Diuretics

Diuretics - Renal tubule transport mechanisms

- Image: renal tubules

Summary of physiology

- Proximal tubule - $NaHCO_3$, NaCl, glucose, amino acids, and other organic solutes are reabsorbed via specific transport mechanisms in the early proximal tubule
- K is absorbed via the paracellular route
- Water is absorbed passively
- Approximately 65% of total Na ions, 65% of potassium and 60% of water is reabsorbed - virtually all filtered glucose and amino acids are reabsorbed in the PCT

Bicarbonate, the proximal tubule and CA inhibitors

- Allows sodium to enter the cell (from the lumen) in exchange for a proton in the cell
- Na is extruded from the cell into the interstitium by Na/K ATPase
- H+ in the lime combines with bicarbonate to form carbonic acid with dehydrates into CO2 and H2O by carbonic anhydrase
- CO2 re enters cell where it is rapidly rehydrated to H2CO3 by intracellular CA
- There is parallel Cl/base exchange resulting in net NaCl reabsorption

Carbonic anhydrase inhibitor

- Predominant location of enzyme is in PCT where is catalyses the dehydration of H2CO3
- By blocking carbonic anhydrase —> decreases NaHCO3 absorption —> causes diuresis
- Acetazolamide is the prototype
- Pharmacokinetics
  - A: well absorbed
  - D: Low Vd, increase in urine pH apparent within 30 minutes
  - M:
  - E: Secretion into the proximate tubule S2 segment, dose reduction in renal failure

- Pharmacodynamics
  - depresses HCO3 in the PCT
  - some HCO3 can still be absorbed via other mechanisms
  - HCO3 depletion leads to enhanced NaCl reabsorption by the remainder of the nephron, the diuretic efficacy of acetazolamide decreases with use over several days
- Clinical idications
  - Glaucoma - decreases aqueous humer formation decreases IOP, can be used topically (brinzolamide)
  - Urinary alkalisations
  - Acute mountain sickness - weakness, dizziness, insomnia, headache - can increase ventilation and decrease symptoms of acute mountain sickness
- Toxicity
  - Hypercholremic acidosis
  - Renal stones
  - Contraindicated in hepatic cirrhosis (can precipitate hepatic encpahlopathy)

Loop of Henle

- PCT empties into the thin descending limb of Henle's loop
- Water extracted from the descending limb of this loop by osmotic forces found in the hypertonic medullary interstitium
- Thin ascending limb is relatively water impermeable
- Thick ascending limb actively reabsorbs Nacl from the lumen via Na/K/2Cl co transporter
  - Responsible for 25% of filtered Na
  - Nearly impermeable to water
  - Therefore dilutes tubular fluid
  - Back diffusion of K causes a lumen +ve electrical potential and that drives Ca and Mg reabsorption too

Loop diuretics

- Pharmacokinetics
  - A: Rapid
  - D: Low Vd
  - M: duration of action is usually 2 - 3 hours, half life depends on renal function
  - E: Eliminated by glomerular filtration and tubular secretion
- Pharmacodynamics
  - Inhibit Na/K/2Cl co transporter in the thick ascending limb of Henle's loop
    - Reduces reabsorption of NaCl and also diminish the lumen positive potential that comes from K recycling - hence increase Mg and Ca excretion
  - Induce synthesis of renal prostaglandins

Loop diuretics

- Most important indications
  - APO
  - Other oedematous conditions
  - Acute hypercalcemia
  - Hyperkalemia
- Toxicity
  - Hypokalemic metabolic alkalosis - inhibiting salt reabsoption in the TAL thus increasig delivery to the collecting duct
    - Leads to secretion of K and H by the duct
  - Ototoxicity - reversible
  - Hyperuricemia - can precipitate gout
  - Hypo mag.
  - Hyponatremia

Distal convoluted tubule

- Only 10% of filtered NaCl is reabsorbed in the DCT and this segment is relatively impermeable to water
- This further dilutes the tubular fluid
- Mechanism of NaCl transport is via an electrically neutral thiazide sensitive co transporter

Thiazide diuretics

- Inhibit NaCl transport predominantly in the DCT
- Chemistry and pharmacokinetics
  - A: well absorbed orally
  - D: Low Vd
  - M: Difference exist
    - Chlorthiazide - the parent group is not very lipid soluble and needs to be given in relatively high doses
    - Chlorthialidone - slowly absorbed and has a longer duration of action
    - Indapamide is excreted primary in the biliary system, enough of the active form is cleared by the kidney to exert its diuretic effect in the DCT
    - All of the thiazides are secreted by the organic acid secretory system in the proximal tubule and compete with uric acid for secretion by this system - hyperuricemia

Thiazide diuretics

- Pharmacodynamics
  - Thiazides inhibit NaCl reabsorption from the luminal side of epithelial cells in the DCT by blocking the Na/Cl transporter
  - Actually enhance Ca reabsorption
    - Net volume depletion leads to increase Na reabsorption in the proximal tubule and therefore passive Ca reabsorption
      - Lower Na intracellularly in DCT enhances Na/Ca exchange in the basolateral membrane and increases overall reabsorption
- Clinical indications: HTN, CHF, Nephrolithiasis due to idiopathic calciuria
- Toxicity: Hypokalemic metabolic alkalosis
  - Impaired carbohydrate tolerance due to impaired pancreatic release of insulin
  - Hyperlipidemia
  - Hyponatremia
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Collecting tubule

- 2 - 5 % of Na reabsorption - it is the final site of Na reabsorption
- Mineralocorticoids act here
- Two cell types; principle and intercalated cells
    - Principle cells: Major sites of Na, K and water transport
    - Intercalated cells: primary sites of H+ secretion
        - 10 - 50mV lumen -ve electrical potential develops - drives chloride back into the blood via paracellular pathway and draws K out of cells
        - Diuretics that act upstream to this site will increase Na delivery to this site and will increase K secretion
- Reabsoprtion of Na via the epithelial Na channel and its coupled secretion of K is regulated by aldosterone (steroid hormone)
- ADH (vasopressin) controls the permeability of this segment to water by regulating the insertion of pre formed water channels (Aquaporins) into the apical cell membrane
    - In the absence of ADH the collecting tubule is impermeable to water and dilute urine is produced

K sparing diuretics

- Spironolactone is a synthetic steroid - competitive antagonist to aldosterone
- Substantial inactivation in the liver
- Slow onset of action
- Pharmacodynamics:
    - Decrease Na reabsorption in the collecting tubules and ducts
    - Similar effects on H+ in the CCT —> hence can cause a metabolic acidosis
- Toxicity:
    - hyperkalemia
    - hypercholremic metabolic acidosis
    - Gyneacomastia
    - ARF
- Contraindications - oral K administration, CRF

Agents that alter water excretion

- Osmotic diuretics
    - Proximal tubule and descending loop of Henle are permeable to water - any osmotically active agent is filtered by the glomerulus and not absorbed causes water to be retained
        - e.g. mannitol
- Pharmacokinetics:
    - A: Poor oral and so given parenterally
    - D: Low Vd
    - M: not metabolised
    - E: really excreted

Pharmacodynamics

- Major effect in proximal tubule and DLH
- Also oppose the action of ADH in the collecting tubule
- Urine volume increases - decreases Na and H20 absorption
- Clinical uses:
    - Increase urine volume in rhabdo and homeless to clear pigment loads
    - Reduction of ICP
- Toxicity:
    - Volume expansion
    - Dehydration, hyperkalemia