THIAZIDE/ THIAZIDE-LIKE DIURETICS

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Thiazide Diuretics | Mechanism of Action, Indications, Adverse Reactions, Contraindications

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OUTLINE

I) MECHANISM OF ACTION

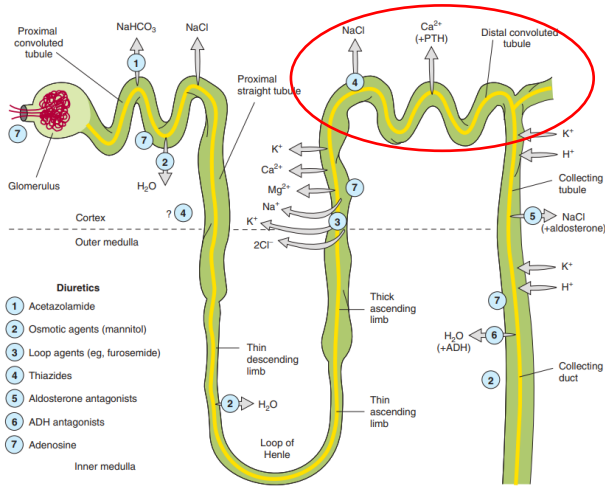

Figure 1. Renal Tubule Transport Systems and Sites of Action of Diuretics in the Nephron [Trevor, Katzung, & Kruidering-Hall, 2015]

(1) Normal Physiology of Distal Convoluted Tubule

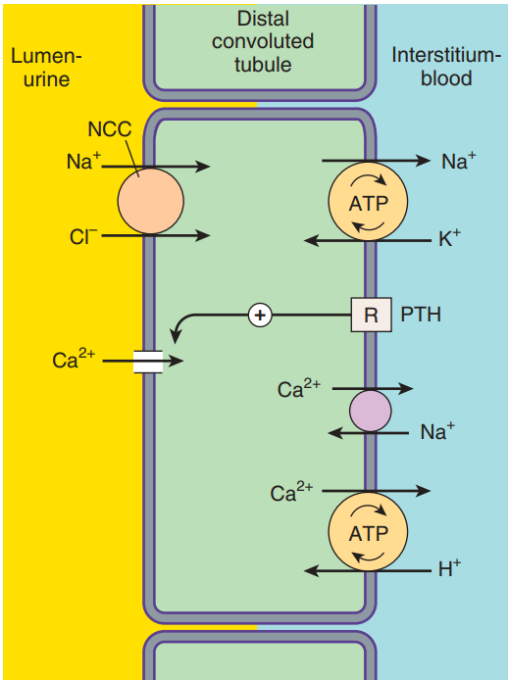

Figure 2. Mechanism of sodium and chloride reabsorption and calcium movement in the distal convoluted tubule [Trevor, Katzung, & Kruidering-Hall, 2015]

- **Distal Convoluted Tubule (DCT)**
  - Part of nephron where **Thiazide and Thiazide-like diuretics** primarily work
  - Responsible for 5-10% of **NaCl reabsorption**
  - Water follows NaCl
- **Thiazide and Thiazide-like diuretics** are mainly used in **high blood pressure** (BP)
- They control BP by **inhibiting NaCl reabsorption** in the DCT; thus, inhibiting water reabsorption → ↓Blood volume → ↓BP
- **Apical/Luminal Surface of DCT**
  - Facing lumen/ tubule containing filtrate
  - **Na^+-Cl^- co-transporter (NCC)**
    - Transports Na^+ and Cl^- from tubular lumen into the cell
  - **Permeable to Ca^{2+}**
- **Basolateral Surface of DCT**
  - Peritubular capillaries present
  - Facing intersitium- blood
  - **Na^+/K^+ ATPase Pump**
    - 3 Na^+ out of the cell (into the blood)
    - 2 K^+ into cell
  - **Na^+/Ca^{2+} exchanger (NCX)**
    - Na^+ back into cell
    - Ca^{2+} out of the cell (into blood)
      - ↓Ca^{2+} in cell
  - **Parathyroid Hormone** controls **Ca^{2+} reabsorption**
    - ↑Ca^{2+} in the DCT lumen compared to ↓Ca^{2+} in the cell due to NCX → concentration gradient
    - Ca^{2+} moves from tubular lumen into the cell (apical surface is permeable to Ca^{2+})
    - Ca^{2+} can again be transported out of the cell via NCX → ↑Ca^{2+} in blood
- **Effects on Electrolytes in the Bloodstream**
  - ↑ Ca^{2+}
  - ↑ Na^+ & Cl^- → osmotic gradient → pull water from tubular lumen into bloodstream via aquaporins

Summary DCT Normal Physiology
- Na^{2+} and Cl^- are retained in blood, pulling water into bloodstream.
- Ca^{2+} levels in blood is regulated via NCX.

(2) Mechanism of Thiazide and Thiazide-Like Diuretics

- **Inhibit NaCl co-transporter (NCC)**
  - ↓Na^+, ↓Cl^- into the cell
    - ↓Cl^- in bloodstream
    - ↓Na^+ that will be pumped out by Na^+/K^+ ATPase
  - ↓Na^+/K^+ ATPase Pump activity
    - ↓K^+ into cell
    - ↓Na^+ pumped out into blood stream
    - but the Na^+ concentration in blood is still higher than the Na^+ in the cell → concentration gradient
  - Na^+ in the bloodstream goes into cell via NCX
    - ↑Na^+ in cell
    - ↑Ca^{2+} is pumped out of the cell → ↑Ca^{2+} into blood, ↓Ca^{2+} in cell
  - ↑Ca^{2+} in lumen than in cell → concentration gradient
  - Ca^{2+} in lumen enters cell and pumped out to the bloodstream via NCX → ↑Ca^{2+} in blood
- **Effects:**
  - **↓Na^+ & Cl^- reabsorption**
    - ↓osmotic gradient to drive water movement
    - **↓H_2O reabsorption**
    - **↓Blood Volume: ↓Blood Pressure (BP)**
  - **↑Ca^{2+} reabsorption**
    - Useful in osteoporosis, osteopenia
    - Useful in people prone to developing calcium oxalate/ calcium phosphate kidney stones

(3) Types

(i) Thiazide Diuretics

- **Hydrochlorothiazide (HCTZ)**
- **Chlorothiazide**

(ii) Thiazide-like Diuretics

- More effective
- **Chlorthalidone**
- **Metolazone**
  - Used in Congestive Heart Failure (CHF), in combination with loop diuretics to get extra sodium and water pull
- Have **Sulfa** component
  - Contraindicated in sulfa allergies → can lead to **acute interstitial nephritis**

(4) Additional Mechanism

- Complete underlying physiology not fully understood yet
- **Promote vasodilation** → ↓**Total Peripheral Resistance** (TPR) → ↓**Blood Pressure**
- Thiazide and Thiazide-like diuretics probably stimulates **Prostaglandin (PG) production**
- PG helps promote the vasodilation

Summary of MOA
- Thiazide and Thiazide-like diuretics inhibits NaCl reabsorption via NCC
  - ↓NaCl in blood
  - ↓water in blood
  - ↓blood volume
  - ↓blood pressure

MECHANISM OF ACTION

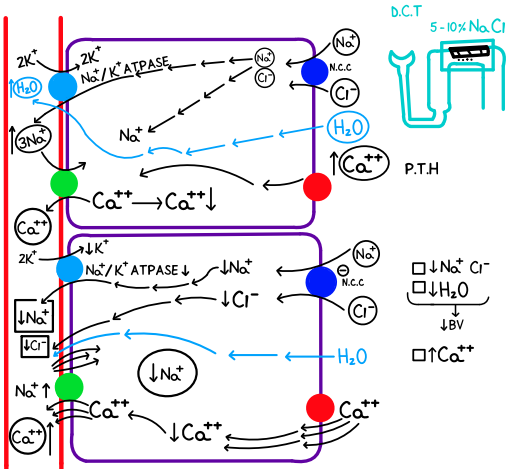

Figure 3. Mechanism of Action of Thiazide and Thiazide-Like Diuretics

II) INDICATIONS

(A) HYPERTENSION

- ↓**Na⁺ & Cl⁻** reabsorption
- ↓**H₂O** reabsorption
- ↓**Blood Volume**
- ↓**Blood Pressure (BP)**

(B) FLUID OVERLOAD

(1) Causes

- Congestive Heart Failure
- Cirrhosis
- Acute Kidney Injury
- Nephrotic syndrome

(2) Manifestations

- **Peripheral Edema**
  - Accumulation of fluid in the tissue spaces in the leg
  - pain, swelling
- **Pulmonary Edema**
  - Accumulation of fluid in the interstitial spaces between alveoli and pulmonary capillaries
  - Difficulty breathing
- **Ascites**
  - Accumulation of fluid in the abdomen

(3) Mechanism

- ↓**Na⁺ & Cl⁻ reabsorption**
- ↓**H₂O reabsorption**
- ↓**excess fluid**
- ↓**blood volume**
- ↓**edema**

- **Loop Diuretics** are the mainstay in the treatment of fluid overload.
- **Thiazides** in fluid overload
  - Monotherapy
  - Dual Therapy with a loop diuretic: more common
    - Ex. Metolazone + loop diuretic (Furosemide)

(C) NEPHROGENIC DIABETES INSIPIDUS (DI)

(1) Pathophysiology of Nephrogenic DI

- **Diabetes Insipidus**: not enough antidiuretic hormone is produced
- **Normal Physiology:**
  - **Antidiuretic hormone (ADH)** or **Vasopressin** is synthesized by the supraoptic nucleus and paraventricular nucleus of the hypothalamus
  - secreted by the posterior pituitary gland
  - ADH binds to **V2 Receptors** of the **collecting duct**
  - Signals production of **aquaporins**
  - Water is pulled from the tubular lumen into the tubular cells, then into the blood → ↓H_2O in urine
- **Nephrogenic Diabetes Insipidus:**
  - **Normal ADH** production
  - **V2 receptors defective**
  - No aquaporin activation
  - ↓H_2O in blood
  - ↑H_2O in urine → ↑urination

Why give a diuretic to someone already losing water?

(2) Paradoxical Mechanism of Thiazide Diuretic

- Induce mild hypovolemia
- ↓Na^+ & Cl^- reabsorption
- ↓H_2O reabsorption
- ↓Blood Volume
- ↓**Blood flow to glomerulus**
- ↓**Glomerular Filtration Rate (GFR)**
- **Proximal Convoluted Tubule (PCT) has more time to reabsorb Na^+, Cl^-, and H_2O**
- ↑**reabsorption of Na^+, Cl^-, H_2O**
- ↓Na^+, Cl^-, and H_2O in urine → ↓water loss

(D) HYPERCALCIURIA

- High calcium in urine, which can combine with phosphates and oxalates
- ↑**risk of kidney stones**
- Thiazide diuretics prevent formation of kidney stones
  - ↑Ca^{2+} reabsorption into blood
  - ↓Ca^{2+} in kidney tubules

(E) OSTEOPENIC/ OSTEOPOROSIS: BRITTLE BONES

- ↑Ca^{2+} reabsorption
- Stimulate **calcitonin** production
- ↑**osteoblast** activity → build bones

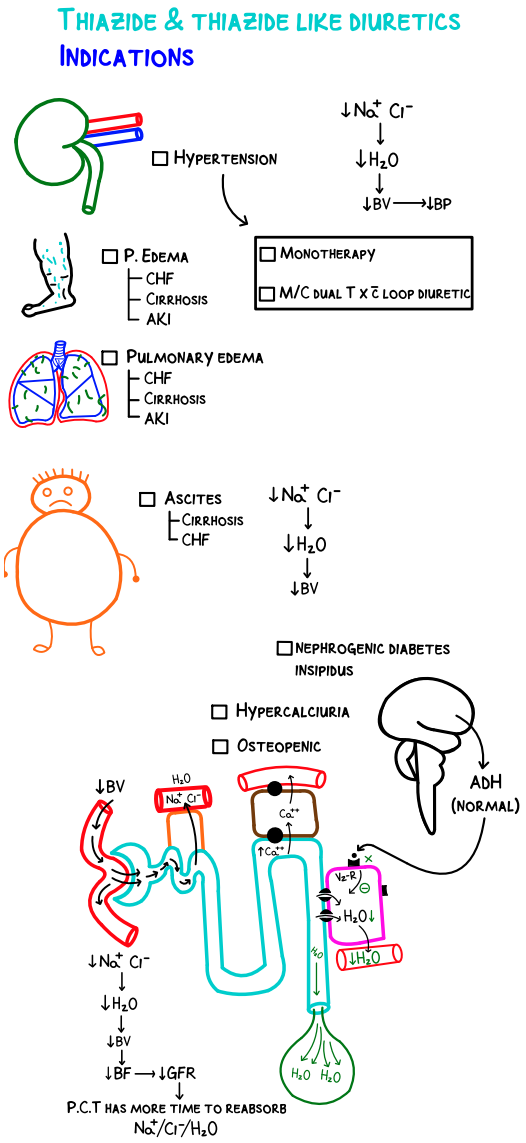

Figure 4. Summary of Indications of Thiazide and Thiazide-like Diuretics

III) ADVERSE DRUG REACTIONS

(A) GOUT

- **Uric Acid** is excreted from the blood into the tubular cells and into the tubular lumen via **Organic Acid/ Anion Transporters (OAT)** in the apical and basolateral surfaces of the **Proximal Convoluted Tubule**
- **Thiazides inhibit OAT**
  - ↑Uric Acid in blood
  - **Hyperuricemia**
  - Gout
    - uric acid (monosodium urate) crystals deposit in joints, especially the first **metatarsophalangeal (MTP) joint** of the big toe
    - causing pain and tenderness

(B) ELECTROLYTE IMBALANCES

- **Inhibition of Na^+-Cl^- Cotransporters**
  - ↓Na^+, Cl^- reabsorption
  - ↑Na^+, Cl^- retained in kidney tubules
  - ↑Na^+, Cl^- excreted in urine
  - ↓Na^+ in blood: **Hyponatremia**
  - ↓Cl^- in blood: **Hypochloremia**
- ↑Ca^{2+} reabsorption: **Hypercalcemia**
  - Inhibition of NCC
  - ↓Na^+, ↓Cl^- into the cell
    - ↓Cl^- in bloodstream
    - ↓Na^+ that will be pumped out by Na^+/K^+ ATPase
  - ↓Na^+/K^+ ATPase Pump activity
    - ↓K^+ into cell
    - ↓Na^+ pumped out into blood stream
    - but the Na^+ concentration in blood is still higher than the Na^+ in the cell → concentration gradient
  - Na^+ in the bloodstream goes into cell via NCX
    - ↑Na^+ in cell
    - ↑Ca^{2+} is pumped out of the cell → ↑Ca^{2+} into blood, ↓Ca^{2+} in cell
  - ↑Ca^{2+} in lumen than in cell → concentration gradient
  - Ca^{2+} in lumen enters cell and pumped out to the bloodstream via NCX → **↑Ca^{2+} in blood**
  - **↓Ca^{2+} in urine**
- **↑Na^+ in urine**
  - More sodium is moving from the distal convoluted tubule to the collecting duct than normal, creating a concentration gradient, where Na^+ levels in the tubular cells of the collecting duct is lower and the tubular lumen has higher Na^+ levels
  - Na^+ moves into tubular cell
  - Na^+/K^+ ATPase pumps Na^+ out of cell into blood
  - If cations (+ charged ions, i.e. Na^+) are moving into the cell and leaving the tubular lumen, the lumen becomes **negatively charged**
  - (-) charged lumen attracts cations (i.e., K^+ and H^+) in the tubular cells to be excreted in the urine
  - ↓K^+ in blood: **Hypokalemia**
  - ↓H^+ in blood: **Metabolic Alkalosis**

Summary: Effects of Thiazide Diuretics on Urine Levels of Electrolytes

- Hyperuricemia
- Hypercalcemia
- Hyponatremia
- Hypochloremia
- Hypokalemia
- Metabolic alkalosis

Table 1. Effect of Thiazide Diuretics on Urine Levels of Electrolytes

↑Urine Levels	↓Urine Levels
Na^+	Ca^{2+}
Cl^-	
H_2O	
K^+	
H^+	

(C) HYPERGLYCEMIA

Pancreatic β-Cell

- **Normal Physiology**
  - **GLUT transporters**: bring glucose into cell
  - Glucose →→→ ATP
  - ATP binds and closes ATP-sensitive K^+ channel
  - K^+ cannot leak out of cell
  - ↑↑↑ (+) charge → activation of voltage gated Ca^{2+} channels
  - Ca^{2+} moves into the cell and stimulate the release of insulin from vesicles into bloodstream
  - Insulin binds to insulin receptor and activate transporters that move glucose into the cell
  - ↓blood glucose
- **Thiazides given**
  - **↓K^+ in blood**
  - K^+ in cells move out to the blood to compensate for ↓serum K^+
  - **↓K^+ in cells**
  - **↓ (+) charge → ↓activation of voltage gated Ca^{2+} channels**
  - ↓Ca^{2+} moves into the cell
  - ↓insulin released into blood
  - ↓glucose movement into cell

- ↑blood glucose → **hyperglycemia**

(D) ACUTE INTERSTITIAL NEPHRITIS

- Allergic reaction to **Sulfa Group of Thiazide-like diuretics**
- Signs and Symptoms (triad):
  - Arthralgia
  - Rash
  - Intrarenal Acute Kidney Injury
  - ↑eosinophil count in CBC

Summary:

Table 2. Effect of Thiazides on Serum levels of Electrolytes/ Substance

↑Serum Levels	↓Serum Levels
Ca^{2+}	Na^+
Uric Acid	Cl^-
Glucose	H_2O
	K^+
	H^+ (metabolic alkalosis)

SIDE EFFECTS / ADRS

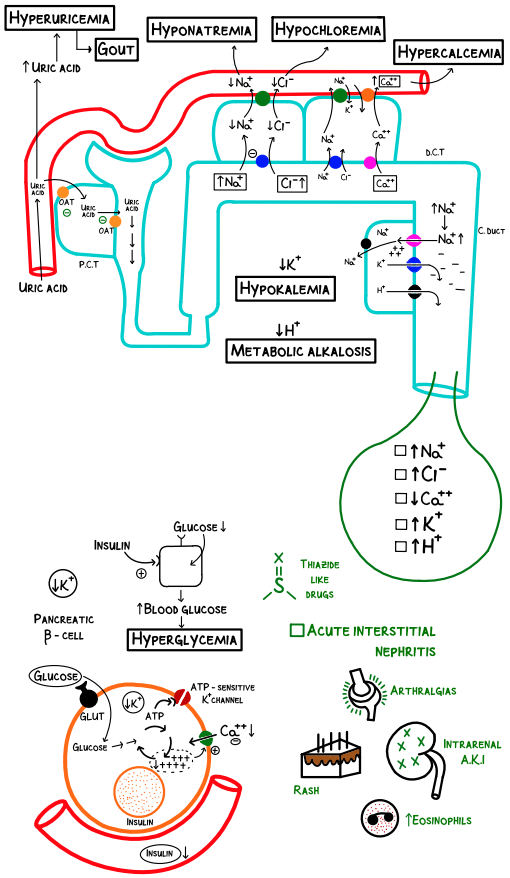

Figure 5. Summary of Adverse Effects of Thiazide and Thiazide-like Diuretics

IV) REVIEW QUESTIONS

1) **Where is the primary site of action of Thiazide Diuretics?**
   a. Proximal Convoluted Tubule
   b. Collecting Duct
   c. Loop of Henle
   d. Distal Convoluted Tubule

2) **Which of the following contain Sulfa group?**
   a. Hydrochlorothiazide
   b. Chlorothiazide
   c. Thiazide Diuretics
   d. Chlorthalidone

3) **True or False: Thiazides cause hypoglycemia.**
   a. True
   b. False

4) **Which of the following is not an effect of thiazides?**
   a. Hypokalemia
   b. Hyponatremia
   c. Hypochloremia
   d. Hypocalcemia

5) **Thiazides are usually combined with what in treating fluid overload?**
   a. Vasopressin
   b. Loop Diuretic
   c. Osmotic Diuretic
   d. Acetazolamide

CHECK YOUR ANSWERS

V) REFERENCES

- Trevor, A., Katzung, B., & Kruidering-Hall, M. (2015). *Katzung & Trevor's Pharmacology Examination & Board Review*. McGraw Hill Education