

DIURETICS-3

Dr. Shariq Syed

Pop Quiz !!

- Diuretics primarily prevent the reabsorption of

K

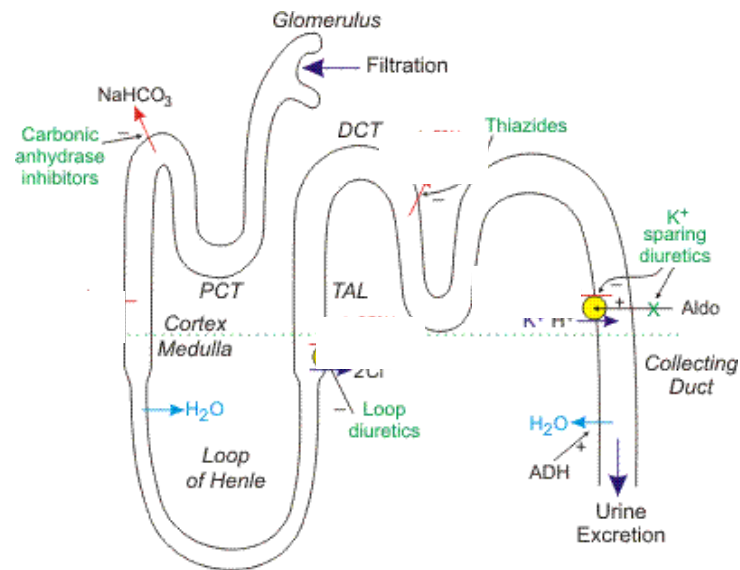
Na

Cl

I Don't know, Too
busy with periodic
exams!

Pop Quiz !!

- In which nephron region max reabsorption of Na^+ takes place ??



Pop Quiz !!

- Carbonic anhydrase inhibitors act in which region of nephron

Loop

DCT

PCT

Sorry, forgot, any
lifeline ??

Pop Quiz !!

- Major use of Carbonic anhydrase inhibitors is in treatment of

Glaucoma

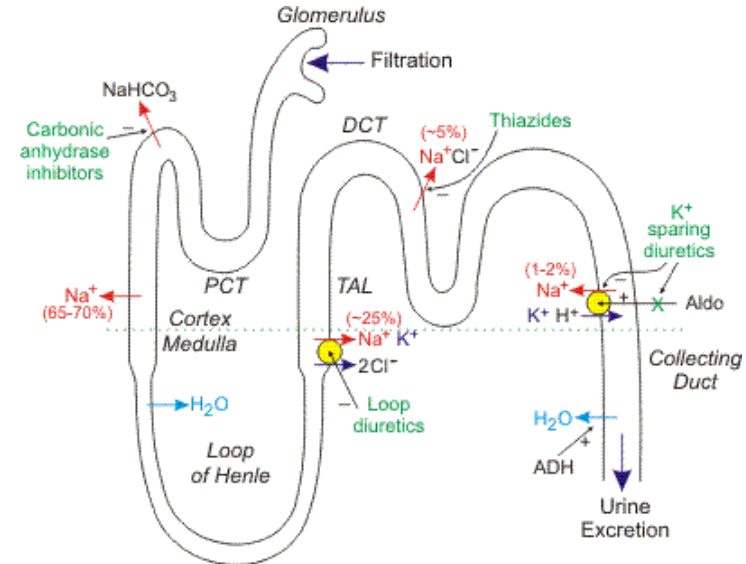
Malaria

Dengue

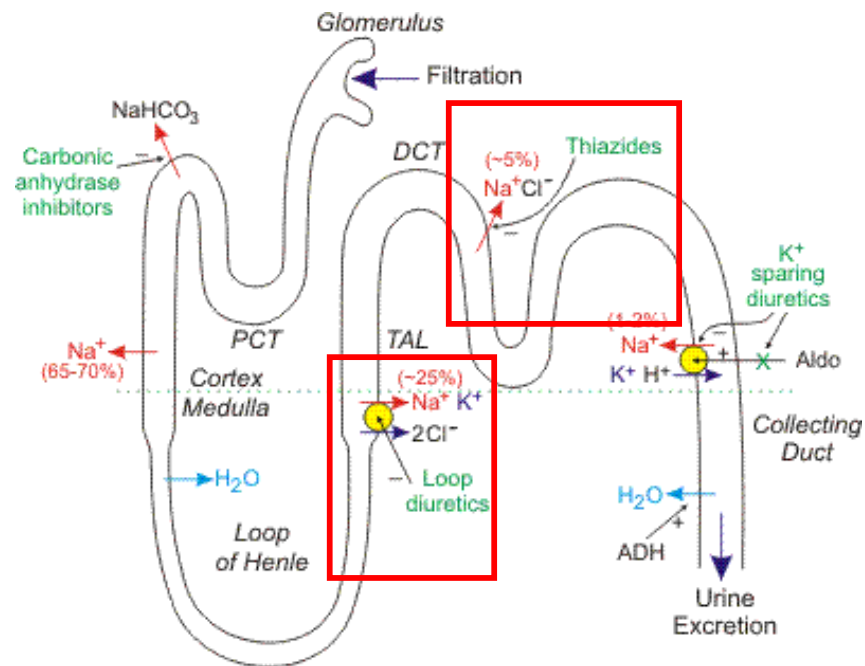
Sorry, forgot, any
lifeline ??

Recap of what we did last time

- Reviewed the structure/function of Nephron
- Basic concept of how diuretics work
- Introduced different classes of Diuretics
- Looked in detail at Carbonic Anhydrase inhibitors

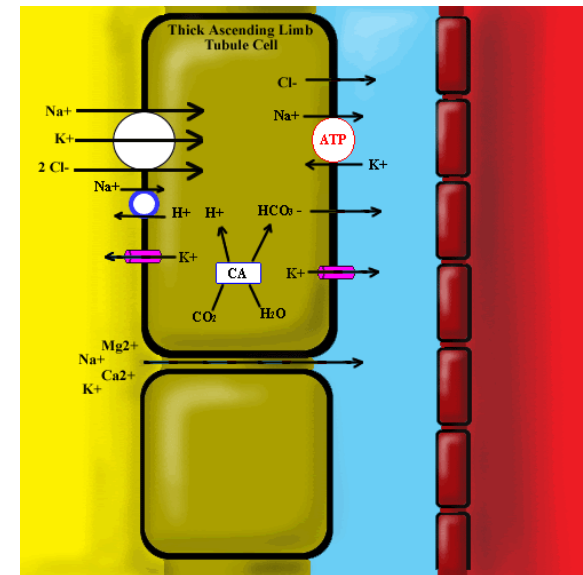


Plan for today



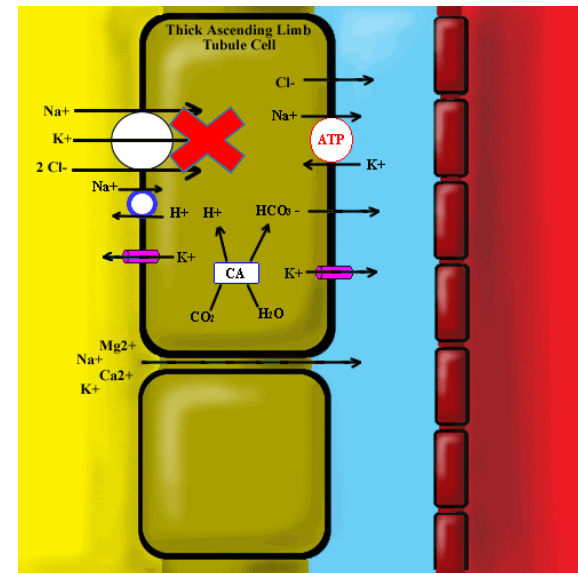
Action at TAL, close look at NKCC2

- NKCC2 electrically neutral transporter (2^+ , 2^-)
- Leads to excess accumulation of K^+ in cells, gets diffused back in lumen
- Positive potential in lumen drive Ca^{2+} , Mg^{2+} reabsorbed via paracellular path

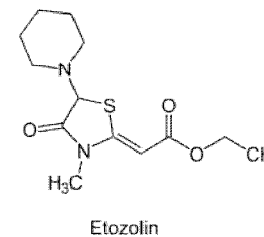
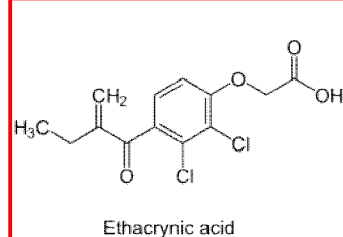
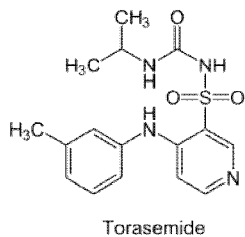
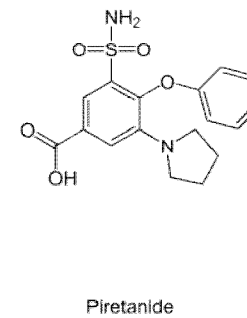
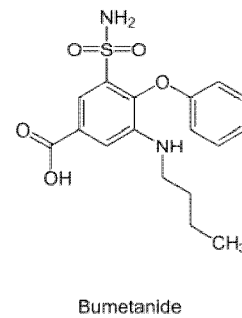
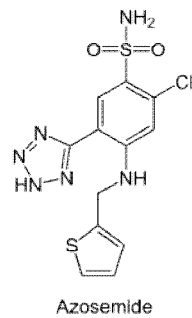
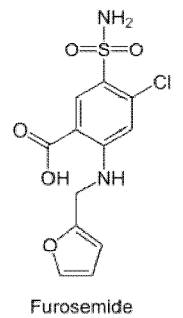


Loop Diuretics, MOA, Site

- 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 of an osmotic driving force to leave the collecting duct system, ultimately resulting in increased urine production



Loop Diuretics, Structures

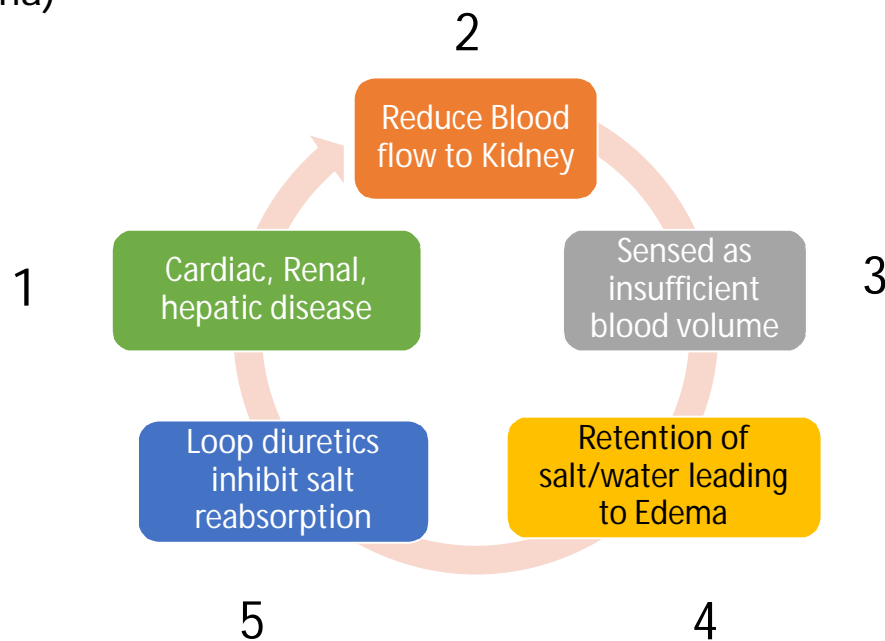


Pharmacokinetics of Diuretics

- 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

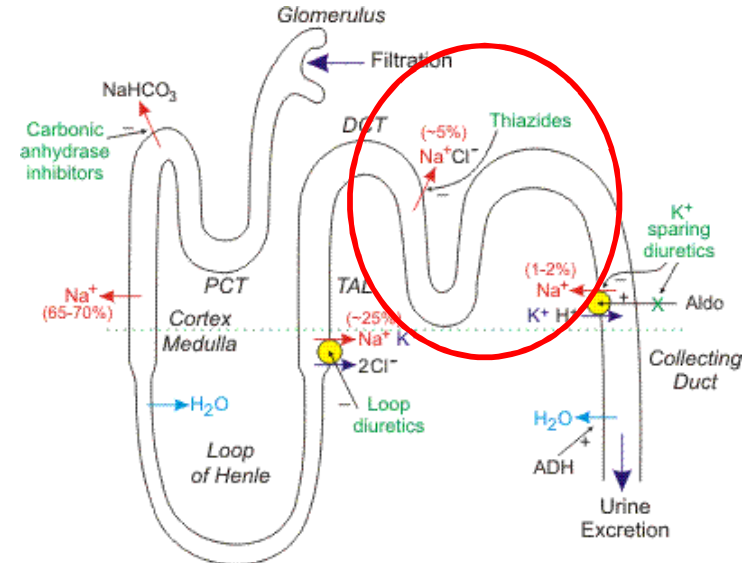
- Hyperkalemia:
 - Loop diuretics significantly enhance urinary excretion of K^+
- Acute renal failure
 - Increase in urinary flow to flush out intra-tubular casts , obstructions
- Anion overdose
 - Br, FI, I
 - Saline must be co-administered to replenish Na, Cl loss

Toxicity

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

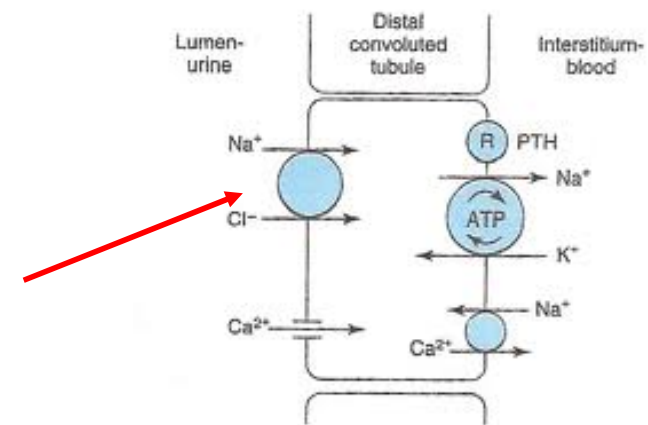
Thiazide Diuretics

- 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

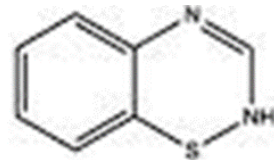


Thiazide action at DCT

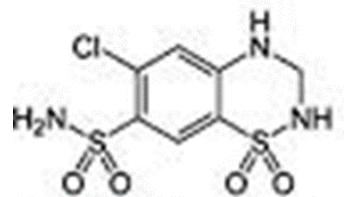
- Na^+ , Cl^- reabsorbed by Na^+/Cl^- co-transporter (NCC)
- Ca^{++} actively reabsorbed by Ca^{++} channel & basolateral $\text{Na}^+/\text{Ca}^{++}$ exchanger
- Thiazides bind to Cl^- inhibiting NCC & thus prevent Na^+ reabsorption



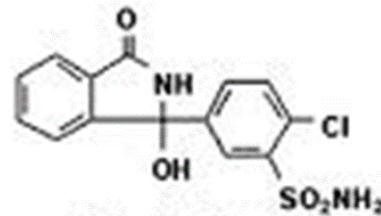
Thiazide Diuretics, Structures



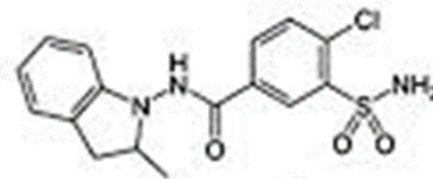
Benzothiadiazine ring



Hydrochlorothiazide



Chlorthalidone



Indapamide

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
 - Levels typically return to baseline after prolonged use
- Hyponatremia
 - Important side effect
 - Prevented by reducing the dose or fluid intake