LOOP DIURETICS

Last edited: 9/27/2021

[Loop Diuretics | Mechanism of Action, Indications, Adverse Reactions, Contraindications]

Medical Editor: Abigail S. Xu, RPh

OUTLINE

I) MECHANISM OF ACTION

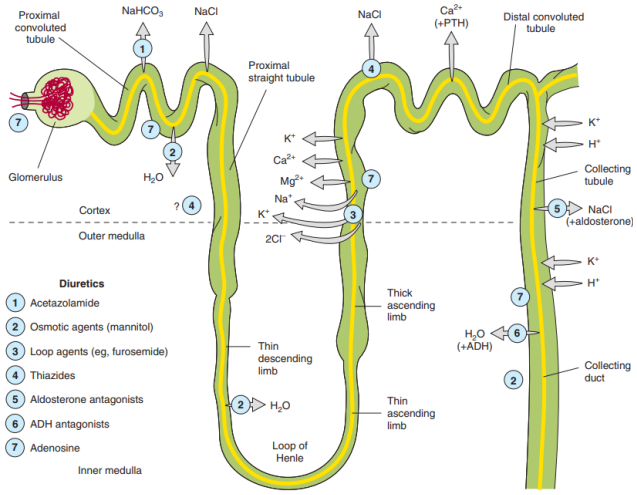

Figure 1. Renal Tubule Transport Systems and Sites of Action of Diuretics [Trevor, Katzung, & Kruidering-Hall, 2015, p. 133, Fig. 15-1]

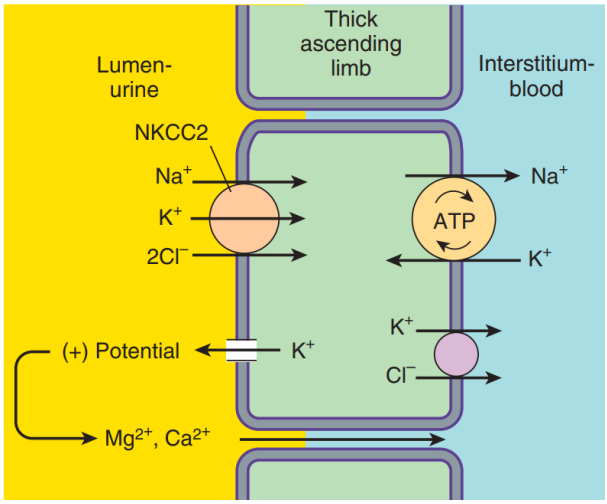

Figure 2. Mechanism of sodium, potassium, and chloride reabsorption in the thick ascending limb of loop of Henle

[Trevor, Katzung, & Kruidering-Hall, 2015, p. 135, Fig. 15-3]

(1) Normal Physiology of the Loop of Henle

(i) Thick Ascending Limb of the loop of Henle (TAL)

- **Site of Action of Loop Diuretic**
- The lumen is lined by tubular cells (type of cuboidal cells)
- Responsible for the **reabsorption of 25% of NaCl**
- Pumps **sodium, potassium, and chloride** out of the lumen **into the interstitium** of the kidney [Trevor, Katzung, & Kruidering-Hall, 2015]
- Major site of **calcium and magnesium reabsorption** [Trevor, Katzung, & Kruidering-Hall, 2015]
- **Na^+/ K^+/ $2Cl^-$ Cotransporter (NKCC2)**
  - Transports Na^+, K^+, $2Cl^-$ into cell
- **Na^+/ K^+ ATPase**
  - Found on every nucleated cell in the body
  - Pumps **3 Na^+ out** of cell → **↑Na^+ in interstitium**
  - Pumps **2 K^+ into cell**
- **Cl^- Transporter**
  - Cl^- out of cell → **↑Cl^- in interstitial space**
- **↑NaCl in medullary interstitium** → "salty"

Recall Renal Physiology
- **Renal Cortex**
  - Bowman's capsule
  - Proximal Convoluted Tubule
  - Distal Convoluted Tubule
- **Renal Medulla**
  - Loop of Henle

- **K^+- selective channel**
  - Escape route of K^+
  - K^+ is pumped into the cell from both the luminal (via NKCC2) and basal side (via Na^+/ K^+ ATPase) [Trevor, Katzung, & Kruidering-Hall, 2015]
  - **K^+ diffuse to tubular lumen**
  - ↑↑↑ (+) potential in the lumen
  - **Ca^{2+}** and **Mg^{2+}** flow from descending limb to the ascending limb
    - move out of the tubular lumen and into the interstitial space via **pericellular process** (space between the cells)
  - **↑Ca^{2+} & Mg^{2+} in blood**

(ii) Descending Limb of the Loop of Henle

- Major component is **water**
- Water flows from areas of ↓salt concentration to areas of ↑salt concentration
- Water moves to "salty" interstitium via **aquaporins**

Counter-current Multiplier Mechanism
- **Ascending limb**
  - NaCl is pumped out of cell and into interstitium, creating a concentration gradient
- **Descending limb**
  - salty environment in the interstitium draws water into the interstitium
  - ↑water reabsorption
  - ↓water in urine → concentrated urine

Summary: Reabsorption in the Loop of Henle
- ↑↑↑Na^+
- ↑↑↑Cl^-
- ↑↑↑H_2O
- ↑↑↑Ca^{2+}
- ↑↑↑Mg^{2+}
- ↑K^+

- **↑NaCl in blood → ↑H_2O in blood → ↑Blood Volume (BV) → ↑ Blood Pressure (BP)**

(2) Mechanism of Loop Diuretics

- **Inhibit Na^+/ K^+/ $2Cl^-$ Cotransporter (NKCC2) in TAL**
  - **↓Na^+ in cell**
    - ↓Na^+ pumped out by Na^+/ K^+ ATPase
    - ↓K^+ pumped in by Na^+/ K^+ ATPase
  - **↓Cl^- in cell**
    - ↓Cl^- transported out of cell and into interstitium
  - ↓NaCl in interstitium
  - ↓movement of water into interstitial space
  - **↓K^+ in cell**
    - ↓K^+ that diffuse to tubular lumen
    - ↓ (+) charge in lumen

- ↓ Ca^{2+} and Mg^{2+} would move by the pericellular route and they will move along the course of the ascending limb to the distal convoluted tubule
- Ca^{2+} and Mg^{2+} would be excreted in the urine instead of being reabsorbed
- **↓Ca^{2+} & Mg^{2+} in interstitium**

Effects of Loop Diuretics on Reabsorption

- ↓NaCl
- ↓H_2O
- ↓Ca^{2+}
- ↓Mg^{2+}

- **↓NaCl in blood → ↓H_2O in blood → ↓BV → ↓BP**

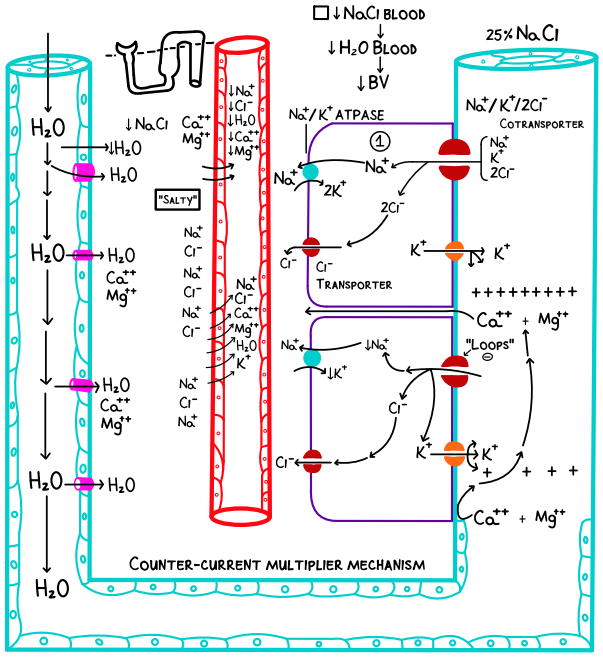

Figure 3. Mechanism of Action of Loop Diuretics

(3) Additional Mechanism

We don't know the exact mechanism of how the thiazides and loop diuretics cause vasodilation. What they think is that they might cause:

- **↑Prostaglandin Production**
- **Vasodilation** of arterioles
- **↓Total Peripheral Resistance (TPR)**
- **↓Blood Pressure (BP)**

Recall

- $BP = CO \times TPR$
  - BP: Blood Pressure
  - CO: Cardiac Output
  - TPR: Total Peripheral Resistance

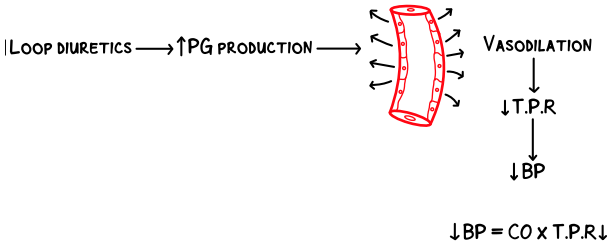

Figure 4. Mechanism of Loop Diuretics on Lowering Blood Pressure

(4) Types of Loop Diuretics

(i) Type 1 Loop Diuretic

- Sulfonamide derivatives

a. **Furosemide (Lasix)**
b. **Torsemide**
c. **Bumetanide**

(ii) Type 2 Loop Diuretic

- No sulfa component
- Phenoxyacetate derivative [Trevor, Katzung, & Kruidering-Hall]

a. **Ethacrynic Acid**

II) INDICATIONS

(A) FLUID OVERLOAD STATES

(1) Causes

- **Congestive Heart Failure (CHF)**
- **Cirrhosis**
  - Liver failure
  - ↓*albumin* production
  - ↓*osmotic pressure* to keep water in blood vessels
- **Acute Kidney Injury/ Nephrotic syndrome**
  - ↓kidney function
  - ↓*urine output*
  - *fluid build-up*

(2) Manifestations

- **Pulmonary Edema**
  - Accumulation of fluid in the **interstitial spaces** between alveoli and pulmonary capillaries
  - Usually caused by **left-sided heart failure** (cause fluid to back up in the pulmonary circulation)
- **Peripheral Edema**
  - Accumulation of fluid in the **tissue spaces** in the leg
  - Usually caused by **right-sided heart failure**
- **Ascites**
  - Accumulation of fluid in the **peritoneum/ abdominal cavity**
  - CHF is **right-sided heart failure**
  - In **cirrhosis** because of **hepatic portal hypertension** (blood is back flowing to the hepatic portal system)

(3) Mechanism

- **↑Na^+ & Cl^- excretion**
- **↑H_2O excretion**
- **↓excess fluid**
- **↓edema**

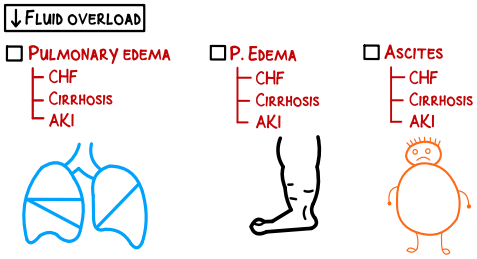

Figure 5. Summary of Fluid Overload States

(B) HYPERTENSION

- In hypertensive patients with **decreased kidney function → ↓fluid in kidney**
- **Loop diuretics**
  - more effective than thiazides if patient has ↓**kidney function**
    - loop diuretics have more access to fluid and salt
  - **Loop diuretics** act on **Thick Ascending Loop of Henle**, where **25% of fluid and salt are reabsorbed**
  - **Thiazides** act on **Distal Convoluted Tubule** and can only access **5-10% of fluid and salt**
- **↑fluid and salt loss → ↓BV → ↓BP**
- Watch out for dehydration since more fluid and salt are excreted in the urine
- It's **not always or commonly utilized in hypertension** but it could be.

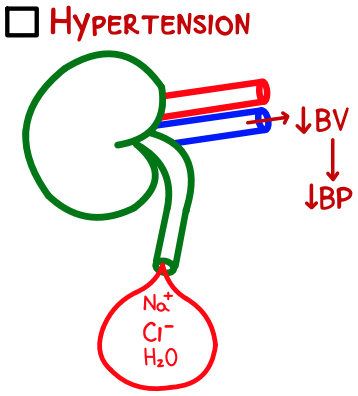

Figure 6. Effect of Loop Diuretics on Blood Volume and Blood Pressure

(C) ELIMINATION OF TOXINS/ EXCESS IONS

(1) Conditions of Excess Ions/ Toxins

a. Hypercalcemia
- ↑Ca^{2+}

b. Hyperkalemia
- ↑K^+

c. ↑↑Li+
- Bipolar disorder medication

d. ↑↑ Myoglobin (Rhabdomyolysis)
- Destruction of skeletal muscle or cardiac muscle (release myoglobin into the blood stream)
- **Acute Tubular Necrosis**
  - Myoglobin accumulates in tubular cells of Proximal Convoluted Tubule
  - Alter filtration process
  - Accumulation of waste products in blood
    - Urea
    - Creatinine

(2) Treatment

- ↑**Fluids: Normal Saline (IV)** (1L/hr.)
  - Allows for more filtration of the excess ions and toxins
- **Loop diuretic**
  - ↑NaCl & water excretion
  - Pull excess ions and toxins into nephron
  - Excretion of excess ions and toxins into the urine

Fun Fact!
- Myoglobin excreted in urine
  - brown tinged urine due to heme

Hyperkalemia Treatment
- **Loops Diuretics and Fluids**
  - Increase renal excretion of K^+
- **Calcium Gluconate**
  - Antagonize cardiotoxicity of hyperkalemia (it can cause dysrhythmia and cause them to go into ventricular fibrillation)
  - Stabilize cardiac cell membrane
- **Insulin**
  - Push K^+ into cells → ↓K^+ in blood
  - D50 (dextrose) is added to maintain glucose level in blood since insulin can cause hypoglycemia (excessive correction)
- **Albuterol**
  - Move K^+ into cells → ↓K^+ in blood
- **Bicarbonate**

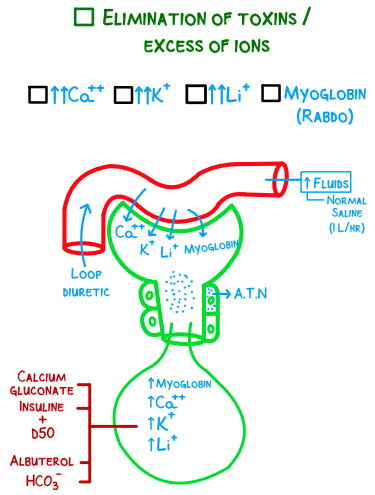

Figure 7. Elimination of Calcium, Potassium, Lithium, and Myoglobin via the Urine by Loop Diuretics

III) ADVERSE DRUG REACTIONS

(A) HYPERURICEMIA/ GOUT

- Loop diuretics **alter organic anion transporter** (OAT) in **proximal convoluted tubule**
  - **OAT**: responsible for the **excretion of uric acid** into tubular lumen
- ↓**Uric Acid Excretion**
- ↑**Uric Acid in blood (Hyperuricemia)** → **Gout**
  - due to deposited uric acid in particular joints in the body

(B) HYPOVOLEMIA

(C) HYPONATREMIA

(D) HYPOCHLOREMIA

- **Thick Ascending Limb** of the Loop of Henle (TAL) is responsible for **25% of NaCl reabsorption**
- Loop Diuretic **inhibits Na^+/ K^+/ $2Cl^-$ Cotransporter** in TAL
- ↓NaCl & H_2O reabsorption
  - ↓Na^+ in blood → **Hyponatremia** (<135 mEq/L)
  - ↓Cl^- in blood → **Hypochloremia**
  - ↓H_2O in blood → **Hypovolemia**
- ↑NaCl excretion → ↑NaCl in urine → ↑H_2O in urine

(E) HYPOKALEMIA

(F) METABOLIC ALKALOSIS

- ↑**Na^+ in the lumen** of collecting duct
- Concentration gradient
- **Na^+ moves from the lumen into the tubular cells** of the collecting duct
- **Tubular lumen** becomes more **negatively charged**
- **K^+ and H^+ move out of the tubular cells** into the negatively charged lumen
- ↑excretion of K^+ → ↓K^+ in blood → **Hypokalemia**
- ↑excretion of H^+ → ↓H^+ in blood → **Metabolic alkalosis**

Carbonate-Bicarbonate Buffer System in Blood
- $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$
- **Loop diuretics**
  - ↓$\boldsymbol{H^+}$ in blood
  - ↑$\boldsymbol{HCO_3^-}$ in blood since there is not enough H^+ to make H_2CO_3
  - ↑**pH**
  - **Metabolic alkalosis**

Anion Gap (AG)
- $AG = Na^+ + (Cl^- + HCO_3^-)$
- Cl^- & HCO_3^- changes are inverse of each other
- **Loop Diuretic**
  - Causes **hypochloremia** → $\downarrow Cl^-$
  - Inverse relationship between Cl^- & HCO_3^-
  - $\uparrow \boldsymbol{HCO_3^-}$ → **Metabolic alkalosis**

(G) OTOTOXIC EFFECT

- **Na^+/ K^+/ $2Cl^-$ Cotransporter (NKCC2)**
  - Loop of Henle
  - Inner ear
- High concentration of Loop Diuretics can affect **NKCC2 in inner ear**
- **↓endolymph concentration**
- **Damage hair cells** in inner ear → **ototoxicity**

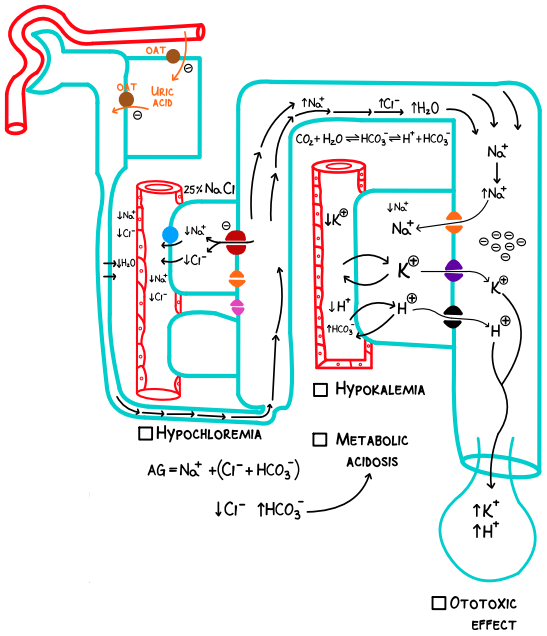

Figure 8. Mechanism of Loop Diuretics Causing Hyperuricemia, Hypovolemia, Hyponatremia, Hypochloremia, Hypokalemia, Metabolic Acidosis, and Ototoxicity

(H) HYPERGLYCEMIA

Pancreatic β-Cell
- **Normal Physiology**
  - **GLUT transporters**: bring glucose into cell
  - **Glucose →→→ ATP**
  - ATP 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**
  - **Release of insulin** from vesicles into bloodstream
  - Insulin binds to receptor in cells
  - Activate transporters that move glucose into the cell
  - **↓blood glucose**
- **Loop Diuretics**
  - **Hypokalemia**
  - **↓K^+ in cell**
  - **↓ (+) charge**
  - **↓activation of voltage gated Ca^{2+} channels** (not enough K^+ to cause it to depolarize)
  - **↓Ca^{2+} enters cell**
  - **↓insulin release**
  - ↓glucose movement into cell
  - **↑blood glucose → hyperglycemia**

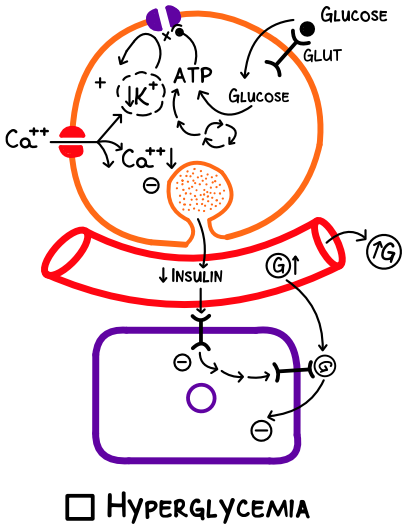

Figure 9. Mechanism of Loop Diuretics Causing Hyperglycemia

(I) ACUTE INTERSTITIAL NEPHRITIS

- **Sulfa derivatives/ Type I Loop Diuretics**
- Hypersensitivity reactions to Sulfa drugs
- Triad of Symptoms
  - Arthralgia (joint pain)
  - Rash
  - Acute Kidney Injury (due to inflammation of interstitial spaces within the kidney tubules)
    - Elevated BUN and Creatinine
- ↑eosinophil: due to hypersensitivity reaction

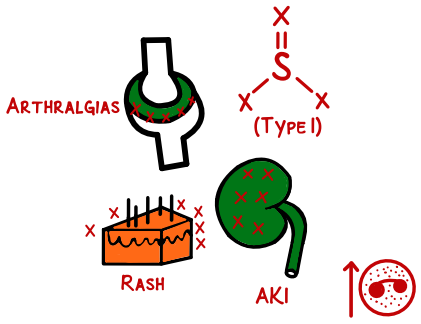

Figure 10. Manifestations of Acute Interstitial Nephritis

Summary:
Loop Diuretics
- Site of Action: Thick Ascending Limb of Loop of Henle
- Mechanism: Inhibition of NKCC2
- Indications
  - Fluid Overload State
  - Hypertension
  - Elimination of Toxins and Excess Ions
- Effects

Table 1. Effects of Loop Diuretics on Serum levels of Electrolytes/ Substance

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

IV) REVIEW QUESTIONS

1) **Which of the following is an important effect of chronic therapy with loop diuretics?**
   a. Decreased urinary excretion of calcium
   b. Elevation of blood pressure
   c. Elevation of pulmonary vascular pressure
   d. Metabolic alkalosis

2) **Which of the following loop diuretics can be used in patients with sulfa allergy?**
   a. Furosemide
   b. Lasix
   c. Ethacrynic acid
   d. Torsemide

3) **What transporter does loop diuretics inhibit?**
   a. Na^+/ K^+/ $2Cl^-$ Cotransporter
   b. Na^+/ K^+ ATPase
   c. K^+- selective channel
   d. Cl^- Cotransporter

4) **Loop diuretics cause diuresis by mainly affecting which part of nephron?**
   a. Thick ascending limb of loop of Henle
   b. Descending limb of loop of Henle
   c. Proximal convoluted tubule
   d. Distal convoluted tubule

5) **Which of the following is an ADR of loop diuretic?**
   a. Hypoglycemia
   b. Hyperuricemia
   c. Hypernatremia
   d. Hyperkalemia

CHECK YOUR ANSWERS

V) REFERENCES

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