Diuretics

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Diuretics

- Diuretics (natriuretics) are drugs which cause a net loss of Na+ and water in urine.
- Application of diuretics in the management of hypertension has outstripped their use in edema.

Renal tubule transport mechanism

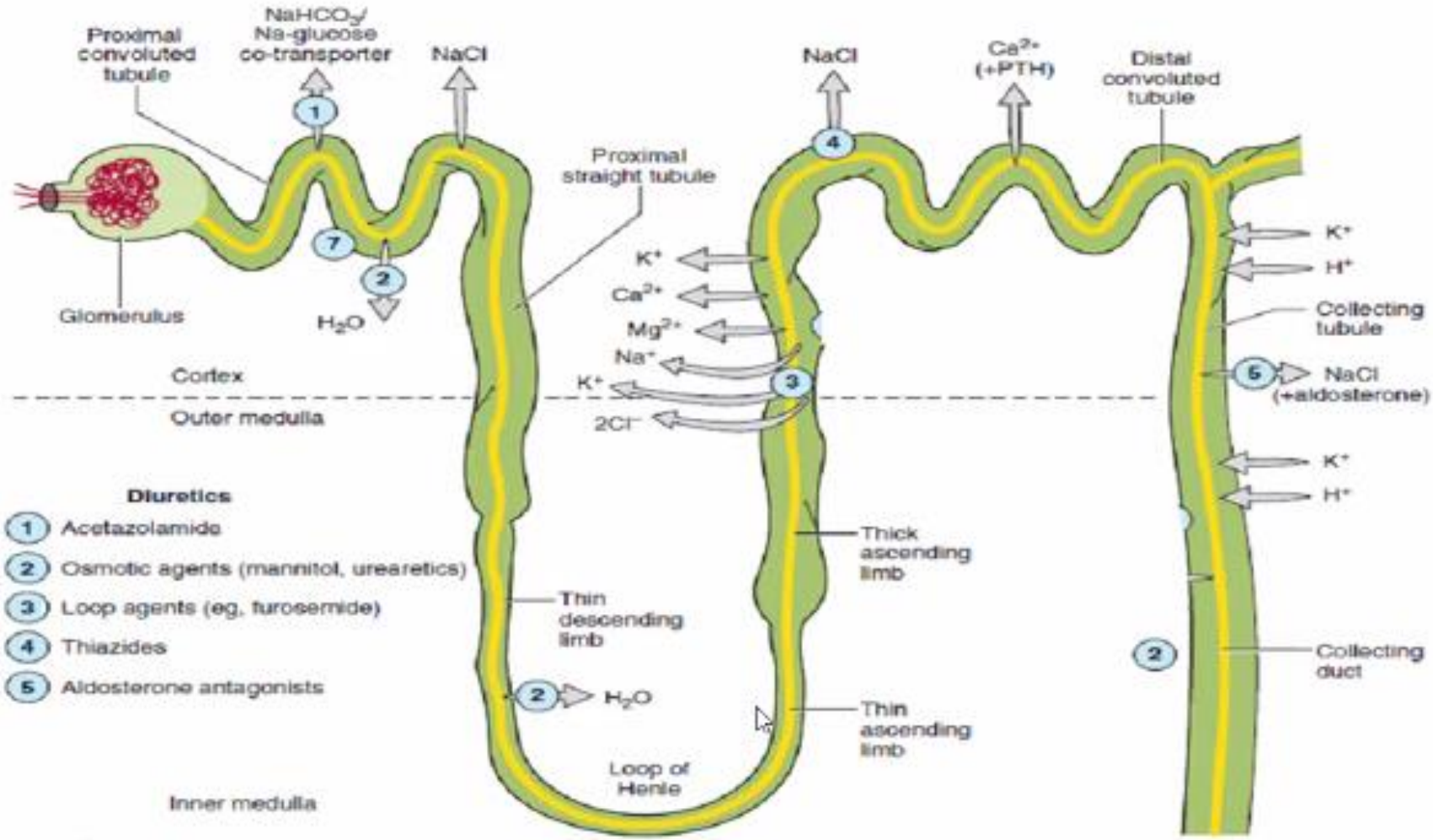


FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

CLASSIFICATION

1. **High efficacy diuretics (Inhibitors of Na+- K+-2Cl⁻ cotransport):**
   Sulphamoyl derivatives: (@BTF)

- Furosemide,
- Bumetanide,
- Torasemide

2. **Medium efficacy diuretics (Inhibitors of Na+-Cl⁻ symport)**

a) Benzothiadiazines (thiazides): (@H2B2)

- Hydrochlorothiazide,
- Benzthiazide,
- Hydroflumethiazide,
- Bendroflumethiazide

b) Thiazide like (related heterocyclics) (@ CC MIX)

- Chlorthalidone,
- Metolazone,
- Xipamide,
- Indapamide,
- Clopamide

3. Weak or adjunctive diuretics (@ A SETA MIG)

a) Carbonic anhydrase inhibitors

- Acetazolamide

b) Potassium sparing diuretics

i. Aldosterone antagonist:

- Spironolactone
- Eplerenone

ii. Inhibitors of renal epithelial Na+ channel:

- Triamterene
- Amiloride.

iii. Osmotic diuretics

- Mannitol
- Isosorbide
- Glycerol

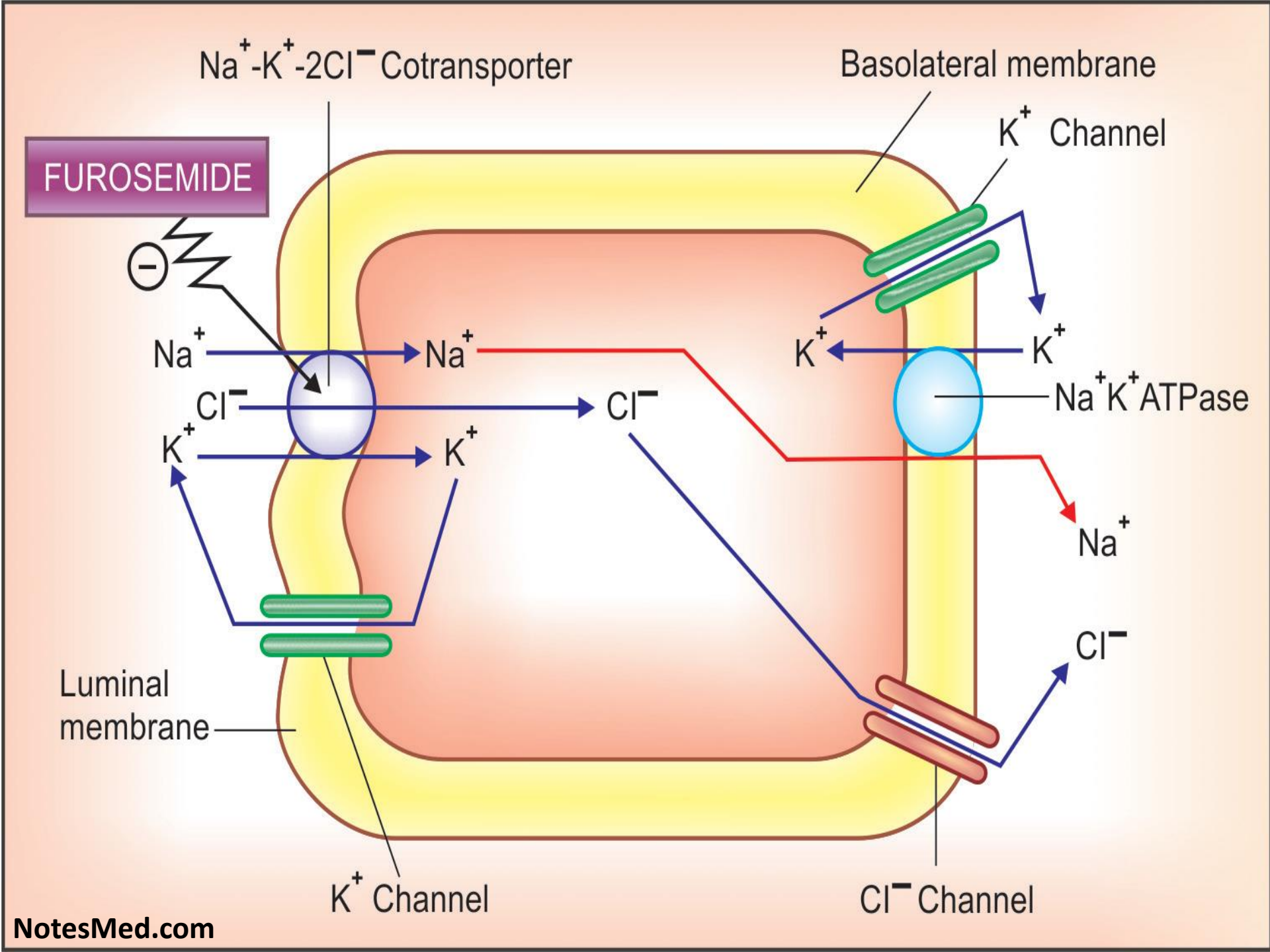
High Ceiling (Loop) Diuretics

(Inhibitors of Na+-K+-2Cl⁻ Cotransport

- High efficacy diuretics .
  - 25% of Na reabsorbed in thick ascending loop (TAL).
  - Past the thick ascending loop (TAL) do not posses the resorptive capacity.

Mechanism of action:

- It inhibits Na+-K+-2Cl⁻ Cotransport from luminal side of thick ascending limb of loop of Henle.
- Decreased absorption of Na+ and Cl⁻.
- High amounts of Na+ and water excreted in urine.
- K+ excretion increased due to exchanged with Na+ in distal tubule.
- Enhance excretion of **Ca^{2+}** and **Mg^{2+}** by abolishing the transepithelium potential difference in thick ascending loop (TAL).



Other Action

- Inhibits carbonic anhydrase enzymes in proximal tubule (PT) and increase HCO_3- excretion.

Pharmacokinetics of furosemide

- Furosemide is rapidly absorbed orally but bioavailability is about 60%.
- severe CHF oral bioavailability may be markedly reduced necessitating parenteral administration.
- Low lipid solubility and highly bound to plasma proteins.
- It is partly conjugated with glucuronic acid and mainly excreted unchanged by glomerular filtration as well as tubular secretion.
- Plasma t½ averages 1–2 hour but is prolonged in patients with pulmonary edema, renal and hepatic insufficiency.

Bumetanide

- similar to furosemide in all respects, but is 40 times more potent.
- Induces very rapid diuresis and is highly effective in pulmonary edema.
- Bumetanide is more lipid-soluble; oral bioavailability is 80–100%.
- t is preferred for oral use in severe CHF, because its bioavailability is impaired to a lesser extent than that of furosemide.
- extensively bound to plasma proteins, partly metabolized and partly excreted unchanged in urine.
- Plasma t½ ~60 min.

Torasemide (Torsemide)

- High ceiling diuretic with properties similar to furosemide, but 3 times more potent.
- Oral absorption is more rapid and more complete.
- The elimination t½ (3.5 hours) and duration of action (4–8 hours) are longer.

Use of high ceiling diuretics

1. **Edema:**
   Diuretics are preferred in CHF for rapid mobilization of edema fluid. For nephrotic and other forms of resistant edema, high ceiling diuretics are effective, and are the drugs of choice.
2. **Acute pulmonary edema (acute LVF, following MI):**
   Increase PG synthesis →venodilation → shift of blood from pulmonary to systemic circulation.
3. **Cerebral edema:**
   Along with osmotic diuretics are primarily used to lower intracranial pressure by withdrawing water, furosemide may be combined to improve efficacy.
4. **Hypertension:**
   Only in the presence of renal insufficiency, CHF, or in resistant cases and in hypertensive emergencies.
5. **Forced diuresis:** Poisoning due to drugs like barbiturates, salicylates.
6. **Hypercalcaemia of malignancy:** Along with saline infusion**.**
7. **Blood transfusion:** To avoid volume overload.

Adverse effects

A) Electrolyte disturbance (more common adverse effects).

a) Hypokalemia:
Most common and it can causes fatigue, muscle weakness and cardiac arrhythmias. Hypokalemia can be prevented by using a combination of loop diuretics with potassium sparing diuretic. It can also treated by K+ supplementation.

b) Hyponatraenia:
Loop diuretics can cause depletion of sodium from the body.

c)Hypocalcaemia and hypomagnesaemia:
If chronic used of this drugs due to the increasing urinary excretion of **Ca^{2+}** and **Mg^{2+}** respectively.
Hypomagnesaemia can predispose to arrhythmias.

Adverse effects

B. **Metabolic disturbance**:
   a) **Hyperglycaemia**: can occur due to decreased insulin secretion.
   b) **Hyperuricaemia**: Drugs decrease the renal excretion of uric acid and may precipitate attack of gout.
   c) **Hyperlipidaemia**: Increased plasma triglycerides and LDL cholesterol level.

C. **Ototoxicity**: Deafness, vertigo and tinnitus due to **direct damage to hair cells** in inner ear. Symptoms are usually reversible on stoppage of therapy.
   Note: Drugs contraindicated with drugs like cyclosporine, aminoglycosides, etc.

D. **Hypersensitivity**: Skin rashes, eosinophilia, photosensitivity, etc. may occurred.

Interactions

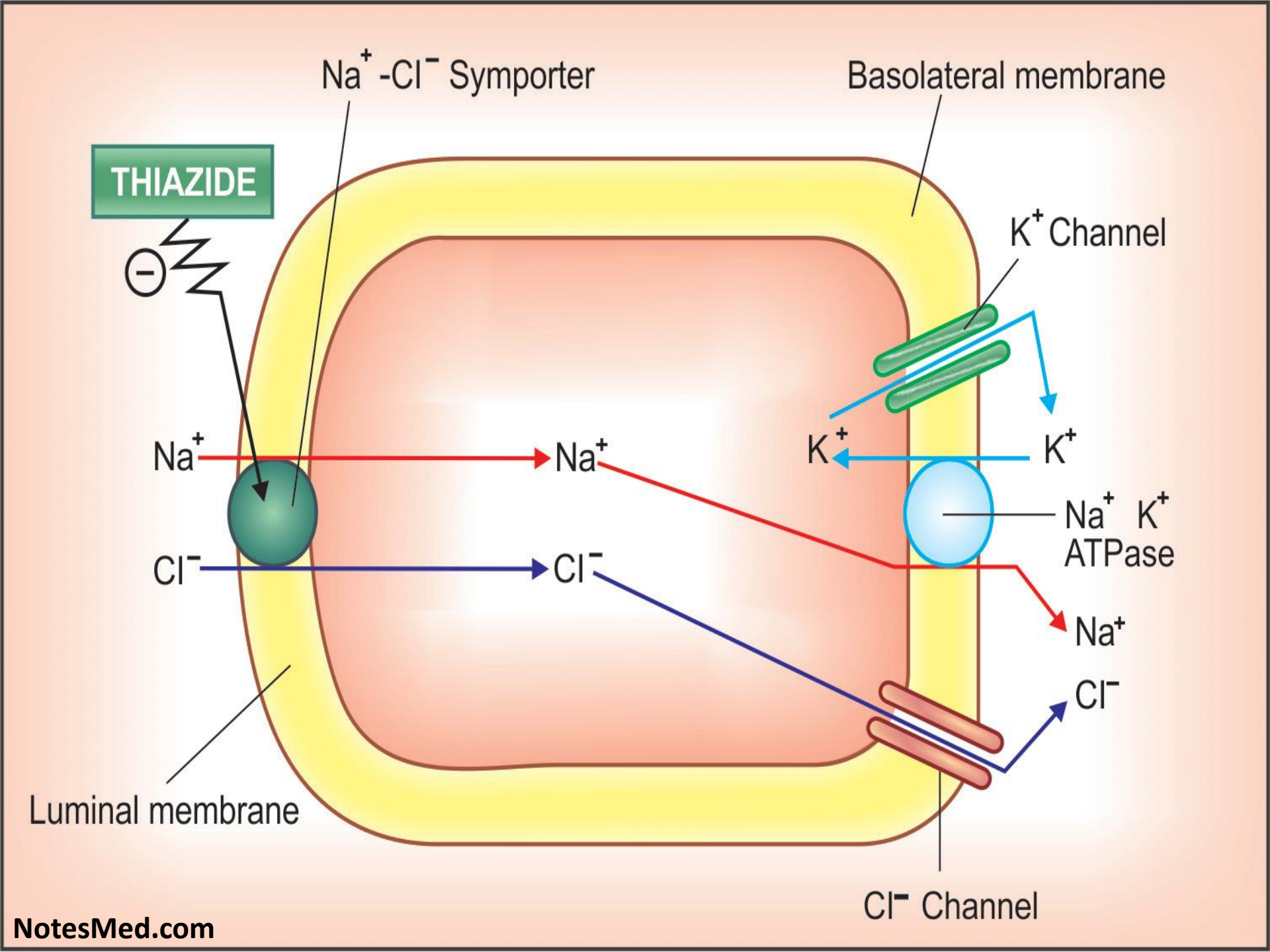
1. Aminoglycosides (synergism of ototoxicity).
2. Lithium (Increased plasma levels of Li+).
3. Digitalis glycosides (increased digitalis induced arrhythmias).
4. NSAIDs (blunted diuretic response).
5. Thiazide diuretics (synergism of diuretic activity of both drugs).

Medium efficacy diuretics
Thiazides and related diuretics

- Medium efficacy; 90% Na+ already absorbed.

Mechanism of action

- Inhibits NaCl reabsorption from the luminal side of epithelium cells in the distal convulating tubules (DCT) by blocking the Na+-Cl^- cotransporter.
- K+ Excretion increased due changed with Na+ in distal tubule.
- Enhanced reabsorption of **Ca^{2+}** due to enhancement of Na+/ **Ca^{2+}** pump.
- Other action: inhibits carbonic anhydrase enzyme in PT and increase HCO_3- excretion.



Pharmacokinetics

- well absorbed orally and more lipid-soluble agents have larger volumes of distribution (some are also bound in tissues), lower rates of renal clearance and are longer acting.\
- T½ of hydrochlorothiazide is 3–6 hours, but action persists longer (6–12 hours).
- *Chlorthalidone:* long acting compound with a t½ 40–50 hours, used exclusively as antihypertensive.
- *Metolazone:* t½ 12–24 hours.
- Xipamide: t½ 12 hours.
- Indapamide: t½ 12–24 hours.
- Clopamide: t½ 12–18 hours

Uses

1) Edema: for maintenance therapy.
2) Hypertension: Especially chlorthalidone are one of the first line drugs.
3) Hypercalciuria: Renal calcium stones in the kidney. Thiazides act by reducing Ca2+ excretion.
4) Diabetes insipidus: Reduction in blood/ECF volume→ reduction in GFR → increased reabsorption of NaCl and water from proximal tubule (compensatory) →less delivery of NaCl and water to the distal tubule → decreased diuresis.

Adverse effects

1. **Hypokalaemia and metabolic alkalosis:** weakness, fatigue, muscle cramps; cardiac arrhythmias are the serious complications. Hypokalaemia can be prevented and treated by:
   (a) High dietary K+ intake or
   (b) Supplements of KCl (24–72 mEq/day) or
   (c) Concurrent use of K+ sparing diuretics.
2. Acute saline depletion.
3. *Dilutional hyponatraemia*
4. *GIT and CNS disturbances:* ausea, vomiting and diarrhoea, Headache, giddiness, weakness, paresthesias, impotence, etc.
5. *Hearing loss:* Increased salt content of endolymph and a direct toxic action on the hair cells in internal ear.
6. *Allergic manifestations:* Rashes, photosensitivity.

Adverse effects

7. Hyperuricaemia (long term used of higher dose).
8. Hyperglycaemia and hyperlipidemia.
9. Hypocalcaemia.
10. Hypomagnesaemia.
11. Aggravated renal insufficiency, probably by reducing GFR.
12. Mental disturbances and hepatic coma.

Interactions

- Digitalis glycosides (increased digitalis induced arrhythmias).
- Sulfonylurea (Reduced action).
- Cotrimoxazole (higher incidence of thrombocytopenia).
- NSAIDs (blunted diuretic response).

Carbonic anhydrase inhibitors

- Acetazolamide.
- Reversible but non-competitive inhibitors of carbonic anhydrase.

Mechanism of action

- **Inhibits carbonic anhydrases (Cas) enzymes at multiple sites,**

1. Type II in cells of proximal tubules (PT) resulting in slowing of hydration of CO_2 →decreased availability of H^+ to exchange with luminal Na^+ through the Na^+-H^+ antiporter.
2. Inhibition of brush border CAse (type IV) retards dehydration of H_2CO_3 in the tubular fluid so that less CO_2 diffuses back into the cells.

- Inhibition of Na^+ and HCO_3 reabsorption in proximal tubule due to Na^+ gets absorbed in exchange with K^+ in distal tubule(DT), collecting duct (CD) and HCO_3^- lost in excess in urine.

3. Present in intercalated cells of DT and CD due to less H^+ available for secretion by H^+ -ATPase and decrease Na^+ reabsorption.

Extra-renal actions of acetazolamide

(i) Lowering of intraocular tension due to decreased formation of aqueous humour (aqueous is rich in $HCO3^-$).

(ii) Decreased gastric HCl and pancreatic NaHCO3 secretion: This action requires very high doses—not significant at clinically used doses.

(iii) Raised level of CO2 in brain and lowering of pH→ sedation and elevation of seizure threshold.

(iv) Alteration of CO2 transport in lungs and tissues. These actions are masked by compensatory mechanisms.

Pharmacokinetics

- Well absorbed orally and excreted unchanged in urine.
- t½ : 8–12 hours.

Uses

1. Glaucoma: Carbonic anhydrase mediates formation of HCO3- in aqueous humor. Inhibition of carbonic anhydrase →decreases the rate of formation of aqueous humor →reduced intraocular pressure.
2. Acute mountain sickness: Development of alkalosis, hypoxia and hyperventilatory responses to decreased O2 tension. Acetazolamide affords relief by inducing metabolic acidosis and also decreases the pH and quantity of CSF and affords the relief.
3. To alkaline urine: Overdose of acidic drugs.
4. Epilepsy and periodic paralysis: Due to lowering of pH.

Adverse effects

- Metabolic acidosis.
- Hypokalaemia.
- Drowsiness
- Paresthesias
- Fatigue
- abdominal discomfort.
- Hypersensitivity reactions—fever, rashes.
- Renal stone due to hypercalciuria.

Contraindications

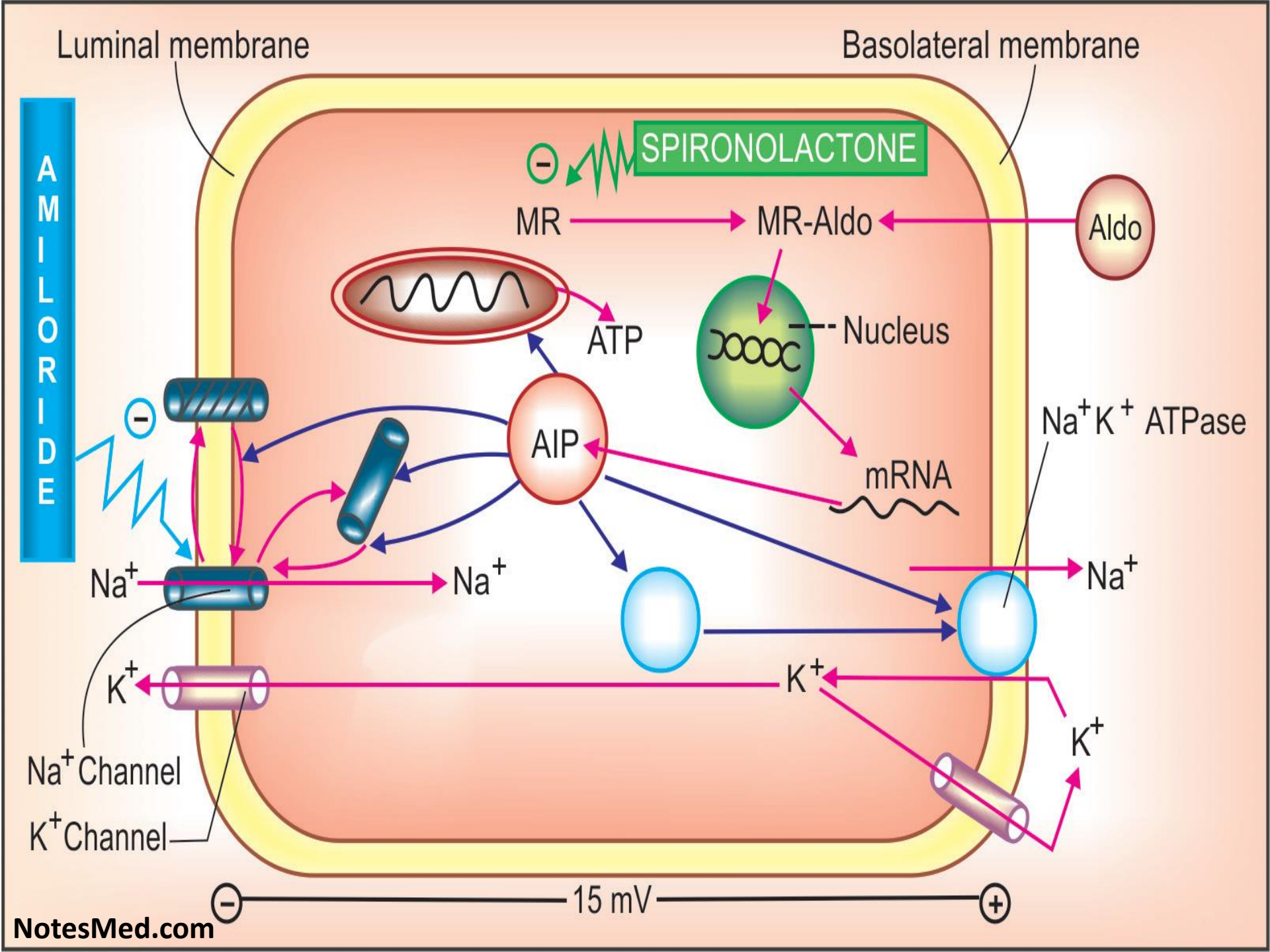
- **Liver failure**
- **COPD.**

POTASSIUM SPARING DIURETICS

Aldosterone antagonist: **Spironolactone & Eplerenone**.

Aldosterone:

- Regulates Na+ reabsorption and K+ & H+ secretion in collecting tubule and duct.
- Enters cells and binds to the mineralocorticoid receptor (MR)→Aldosterone MR complex moves to the nucleus →direct synthesis of aldosterone induced proteins (AIPs) → increases expression and function of Na+ channel and Na+/K+ pump.



Spironolactone

Mechanism of action

- **It acts from the interstitial side of the tubular cells and combines with** mineralocorticoid receptor (MR) and competitively inhibits the binding of aldosterone to MR.
- **MR-Spironolactone complex not able to induce the synthesis of** *aldosterone-induced proteins' (AIPs).*
- It has no effect on Na+ and K+ transport in the absence of aldosterone, while under normal circumstances, it increases Na+ and decreases K+ excretion.
- Also increases Ca2+ excretion by a direct action on renal tubules.

Pharmacokinetics

- Oral bioavailability of spironolactone from microfine powder tablet is 75%.
- Highly bound to plasma proteins and completely metabolized in liver.
- t½-1-2 hours

Use

- Used only in combination with other more efficacious diuretics.

1. To counteract K+ loss due to thiazide and loop diuretics.
2. Edema: cirrhotic and nephrotic edema in which aldosterone levels are generally high.
3. Hypertension: Along with thiazides to avoid hypokalaemia and for additive effect.
4. CHF: Retard disease progression and lower mortality.
5. Resistant hypertension with primary hyperaldosteronism.

Adverse effects

- Hyperkalaemia
- Gynecomastia, loss of libido and erectile dysfunction in male.
- Menstrual irregularities in female.
- Gastric ulcer.
- Drowsiness, ataxia.
- Mental confusion.
- Epigastric distress.
- Loose motions

Interactions

1. Given together with K+ supplements dangerous hyperkalaemia can occur.
2. Aspirin blocks spironolactone action by inhibiting tubular secretion of its active metabolite canrenone.
3. More pronounced hyperkalaemia can occur in patients receiving ACE inhibitors/ARBs.
4. Spironolactone increases plasma digoxin concentration.

Eplerenone

- A newer and more selective aldosterone antagonist which has much lower affinity for other steroidal receptors.
- Eplerenone is well absorbed orally, inactivated in liver by CYP3A4, and excreted in urine well as faeces.
- t½ is 4–6 hours

Inhibitors of renal epithelial Na+ channel (*Triamterene* and *amiloride)*

Mechanism of action

- Block the renal epithelial Na+ channels (ENaCs) in the luminal membrane of principal cells in late distal tubules and collecting ducts.
- Increase Na+ excretion and decrease K+ and H+ excretion (acidosis).

Triamterene

- incompletely absorbed orally.
- partly bound to plasma proteins, largely metabolized in liver to an active metabolite and excreted in urine.
- Plasma t½ is 4 hours.
- *Side effects:* nausea, dizziness, muscle cramps and rise in blood urea, Impaired glucose tolerance and photosensitivity.

Amiloride

- 10 times more potent than triamterene.
- At higher doses it also inhibits Na+ reabsorption in PT, but this is clinically insignificant. It decreases Ca2+ and Mg2+ excretion but increases urate excretion.
- Only ¼ of an oral dose is absorbed.
- Not bound to plasma proteins and not metabolized.
- t½ (20 hours) and duration of action are longer than triamterene.
- Side effects: nausea, diarrhoea and headache.
- Blocks entry of Li+ through Na+ channels in the CD cells and mitigates diabetes insipidus induced by lithium.

Uses

- In combination with loop and thiazide diuretics: to avoid hypokalemia and for additive effect in hypertension.
- Amiloride: lithium induced diabetes inspidius- block the entry of Li+.
- Amiloride: Aerosol in cystic fibrosis increase fluidity of respiratory secretions.

OSMOTIC DIURETICS (Mannitol, isosorbide, glycerol)

Mannitol: pharmacologically inert and given IV.

Mechanism of action

- Site: In proximal tubule (PT) and loop of Henle.
- In proximal tubule: limit the osmosis of water into the interstitial space and reduce the luminal Na+ concentration and oppose the Na+ reabsorption.
- Increases osmotic pressure - remove of excess water from cells-increases blood flow and GFR.

- Increase in renal medullary blood flow→removes NaCl and urea from the renal medulla → reduce medullary hypertonicity → decrease in extraction of water from the descending thin limb → limits the concentration of NaCl in the tubular fluid entering the ascending thin limb (ATL) → diminishes the passive reabsorption of NaCl in the ATL.
- Along with water, excretion of all cations (Na+, K+, Ca2+, Mg2+ and anions (Cl-, HCO3-, PO_4^{3-}) is also enhanced.

Uses

1. Acute congestive glaucoma, head injury: encourages movement of water from brain parenchyma, CSF and acqueous humor.
2. To maintain GFR and urine flow in impending acute renal failure. E.g. in shock, severe trauma, cardiac surgery, haemolytic reactions.
3. To counteract low osmolality of plasm/ECF due to rapid dialysis.

Adverse effects

- Pulmonary edema
- Headache
- Nausea, vomiting

Contraindications

- **Acute renal failure**
- **CHF**
- **Active cranial bleeding.**

Isosorbide and glycerol

- Orally active osmotic diuretics which may be used to reduce intraocular or intracranial tension.
- Intravenous glycerol can cause haemolysis.

The end