d. Decreased urinary calcium excretion.

e. Reduced peripheral vascular resistance

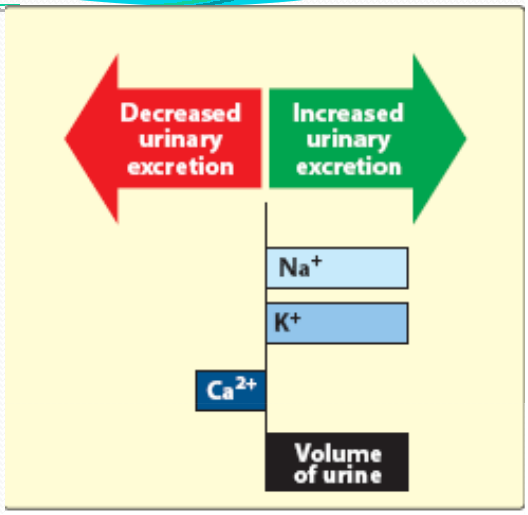


Figure 18.4
Relative changes in the composition of urine induced by thiazides and thiazide-like diuretics.

➢ **The efficacy may be diminished with concomitant use of NSAIDs.**

3. Therapeutic uses:

a. **Hypertension**

b. **Heart failure**

c. **Hypercalciuria**

d. **Diabetes insipidus:** Thiazides can substitute for ADH.

5. Adverse effects:

a. **Potassium depletion**
b. **Hyponatremia**
c. **Hyperuricemia.**
d. **Volume depletion**
e. **Hypercalcemia**
f. **Hyperglycemia:** can lead to glucose intolerance, due to impaired release of insulin and tissue uptake of glucose.

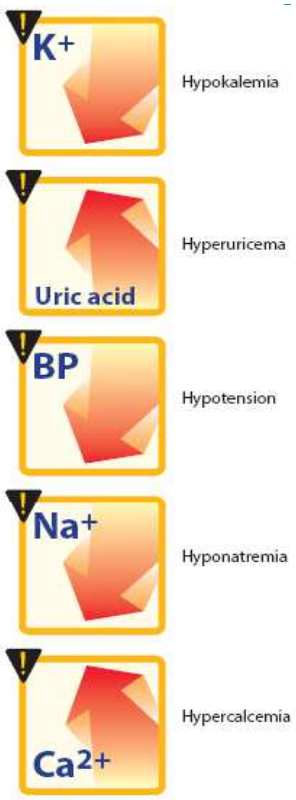


Figure 18.5
Summary of some adverse effects commonly observed with thiazides and thiazide-like diuretics. BP = blood pressure.

B. Thiazide-like diuretics

- These compounds lack the thiazide structure,
- Like the thiazides : sulfonamide group, their mechanism of action.
- The therapeutic uses and adverse effect profiles are similar to thiazides.

1. Chlorthalidone:

- It has a long duration of action
- Often used once daily to treat hypertension.

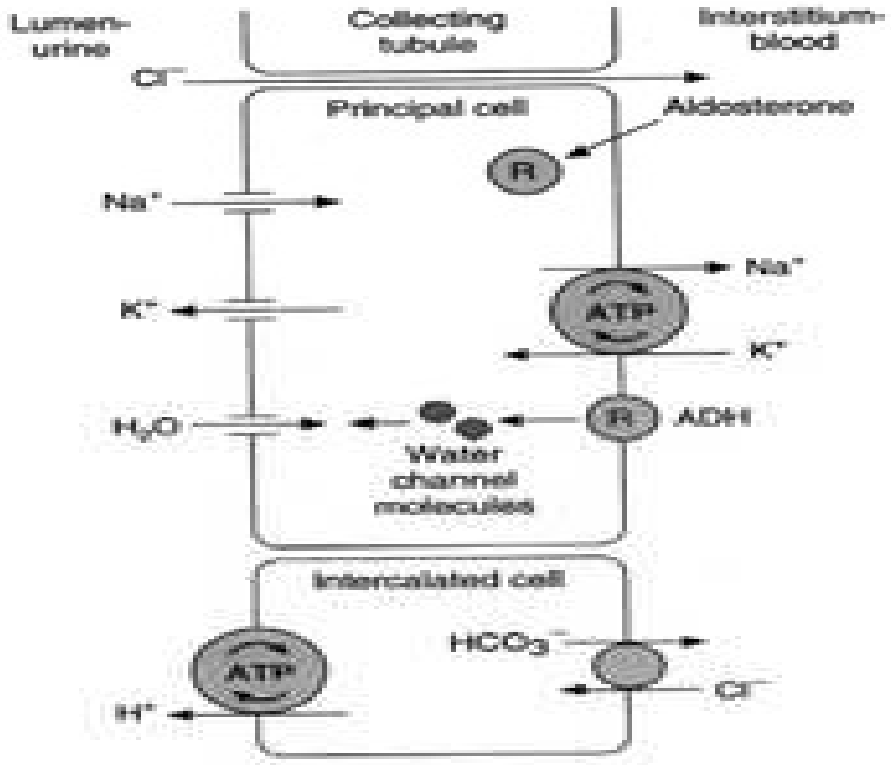
2. Metolazone:

- *More potent than* the thiazides.

3. Indapamide:

- Long duration of action.
- At low doses, significant antihypertensive action with minimal diuretic effects.

Collecting tubule and duct

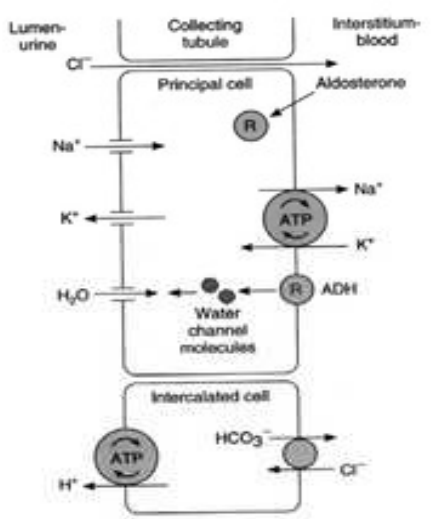


POTASSIUM-SPARING DIURETICS

- Act in the collecting tubule to inhibit Na+ reabsorption and K+ excretion.
- The major use is in the treatment of hypertension (most often in combination with a thiazide) and in heart failure (aldosterone antagonists).
- It is extremely important that potassium levels are closely monitored.
- There are drugs with two distinct mechanisms of action:
  - aldosterone antagonists and
  - sodium channel blockers.

A. Aldosterone antagonists:

1. Mechanism of action:



Spironolactone (Synthetic steroid):

- antagonizes aldosterone receptor rendering the spironolactone–receptor complex inactive.
- a lack of mediator proteins prevents Na+ reabsorption and K+ and H+ secretion.

Eplerenone:

- Aldosterone receptor antagonist,
- Has actions comparable to those of spironolactone,
- have less endocrine effects than spironolactone.

2. Actions:

- In most edematous states, blood levels of aldosterone are high, causing retention of Na+.
- Spironolactone antagonizes the activity of aldosterone, resulting in retention of K+ and excretion of Na+.
- the effect of these agents may be diminished by administration of NSAIDs.

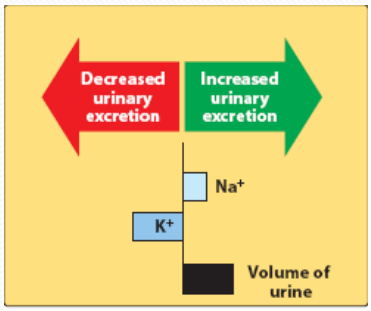


Figure 18.8
Relative changes in the composition of urine induced by potassium-sparing diuretics.

3. Therapeutic uses:

a. Diuretic:

- low efficacy in mobilizing Na+ from the body. / useful retention of K+.

b. Secondary hyperaldosteronism:

- clinical situations associated with secondary hyperaldosteronism (hepatic cirrhosis and nephrotic syndrome).

c. Heart failure:

- Aldosterone antagonists prevent remodeling in heart failure.
- Aldosterone antagonists are indicated in patients with severe stages of HF and recent myocardial infarction.

d. Resistant hypertension.

e. Ascites:

- Accumulation of fluid in the abdominal cavity (hepatic cirrhosis).

4. Pharmacokinetics:

- absorbed after oral administration and significantly bound to plasma proteins.
- Spironolactone is extensively metabolized and converted to several active metabolites.
- The metabolites, along with the parent drug, are thought to be responsible for the therapeutic effects.
- Spironolactone is a potent inhibitor of P-glycoprotein.
- Eplerenone is metabolized by cytochrome P450 3A4.

5. Adverse effects:

- Spironolactone can cause gastric upset.
- Spironolactone (chemically resembles some of the sex steroids) may induce gynecomastia in male patients and menstrual irregularities in female patients.
- Hyperkalemia, nausea, lethargy, and mental confusion can occur.
- Should be used with caution with other medications that can induce hyperkalemia, such as ACE inhibitors and potassium supplements.

B. Triamterene and amiloride

- Block Na+ transport channels in the collecting tubule, resulting in a decrease in Na+/K+ exchange , prevent the loss of K+.
- These agents are not very efficacious diuretics.
- Both triamterene and amiloride are commonly used in combination with other diuretics, usually for their potassium sparing properties.
- The side effects of triamterene include increased uric acid, renal stones, and K+ retention.

OSMOTIC DIURETICS

- Simple, hydrophilic chemical substances that are filtered through the glomerulus, such as mannitol and urea , result in some degree of diuresis.
- The presence of these substances results in a higher osmolarity of the tubular fluid and prevents further water reabsorption, resulting in osmotic diuresis.
- Used to increase water excretion rather than Na+ excretion, so they are not useful for treating conditions in which Na+ retention occurs.
- Are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma.
- Mannitol is not absorbed when given orally and should be given intravenously.
- Adverse effects include dehydration, hypo- or hypernatremia.