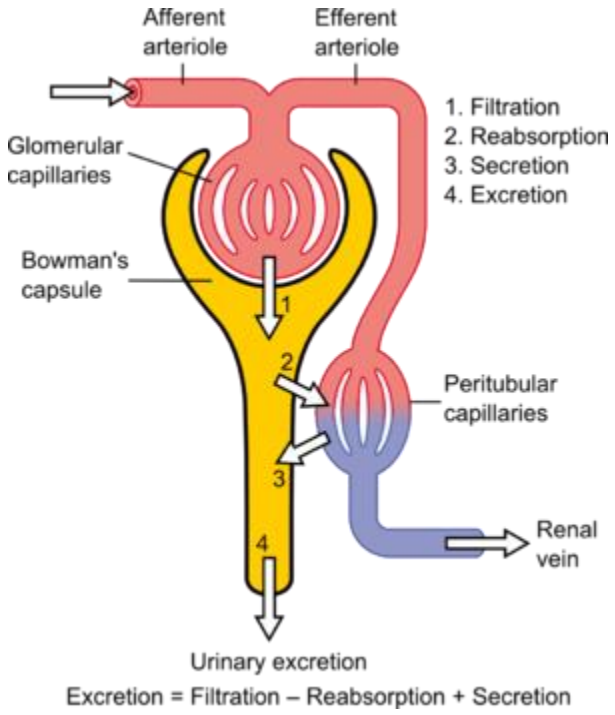
DIURETICS-2

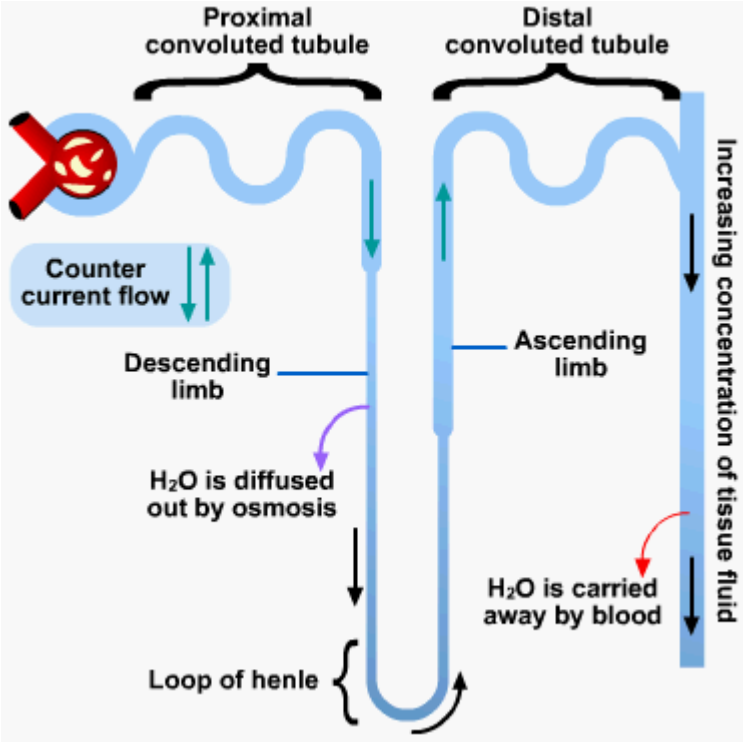
Dr. Shariq Syed

Structure of Kidney

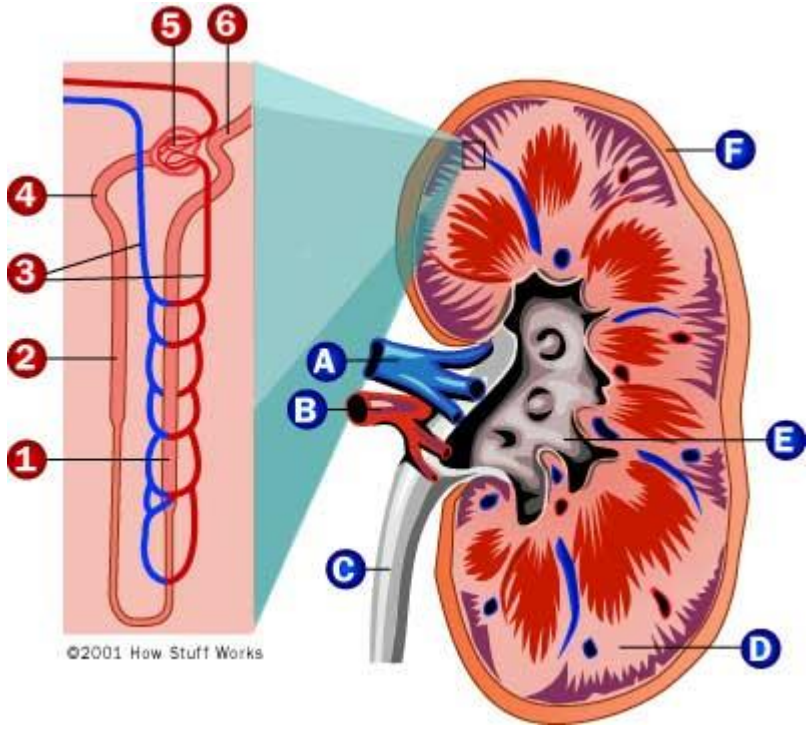


- Blood filtered by functional unit: Nephron
- Except for cells, proteins , other large molecules, rest gets filtered

Structure of Kidney

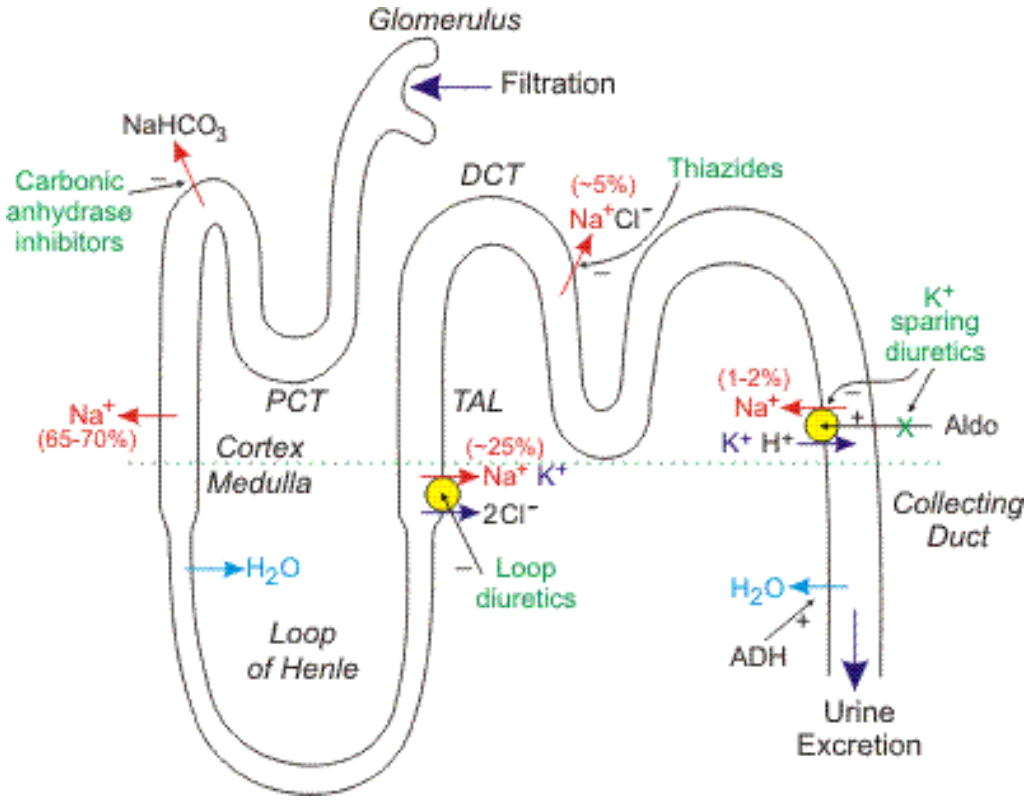


- 3 major regions of nephron
  - PCT (Proximal Convoluted Tubule)
  - Loop of Henle
  - DCT (Distal convoluted Tubule)



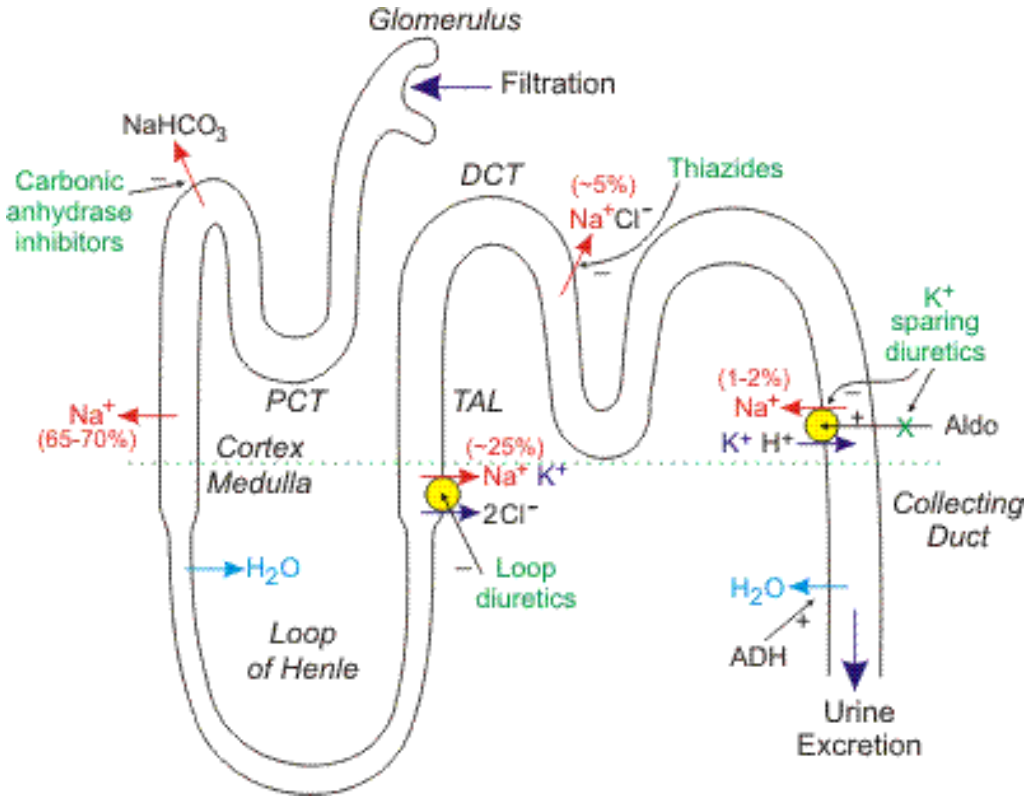
Role of Kidneys in Water/ Na reabsorption

- 20 % of plasma filtered in to PCT
- 65- 70 % of filtered Na removed iso-osmotically
- Medulla hyperosmotic , loop is permeable to water, water reabsorption takes
- The 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

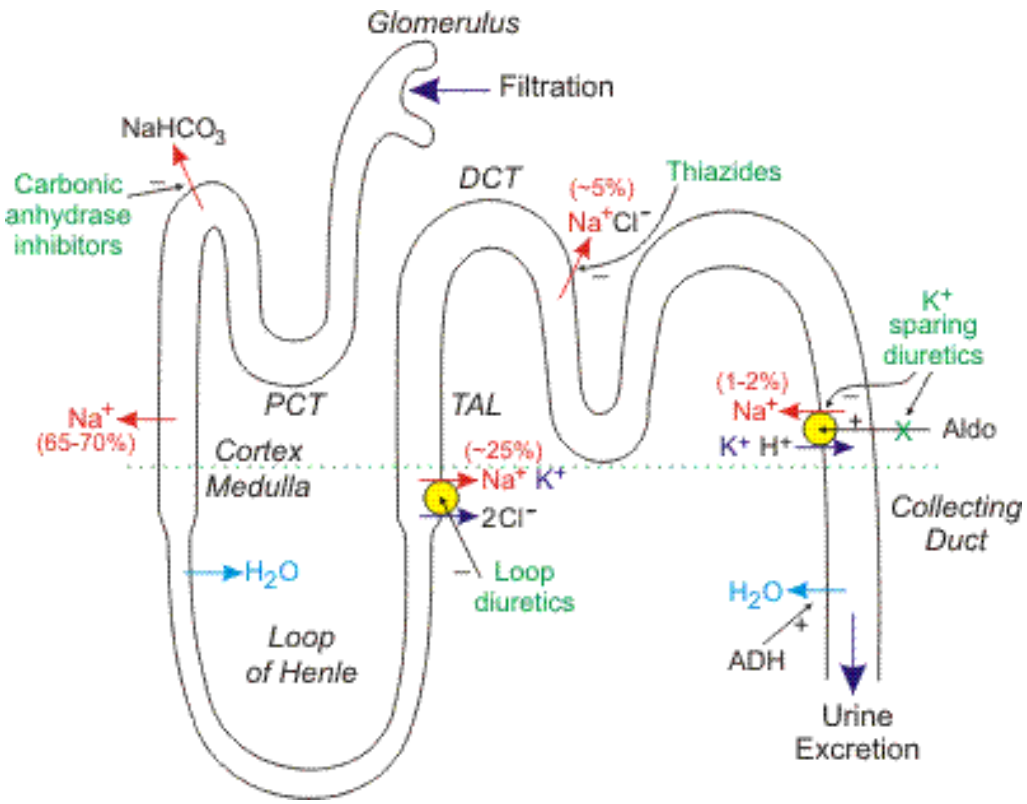


Mechanism of Action

- 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

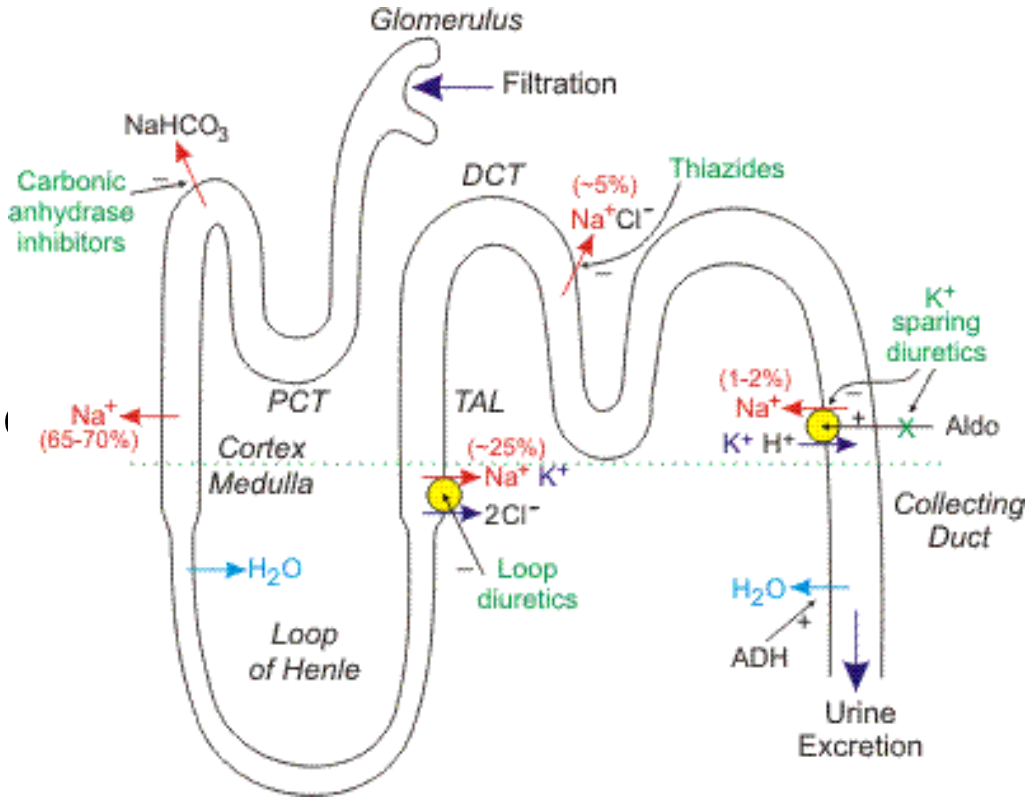
Different Classes of Diuretics

- Loop Diuretics:
  - inhibit the sodium-potassium-chloride co-transporter in the thick ascending limb
  - 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:
  - Inhibit the transport of bicarbonate out 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



Carbonic Anhydrase inhibitors

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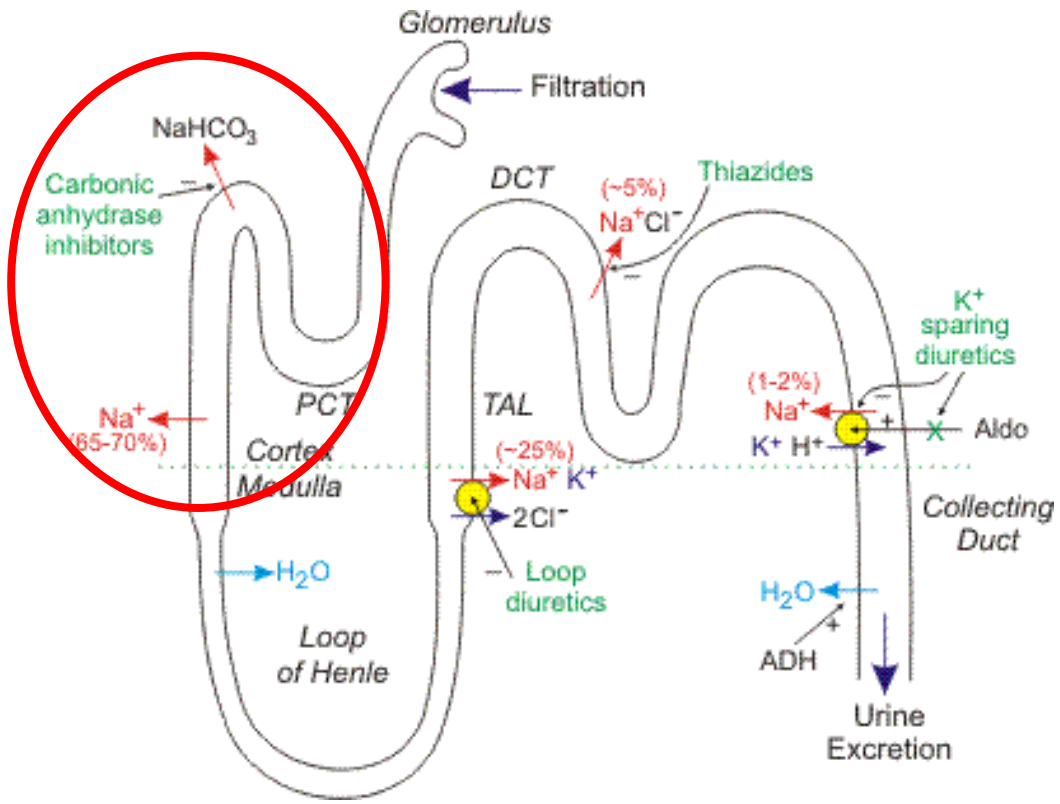
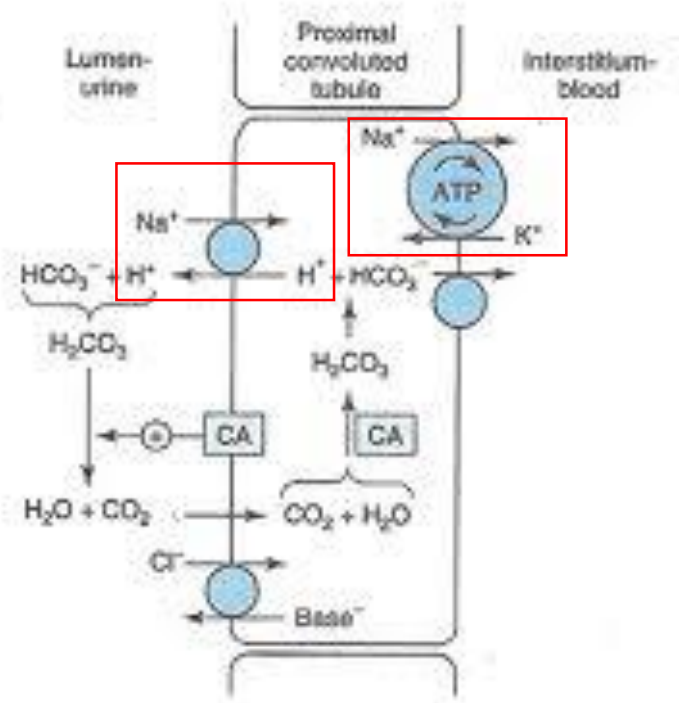
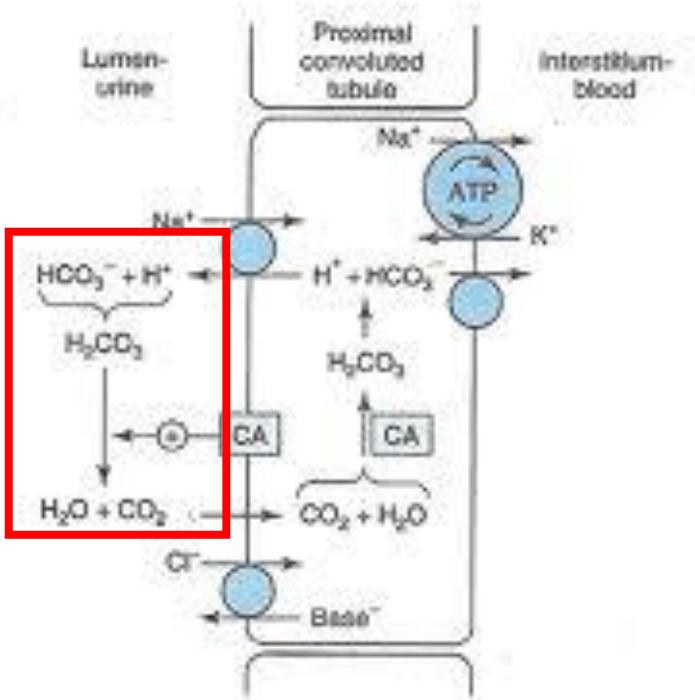


Proximal Convoluted Tubule



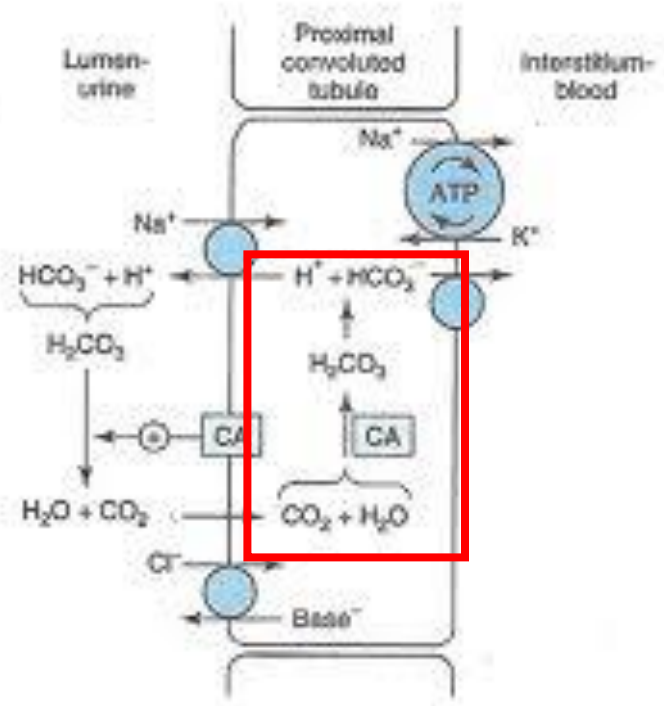
- <u>Step 1</u>
- Na^+/H^+ exchanger (NHE3) allows Na^+ to enter for exchange of H^+
- Na/K/ATPase pumps Na back in to interstitial space to maintain low intracellular Na^+ conc

Proximal Convoluted Tubule



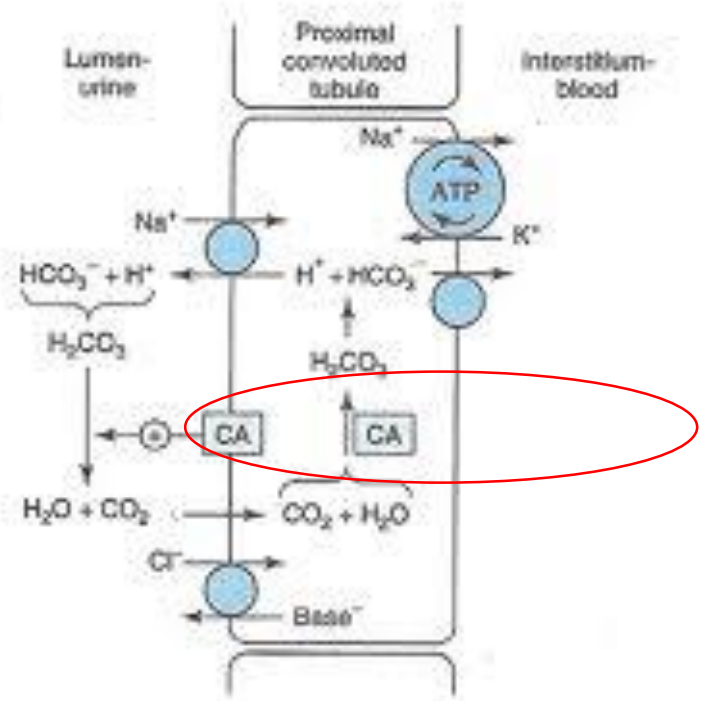
- <u>Step 2</u>
- H^+ secreted in lumen combines with bicarbonate (HCO^-_3) to form carbonic acid
- Carbonic acid rapidly dehydrated to form H_20 and CO_2 catalyzed by carbonic anhydrase (CA)

Proximal Convoluted Tubule



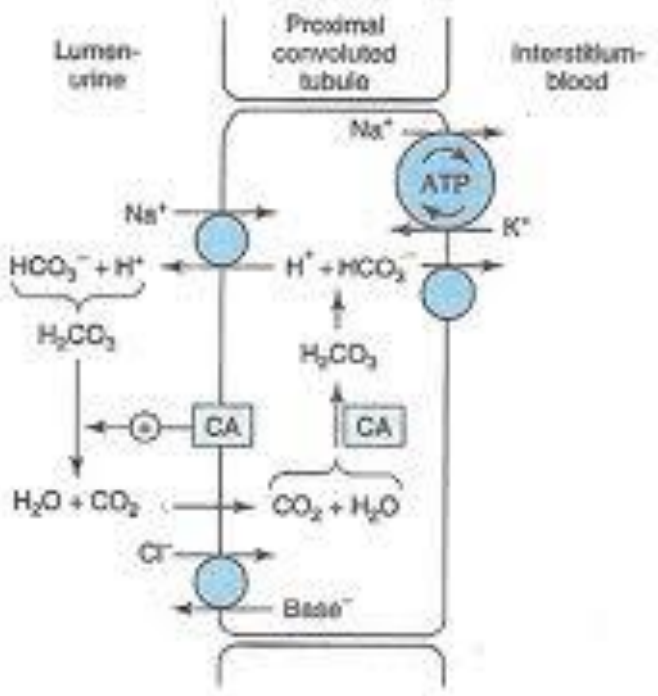
- <u>Step 3</u>
- CO_2 diffuses inside the cell, rehydrated back by CA
- Carbonic acid dissociates to form $HCO3^-$ and H^+
- $HCO3^-$ is transported out by basolateral transporter
- H^+ is available for exchange with Na^+

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

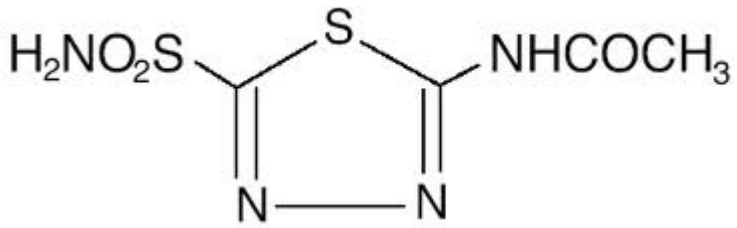


- In presence of CA inhibitors, carbonic acid levels build up
- Also, decrease in the body's ability to reabsorb serum bicarbonate, resulting in urinary bicarbonate wasting
- At max doses, almost 85 % capacity to reabsorb is HCO_3^- at PCT is inhibited
- Activity decreases over a period of time as body increases NaCl reabsorption in later tubule segments

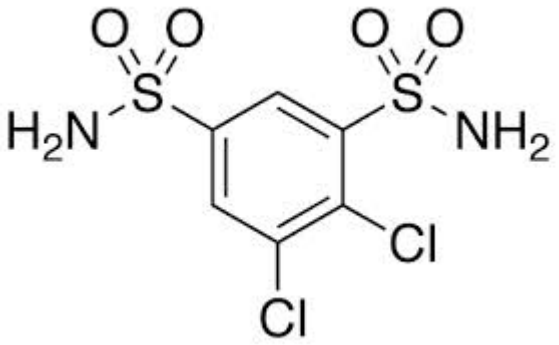
Carbonic Anhydrase (CA) Inhibitor Drugs

- This class was the forerunner of modern diuretics
- Discovered in 1937 , sulfonamides caused diuresis
- Drugs in use
  - Actezolamide (prototype of this class)
  - Dichlorphenamide
  - Methazolamide
- This class now rarely used as diuretics but do have other applications

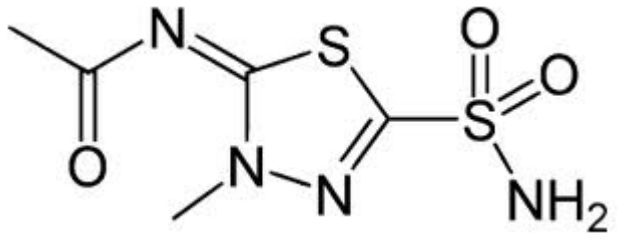
Carbonic Anhydrase (CA) Inhibitor Drugs



Acetazolamide



Dichlorphenamide



Methazolamide

Clinical Indications and doses

- Major clinical applications involving CA inhibitors
- 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 prevent stones formation due to cystinuria or 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