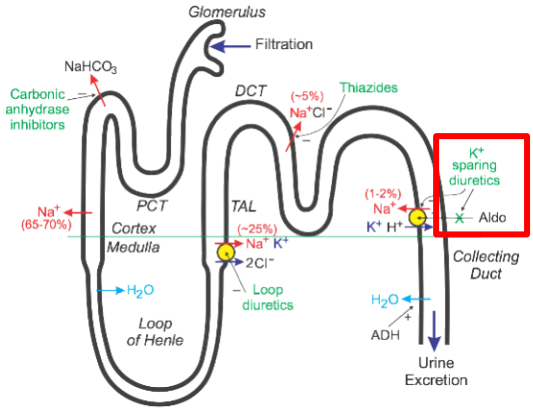
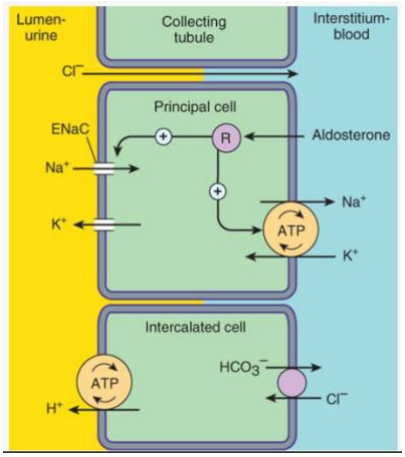
Clinical Pharmacology & Toxicology Pearl of the Week

~Antihypertensives, Part 4: Mineralocorticoid Receptor Antagonists (MRAs)~



- ✓ MRAs are synthetic steroids that competitively antagonizes aldosterone
- ✓ Members: Spironolactone, eplerenone, finerenone
- ✓ Cardiovascular indications:
  - Heart failure
  - Myocardial infarction
  - **Resistant hypertension** (After: Thiazide/thiazide-like diuretic, ACEi/ARB, CCB)
  - **Aldosterone-mediated hypertension** (e.g., primary hyperaldosteronism, secondary aldosterone excess from metabolic syndrome, OSA, cirrhosis, etc.)

Mechanism of action: (Blood pressure)



- ✓ RAAS system: Objective - maintain kidney perfusion. Renin is secreted by the kidney → converts angiotensinogen to angiotensin I → endothelial angiotensin converting enzyme (ACE) coverts angiotensin I → angiotensin II → adrenal cortex release of aldosterone
- ✓ Aldosterone is a steroid hormone – predominant site of action is the distal convoluted tubule
  - Upregulate Na+/K+ ATP pump on basolateral membrane (3Na: 2K)
  - Migration of ENAC sodium channels to apical membrane
  - Result: sodium is pumped out of the principle cell creating a concentration gradient that promotes reabsorption of sodium from the tubule
  - Increased sodium reabsorption causes water to be re-absorbed from the tubule in the collecting duct (via aquaporins).
  - Result: Increased salt and fluid retention → increased blood volume
  - MRAs antagonize aldosterone: Result is a reduced sodium concentration gradient at the distal convoluted tubule → reduced potassium efflux (Potassium sparing) and less sodium reabsorption → increased sodium excretion → lower blood pressure
  - Effect: Natriuresis (and decreased blood pressure), potassium sparing, and mild diuresis

Pharmacokinetics/Pharmacodynamics:

- ✓ Spironolactone → metabolized (deacetylated) to canrenone and 7-α-spirolactone (metabolites are active)
    - Spironolactone half-life: ~4hrs
    - Metabolite half-life: (12-20hrs)
- ✓ Eplerenone → metabolized by CYP 3A4 (Metabolites inactive)
    - Half-life: 4-6hrs
- ✓ Effect on blood pressure is longer than the half-life of agents (Blocks the hormone aldosterone, which triggers multiple downstream effects).
    - After cessation: medication effect can be prolonged (up to 4 weeks)
- ✓ Typical dosing: (for hypertension)
    - Spironolactone: 50-300mg Po Daily
    - Eplerenone: 25-150mg Po BID
    - Dosing: Linear dose response (the higher the dose, the greater the anti-hypertensive effect)

Adverse effects/Toxicity:

- ✓ Spironolactone: Cross affinity to androgen-receptors, which results in androgen blockade → can result in gynecomastia and low-libido
    - Eplerenone has less affinity for androgen receptors and so less androgen-blockade associated side-effects (e.g., Gynecomastia and low libido)
- ✓ Hyperkalemia (Potassium 'sparing' diuretic)
- ✓ Acidosis (Type IV RTA) Aldosterone mediates H^+ excretion and $HCO3^-$ synthesis at intercalated cells
- ✓ Volume depletion and acute kidney injury (rare) Other:
- ✓ Diarrhea, nausea, vomiting
- ✓ Drug interactions: Caution when using with other agents that increase serum potassium, e.g., ACEi/AEB, amiloride, septra, NSAIDs

Take-home points:

- ✓ Antagonizes effect of aldosterone
- ✓ Effective anti-hypertensive for aldosterone-excess hypertension
- ✓ Spironolactone has partial affinity to androgen receptors; blockade leads to gynecomastia/low libido. Eplerenone has much higher specificity for aldosterone receptors
- ✓ Linear dose response curve (the higher the dose, the greater the anti-hypertensive effect)

References:

1. Reilly RF, Jackson EK. Regulation of Renal Function and Vascular Volume. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw-Hill
2. Benowitz NL. Antihypertensive Agents. In: Katzung BG. eds. *Basic & Clinical Pharmacology, 14e*. McGraw-Hill
3. Drugbank: https://go.drugbank.com/drugs
4. Micromedex: https://www-micromedexsolutions-com.ahs.idm.oclc.org
5. Indiana University Department of Medicine Clinical Pharmacology - Flockhart Tables: https://drug-interactions.medicine.iu.edu/MainTable.aspx

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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