Diuretics

BOK 287

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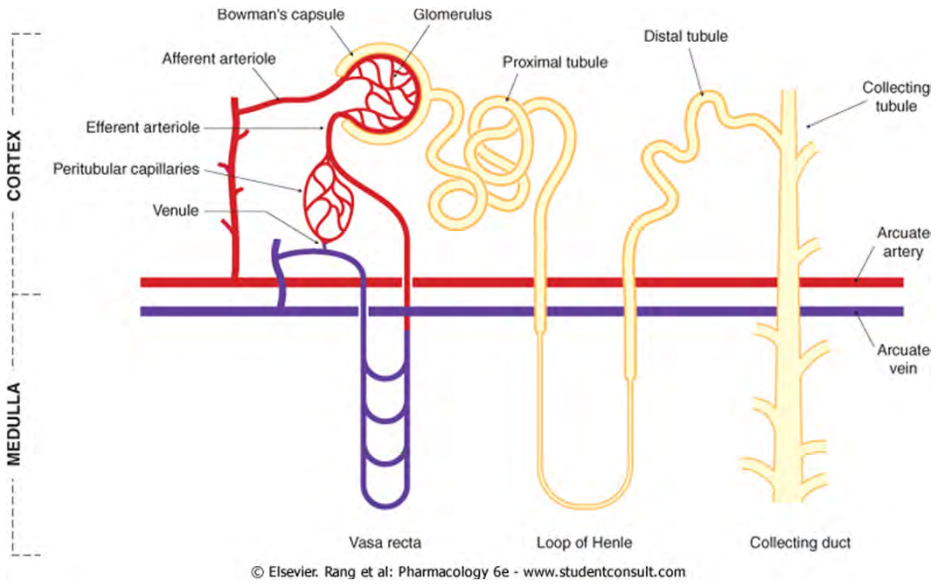
Introduction

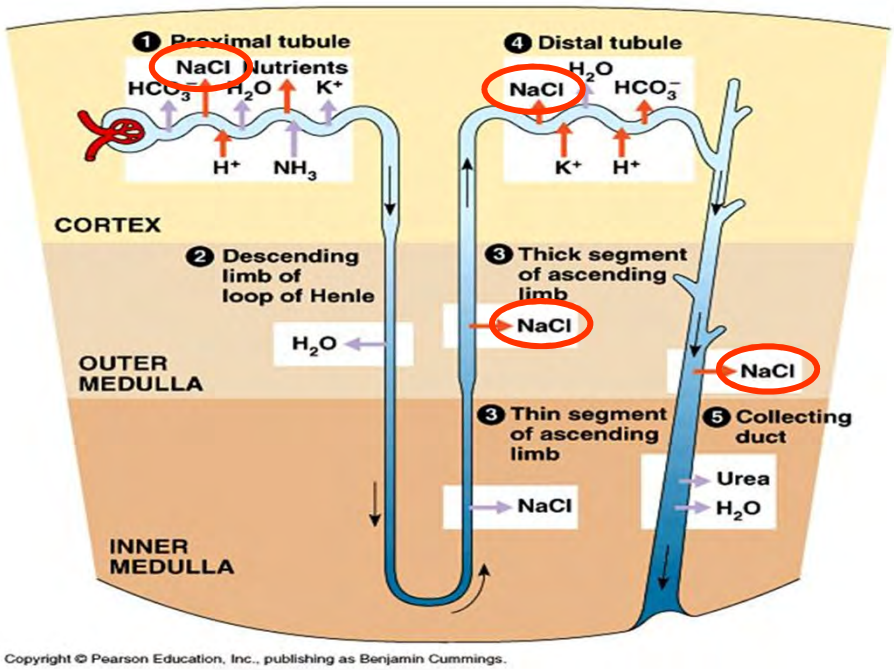
- Diuretics treatment is volume-related
- Oedema (body cavity)
  - Pulmonary
  - Intraocular
  - Intracranial
- Hypertension

Kidney functions

- Excrete waste products
- Maintains acid-base balance
- Regulate salt and electrolyte balance
- Control the volume of extracellular fluid
  - i.e. amount of H_2O in the body

Nephron (Functional unit of the kidney)



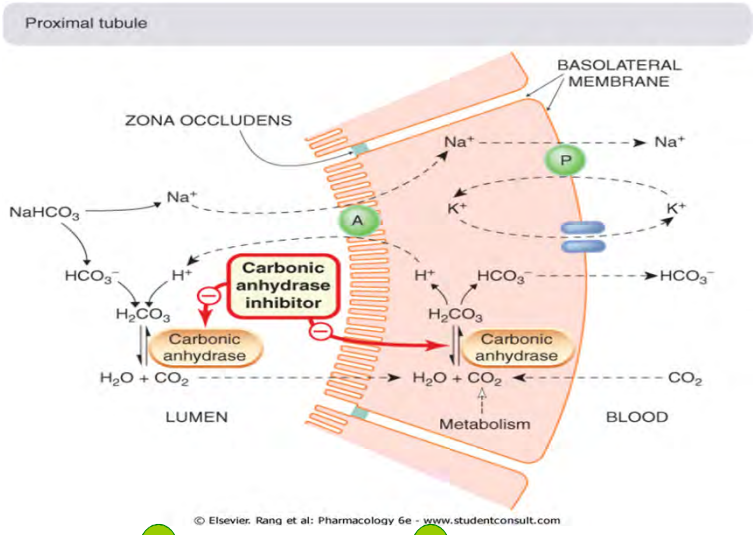


Sites of diuretic action

1. Proximal convoluted tubule
2. Ascending limb (loop of Henle)
3. Distal convoluted tubule
4. Collecting ducts

- All concerned with Na^+ reabsorption

Proximal tubule



A = Na^+/H^+ antiport **P = Na^+/K^+-ATPase**

Proximal tubule

- 60 – 70% of Na^+ actively absorbed
  → Na^+/H^+ exchange
  - Carbonic anhydrase produces H^+ for exchange

  Carbonic anhydrase inhibitors

  (Acetazolamide)

- H_2O follows reabsorbed Na^+
  → osmotic pressure

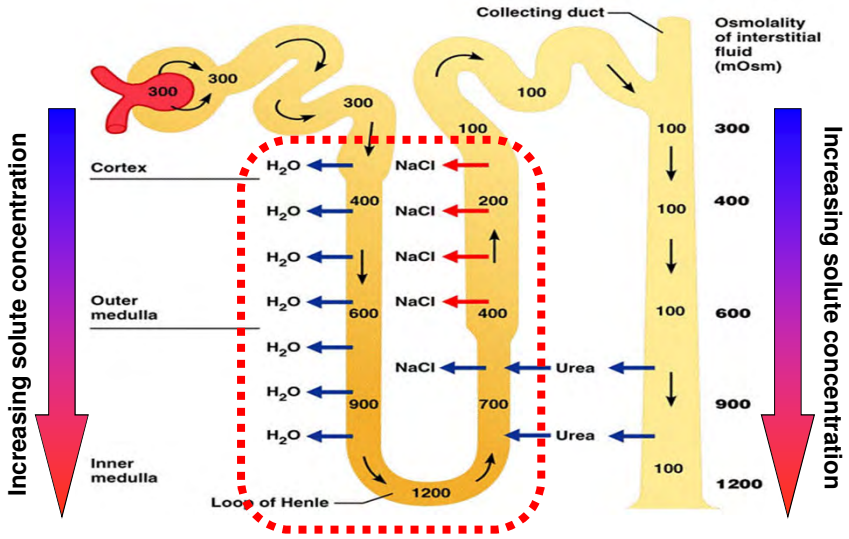
  Osmotic diuretics

  (Mannitol)

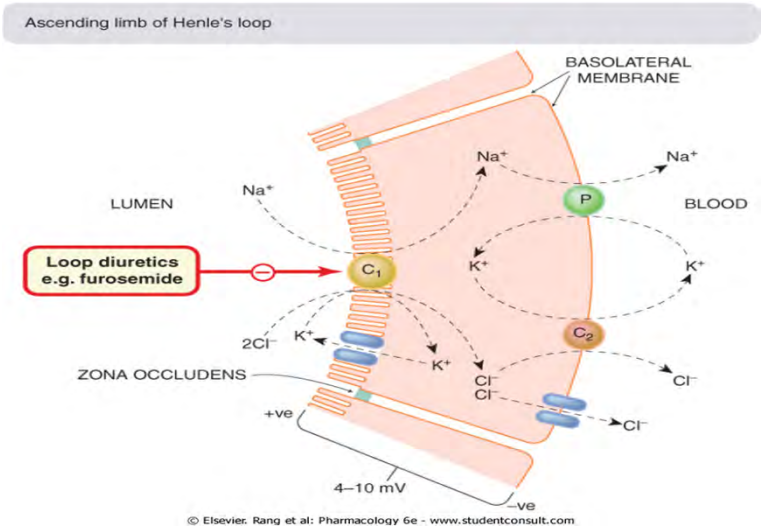
Loop of Henle

- Interstitial fluid has concentration gradient
  - Cortex → Medulla
  - Low [mOsm] → High [mOsm]
- Ascending limb
  - Permeable to Na^+ → transported to interstitium
  - Creates concentration gradient
- Descending limb
  - Impermeable to Na^+ but permeable to H_20
  - H_2O moves into interstitium → concentrates urine

Loop of Henle



Ascending limb



C_1 = $Na^+/K^+/2Cl^-$ symporter **P = Na^+/K^+-ATPase**

Loop of Henle

Ascending limb

- Impermeable to H_2O
- Permeable to Na^+
- Active reabsorption of Na^+
  - $Na^+/K^+/2Cl^-$-symporter
  - Creates hyperosmotic state

Descending limb

- Permeable to H_2O
- Impermeable to Na^+
- Osmotic H_2O reabsorption
  - Due to hyperosmotic state

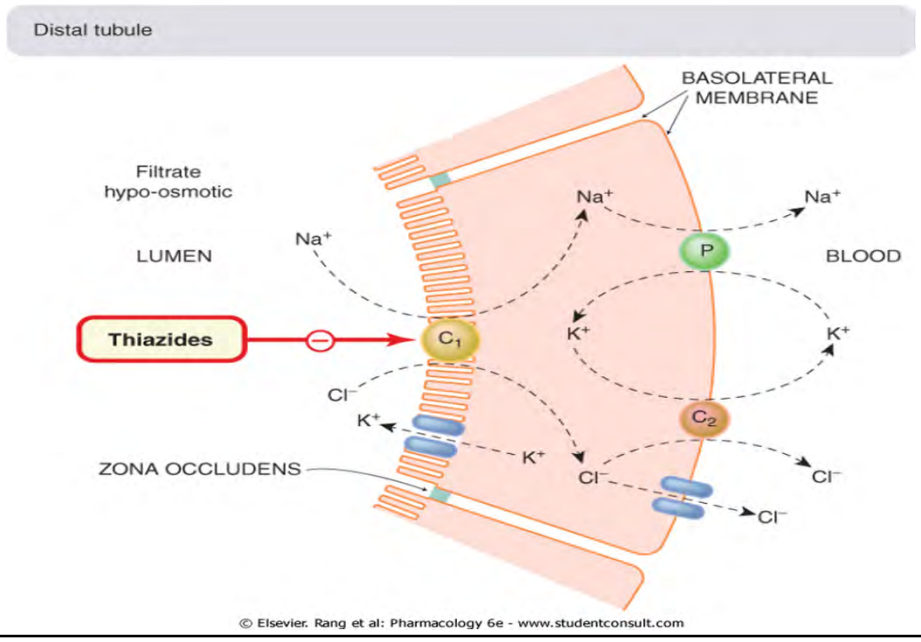
- **Site of action = $Na^+/K^+/2Cl^-$-symporter**

Loop diuretics

- **Loop diuretics** inhibit $Na^+/K^+/2Cl^-$-symporter
- Fail to create hyperosmotic state in interstitium
- Less H_2O reabsorbed → passed with urine

- **Furosemide**
- **Bumetanide**

Distal tubule



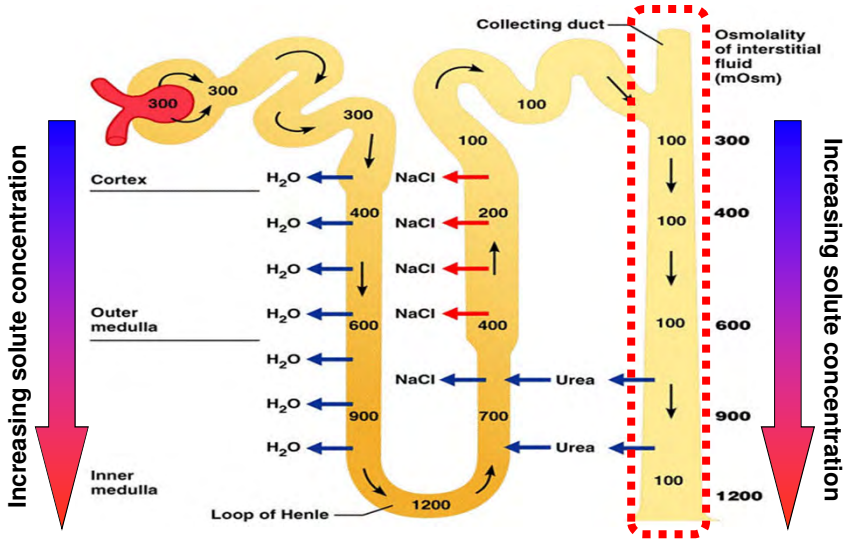
Distal tubule

- Na^+ reabsorbed into tubular cell by the Na^+/Cl^--carrier
- Na+ actively transported into interstitium by Na^+/K^+-ATPase

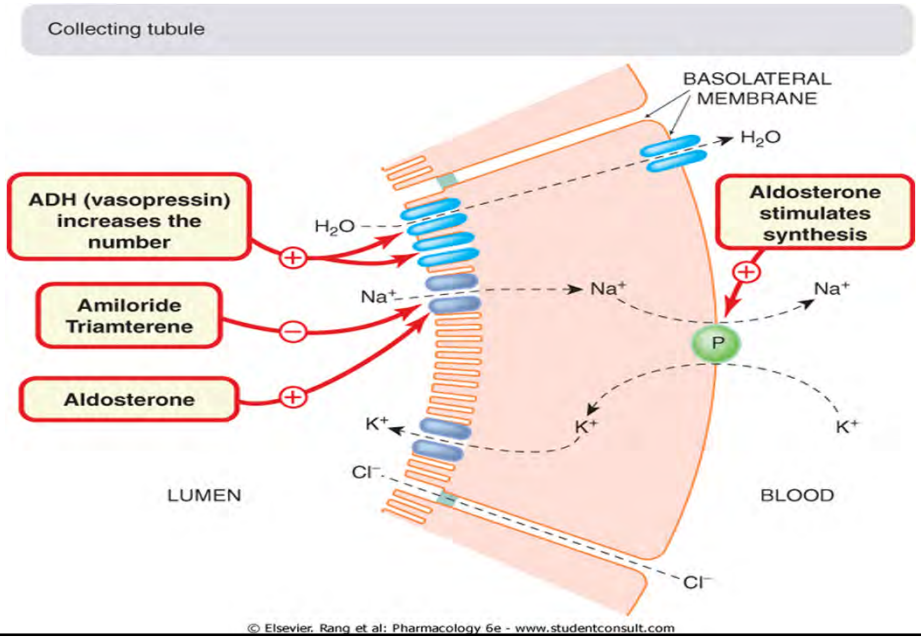
- Site of action = Na^+/Cl^--carrier
- **Thiazides**

- **Indapamide**
  - **Metabolised and excreted in the GIT**
  - **NB! ↓ chance to accumulate with renal impairment**

Collecting tubules



Collecting tubule



Collecting tubule

<u>2 factors working on H_2O reabsorbtion</u>

- Na^+ channels → Na^+ reabsorption
- Aquaporins

- Amiloride
- Triamterene
- Aldosterone antagonists
  - ↓ # of Na^+ channels
  - ↓ # of Na^+/K^+-ATPase pumps (Spironolactone)

- ADH (vasopressin) antagonists
  - ↓ # of aquaporins

Carbonic anhydrase inhibitors

- Blocks formation of H^+ in proximal tubule
  → Indirectly blocks Na^+/H^+-antiport
  → Blocks Na^+ reabsoption

- ***Glaucoma (↓ aqueous humour formation)***

- SE
  - Metabolic acidosis because of loss if bicarbonate ions

- Acetazolamide

Loop diuretics

- Most potent of the diuretics
- Inhibit $Na^+/K^+/2Cl^-$-symporter in ascending limb
  →Less Na^+ reabsorption

- ***Heart failure, hypertension (with renal failure), pulmonary oedema, hypercalcaemia***

- SE
  – Hypovolaemia, hypotension
  – Hypokalaemia, hypomagnesaemia, hypocalcaemia
  – Hyperuricaemia

Thiazides & Co. that act on Distal tubule

- Blocks Na^+/Cl^--carrier in distal tubule
  →Less Na^+ reabsorption
- ***Hypertension (intact renal function), mild heart failure***
- SE
  – Hyponatraemia, hypokalaemia, hypoclaciuria
  – Erectile dysfunction, hyperglycaemia
- Hydrochlorothiazide

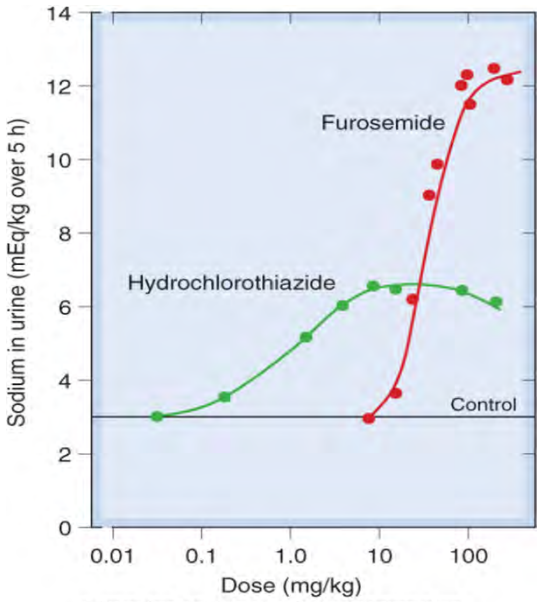
Aldosterone antagonists & Na^+ channel blockers

- Competitive aldosterone antagonists
- Not potent diuretics but effective in hypertension
- NB! = K^+ sparing
- ***Heart failure when hypokalaemia is unwanted***
  – ***NB! Used in conjunction with loop diuretics to maintain K+***
- ***Hypertension***
- ***Hyperaldosteronism***
- SE
  – Hyperkalaemia, gynecomastia (Spironolactone)
  – NB! Triamterene ↓ folic acid levels - contraindicated for pregnancy

Osmotic diuretics

- Pharmacologically inactive compounds
- Increases osmolarity inside tubules
  - "Holds" H_2O in tubule, less reabsorption
- ***Acute elevated intracranial- & intraocular pressure → extract H2O from those body compartments***
- SE
  - ↑ extracellular fluid volume (risk left ventricular failure)
  - Hyponatraemia
- Mannitol

High *vs* low ceiling diuretics



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Class	Site of action	Drugs	Indication
Carbonic anhydrase inhibitors	Proximal tubule	Acetazolamide	Glaucoma Mountain sickness
Loop diuretics	Ascending limb	Furosemide Bumetanide	Pulomonary oedema Heart failure Hypertension Hypercalcaemia
Thiazides	Distal tubule	Hydrochlorothiazide	Heart failure Hypertension
Other	Distal tubule	Indapamide Metalazone Chlorthalidone	Hypertension Synergistic effect with loop diuretics
Aldosterone antagonists	Collecting tubule	Spironolactone Eplerenone	Heart failure Sever hypertension Hyperaldosteronism
Na^+ channel blockers	Collecting tubule	Amiloride Triamterene	Used in conjunction with loop diuretics (K^+ sparing)
Osmotic diuretics	Proximal tubule Descending limb Collecting tubules	Mannitol Isosorbide Urea	Acute elevated intracranial-, intraocular pressure
Acid forming salts	Diverse	Ammonium chloride	Alkaline substance poisoning
Indirect urine drivers	Diverse	Cardiac glycosides Methylxanthines	-