Renal Pharmacology

Diuretics:
- Carbonic Anhydrase Inhibitors
- Thiazides
- Loop Diuretics
- Potassium-sparing Diuretics
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Kidneys:
• Represent 0.5% of total body weight, but receive ~25% of the total arterial blood pumped by the heart
• Each contains from one to two million nephrons:
  – The glomerulus
  – The proximal convoluted tubule
  – The loop of Henle
  – The distal convoluted tubule
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Functions

• Clean extracellular fluid and maintain ECF volume and composition
• Acid-base balance
• Excretion of wastes and toxic substances

• Renal processes
• Filtration - glomerulus
• Reabsorption
• Tubular secretion

In 24 hours the kidneys reclaim:
- ~ 1,300 g of NaCl
- ~ 400 g NaHCO₃
- ~ 180 g glucose
- almost all of the 180 L of water that entered the tubules
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- Blood enters the glomerulus under pressure
- This causes water, small molecules (but not macromolecules like proteins) and ions to filter through the capillary walls into the Bowman's capsule
- This fluid is called nephric filtrate
  - Not much different from interstitial fluid
- Nephric filtrate collects within the Bowman's capsule and flows into the proximal tubule:
  - Here all of the glucose and amino acids, >90% of the uric acid, and ~60% of inorganic salts are reabsorbed by active transport
    - The active transport of Na⁺ out of the proximal tubule is controlled by angiotensin II.
    - The active transport of phosphate (PO₄)³⁻ is regulated (suppressed by) the parathyroid hormone.
- As these solutes are removed from the nephric filtrate, a large volume of the water follows them by osmosis:
  - 80–85% of the 180 liters deposited in the Bowman's capsules in 24 hours
- As the fluid flows into the descending segment of the loop of Henle, water continues to leave by osmosis because the interstitial fluid is very hypertonic:
  - This is caused by the active transport of Na⁺ out of the tubular fluid as it moves up the ascending segment of the loop of Henle
- In the distal tubules, more sodium is reclaimed by active transport, and still more water follows by osmosis.
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**Diuretics:**
- Increase output of urine
- Primary indications are hypertension and mobilization of edematous fluid (e.g. kidney problems, heart failure, cirrhosis,…)

**Basic mechanism:**
- Block reabsorption of sodium and chloride => water will also stay in the nephron
- Diuretics that work on the earlier nephron have greatest effect, since they are able to block more sodium and chloride reabsorption
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**Diuretics:**

**Carbonic anhydrase inhibitors:**

- **Azetazolamide**
  - Can trigger metabolic acidosis
  - Not in use as diuretic anymore
  - Primary indications is glaucoma (prevents production of aequous humor)

  ![Chemical structure of azetazolamide]

- **Dorzolamide**

CA-inhibitors are sulfonamides => cross-allergenic with antibiotics etc.
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Diuretics:

**Loop diuretics (= high ceiling diuretics):**
- Strong, but brief diuresis (within 1 hr, lasts ~ 4hrs)
- Used for moderate to severe fluid retention and hypertension
- Most potent diuretics available
- Act by inhibiting the Na⁺/K⁺/2Cl⁻ symporter in the ascending limb in the loop of Henle
- Major side effects: loss of K⁺ (and Ca++ and Mg++)

- **Furosemide**
- **Bumetanide**
- **Torasemide**
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Diuretics:

Thiazide diuretics:
- Used for mild to moderate hypertension, mild heart failure,
- Medium potency diuretics
- Act by inhibiting the Na⁺/Cl⁻ symporter in the distal convoluted tube
- Major side effects: loss of K⁺ (and Mg²⁺, but not Ca²⁺)

- Hydrochlorothiazide
- Benzthiazide
- Cyclothiazide …
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Major side effects of these diuretics:
- Hypokalemia, hyponatremia, hypochloremia
- Hypotension and dehydration
- Interaction with Cardiac Glycosides

=> Potassium can be given orally or IV
   or

Potassium-sparing diuretics:
- Often used in combination with high-ceiling diuretics or thiazides due to potassium-sparing effects
- Produce little diuresis on their own
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**Diuretics:**

**Potassium-sparing diuretics:**
- Act on the distal portion of the distal tube (where Na\(^+\) is exchanged for K\(^+\))
- Aldosterone promotes reabsorption of Na\(^+\) in exchange for K\(^+\)
  (transcriptionally upregulates the Na\(^+\)/K\(^+\) pump and sodium channels)

- **Spironolactone**
  - Aldosterone receptor antagonist
  - Onset of action requires several days

- **Amiloride; Trimterene**
  - Block sodium channels
  - Quick onset
Diuretics:

Osmotic diuretics:

- Small, non-reabsorbable molecules that inhibit passive reabsorption of water
- Predominantly increase water excretion without significantly increasing Na\(^+\) excretion ⇒ limited use
- Used to prevent renal failure, reduction of intracranial pressure
  (does not cross blood-brain barrier ⇒ water is pulled out of the brain into the blood)

• Mannitol
  - Only given IV – can crystallize (⇒ given with filter needle or in-line filter)
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Uric acid

• only slightly soluble in water and easily precipitates out of solution forming needle-like crystals of sodium urate
  – sodium urate crystals contribute to the formation of kidney stones and
  – produce the excruciating pain of gout when deposited in the joints.

• Curiously, our kidneys reclaim most of the uric acid filtered at the glomeruli. Why, if it can cause problems?
  – Uric acid is a potent antioxidant and thus can protect cells from damage by reactive oxygen species (ROS).
  – The concentration of uric acid is 100-times greater in the cytosol than in the extracellular fluid. So when lethally-damaged cells release their contents, crystals of uric acid form in the vicinity. These enhance the ability of nearby dendritic cells to "present" any antigens released at the same time to T cells leading to a stronger immune response.
  => risk of kidney stones and gout may be the price we pay for these protections.

• Most mammals have an enzyme — uricase — for breaking down uric acid into a soluble product. However, during the evolution of great apes and humans, the gene encoding uricase became inactive.
  – Uric acid is the chief nitrogenous waste of insects, lizards, snakes and birds
    (the whitish material that birds leave on statues)
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**Uricosuric agents:**
- At therapeutic doses promote excretion and inhibit reabsorption of uric acid (normally, only 8-12% of the initially filtered urates are eliminated)
- At low, subtherapeutic doses, both excretion and reabsorption are inhibited => possibility of an increase in uric acid concentration

- **Probenicid**
  - Inhibits reabsorption of urates in the proximal convoluted tubule
  - Strong inhibitory effect on penicillin excretion

- **Sulfinpyrazone**