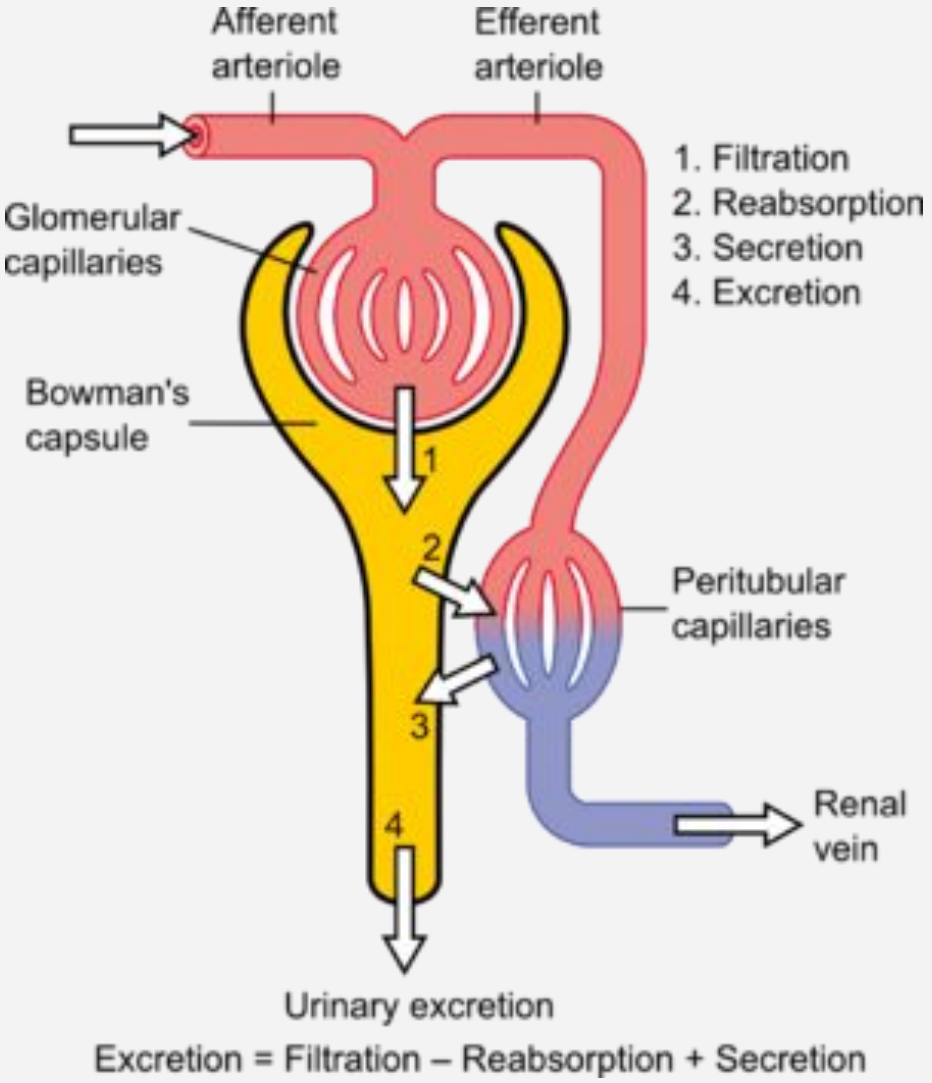
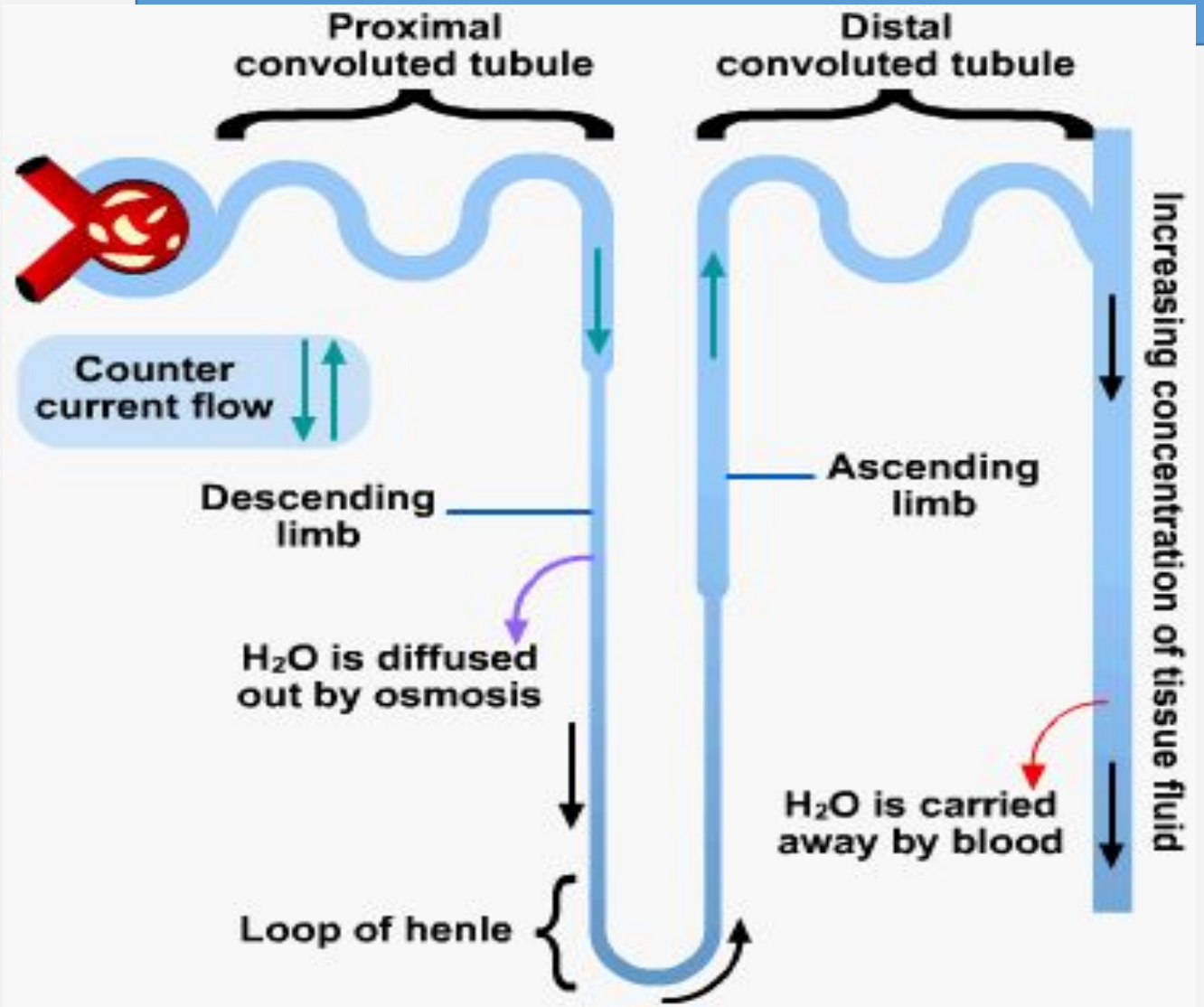
DIURETICS

Structure of Kidney



- Blood filtered by functional unit: Nephron
- Except for cells, proteins , other large molecules, rest gets filtered

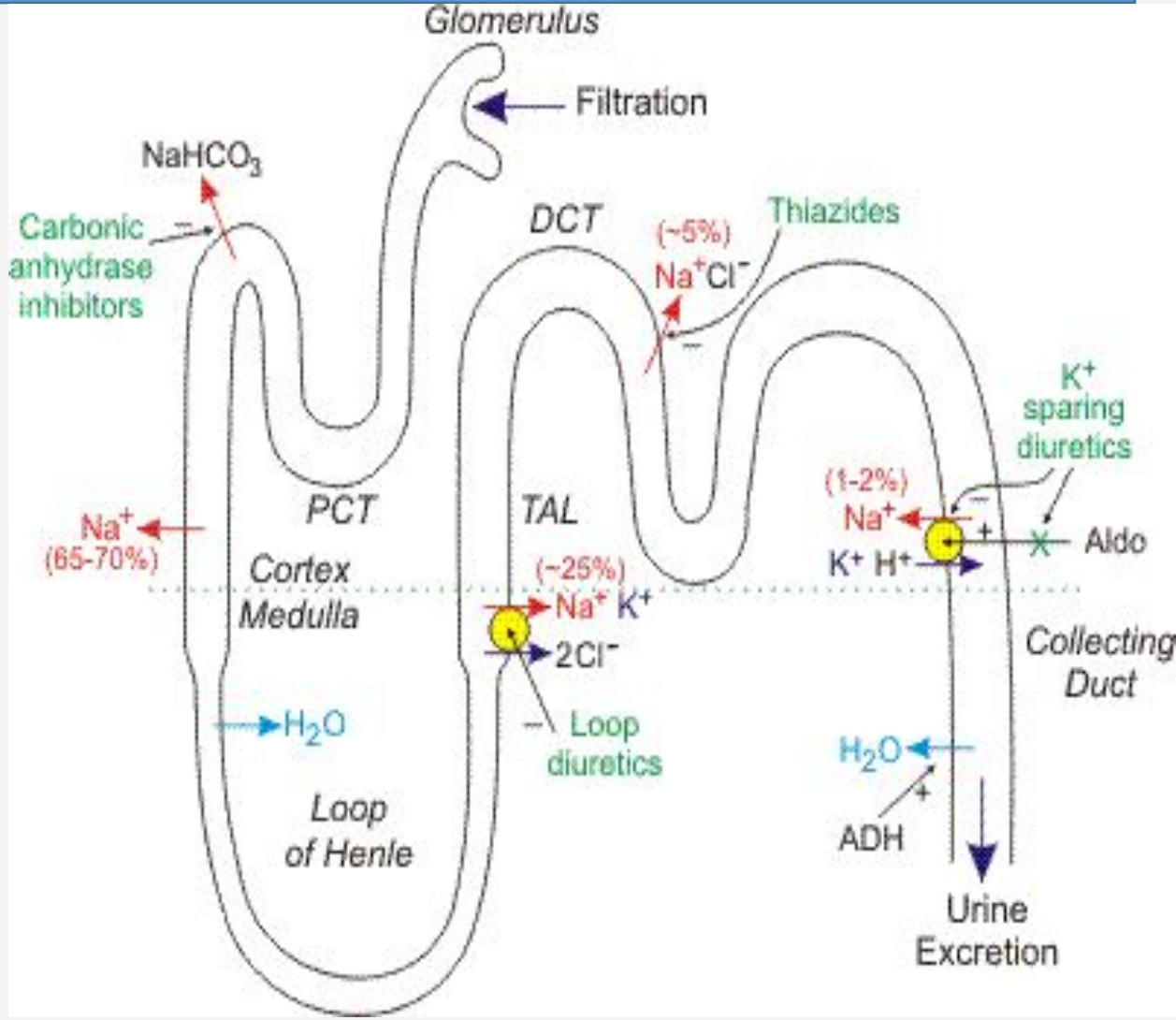
Structure of Kidney



- 3 major regions of nephron
  - PCT (Proximal Convoluted Tubule)
  - Loop of Henle
  - DCT (Distal convoluted Tubule)

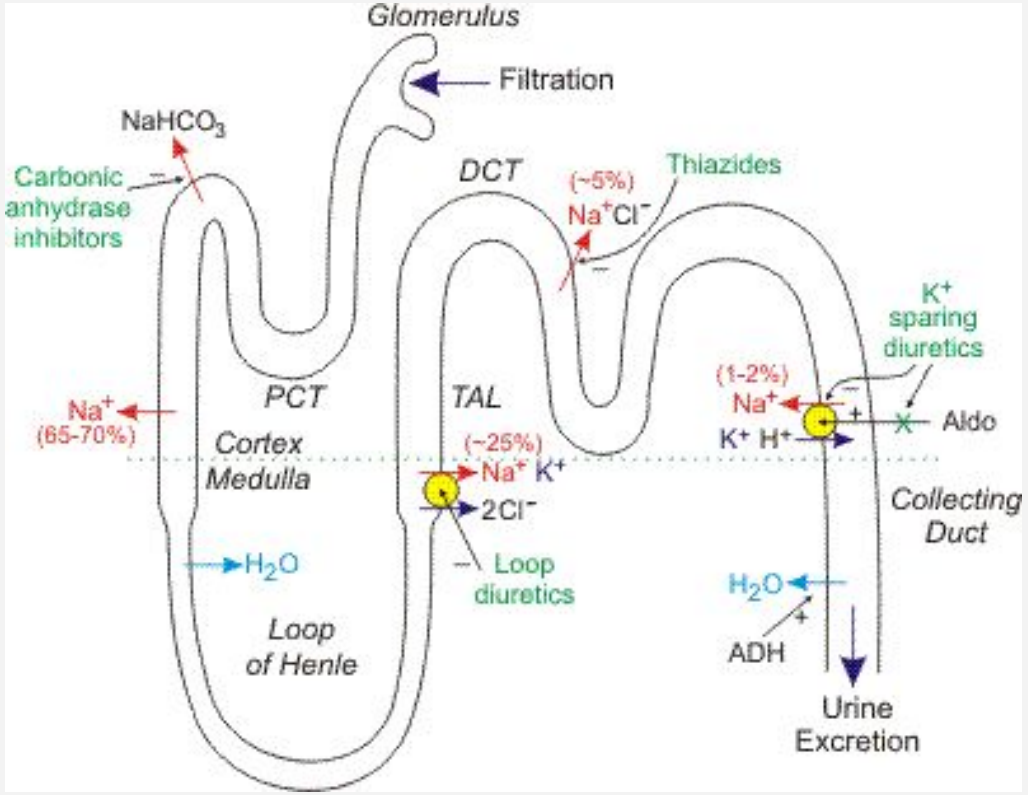
Role of Kidneys in Water/ Na reabsorption

- 20 % of plasma filtered in to PCT
- 65- 70 % of filtered Na removed iso-osmotically
- The Thick Ascending Loop (TAL), which is impermeable to water, has a **cotransport system** that reabsorbs sodium, potassium and chloride
- Approximately 25% of the sodium load of the original filtrate is **reabsorbed at the TAL**



Role of Kidneys in Water/ Na reabsorption

- 5 % Na reabsorbed in DCT
- 1-2 % Na reabsorbed in remaining region

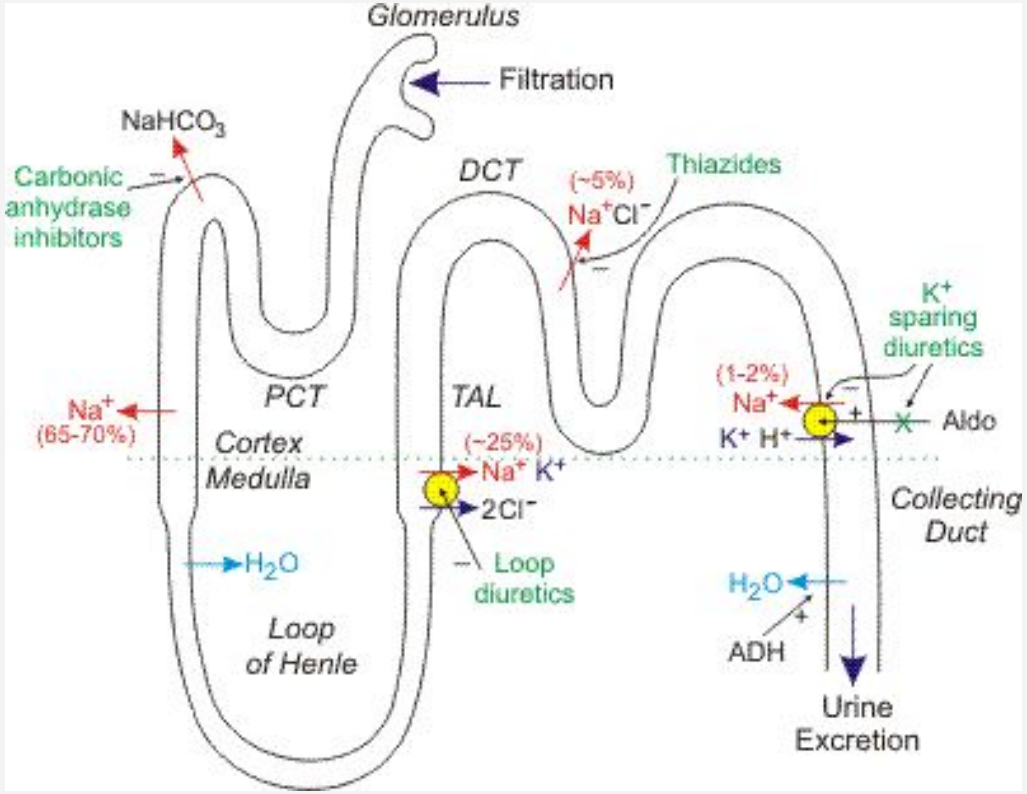


Mechanism of Action

- Diuretics act by changing the way kidney handles Sodium
- Most Diuretics acts by blocking reabsorption of Sodium
- Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect) of Na

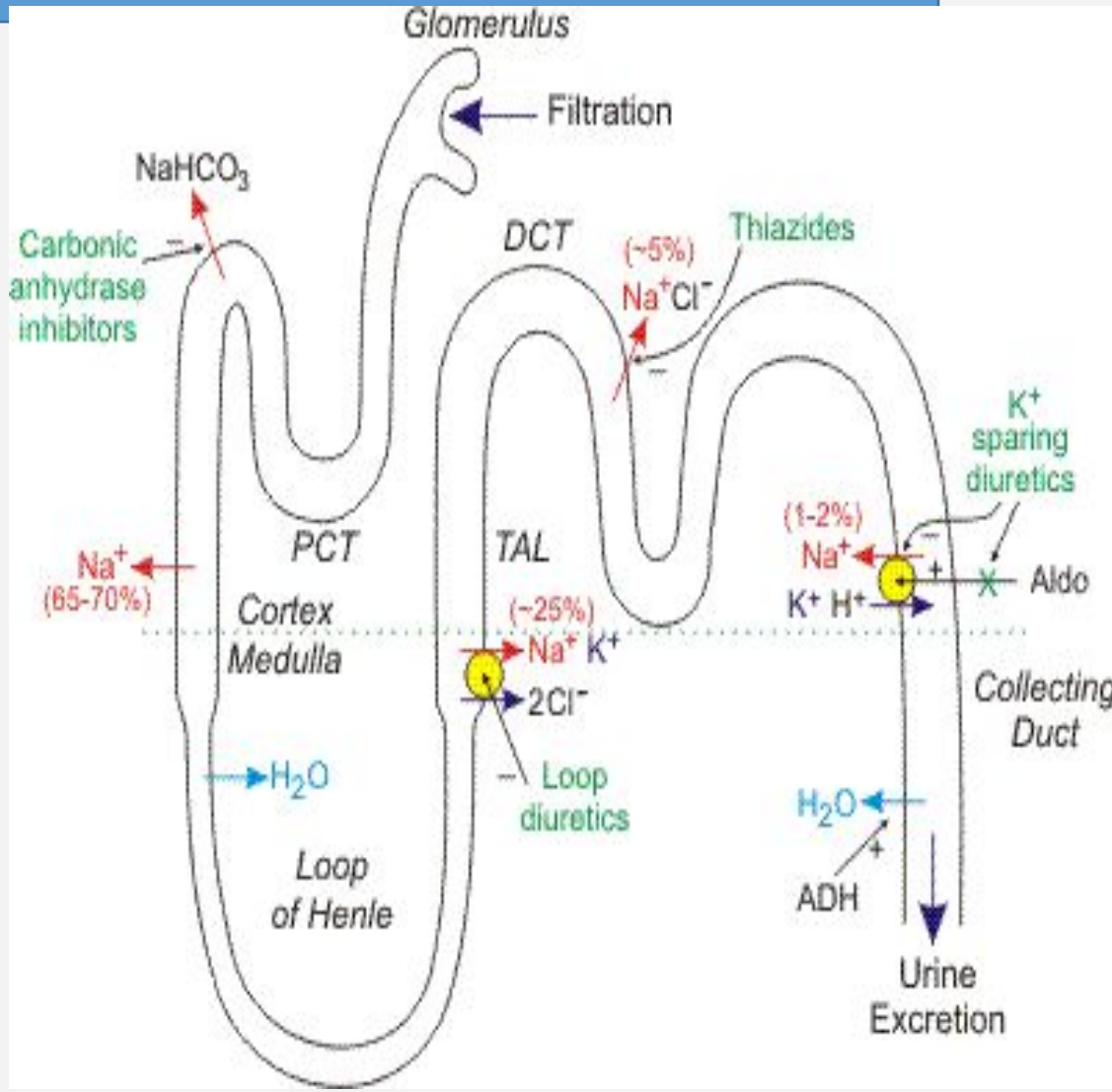
Different Classes of Diuretics

- **Loop Diuretics:**
  - inhibit the sodium-potassium-chloride co-transporter in the TAL
  - This transporter normally reabsorbs about 25% of the sodium
- **Thiazide Diuretics:**
  - Commonly used, act in DCT (5% Na)
  - Less powerful



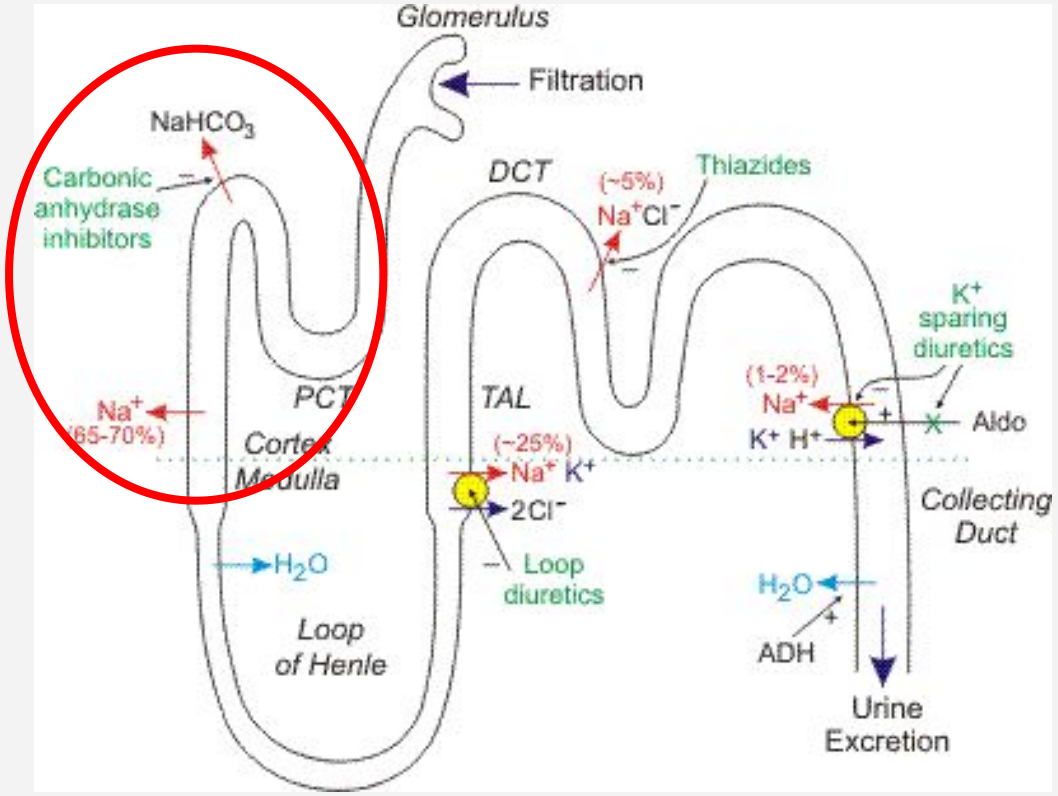
Different Classes of Diuretics

- **K Sparing Diuretics:**
  - Some **do not** act directly on Na transport
  - Antagonize the actions of aldosterone

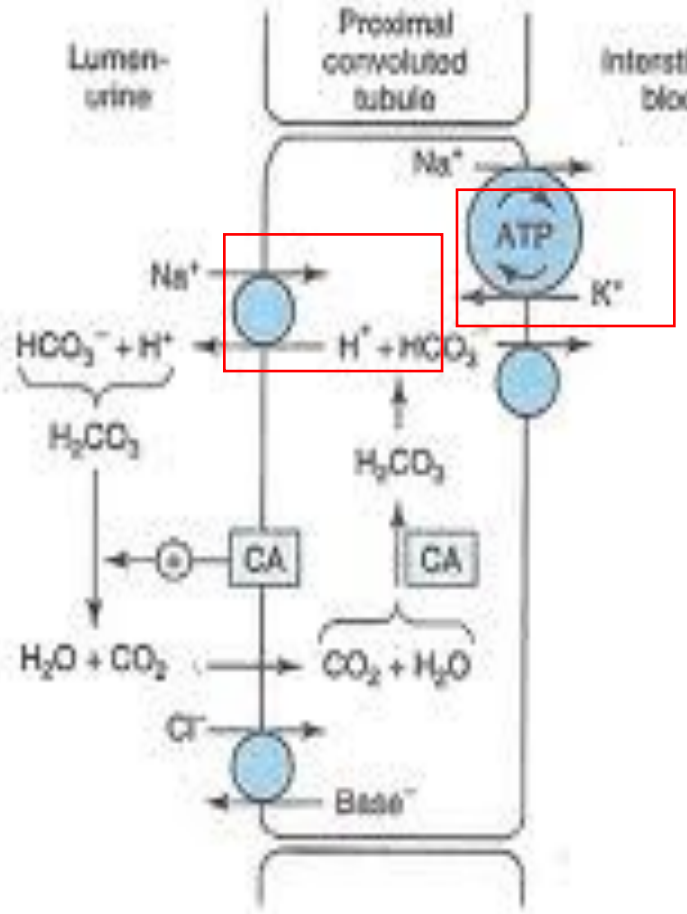


Carbonic Anhydrase inhibitors

- **Carbonic anhydrase inhibitors:**
  - **Inhibit** the transport of bicarbonate out of the proximal convoluted tubule
  - leads to less sodium reabsorption at this site and therefore greater sodium, bicarbonate and water loss in the urine
  - Weakest in class

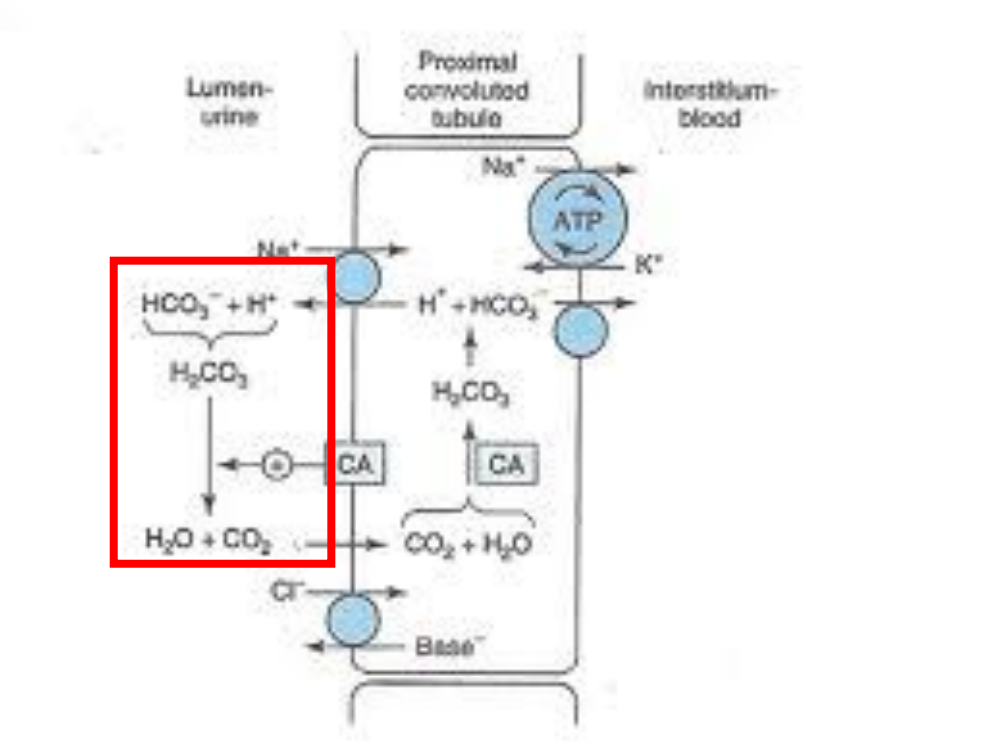


Proximal Convoluted Tubule



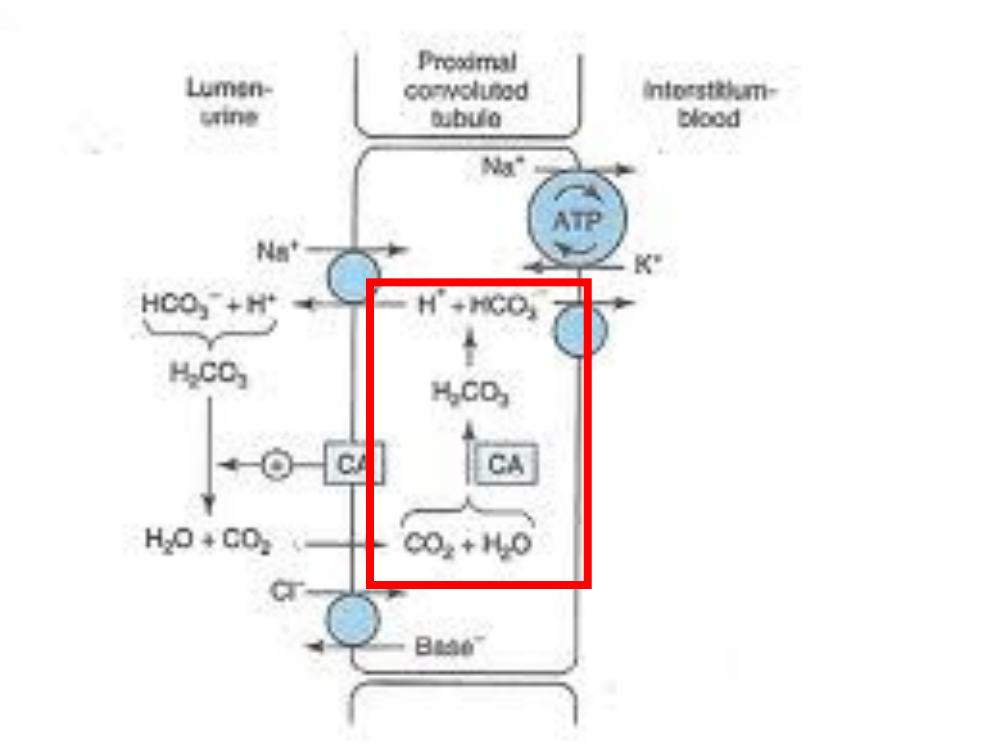
- **<u>Step 1</u>**
- **Na^+/H^+** :exchanger (NHE3) allows **Na^+** to enter for exchange of H^+
- **Na/K/ATPase pumps:** Na back in to interstitial space to maintain low intracellular Na^+ conc

Proximal Convoluted Tubule



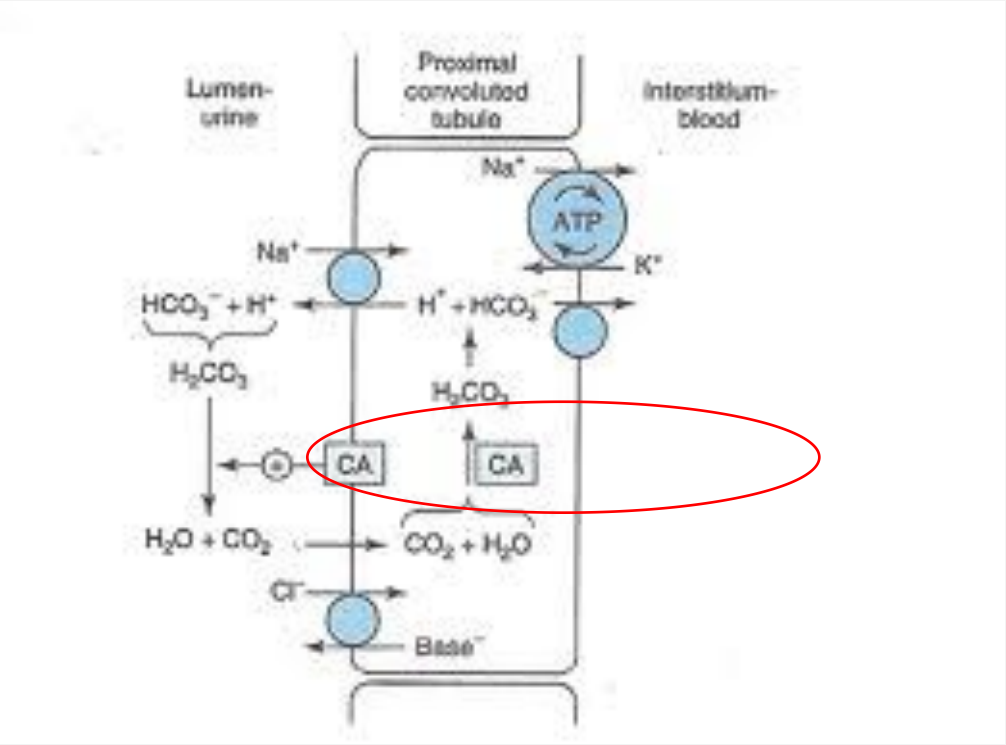
- **<u>Step 2</u>**
- H^+ secreted in lumen combines with bicarbonate (HCO^-_3) to form carbonic acid
- Carbonic acid rapidly dehydrated to form H_20 and CO_2 catalyzed by carbonic anhydrase (CA)

Proximal Convoluted Tubule



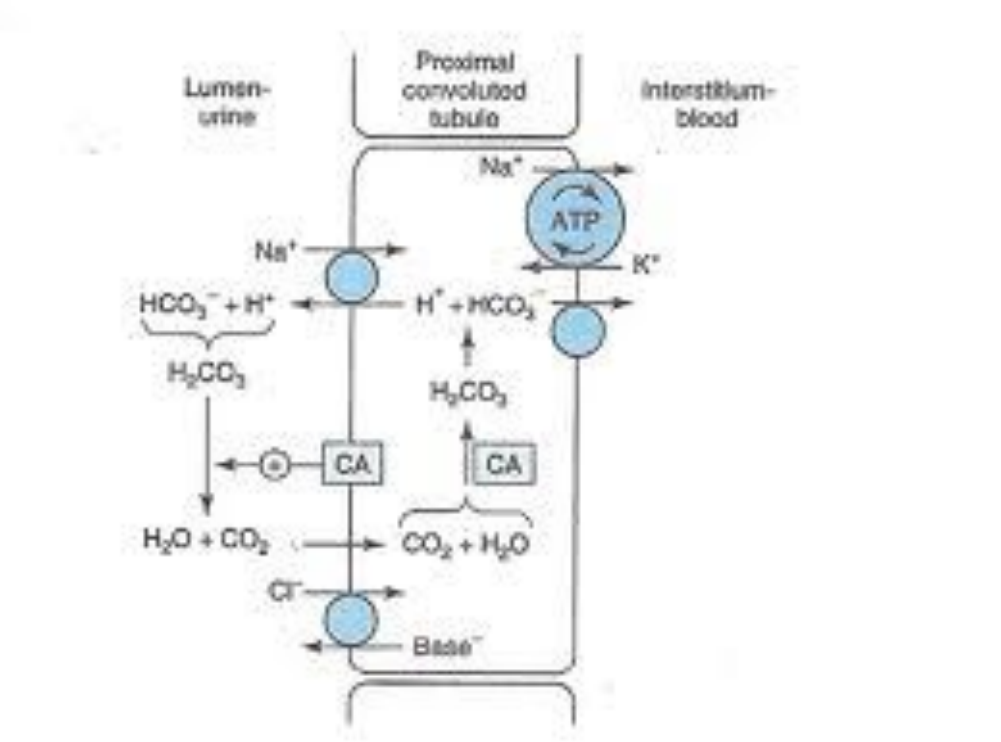
- **<u>Step 3</u>**
- CO_2 diffuses inside the cell, rehydrated back by CA
- Carbonic acid dissociates to form $HCO3^-$ and H^+
- $HCO3^-$ is transported out by basolateral transporter
- H^+ is available for exchange with Na^+

Carbonic Anhydrase (CA) Inhibitors



- Carbonic anhydrase catalyses the following reversible reaction
- $CO_2 + H_2O$ <--^{CA}--> H_2CO_3
- CA inhibitors inhibit this reaction
- This leads to a decreased ability to exchange Na^+ for H^+ in the presence of CA inhibitors resulting in a **mild diuresis**

Carbonic Anhydrase (CA) Inhibitors



- In presence of CA inhibitors, carbonic acid levels build up

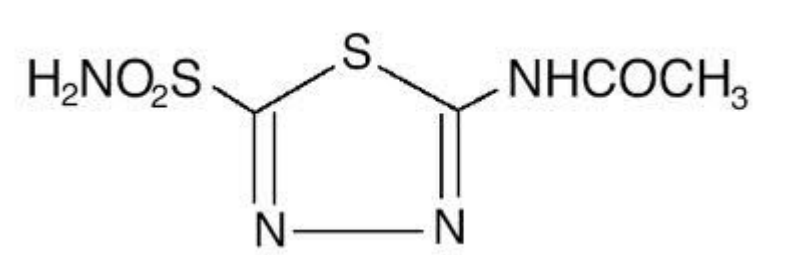
- Also, decrease in the body's ability to reabsorb serum bicarbonate, resulting in urinary bicarbonate wasting

- At max doses, almost 85 % capacity to reabsorb is HCO_3^- at PCT is **inhibited**

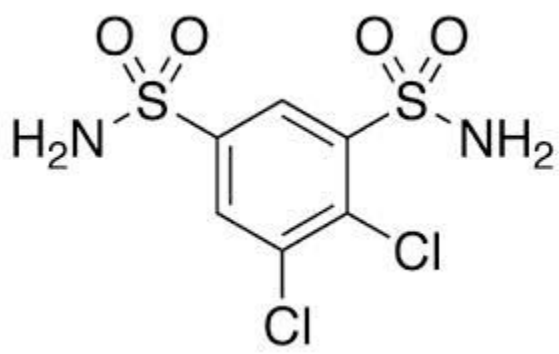
Carbonic Anhydrase (CA) Inhibitor

- Discovered in 1937
- Drugs in use
  - Actezolamide (prototype of this class)
  - Dichlorphenamide
  - Methazolamide
- This class now rarely used as diuretics but do have other applications

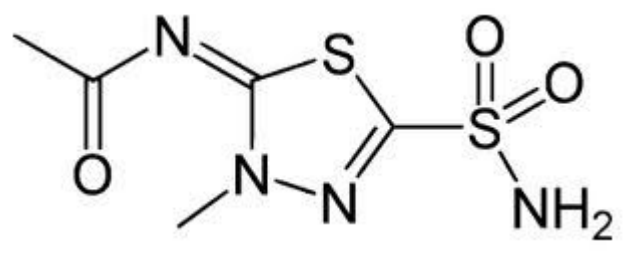
Carbonic Anhydrase (CA) Inhibitor Drugs



Acetazolamide



Dichlorphenamide



Methazolamide

Clinical Indications and doses

Major clinical applications:

- **Glaucoma**:
  - Reduction in aqueous humor by CAI decreases intra-ocular pressure
  - Valuable in management of glaucoma
  - Typical doses: 50 – 150 mg/ 1-3 times daily
- **Urinary alkalization**:
  - Increase urine pH to and avoid stone formation due to uric acid
- **Acute mountain sickness**:
  - Lowers the production of cerebrospinal fluid (CSF) leading to increase ventilation
- **Adjuvant uses**:
  - Epilepsy, CSF leakage

Toxicity

- **Metabolic acidosis**:
  - Condition where the blood becomes slightly acidic
  - Results due to imbalance in acid-base balance
- **Renal stones**:
  - Phosphaturia, calciuria in response to CAI
  - Ca stones relatively insoluble in alkaline urine
- **Renal K wasting**:
  - Increased Na+ reabsorption, increase negative potential in lumen
  - K secreted to counter

Loop Diuretics, MOA, Site

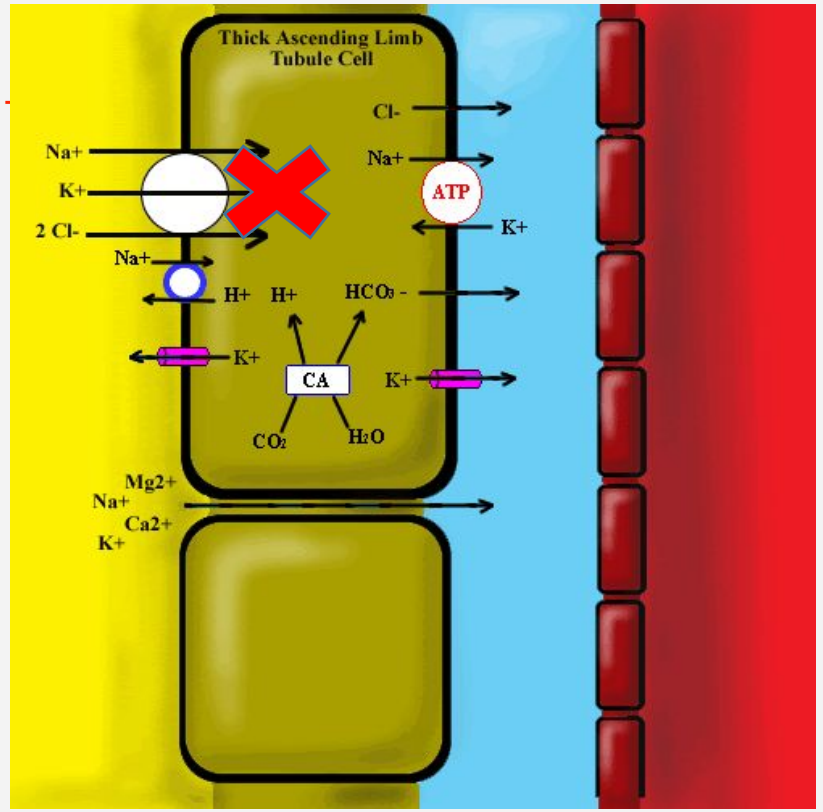
- Loop diuretics blocks the NKCC2 transporter leading to

Decreased reabsorption of Na^+ along with Ca^{2+} Mg^{2+}

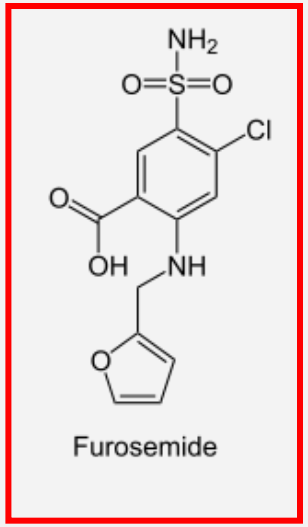
By disrupting the reabsorption of these ions, loop diuretics prevent the generation of a hypertonic renal medulla

Without such a concentrated medulla, water has less osmotic driving force to leave the collecting duct system

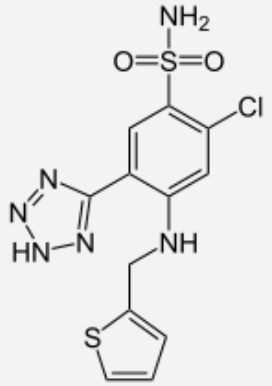
Resulting in increased urine production



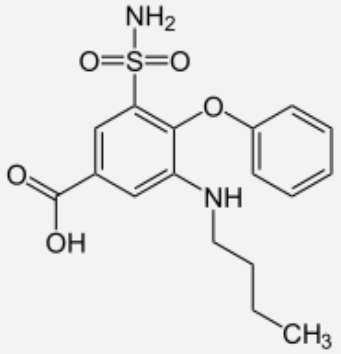
Loop Diuretics, Structures



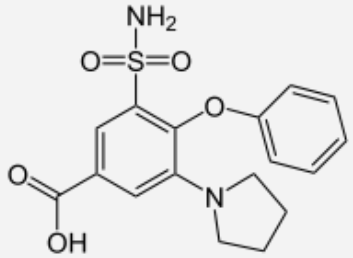
Furosemide



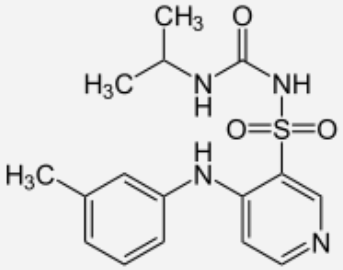
Azosemide



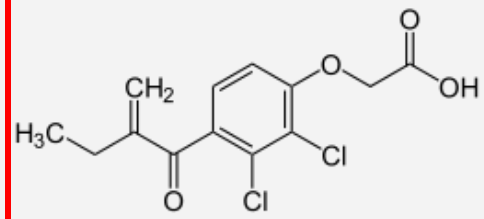
Bumetanide



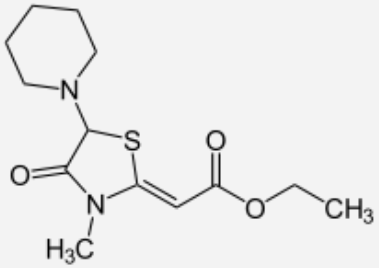
Piretanide



Torasemide



Ethacrynic acid



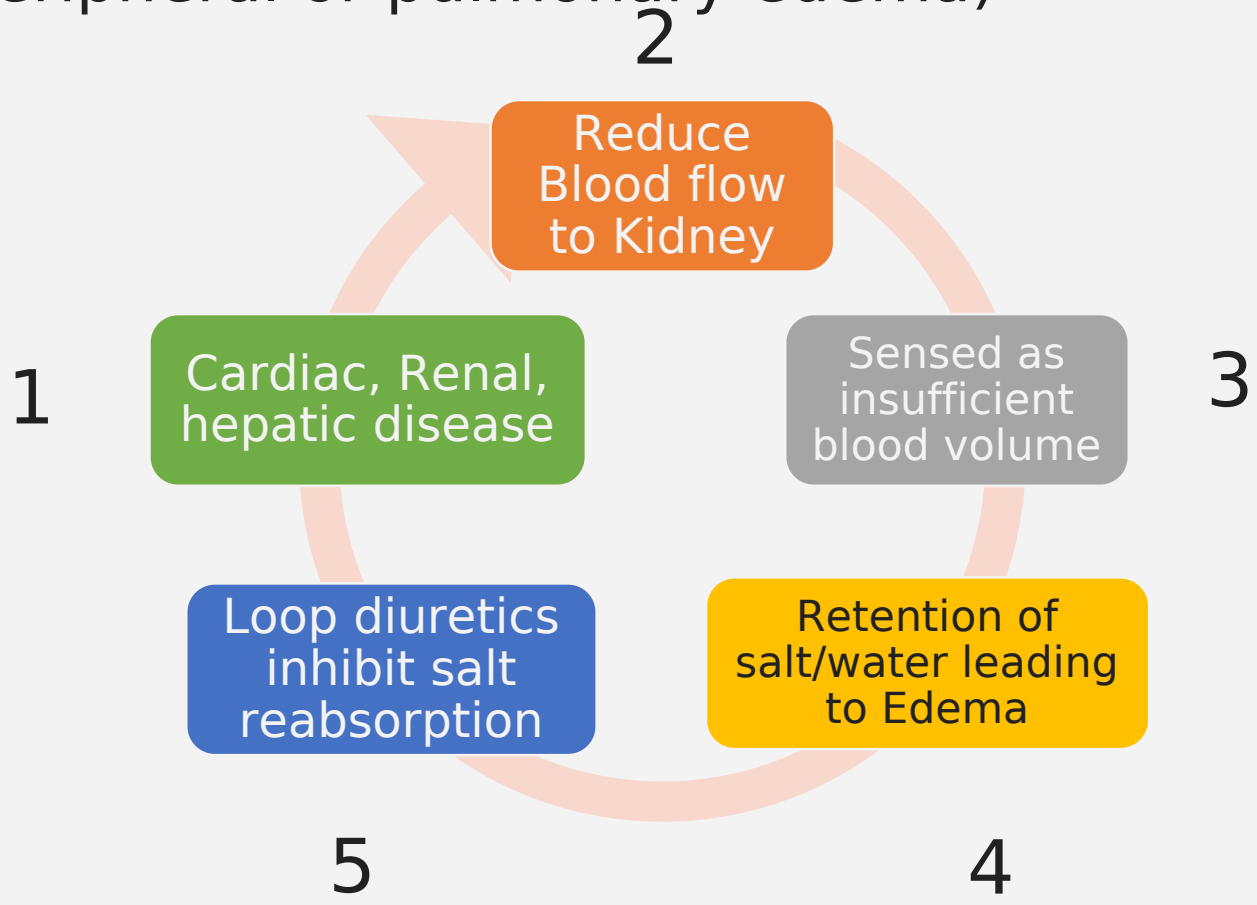
Etozolin

Pharmacokinetics of Diuretics

- Loop diuretics are rapidly absorbed (1-3 hours)
- Eliminated by glomerular filtration and secretion
- Duration of effect is 2- 3 hours
- Half life depends on renal function

Clinical Indications

- Most important use of loop diuretics in treating EDEMATOUS conditions (peripheral or pulmonary edema)



Clinical Indications

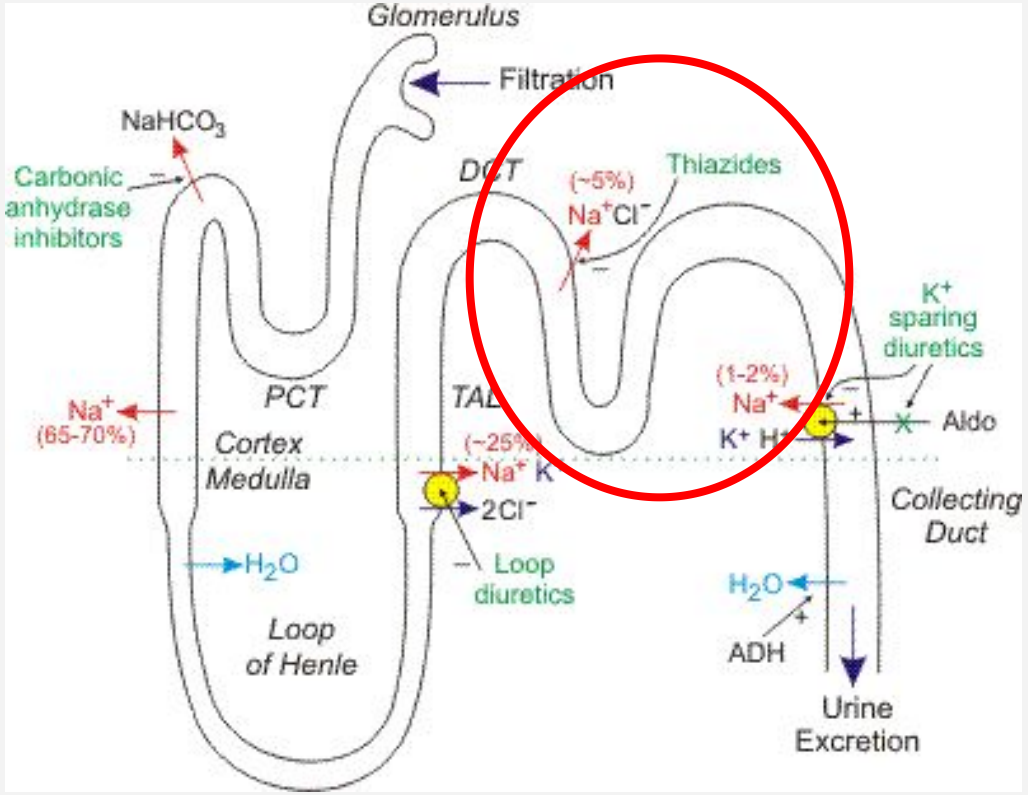
- **Hyperkalemia**:
  - Loop diuretics significantly **increases** urinary excretion of K^+
- **Acute renal failure**
  - Increase in urinary flow to flush out intra-tubular casts, obstructions
- **Anion overdose**
  - Br, Fl, I
  - Saline must be **co-administered** to replenish Na, Cl loss

Toxicity

- **Hypokalemia Metabolic Alkalosis**
  - Increased excretion of K^+ due to increased excretion of Na^+
- **Hypomagnesaemia**
  - Increased excretion of Mg^+
- **Allergic and other reactions**

Thiazide Diuretics

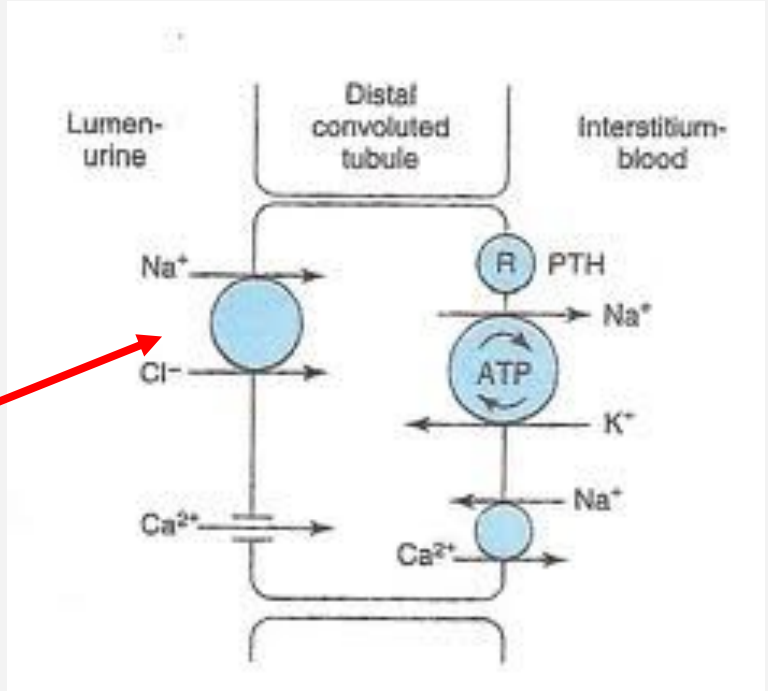
- 5- 10 % Na reabsorbed at DCT
- Impermeable to water, leads to dilution
- Thiazide diuretics originally synthesized to create more potent carbonic anhydrase inhibitors
- Act at DCT



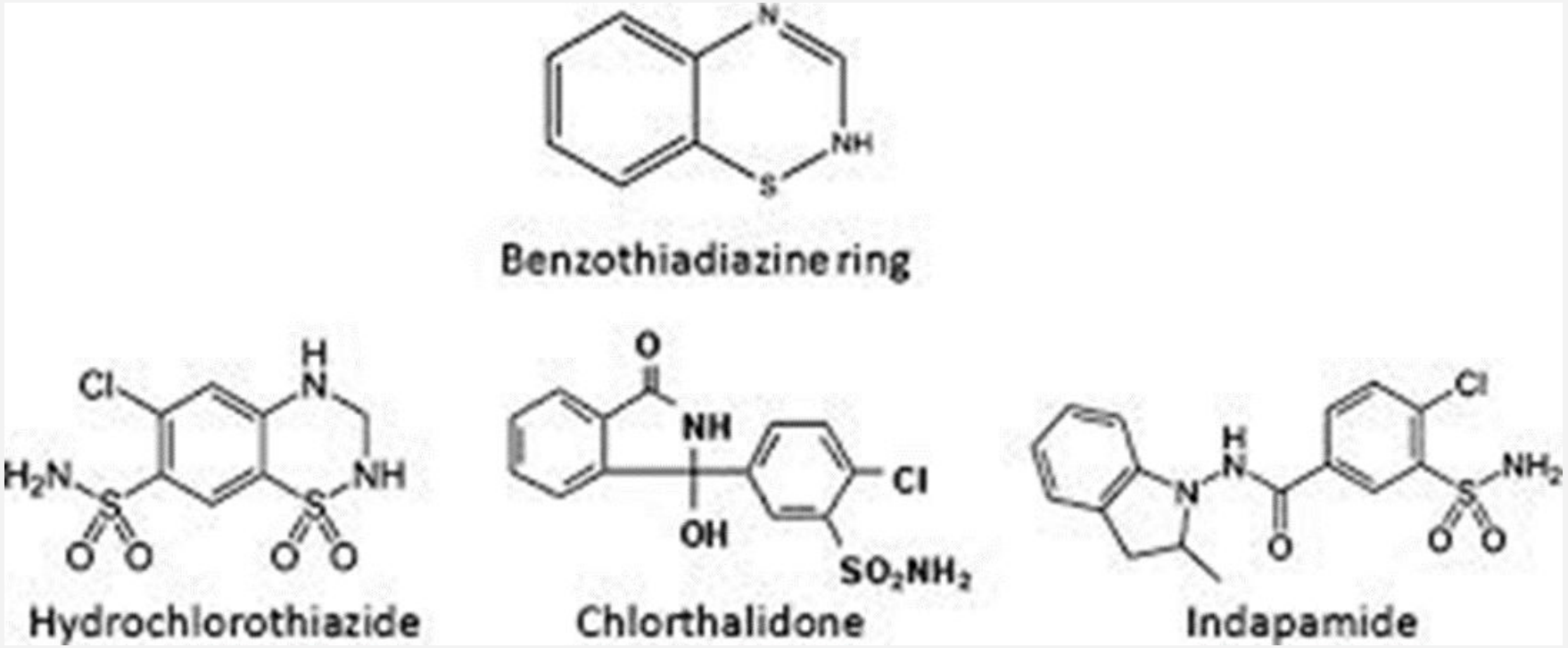
Thiazide action at DCT

- **Na^+, Cl^-** reabsorbed by Na^+/Cl^- co-transporter (NCC)

- Thiazides bind to Cl^- inhibiting NCC & thus prevent Na^+ reabsorption



Thiazide Diuretics, Structures



Clinical Indications

- Less powerful than loop diuretics but preferred in treating Hypertension
  - Decreased blood volume, vasodilation
  - Amongst the group, Hydrochlorothiazide is the most widely used
  - Usually reserved for patients with mild renal insufficiency
- Mild heart failure

Toxicity

- **Hypokalemic Metabolic acidosis**
- **Hyperlipidemia**
  - Increase in cholesterol and LDL
- **Hyponatremia**
  - Important side effect
  - Prevented by reducing the dose or fluid intake

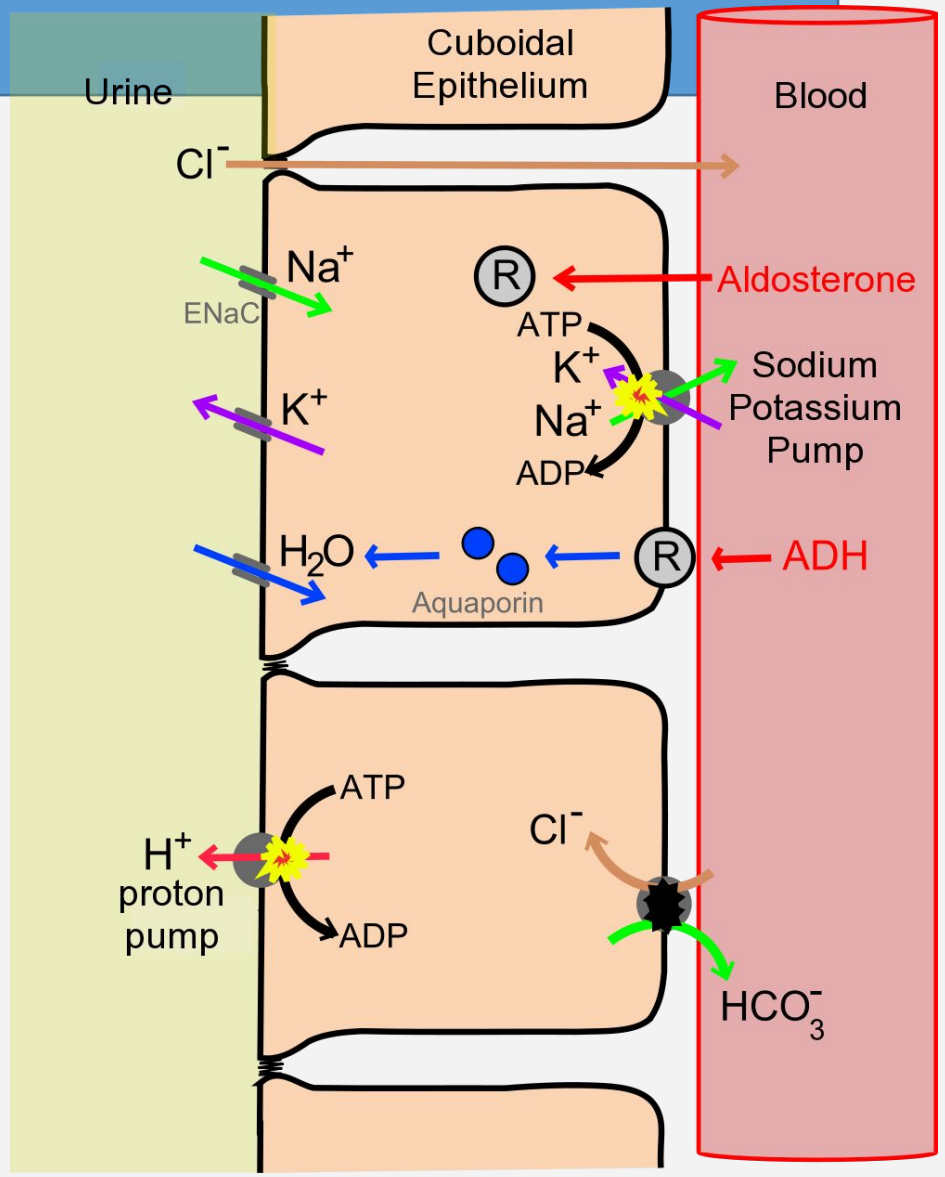
Activity at Collection tubule

- 3 components:
  - connecting tubule
  - collecting tubule
  - collecting duct

- 2.5 % Na reabsorption, final site of Na^+ reabsorption

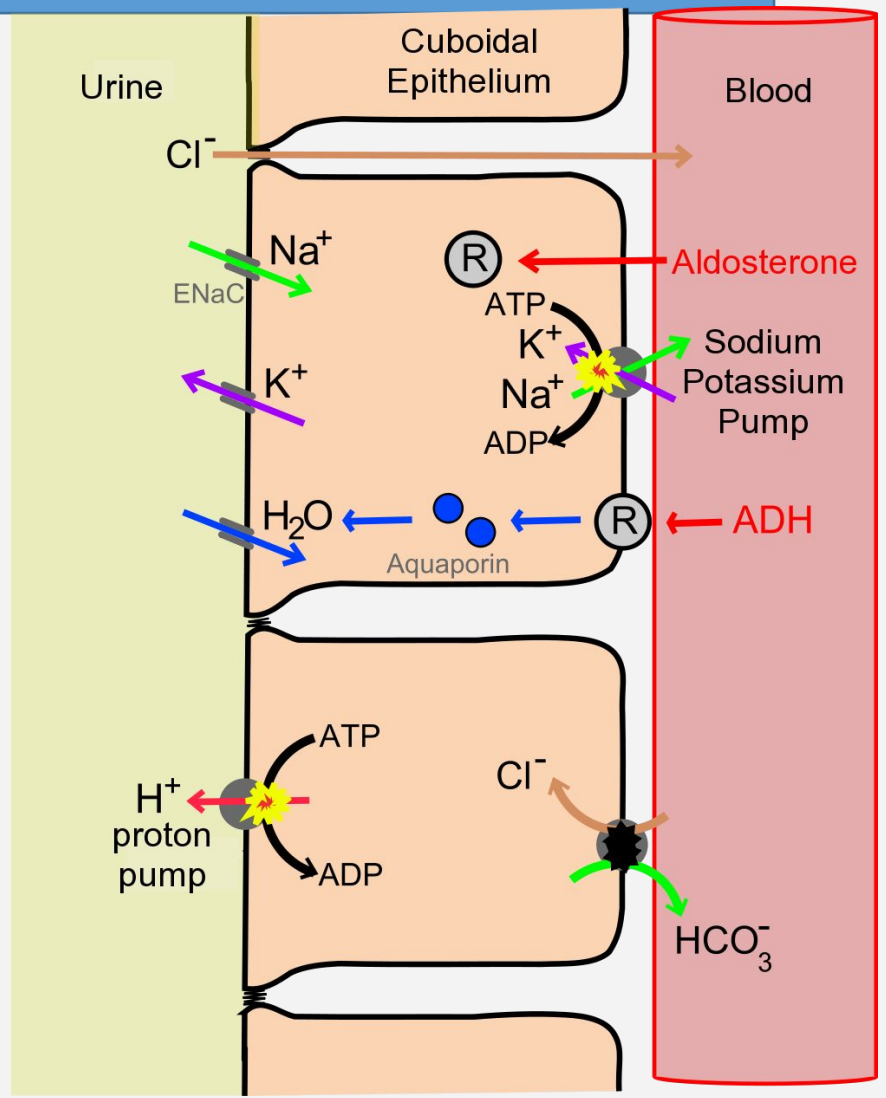
- **Mineralocorticoids** have the largest influence at this site

- Most important site of K^+ secretion in kidney



Activity at Collection tubule

- Mechanism of ion reabsorption different from other regions
- Separate channels for Na^+ & K^+
- Na^+ entry preferred, movement creates a negative lumen potential
- Cl get's in via paracellular route, K^+ goes out of cell
- Aldosterone increases activity of these channels
- Diuretics and Aldosterone activity leads to K^+ wasting

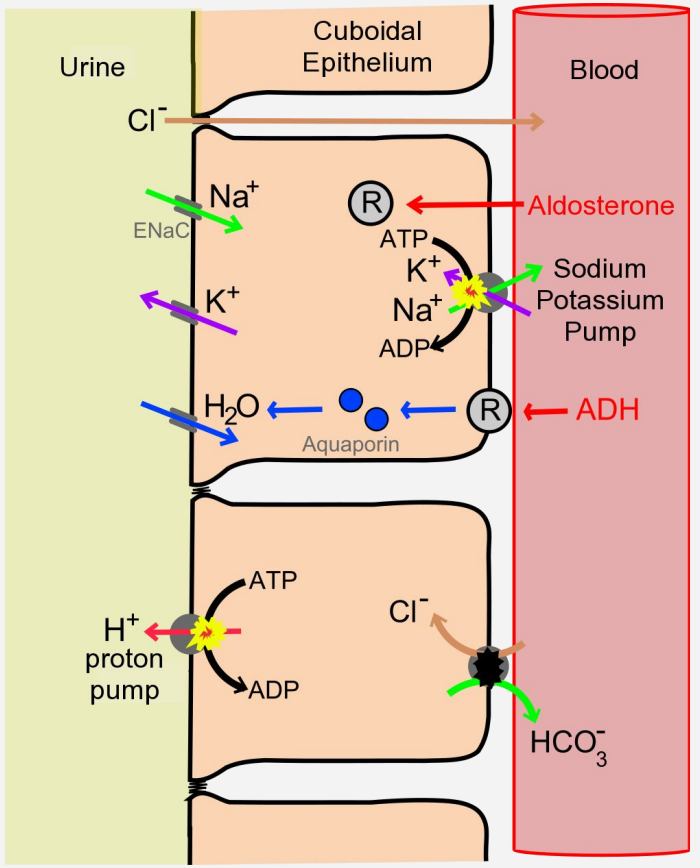


K/ Sparing diuretics

- K-Sparing diuretics mainly act by 2 ways

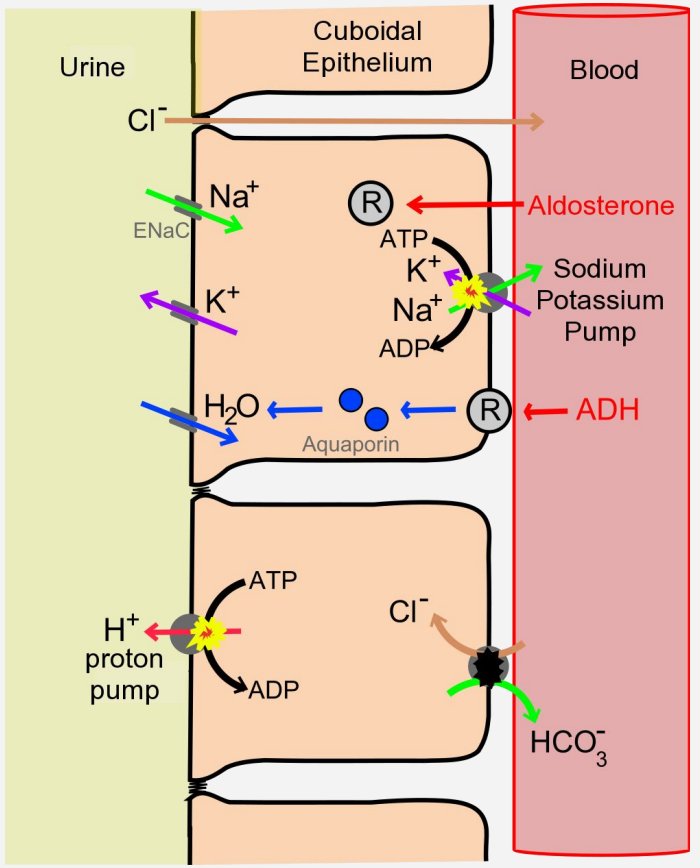
  1. Competitive antagonist of Aldosterone

  2. Directly block Na channels



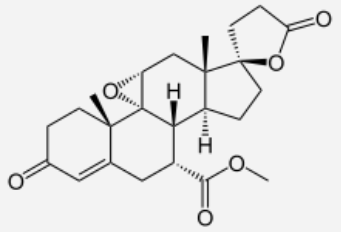
Competitive Aldosterone antagonist

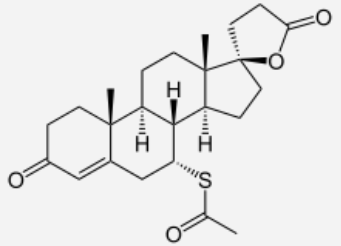
- These directly compete with aldosterone for intracellular cytoplasmic binding sites
- Thus prevent formation of proteins that are normally synthesized in reaction to aldosterone
- As a result mediator proteins are not produced and so stimulation of sodium-potassium exchange does not occur

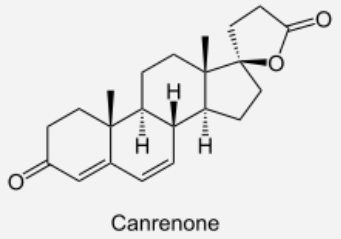


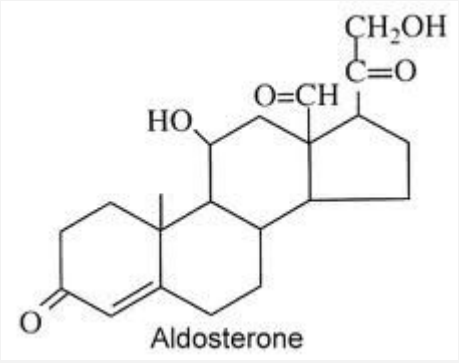
Competitive Aldosterone antagonist

- Synthetic steroidal molecules
- Spironolactone has a slower onset, takes days for full therapeutic effect
- Eplerenone is much selective for ADH receptor, **lower side effects**



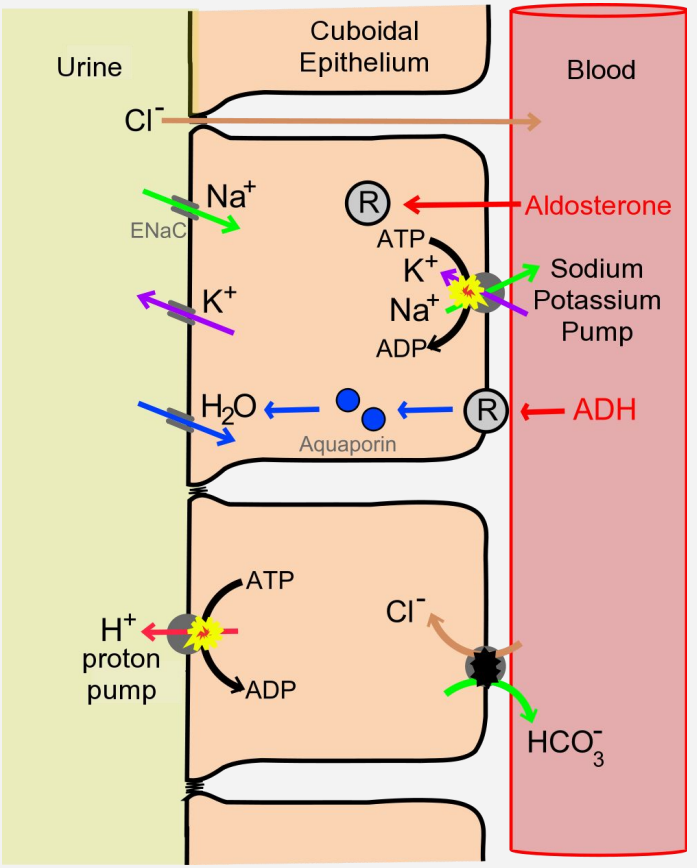




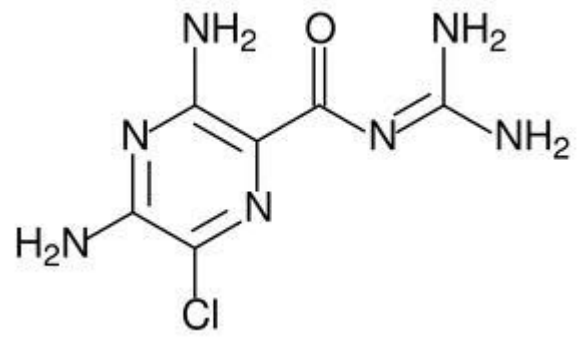


Direct channel blockers

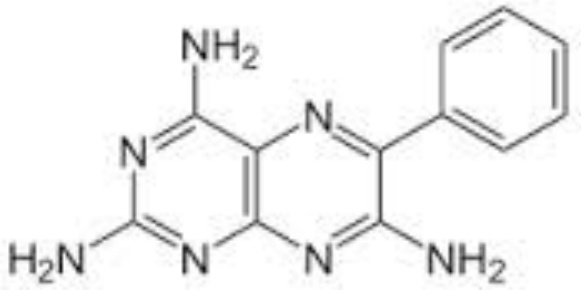
- Directly interfere with Na entry through **epithelial Na $^{+}$ channels (eNaC)**
- Since K^{+} secretion is coupled with Na $^{+}$ entry in this region
- Both categories are thus K^{+} –sparing diuretics



Direct channel blockers



Amiloride



Triamterene

Clinical Indications

- Most useful in conditions of hyperaldosteronism
  - Primary hypersecretion (Conn's syndrome)
  - Secondary hypersecretion (evoked by heart failure, liver cirrhosis etc)
  - Due to enhanced Aldosterone, higher Na^+ retension, K^+ wasting occurs ------ K^+-sparing agents prevent wasting
- These drugs have mild action

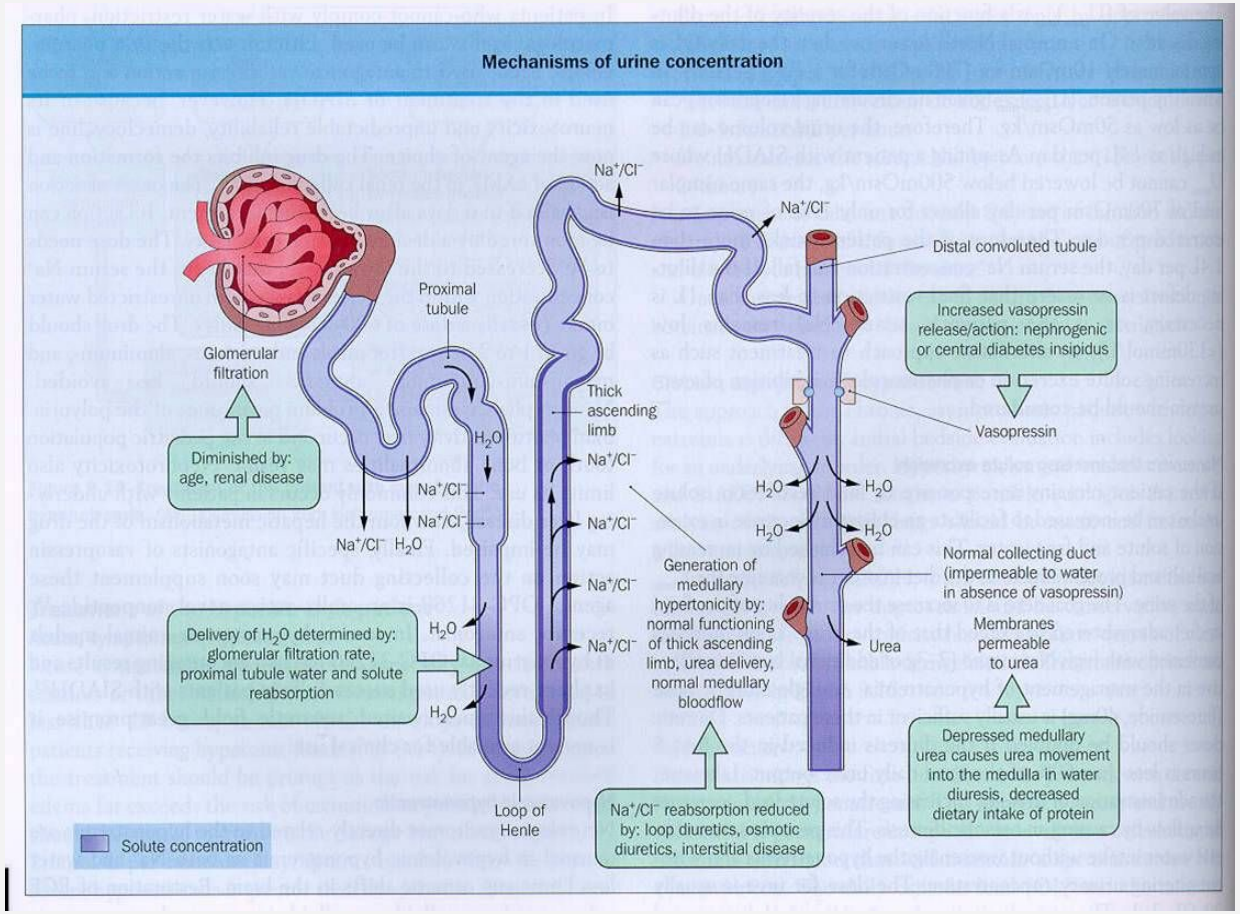
should be avoided in conditions where potent diuretic action is desired

Toxicity

- **Hyperkalemia**
  - Can cause mild, moderate or even life threatening hyperkalemia
  - Risk increased in case of renal disease or renin inhibitors
  - Toxicity more common when used alone
- **Hyperchloremic Metabolic Acidosis**
  - Inhibit H^+ secretion along with K^+ causing **acidosis**
- **Kidney stones**
  - Triamterene is slightly soluble in urine, may ppt causing kidney stones

Agents that alter water excretion Osmotic Diuretics

- Proximal tubule, descending limb are water permeable
- Any osmotic active produces water retention
- **Prototype agent** : Mannitol



Pharmacodynamics & Pharmacokinetics

- PD:
  - Major effect on Proximal tubule & descending limb
  - Increase in urine flow

  ⇩

  decreases the contact time for Na^+, water reabsorption

  ⇩

  Less Reabsorption

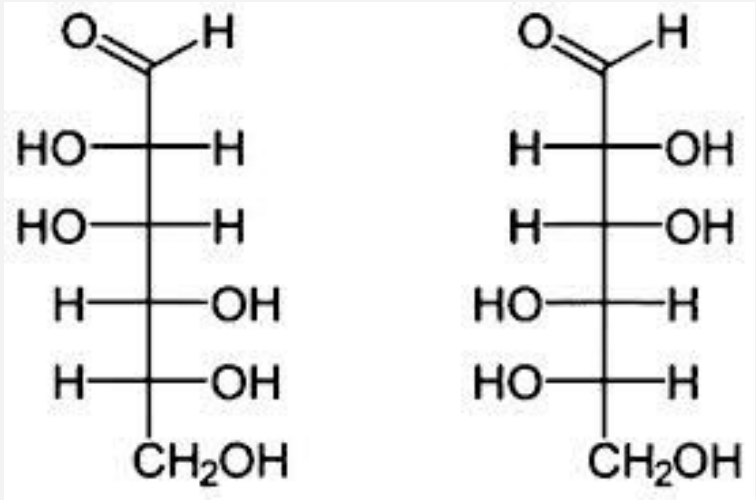
  ⇩

  Enhances the Uresis

- PK:
  - Mannitol ---- poorly absorbed in GI, given IV
  - Not metabolized, excreted by filtration within 30- 60 min

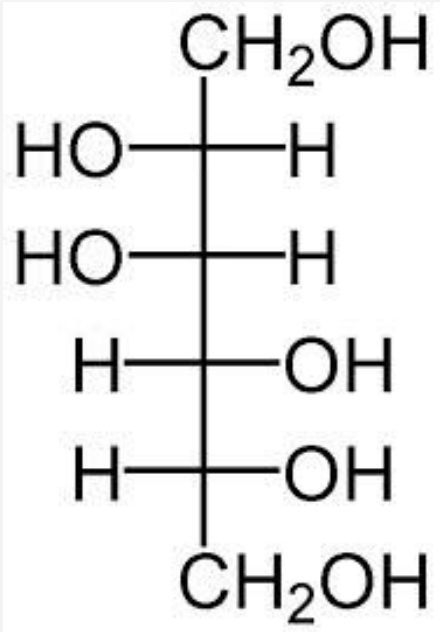
Mannitol Structure

- Sugar alcohol derived from sugar Mannose by reduction



Mannose

Red



Mannitol

Clinical Indications

- To Increase Urine Volume
  - Used to increase water excretion in preference to Na^+ excretion
  - To maintain urine volume & prevent anuria (No urine formation)
- Reduction of intra-cranial, intra-ocular pressure
  - Osmotic diuretics alter osmotic forces; water leaves cell reducing intra-cellular volume

Lower intra-cranial & intra-ocular pressure

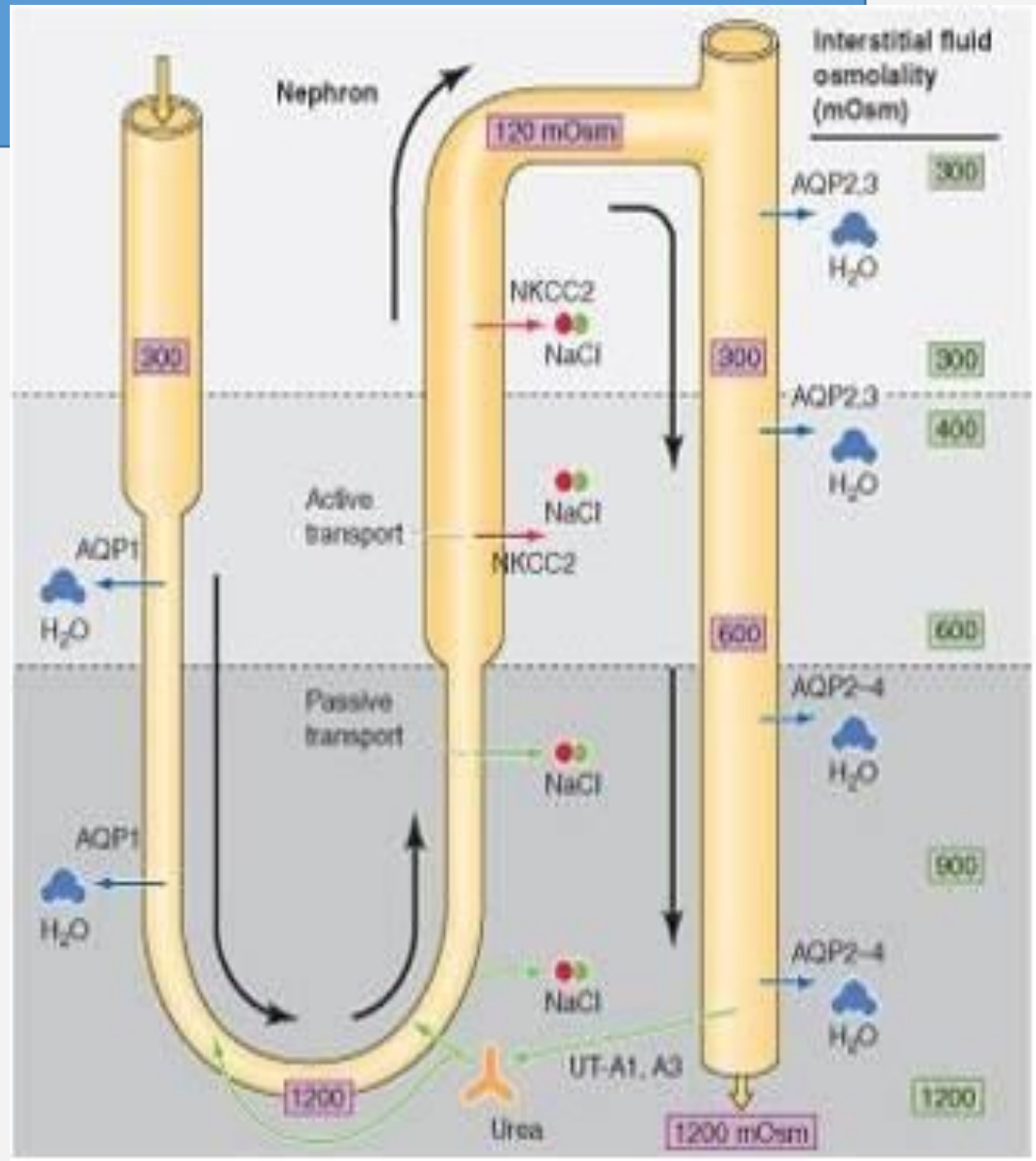
Toxicity

- **Extracellular Volume expansion**:
  - Mannitol rapidly distributed in extracellular compartment, extracts water from cells
  - Leads to expansion of extracellular volume
  - This can complicate heart failure, lead to edema

- Dehydration, Hyperkalemia, Hypernatremia:
  - Excessive use leads to water losses leading to dehydration, **hypernatremia**
  - Water extraction from cells leads to hyperkalemia (increase in K^+ conc)

Water extraction at Collection tubule

- **<u>ADH or arginine vasopressin</u>** controls the movement of water by inserting pre-formed water channels (Aquaporins)
- In absence of ADH, collecting tubule is impermeable to water
- ADH increases water permeability leads to formation of conc urine



ADH Antagonist

- ADH antagonist -: block effects of ADH leading to diuresis
- Non-selective agents:
  - Lithium, demeclocycline
- Selective agents:
  - Vasopressin receptor (V2) antagonist
  - Conivaptan, tolvaptan
  - **Conivaptan** is administered IV
  - **Tolvaptan** is administered orally, half life of 12-24 hrs

Clinical Indications

- Syndrome of Inappropriate ADH secretion (SIADH)

- Other causes of elevated ADH:
  - Low blood volume due to various reasons leads to elevated ADH levels

  - ADH antagonist useful in this setting