**Angiotensin Converting Inhibitors** and **Angiotensin Receptor Blockers**

- **Drugs**
  - ACE-is **Capsopril**, Lisinopril, any other “-prils”
    - Block the formation of ANG II by inhibiting ACE
    - Results in prevention of AT-1 receptor stimulation
    - ↓ Aldosterone synthesis and ↑ Vasodilation
    - ACE-is also prevent bradykinin degradation
  - ARBs **Losartan, Candasartan**, and other “-sartans”
    - Block the AT-1 Receptor, but allow ANG II to be made
    - Same effect on aldosterone and vasodilation
    - ARBs do not prevent bradykinin degradation

- **Uses**
  - Mild-to-moderate HTN; “everyone with HTN gets ACE-I”
  - Protective of diabetic nephropathy
  - CHF
  - Use ACE-is first because they are cheaper, if not tolerated, switch to ARB

- **Side Effects**
  - Dry Cough (ACE-I only, usual indication for switch to ARB)
  - Hyperkalemia as a result of aldosterone inhibition “K-sparing”

- **Contraindications**
  - Bilateral renal artery stenosis can cause Acute Renal Failure
  - Pregnancy. It is class D, switch to α-methyldopa (cardio block)

A brief review of the RAS axis is required. **Angiotensinogen** is produced by the liver. In response to a decreased flow rate or ischemia, the JGA of the kidney produces **Renin**. Renin chops off the “ogen” propeptide portion of Angiotensinogen to **Angiotensin-I**. This happens everywhere. Angiotensin-1 is converted to **Angiotensin-2**, the active form, by **angiotensin converting enzyme** (ACE) which is found everywhere, but primarily in the lungs. **Angiotensin-II** binds to and activates AT-1 receptors (notice that angiotensin roman numeral II binds to angiotensin receptor Arabic numeral 1) in both the adrenal cortex and the blood vessels. Binding to **blood vessels** activates vasoconstriction. Binding to **adrenal cortex** induces aldosterone secretion. Aldosterone then upregulates the Na channels in the Collecting Tubules (see K-sparing diuretics for image and explanation page 5). Aldosterone leads to salt retention, and, under the influence of ADH, retention of water. ANG-II also activates thirst.

**Angiotensin Converting Enzyme-Inhibitors** (ACE-Is) block the effects of this system at the point of formation of Angiotensin II. If ANG II cannot be made, it cannot have its effects. **Angiotensin Receptor Blockers** (ARBs) block this system after the formation of ANG II, but at the site of action of ANG-II.

In either case the effect is vasodilation (reduces BP), and inhibition of aldosterone (effectively potassium sparing diuretics). This means that a potential side effect of both is **hyperkalemia**. Because ACE also degrades bradykinin, and unopposed bradykinin produces cough in the lungs, administration of ACE-I, but not ARB, results in a chronic productive cough that often results in the use of ARBs.
Carbonic Anhydrase Inhibitors = acidotic ineffective diuretic

- Acetazolamide, Dorzolamide, other “-zolamides”
  - Mechanism
    - Carbonic Anhydrase Inhibition
    - $\downarrow$ H$^+$ ion formation inside the PCT cell
    - $\downarrow$ Na/H antiport
    - $\uparrow$ HCO$_3^-$ in lumen (lost in urine)
    - $\uparrow$ Diuresis
  - Uses
    - Glaucoma
    - Acute Mountain Sickness
    - Metabolic Alkalosis
  - Side Effects
    - Acidosis from loss of Bicarb
    - Hypokalemia from increased Na$^+$ delivery to the collecting tubules
    - Hyperchloremia from Na$^+$ stuck in the lumen which draws Cl$^-$
    - Renal Stones (Calcium Oxalate) form in the alkaline urine

Inside the cell, carbonic anhydrase has one purpose. It takes CO$_2$ and H$_2$O to a proton (H$^+$) and bicarbonate (HCO$_3^-$). It gives us the bicarb we use to buffer our blood pH. It also gives us that Hydrogen ion that is transported out for Na reabsorption. Without Hydrogen being made, there is no driving force for the H/Na antiporter to draw Na in. Thus, there is a naturesis.

Here in a fairly permeable tubule, where Na goes, Cl follows. Thus, if there is increased luminal Na there will naturally be increased luminal Cl. As the PCT is the site of most reabsorption, inhibited reabsorption cannot be fully compensated by the rest of the tubules. This results in a diuresis. However, there is the entire nephron to go, so the diuretic effect is minimal. This is why they are not used as diuretics in most cases.

Look at the right side of the cell. Carbonic Anhydrase produces bicarbonate that is resorbed. Well, the happy bicarbonate floating in your blood will naturally be filtered by the nephron. That is how the bicarbonate on the left of the image gets there. In addition to making H$^+$ and HCO$_3^-$ in the cell, carbonic anhydrase makes CO$_2$ and H$_2$O from Bicarbonate and Hydrogen ion in the lumen. HCO$_3^-$ is a large, charged ion, which cannot be reabsorbed. Carbonic Anhydrase takes HCO$_3^-$, turns it into a soluble form, then reconstitutes it back to bicarb once reabsorbed. Without carbonic anhydrase, bicarb cannot be reabsorbed. Thus, you will lose bicarb in your urine, producing a metabolic acidosis.

This is how it gets one of its uses. In acute mountain sickness the pO$_2$ goes down. The body compensates with hyperventilation, dropping the pCO$_2$ (a respiratory alkalosis). By giving a carbonic anhydrase, you lose bicarb (metabolic acidosis) which compensates for the respiratory alkalosis.
Loop diuretics inhibit the Na/K/2Cl transported in the TAL. This transporter is usually electroneutral so that no change in luminal charge occurs. However, the potassium gradient is set up so that there is a potassium back leak into the lumen, creating a positive potential that drives the paracellular reabsorption of Ca$^{2+}$ and Mg$^{2+}$. As always (depicted on the right of the image) is that basal Na/K-ATPase that gets sodium out of the cell, as well as the Na/Cl cotransporter to fully reabsorb everything and maintain concentration gradient in the cell.

By blocking this Na/K/2Cl cotransporter there is no absorption of anything, no back leak, and no positive luminal charge to drive paracellular reabsorption. The result, then, is an increase in the urine content of all these ions. The diuresis is a result of the naturesis. Again, because distal sodium delivery to the collecting tubules is increased, Na will be reabsorbed and K will be lost, producing a hypokalemia.

Ethacrynic Acid is rarely used when Furosamide will work. However, in the cases of sulfa allergies, Furosamide cannot be tolerated, and EA is used instead. They basically do the exact same thing, only one induces an allergy (Furosamide) and one carries a risk of increased ototoxicity (EA).
Thiazides = weak diuretics

- Drugs
  - Hydrochlorothiazide and Indapamide
    - Mechanism
      - Na/Cl Cotransporter inhibition in the DCT
      - Luminal concentrations of Na⁺ and Cl⁻
      - Diuresis
      - Increase in calcium reabsorption
      - Unrelated, there is a potassium channel opening leading to vasodilation of peripheral vasculature (HTN, CHF)
    - Uses
      - Hypertension, CHF
      - Nephrolithiasis (Calcium Stones) by reducing luminal [Ca]
    - Side Effects
      - Sulfonamide Hypersensitivity just like Furosemide
      - Hypokalemia and Alkalosis from increased delivery to collecting tubules of Na
      - Hypercalcemia from increased calcium uptake
      - Hyperglycemia in a mechanism unrelated to kidney
      - Hyperlipidemia (not Indapamide)
  - Drug Interactions
    - Digoxin (hypokalemia increases Dig toxicity)
    - Avoid in patients with diabetes (because of hyperglycemia)

Thiazides inhibit the Na/Cl cotransporter inhibition. Even though this accounts for only 10% of Na reabsorption, it is still carries a significant impact on diuresis. As always, there is a Na/K-ATPase on the basal membrane to allow maintenance of electrochemical gradients. Another pump is important here. There is a Na/Ca antiporter on the basal membrane.

If Thiazides are given, because less sodium comes in on the luminal side (maintaining intracellular concentrations as low), the gradient is stronger for sodium to come in through the basal side. This means that more calcium will be reabsorbed when Thiazides are administered. This is great when it comes to Calcium Oxalate stones, where the concentration of calcium in the urine predisposes to the formation of stones. Thus, Thiazides can be given as a diuretic or in the treatment of calcium stones. On a side note, the Calcium channel that allows Ca into the cell is the PTH induced calcium leak channels, shown on the bottom of the left of the image.

Just as Minoxidil did, Thiazides have an effect on vasodilation of peripheral vasculature. They vasodilate by opening potassium channels. Unfortunately, these drugs also affect potassium channels in the pancreas, leading to a decreased insulin release, resulting in the hyperglycemia.
K-Sparing Diuretics

- **Spironolactone**
  - Mechanism
    - Aldosterone Receptor Antagonist, Collecting Tubules
  - Uses
    - Hyperaldosteronism
    - Adjunct to Potassium wasting diuretics (protects against hypokalemia)
  - Side Effects
    - Hyperkalemia and acidosis (especially with ACE-I / ARBs)
    - Antiandrogen

- **Amiloride and Triameterene**
  - Mechanism
    - Na⁺ Channel Blockers of the Collecting Tubules
  - Use
    - Adjunct to potassium wasting diuretics (protects against hypokalemia)
    - Lithium-induced Nephrogenic diabetes Insipidus
    - When Spironolactone is not possible
  - Side Effects
    - Hyperkalemia and Acidosis (especially with ACE-is / ARBs)

These are called diuretics just for the fun of it. These will not really increase diuresis because they are at the very end of the tubules, once the job of sodium and water retention has been done proximal to the collecting tubules. Therefore, K sparing diuretics will be mild diuretics that do not cause hypokalemia.

Aldosterone is a steroid receptor that binds to its cytoplasmic nuclear receptor via zinc fingers. It upregulates both transcription and insertion of Na channels. In the collecting ducts, the remaining Na is collected. For every Na⁺ passively absorbed, a K⁺ is passively secreted. This is why other diuretics, which increase the concentration of sodium delivered to the collecting ducts, will induce hypokalemia. If aldosterone is blocked, neither the insertion nor the upregulation can happen. The drug that blocks the steroid receptor is **Spironolactone**.

In addition to blocking aldosterone, we can directly inhibit the Na channel. Then, regardless of aldosterone activation of these channels, there will be no Na reabsorption. Without Na reabsorption at this point there will be no K lost. Drugs like **Amiloride** and **Triameterene** do this.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms</th>
<th>Urinary Electrolytes</th>
<th>Blood pH</th>
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<tbody>
<tr>
<td>Acetazolamide</td>
<td>Carbonic Anhydrase Inhibition in PCT</td>
<td>↑ Na</td>
<td>Acidosis from loss of bicarb</td>
</tr>
<tr>
<td>Ethacrynic Acid, Furosemide,</td>
<td>Inhibition of Na/K/2Cl cotransporter in TAL</td>
<td>↑ Na⁺ 𝑾  𝑷  𝐶 Clubs</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>Torsemide</td>
<td></td>
<td>↑ K⁺</td>
<td></td>
</tr>
<tr>
<td>HCTZ, Indapamide, Metolazone</td>
<td>Inhibition of Na⁺/Cl⁻ cotransporter in DCT</td>
<td>↑ Na⁺ 𝑾  𝐶 Clubs</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>Amiloride, Triamterene,</td>
<td>Block Aldosterone mediated insertion of (Spironolactone) or directly block (others) Na⁺⁻ channels in Collecting Tubules</td>
<td>↑ Na⁺ 𝑾  𝐶 Clubs</td>
<td>Acidosis and Hyper K</td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
<td>↓ K⁺</td>
<td></td>
</tr>
<tr>
<td>ACE-I and ARBs</td>
<td>Either inhibits the formation of (ACE-i) or effects of (ARB) Angiotensin II, producing vasodilation and decreased aldosterone</td>
<td>↑ Na⁺ 𝑾  𝐶 Clubs</td>
<td>Acidosis and hyper K</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ K⁺</td>
<td></td>
</tr>
</tbody>
</table>

Pay attention to the fact that the column is **urinary electrolytes** and **blood pH**. What is increased in the urine will be decreased in the blood!

Reminder: This Block includes drugs used in the treatment of hypertension we learned in the Cardiovascular Block. These include Alpha, Beta, and Calcium Channel Blockers. They are not included here because they were included in the Cardio block. Be sure to look over the drug profile, the Pharm Renal By Drug Owl Club handout, and review Cardio!
DRUGS USED IN THE TREATMENT OF BENIGN PROSTATIC HYPERTROPHY

- **α-1-Receptor Blockers**
  - Drugs
    - Doxazosin, Tamulosin, Terazosin
      - Mechanism
        - α-1 receptors are present on vascular smooth muscle & prostate
        - Inhibition results in vasodilation (Tx for HTN) and relaxation of Prostate
      - Uses
        - Benign Prostatic Hyperplasia
        - A poor choice for HTN, though they exist
      - Side Effects
        - Reflex Tachycardia and Orthostatic Hypotension
          - Vasodilation causes drop in BP
          - Tamsulosin is specific for α-1a, selective for prostate
        - Tamsulosin does not cause Reflex Tachycardia nor Orthostatic Hypotension and does not have to be titrated as the other drugs do

- **5-α-reductase inhibitors**
  - Drugs
    - Dutasteride and Finasteride
      - Mechanism
        - Inhibition of 5-α-reductase enzymes
          - Dutasteride is in liver/skin (type 1) and prostate (type 2)
          - Finasteride is specific for type 2
        - Dihydrotestosterone
        - Prostatic growth and eventual shrinkage (over weeks to months)
      - Uses
        - Benign Prostatic Hyperplasia
          - Combination with Tamsulosin shows best results
        - Male Pattern Baldness
      - Side Effects
        - Reduced Libido and impotence
        - Gynacomastia = induced breast enlargement and nipple tenderness
      - Contraindications
        - Women who are pregnant should not handle it (absorbed from skin)
        - Men on it should not donate blood for 6 months
        - Teratogen

5-alpha-reductase inhibitors take a year to take effect, and should be given to anyone who wants to decrease their prostate. **Alpha-1 Blockers** are quick and easy, given to patients who have symptoms they want to get rid of right now. Giving both is the most effective therapy.
DRUGS USED IN THE TREATMENT OF ERECTILE DYSFUNCTION

- **Selective Type 5 Phosphodiesterase Inhibitors**
  - Drugs
    - Sildenafil, Tadalafil, Verdenafil
  - **Mechanism**
    - Phosphodiesterase cancels the effect of Nitric Oxide initiated, Guanylyl Cyclase induced, cGMP mediated vasodilation
    - These drugs inhibit Phosphodiesterase, but are selective for Type V, found in corpus cavernosum of penis
    - cGMP induces relaxation of smooth muscle and vasculature
  - **Uses**
    - Erectile Dysfunction, though requires stimulation for erection
    - Sildenafil is used for Pulm HTN
  - **Side Effects**
    - Orthostatic Hypotension
    - Transient Visual Anomalies (Blue-Green Tinged Objects)
    - Unsafe drop in BP when consumed with Nitrates
  - **Specifics**
    - Sildenafil and Verdenafil are the same
    - Tadalafil has a longer half life, 24 hr duration and less risk of vision disturbances

A review of Nitric Oxide is worthy. In the center of the image, Nitric Oxide (NO) activates guanylyl Cyclase. Regardless of where the NO comes from, guanylyl Cyclase turns GTP into cGMP. cGMP is then responsible for smooth muscle relaxation. This model is fairly common throughout the body. It occurs in the smooth muscle of the vasculature, smooth muscle of the penis, and even in the retina of the eye. cGMP is a fairly ubiquitous signal, which accounts for some of the side effects of these drugs.

Nitric Oxide is normally produced from the **endothelial cells** (shown on the top of the image) via **NO synthase's** affect on arginine, liberating NO which is allowed to diffuse into smooth muscle cells. In addition, when we treat someone for angina, we give them **nitroglycerin**, which, through an unknown pathway, generates NO within the smooth muscle cells. This is shown on the bottom left of the image.

Regardless of where the NO comes from, cGMP is made. Now, we wouldn’t want to have constant smooth muscle relaxation, so there is a second mechanism. The **phosphodiesterase** reverses the effect of Guanylyl Cyclase and takes the active cGMP to the inactive GTP form. The **type is dependent on its location**. Inhibiting type V results in smooth muscle relaxation in the penis. But because these drugs are not specific for a type of phosphodiesterase, there is a dose dependent activation of other types of phosphodiesterase. In the eye PDE-6 can be inhibited producing the vision abnormalities. If someone is taking nitrates and the PDE in the vasculature is inhibited, they can have an unrestrained vasodilation. This is why there is a risk of an unsafe drop in BP and vision disturbances. Note that **Tadalafil** (Cialis) has the longest duration and highest selectivity for PDE-5.