DIUERETICS

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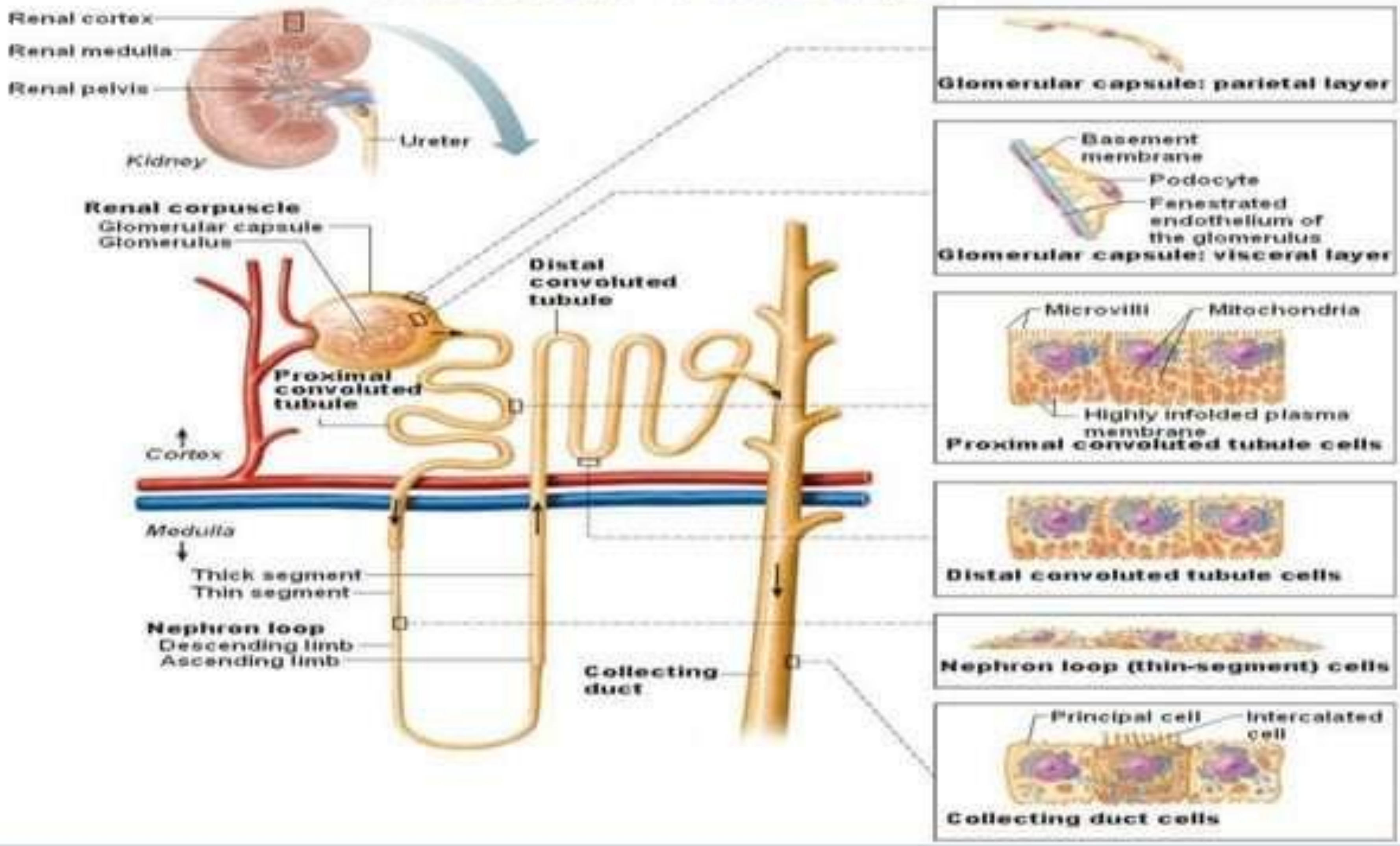
DIURETICS

DEFINITION :

- These are drugs which cause a net loss of Na^+ and water in urine
- There are several categories of diuretics. All diuretics increases the excretion of water from body.

Renal Tubule



CLASSIFICATION

Diuretics are Classified as:

1. High ceiling /Loop diuretics...
2. Thiazides.
3. Carbonic anhydrase inhibitors.
4. Potassium –sparing diuretics.
5. Osmatic diuretics.
6. Low ceiling diuretics.

DIURETICS CLASSIFICATION

1.HIGH EFFICACY DIURETICS:

(Inhibitors of Na^+,K^+,$2Cl^-$ cotransport)

(a) Sulphamoyl deravatives:

Furosemide.

Bumetanide.

Torasemide.

(b) Phenoxyacetic acid derivative:

Ethacrynic acid.

MEDIUM EFFICACY DIURETICS

2.Medium efficacy diuretics :
(Inhibitors of Na+,Cl- symport)

(a) Benzothiadiazines(THIAZIDES):
Hydrochloro thiazide.
Benzthiazide.
Hydroflumethe thiazide.
Ciopamide.
(b) Thiazide: Chlorthalidone.
Metolazone.
Xipamide.
Indapamide.

WEAK OR ADJUNCTIVE DIURETICS

3.Weak or adjunctive diuretics:

(a) Carbonic anhydrase inhibitors:

Acetazolamide.

(b) Potassium –sparing diuretics:

(i)Aldosterone antagonist:

Spironolacton

Eplerenone.

(ii)Inhibitors of renal epithial Na+ channel:

Trimterene.

Amiloride.

(c) Osmotic diuretics:

Mannitol.

Isosorbide.

Glycerol.

(d) Xanthines:

Theophlline.

ANTI- DIURETICS

1.Anti diuretic homone(ADH) and its analogues:

- Vasopressin.
- Desmopressin.
- Lypressin.
- Terlipressin.

2.Diuretics:

- Thiazides.
- Amiloride.

3. Miscellineous:

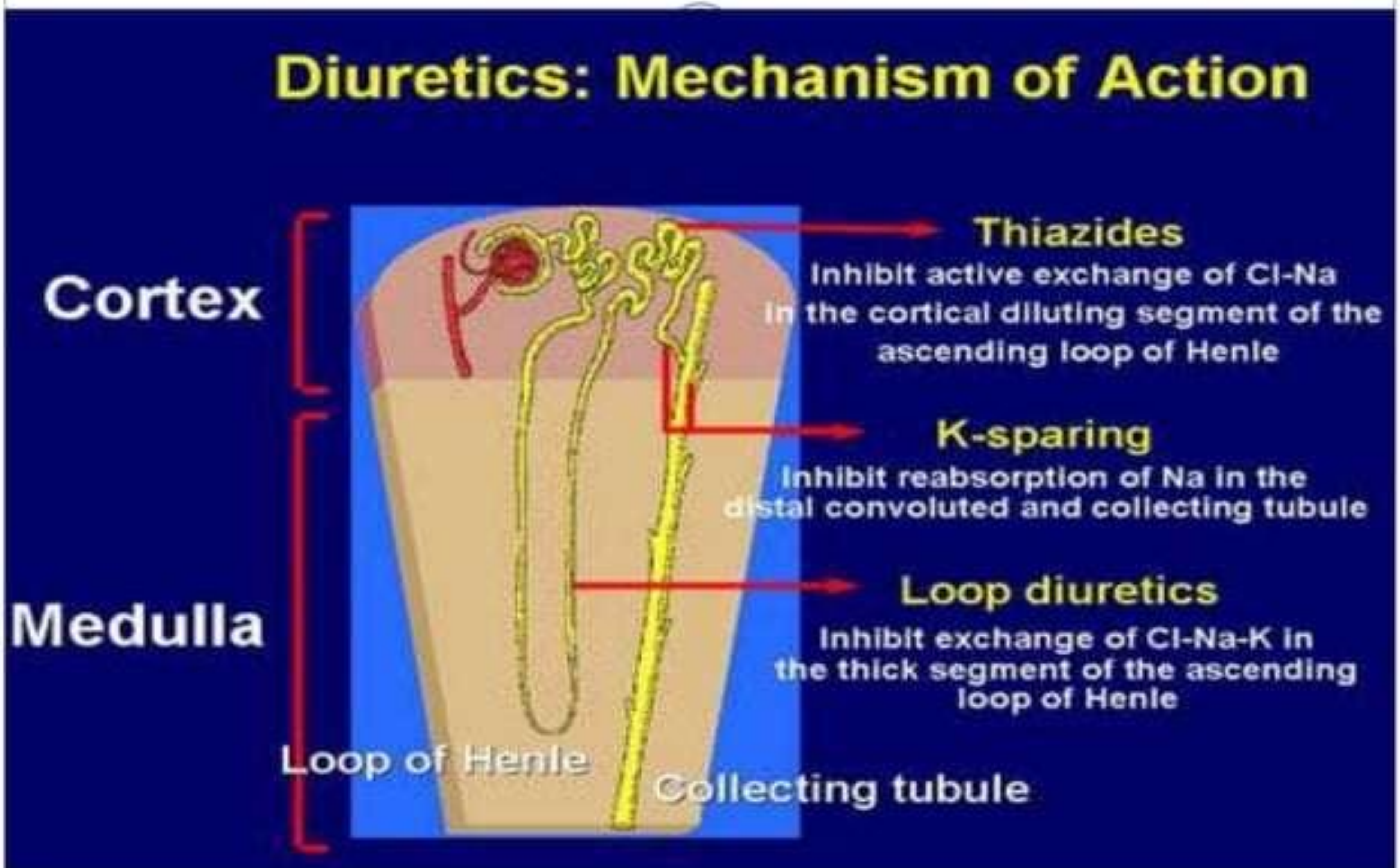
- Chlorpropamide.
- Carbamazepine.

MECHANISM OF DIURETICS

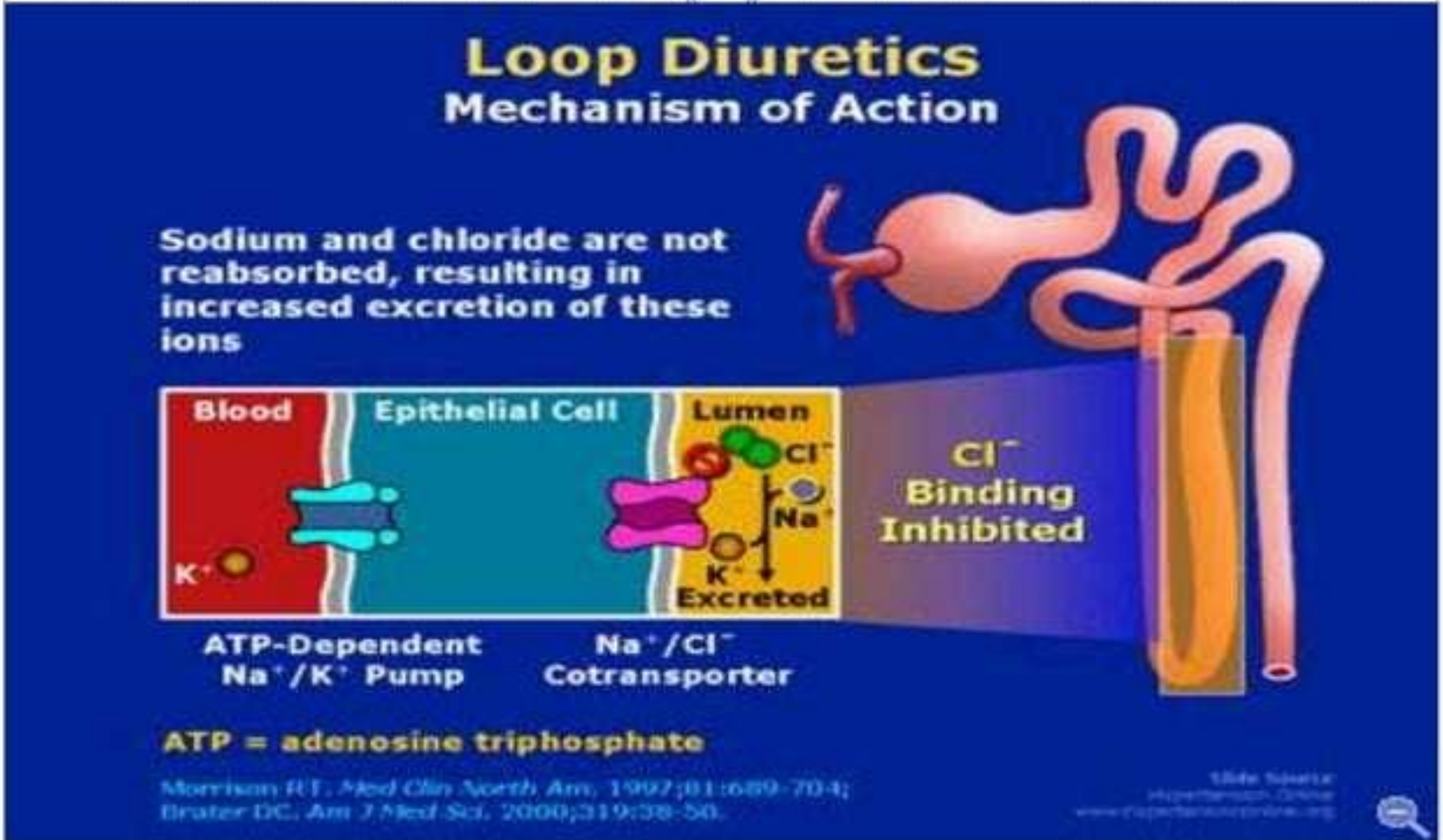
Mechanism of action of commonly used diuretics

Site of Action	Channel Inhibited	Percent Excreted
Loop of Henle Furosemide, bumetanide, ethacrynic acid	Na/K/2Cl	Up to 25
Distal Tubule Thiazides	Na/Cl	Up to 3-5
Cortical Collecting Tubule Spironolactone, amiloride, and triamterine	Na channel	Up to 1-2

MECHANISM OF ACTION



MECHANISM OF ACTION OF LOOP DIURETICS



Loop diuretics

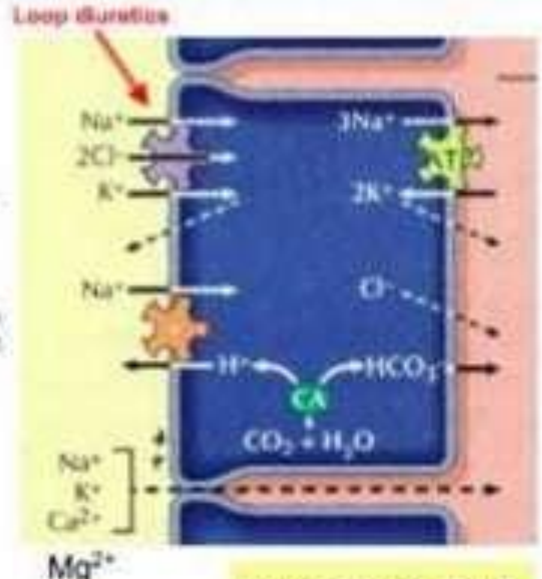
TAHL – thick ascending loop of Henle

impermeable to water!

Transcellular:
Via specialized luminal Na+K+ Cl- co-transporters.

Na/H antiporter continues to reabsorb Na+ and excrete H+

Paracellular: Backleak of K+ creates lumen positive 6mV transepithelial gradient which drives paracellular movement of cations out of the lumen.



MedPhys RL3

Site of action – enter via filtration and secretion by the OATs. Act on TAHL

Mechanism – inhibition of Na+/K+/2Cl- symporter. Positive luminal potential ↓
Mg+, Ca2+ reabsorption ↓
Hypochloremia due to NKCC block
Large doses abolish osmotic gradient
Renal vascular resistance ↓, RBF ↑ via effect on prostaglandins.
Kidney is not able to produce dilute urine.
After initial strong diuresis - *diuretic braking*.

Urine – increased excretion of all ions: Na+, Cl-, K+, H+, Mg2+, Ca2+, as well as HCO_{3-} in case of furosemide (Furosemide is a weak CA inhibitor).

Plasma - hypochloremic alkalosis and hypokalemia
(mechanisms are similar to thiazide duiretics and will be considered shortly)

INDICATIONS AND SIDE EFFECTS

Indications & Side Effects

- Loop diuretics
  - large volume diuresis
  - isotonic urine (as compared to plasma)

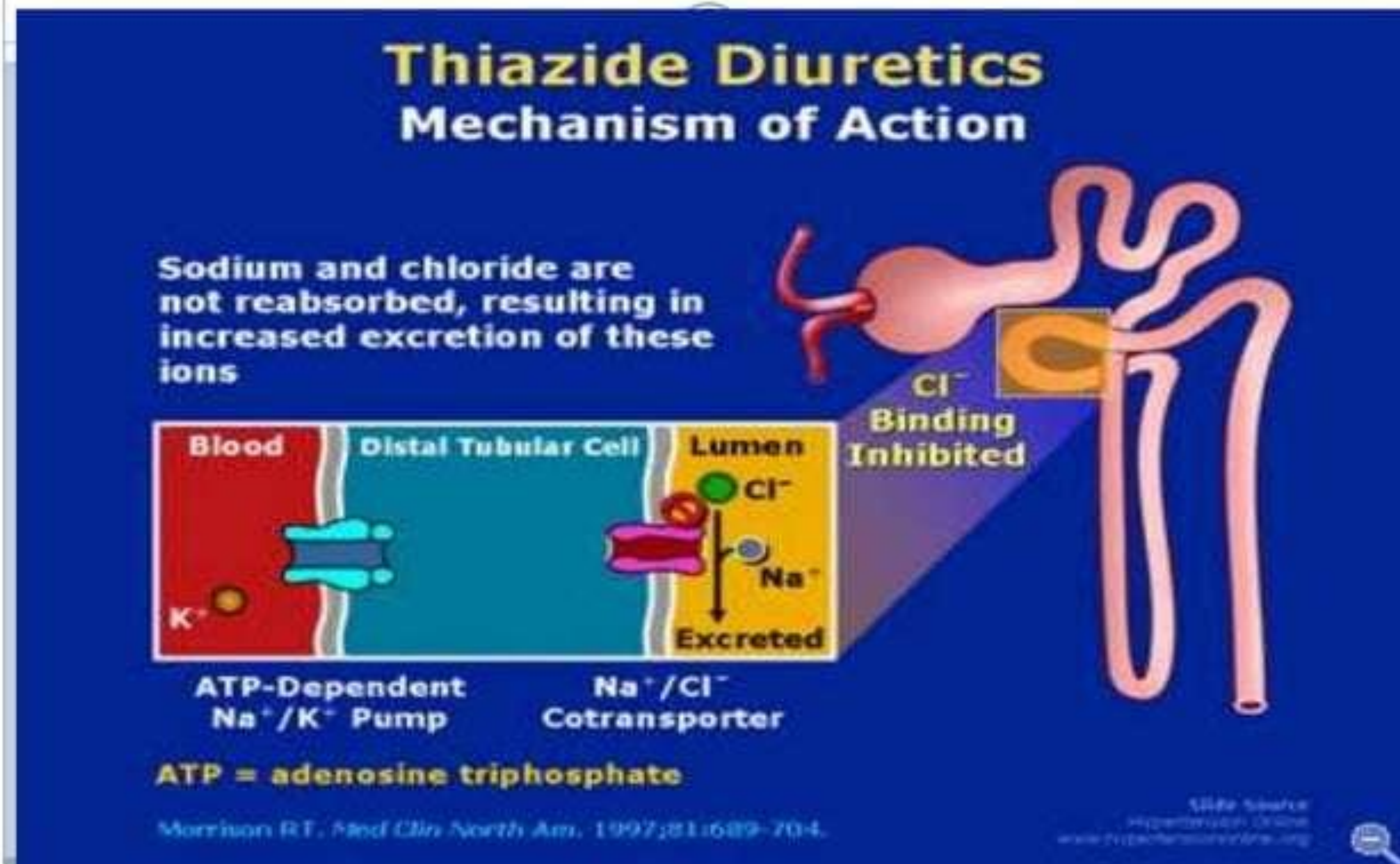
- Indications
  - edema
    - congestive heart failure
    - acute pulmonary edema
    - cirrhosis
    - nephrotic syndrome
  - hypertension
  - hypercalcemia
  - forced diuresis

- Side effects
  - excess volume depletion
    - circulatory collapse
    - azotemia & hyperuricemia
  - hypokalemia
    - cardiac arrhythmias
  - hypocalcemia
  - hypomagnesemia
  - ototoxicity

Thiazides - Mechanism Of Action

- Act In The Distal Tubule
- Inhibit Reabsorption Of Sodium And Potassium
- Stimulate The Reabsorption Of Calcium
- Loss Of Water As Urine

MECHANISM OF THIAZIDE DIURETICS



Thiazide Diuretics (HYDROCHLOROTHIAZIDE)

Therapeutic uses:

Absorbed orally. Bound to plasma proteins, Secreted by the OAT in PT

Hypertension -reduces blood pressure by reducing volume and producing mild vasodilation

Congestive heart failure

Hypercalciuria- to help prevent renal stones.

Nephrogenic diabetes insipidus (renal insensitivity to ADH): thiazides ↓ plasma volume => lowers GFR -> reabsorption of Na in PT ↑. Less Na^+ and water reach CD so overall fluid conservation is obtained.

Adverse effects -

Electrolyte imbalance – hypokalemic metabolic alkalosis, hyponatremia, hypercalcemia, hyperuricemia, hypochloremia, cardiac arrhythmias. Hypokalemia increases risk of torsade de pointes caused by guanidine.

Hypotension -due to volume depletion

Hyperglycemia- in patients with diabetes or abnormal glucose tolerance tests. Mechanisms poorly understood

Hyperlipidemia- an increase in the levels of LDL, total cholesterol and total triglycerides

Hypersensitivity

POTASSIUM- SPARING DIURETICS

Spironolactone - Mechanism Of Action

- Competitively Binds The Aldosterone Receptor Preventing The Hormone From Binding To Its Receptor
- Aldosterone's Normal Steroid-Nuclear DNA Transcription Is Halted

OSMOTIC DIURETICS

Osmotic Diuretics

mannitol

- Raises osmotic pressure of the plasma thus draws H_2O out of body tissues & produces osmotic diuresis
- Does not effect Na^+ excretion

Osmotic Diuretics: Therapeutic Uses

- Used in the treatment of patients in the early, oliguric phase of ARF
- To promote the excretion of toxic substances
- Reduction of intracranial pressure
- Treatment of cerebral edema

PHARMACOLOGICAL ACTIONS OF DIURETICS

HIGH CEILING/LOOP DIURETICS

- High ceiling diuretics may cause a substantial decrease upto 20%of the filtered load of Nacl and water.
- Loop diuretics such as FUROSEMIDE inhibits the body's ability to reabsorb sodium at the ascending loop in NEPHRON.

THIAZIDES

- Thiazide diuretics such as Hydrochlorothiazide act on the distal convoluted tubule and inhibits the sodium-chloride symporter leading to retention of water in the urine.
- Frequent urination is due to the increased loss of water.
- The long term anti –hypertensive action is based on the thiazides which decrease preload and blood pressure.

CARBONIC ANHYDRASE INHIBITORS

- Carbonic anhydrase inhibitors inhibits the enzyme carbonic anhydrase which is found in proximal convoluted tubule.
- This results in several effects including biocarbonate retention in the urine.
- Potassium retention in urine.
- Decreased sodium absorption.

Eg: Acetazolamide.

Methazolamine.

POTASSIUM-SPARING DIURETICS

- These are diuretics which do not promote the secretion of potassium into the urine.
- Potassium is retained and not lost as much as with other diuretics.
- The term potassium sparing refers to an effects rather than a mechanism or location.

Eg: Aldosterone antagonists
Spironolactone

- Which is a competitive antagonist of aldosterone.
- Aldosterone adds sodium channels in the cells of collecting duct and late distal tubule of the Nephron.
- Spirnolactone prevents aldosterone from entering the cells, and preventing sodium reabsorption.

  Eg: Eplerenone.

  Potassium canrenonate.
- Epithelial sodium channel blockers

  Eg: Amiloride.

  Triamterence.

OSMOTIC DIURETICS

The compounds as Mannitol are filtered in the glomerulus, but cannot be reabsorbed.

- Their presence lead to an increases in the osmolarity of the filtrate.
- To maintain osmotic balance ,water is retained in the urine.
- Glucose like mannitol behave as an osmotic diuretic.
- Glucosuria causes a loss of hypotonic water & Na+, leading to a hypertonic state with signs of volume depletion.
- Such as Hypotention,Tachycardia.

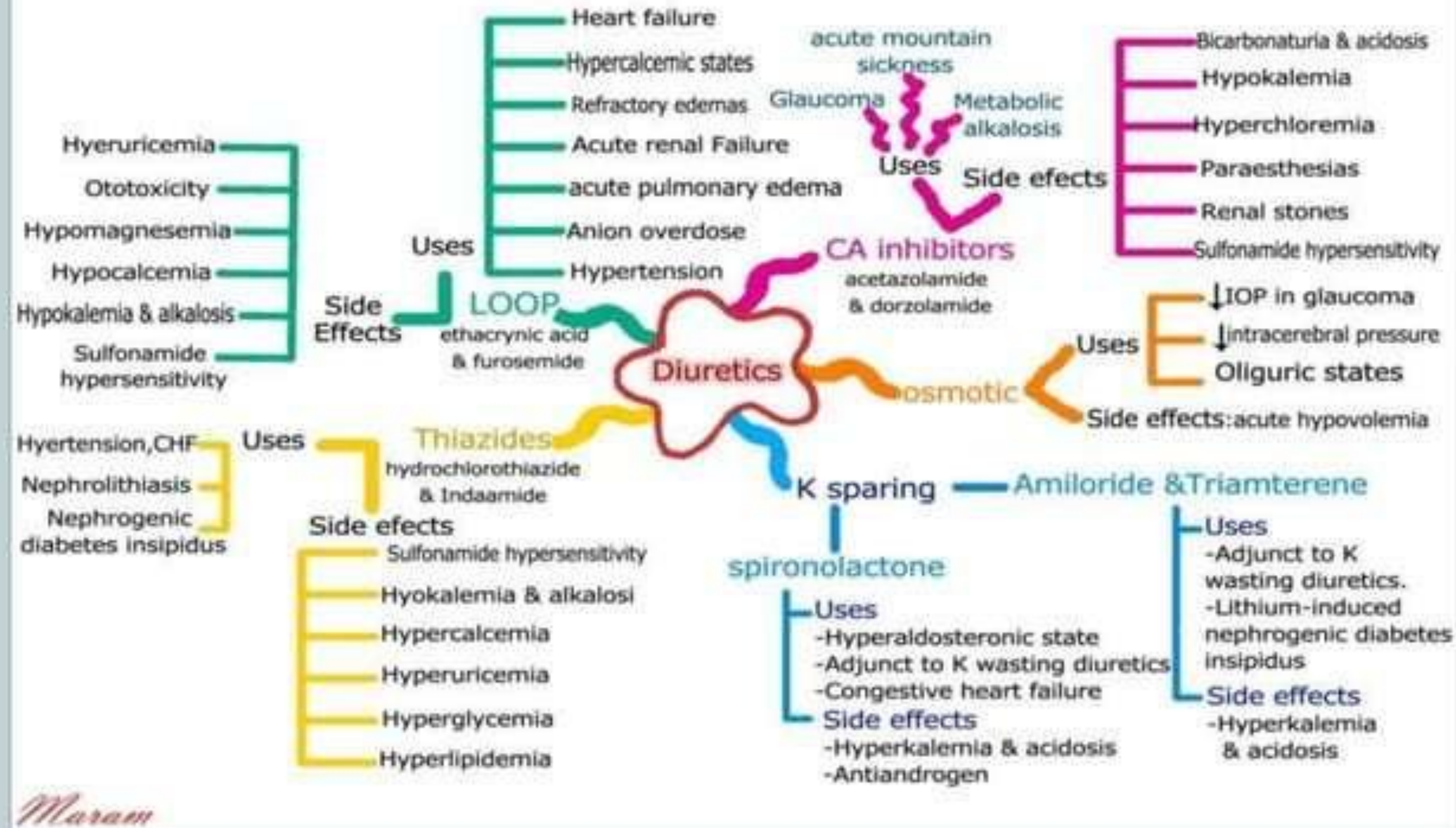
LOW CEILING DIURETICS

- The low celing diuretics are used to indicate an diuretic has a rapid flatting dose effect curve.
- It refers to a pharmacological profile ,not a chemical structure.

MEDICINAL USES

- Diuretics are used to treat
  1. Heart failures.
  2. Liver cirrhosis.
  3. Hypertension.
  4. Certain kidney diseases

USES AND SIDE EFFECTS OF DIURETICS



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