DIURETIC:
- A drug that increases excretion of solutes
  > Increased urine volume is secondary
- All clinically useful diuretics act by blocking Na⁺ reabsorption
  > Has the highest EC to IC ratio = always more sodium on outside as compared to inside

USES OF DIURETICS:
- Edema
- Mild to mod hypertension
- Glaucoma

PRINCIPLES OF DIURETIC ACTIONS:

THREE MAIN PROCESSES IN NEPHRON:
1) Glomerular filtration: afferent arteriole lumen > efferent = glomerular pressure → forced fluid through glomerular membrane
2) Tubular reabsorption: important substances reabsorbed into peritubular capillary
3) Tubular secretion: peritubular capillary → proximal tubule **DRUGS**

1) PROXIMAL TUBULE - CARBONIC ANHYDRASE INHIBITORS: Acetazolamide, Methazolamide, Dorzolamide (topical), Brinzolamide (topical)

MOA: inhibits CA (reversible) in proximal tubule (both membrane bound CA IV and cytoplasmic CA II)

WEAK DIURETIC:
- Large SA of proximal tubule makes it very difficult to block ALL CA IV and II enzymes
- Other segments reabsorb sodium

INDICATIONS:
- Topical for open-angle glaucoma
  o Block CA II (majority in eye) → decrease amount of carbonic acid → decrease HCO₃⁻ → decreased amount of aqueous humor formation = reduce intraocular pressure
- Oral for acute mountain sickness
  o Block CA → reduce H⁺ ions → reduce sodium bicarbonate (basic) → pH becomes acidic = metabolic acidosis
  o Causes compensatory hyperventilation and improved oxygenation

ADVERSE EFFECTS:
- Metabolic acidosis: reduced HCO₃ buffering capacity of blood
- Rash: sulfa derivative
- Renal stones: increased excretion of HCO₃ → rise in urine pH up to 8 → urine alkalosis → precipitation of calcium phosphates
- Hypokalemia

HYPOKALEMIA:
Below 3 mEq/L:
- Neurological: drowsiness, irritability, confusion
- Neuromuscular: loss of sensation, muscular weakness
- Cardiac: arrhythmias

TREATMENT:
- Increased dietary potassium
- Fresh fruits (banana, cantaloupe) & veggies (beans, potatoes)
- K⁺ salts (KCl)
- K⁺ sparing diuretic concomitantly

PATHOPHYS: explained in collecting duct diuretics
LOOP (of Henle) DIURETICS: *Furosemide, Bumetanide, Ethacrynic acid*
- MOST EFFECTIVE DIURETIC AGENTS – the sodium that is blocked from reabsorption here is not reabsorbed later

**USES OF LOOPS:** acute relief of pulmonary and peripheral edema in context of heart failure

1) heart failure
2) low blood pressure
3) low BP → baroreceptors stop firing
4) adrenergic stimulation
5) renin released from juxtaglomerular cells
6) renin converts AI to AII
7a) All is a powerful vasoconstrictor → increases afterload → hard has to pump harder → increase BP → BUT failing heart has to beat against higher afterload = further deterioration
7b) AII causes release of aldosterone → Na and H2O retention → excess blood volume → increased preload → increased BP → causes filling of heart that is already failing = VISCIOUS CYCLE
7c) All also causes release of ADH → binds to V2 receptors on collecting duct membrane → V2R activates cAMP → cell inserts AQP2 water pores into peritubular capillary membrane → water absorbed by osmosis

**ADVERSE EFFECTS:**
- Decreased blood volume (drugs are so efficacious)
- Dehydration (weakness, dizziness)
- Dose related ototoxicity (rare, reversible)
  - Caution when using other drugs that can also cause ototoxicity (ex// aminoglycosides)
- Hypokalemia
- Hyperuricemia
  - Uric acid competitively binds with loop & thiazide diuretics for the transporter used in tubular secretion
  - Uric acid not secreted → stays in peritubular capillaries
- Hypomagnesemia

**MOA:** inhibits NKCC2 in ascending limb

**HYPOMAGNESEMIA:**
- A drug that blocks NKCC2 blocks Na and K ENTRY
- Decrease Na-K-ATPase activity
- Block K backflow = lose positive charge potential = Mg and Ca can't be reabsorbed
- High concentrations of K in cell cause backflow of K moving back out into lumen

However, calcium can be reabsorbed in the distal tubule in presence of parathyroid hormone.

BUT magnesium cannot be reabsorbed = causes hypomagnesemia
DISTAL TUBULE: THIAZIDES – Hydrochlorothiazide (> 150 products); Indapamide, Metolazone, Chlorthalidone

MOA: inhibits Na-Cl co-transporter in distal tubule

USES OF THIAZIDES:
- Antihypertensive effects
  - Although distal tubule only reabsorbs 5% of sodium, these drugs are effective hypertensives due to other non-specific actions
- Edema
- Treatment of renal stones (caused by hypercalciuria)
  - Thiazides increase amount of TRP5 calcium channels in distal tubule → calcium reabsorption → prevent hypercalcemia and renal stone formation

THIAZIDE ANTIHYPERTENSIVE EFFECTS:
As thiazides are given for months, the effects of blood pressure lowering is not related to its ability to block sodium reabsorption but rather its ability to cause smooth muscle relaxation

ADVERSE EFFECTS:
- Excess pharmacological effect (decreased blood volume, dehydration)
- Hyperglycemia (decreased release of insulin or blockade of peripheral glucose utilization) – transient
  - Normally glucose enters beta cell → converted to ATP → closes ATP sensitive K+ channel → depolarization → calcium moves in → insulin secretion
  - Long-term hypokalemia = lose extracellular potassium → lose intracellular potassium because it leaves the cell → hyperpolarization → decreased calcium entry → decreased insulin secretion
- Hyperlipidemia (returns to normal with prolonged use)
- Hypokalemia
- Gout (due to competitive tubular secretion of thiazides and uric acid)
### Collecting Duct: Potassium Sparing Diuretics

#### Potassium Loss:

<table>
<thead>
<tr>
<th>Luminal Side</th>
<th>Basolateral Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ increase sodium channels at collecting duct</td>
<td>ATPase pump ( \rightarrow ) Na⁺ uptake</td>
</tr>
<tr>
<td>2) MR-aldosterone complex is internalized into nucleus</td>
<td>4) Aldosterone induced proteins made</td>
</tr>
<tr>
<td>MR</td>
<td>ATPase pump ( \rightarrow ) K⁺ uptake</td>
</tr>
<tr>
<td>3) Gene transcription is turned on</td>
<td>Na⁺ pump ( \rightarrow ) Na⁺ uptake</td>
</tr>
<tr>
<td>mRNA</td>
<td>Mito</td>
</tr>
<tr>
<td>Aldosterone binds to mineralocorticoid receptor at collecting duct</td>
<td>ATPase pump ( \rightarrow ) K⁺ uptake</td>
</tr>
<tr>
<td>ALDO</td>
<td>Na⁺ uptake</td>
</tr>
</tbody>
</table>

**Aldosterone Antagonists:** Spironolactone, Eplerenone
- Competitively inhibit aldosterone binding in collecting duct
- Promotes modest Na⁺ excretion but this promotes K⁺ retention

**Uses:**
- Diseases with elevated aldosterone (CHF)
- Hypokalemia
- Combined with other diuretics to prevent K⁺ loss

**Adverse Effects:**
- **Males:** Gynecomastia, impotence, decreased libido
- **Females:** Menstrual irregularities

**Na⁺ Channel Inhibitors:** Triamterene, Amiloride
- Inhibits Na⁺ reabsorption in collecting duct \( \rightarrow \) prevents negative lumen \( \rightarrow \) reduces K⁺ loss

**Uses:**
- Useful in edema
- Combined with another diuretic to prevent K⁺ loss

*“Few Side Effects“*
OSMOTIC DIURETIC: PROXIMAL TUBULE & DESCENDING LOOP – Mannitol

- Water soluble
- Freely filtered and poorly absorbed = stays in bloodstream
  - As it comes down into proximal tubule & descending limb of Loop of Henle, it can cause an osmotic disequilibrium
  - Water cannot be reabsorbed because of the presence of mannitol solute → mannitol leaves in urine and water leaves with it
- No pharmacological effects

USES:
- Draws fluid by osmotic effect only
- Used to prevent acute renal failure (ex// removal of tubular obstructions)
- Also to relieve increased intracranial pressure (draw out water)

SUMMARY OF DIURETICS: