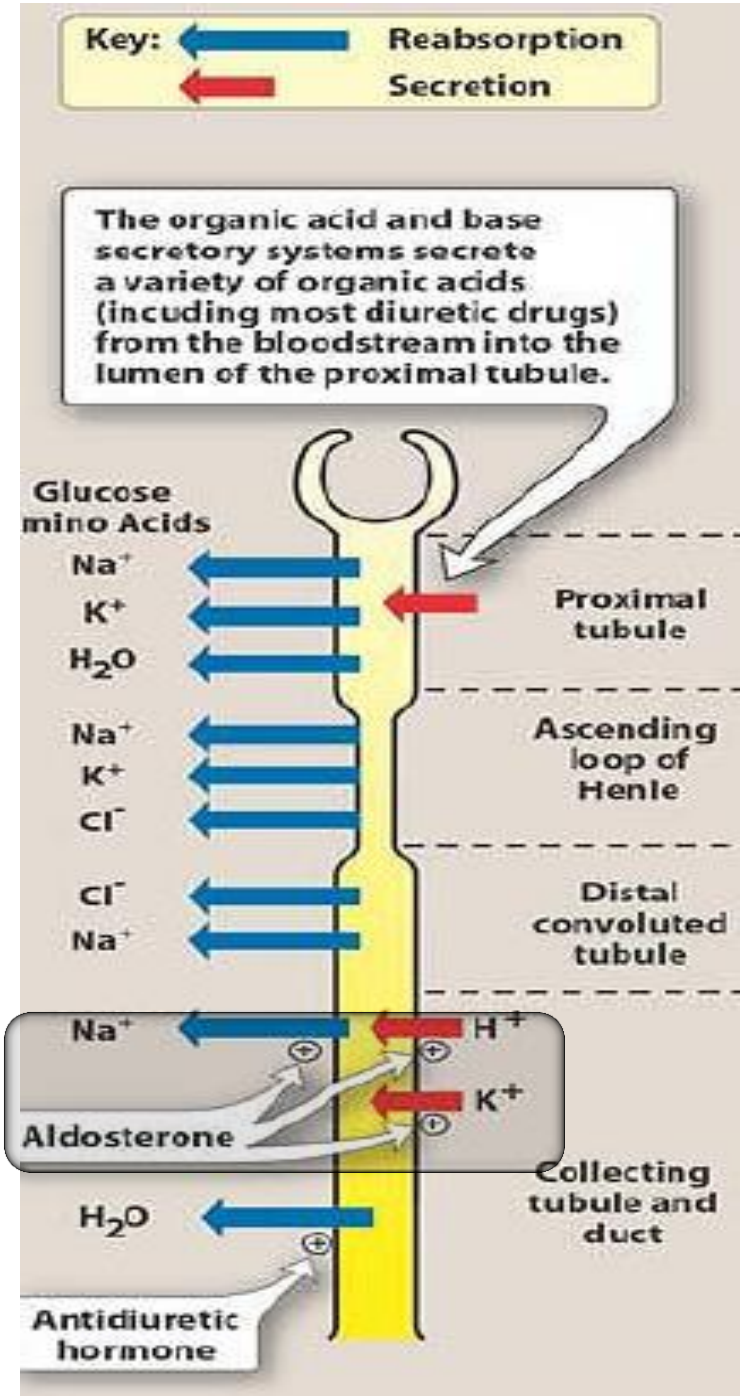
DIURETICS

Assoc. Prof. Bilgen Başgut


Key:
Reabsorption
Secretion
The organic acid and base secretory systems secrete a variety of organic acids (incuding most diuretic drugs) from the bloodstream into the lumen of the proximal tubule.
Glucose
mino Acids
Na+
K+
H2O
Proximal tubule
Na+
K+
Cl-
Ascending loop of Henle
Cl-
Na+
Distal convoluted tubule
Na+
H+
K+
Aldosterone
Collecting tubule and duct
H2O
Antidiuretic hormone

Classification of Diuretics

- **The best way to classify diuretics is to look for their Site of action in the nephron**

A. **Diuretics that inhibit transport in the Proximal Convoluted Tubule (Osmotic diuretics, Carbonic Anhydrase Inhibitors)**

B. **Diuretics that inhibit transport in the Medullary Ascending Limb of the Loop of Henle(Loop diuretics)**

C. **Diuretics that inhibit transport in the Distal Convoluted Tubule(Thiazides : Indapamide , Metolazone)**

D. **Diuretics that inhibit transport in the Cortical Collecting Tubule (Potassium sparing diuretics)**

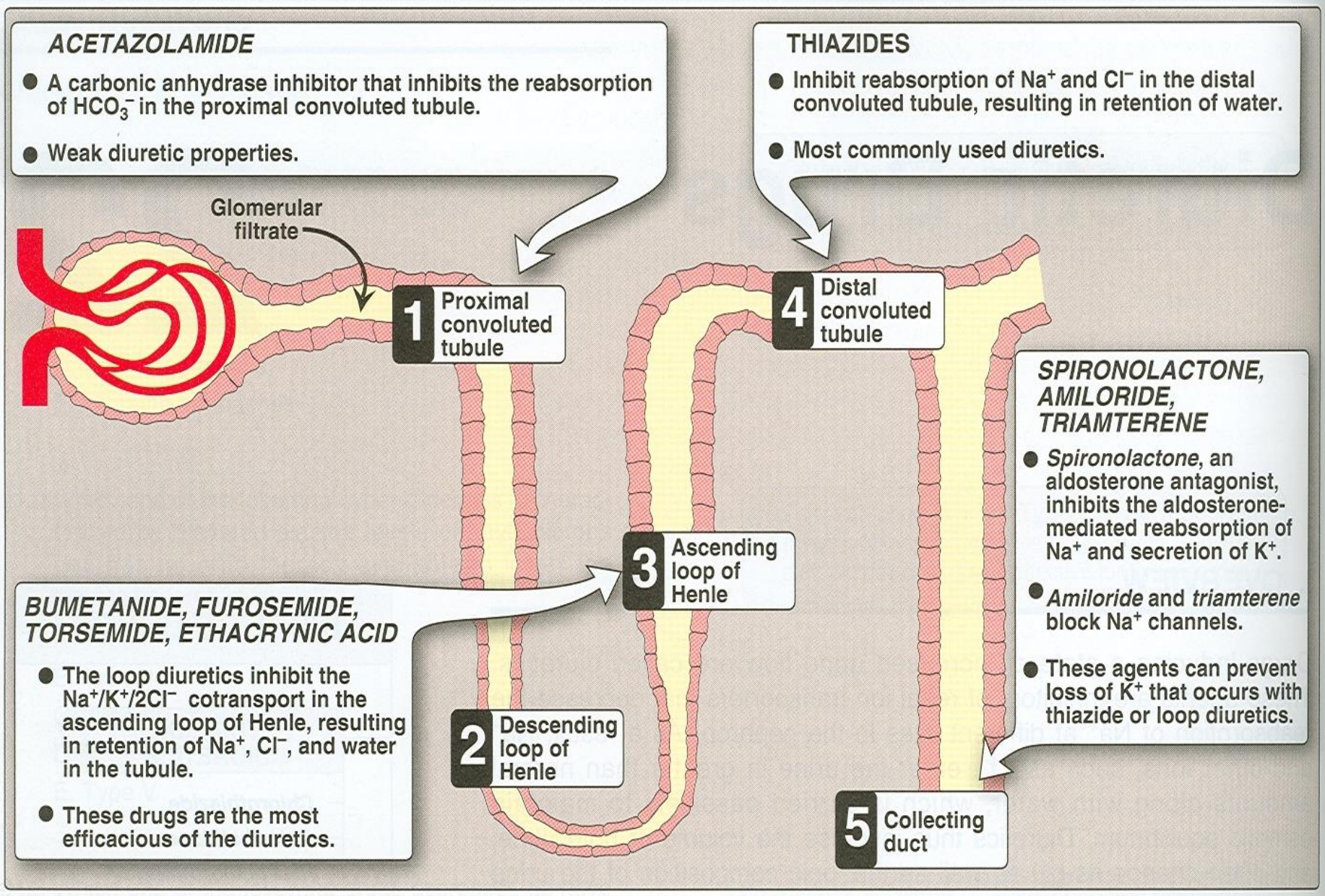


Figure 22.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

A. Diuretics that inhibit transport in the Convoluted Proximal Tubule

1. Osmotic Diuretics (e.g.: Mannitol)

Mechanism of action: They are hydrophilic compounds that are easily filtered through the glomerulus with little re-absorption and thus increase urinary output via osmosis.

PK: Given parenterally. If given orally it will cause osmotic diarrhea.

Indications:

- to decrease intracranial pressure in neurological condition
- to decrease intraocular pressure in acute glaucoma
- to maintain high urine flow in acute renal failure during shock

Adverse Reactions:

- Extracellular water expansion may complicate heart failure and produce pulmonary edema.
- Dehydration
- Hypernatremia due to loss more water than sodium

Contraindications: 1- heart failure

2- renal failure

2. Carbonic Anhydrase Inhibitors

(Acetazolamide (Oral) ; Dorzolamide (Ocular) ; Brinzolamide (Ocular)

Mechanism of action Simply inhibit reabsorption of sodium and bicarbonate.

- Inhibition of HCO_3 reabsorption → metabolic acidosis.
- HCO_3 depletion → enhance reabsorption of Na and Cl → hyperchloremea.
- Reabsorption of Na → ↑ negative charge inside the lumen → ↑K secretion

Clinical uses of carbonic anhydrase inhibitors

- Weak diuretic : because depletion of HCO_3 → enhance reabsorption of Na and Cl

- In glaucoma :

✓The ciliary process absorbs HCO_3 from the blood.

✓ ↑HCO_3 → ↑aqueous humor.

✓Carbonic anhydrase inhibitors prevent absorption of HCO_3 from the blood.

- Urinary alkalinization : to increase renal excretion of weak acids e.g.cystin and uric acid.

- In metabolic alkalosis.

- Epilepsy : because acidosis results in ↓seizures.

- Acute mountain sickness.

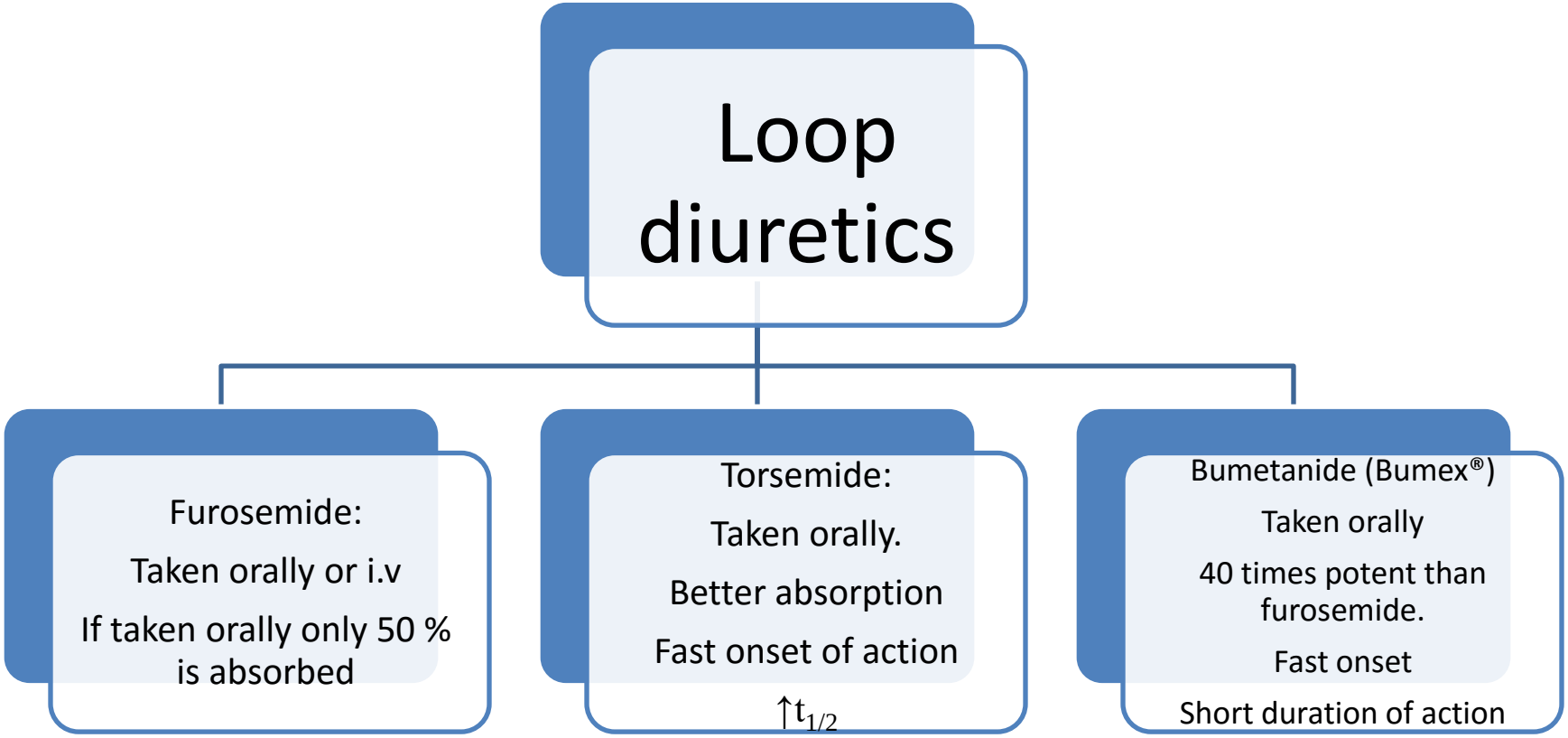
- Benign intracranial hyper tension.

Dorzolamide and brinzolamide are mixed with β blockers (Timolol) to treat glaucoma (as topical drops)

►Side Effects of Acetazolamide:

- Sedation and drowsiness;
- Hypersensitivity reaction (because it contains sulfur)
- Acidosis (because of decreased absorption of HCO_3),
- Renal stone (because of alkaline urine);
- Hyperchloremia,
- hyponatremia and
- hypokalemia

B. Diuretics Acting on the Thick Ascending Loop of Henle (loop diuretics) High ceiling (most efficacious)



- e.g. Furosemide (Lasix^{R}), Torsemide, Bumetanide (Bumex^{R}), Ethacrynic acid.

- **Pharmacodynamics:**

1) **Mechanism of Action** : Simply inhibit the coupled Na/K/2Cl cotransporter in the loop of Henle. Also, they have potent pulmonary vasodilating effects (via prostaglandins).
2) They eliminate more water than Na.
3) They induce the synthesis of prostaglandins in kidney and NSAIDs interfere with this action.

They are the best diuretics for 2 reasons:

1- they act on thick ascending limb which has large capacity of reabsorption.

2- action of these drugs is not limited by acidosis

LOOP DIURETICS

- Secreted in proximal tubule by acid mechanisms
- Act on the ascending loop of Henle to inhibit sodium and chloride transport
- Cause a **greater natriuresis than thiazides**
- Effective at low glomerular filtration rates (as occur in chronic renal failure), where thiazides are ineffective
- Increase potassium, **calcium** and magnesium excretion
- Decrease urate excretion
- Impair maximal concentrating and diluting capacity

LOOP DIURETICS

- Additional non-tubular effects
    1. Renal Vasodilation and redistribution of blood flow
    2. Increase in renin release
    3. Increase in venous capacitance

These effects mediated by release of prostaglandins from the kidney.

CLINICAL USES OF LOOP DIURETICS

- **EDEMA** due to CHF, nephrotic syndrome or cirrhosis
- Acute heart failure with **PULMONARY EDEMA**
- **HYPERCALCEMIA**
- not in widespread use for the treatment of hypertension (except in a few special cases e.g. hypertension in renal disease)
- **Acute renal failure**
- **Hyperkalemia**

Adverse Effects of Loop Diuretics

similar to thiazides in many respects

- Hypokalemia, metabolic alkalosis, hypercholesterolemia, hyperuricemia, hyperglycemia, hyponatremia, hypomagnesemia; hypochloremia; Hypovolemia

- **Dehydration** and postural hypotension
- **Hypocalcemia** (in contrast to thiazides)
- **Hypersensitivity (contain sulfur)**
- **OTOTOXICITY** (especially if given by rapid IV bolus)

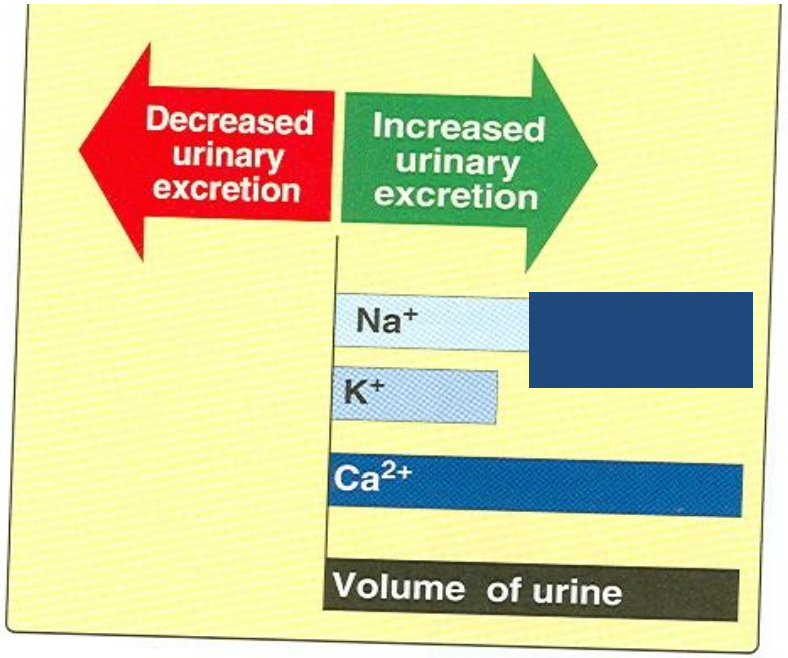


Figure 22.6
Relative changes in the composition of urine induced by loop diuretics.

C. Diuretics that Inhibit Transport in the Distal Convoluted Tubule (e.g.: Thiazides and Thiazide-like (Indapamide; Metolazone)

- Pharmacodynamics:
  - Mechanism of action: Inhibit Na^+ via inhibition of Na^+/Cl^- cotransporter.
  - They have natriuretic action.

CLINICAL USES Of THIAZIDES-1

1) HYPERTENSION

- Thiazides reduce blood pressure and associated risk of CVA and MI in hypertension
- they should be considered first-line therapy in hypertension (effective, safe and cheap)
- Mechanism of action in hypertension is uncertain – involves vasodilation that is not a direct effect but a consequence of the diuretic/natriuretic effect
- Hydrochlorthiazide; Indapamide (Natrilex^{R})

CLINICAL USES OF THIAZIDES-2

2) **EDEMA** (cardiac, liver renal) Edema(doesn't respond well to ordinary treatment) together with the Loop diuretics (Metolazone)

3) **IDIOPATHIC HYPERCALCIURIA**

- condition characterized by recurrent stone formation in the kidneys due to excess calcium excretion
- thiazide diuretics used to prevent calcium loss and protect the kidneys

4) **DIABETES INSIPIDUS**

ADVERSE EFFECTS OF THIAZIDES-1

Initially, they were used at high doses which caused a high incidence of adverse effects. Lower doses now used cause fewer adverse effects. Among them are:

- **HYPOKALEMIA**
- **DEHYDRATION** (particularly in the elderly) leading to POSTURAL HYPOTENSION
- **HYPERGLYCEMIA** possibly because of impaired insulin release secondary to hypokalemia (due to both impaired pancreatic release of insulin and diminished utilization of glucose)
- **HYPERURICEMIA** because thiazides compete with urate for tubular secretion

ADVERSE EFFECTS OF THIAZIDES-2

- **HYPERLIPIDEMIA**; mechanism unknown but cholesterol increases usually trivial (1% increase)
- **IMPOTENCE**
- **HYPONATREMIA** due to thirst, sodium losloss, inappropriate ADH secretion (can cause confusion in the elderly), usually after prolonged use

ADVERSE EFFECTS OF THIAZIDES-3

Less common problems

- **HYPERSENSITIVITY** - may manifest as interstitial nephritis, pancreatitis, rashes, blood dyscrasias (all very rare)
- **METABOLIC ALKALOSIS** due to increased sodium load at the distal convoluted tubule which stimulates the sodium/hydrogen exchanger to reabsorb sodium and excrete hydrogen
- **HYPERCALCEMIA** due to ↑PTH

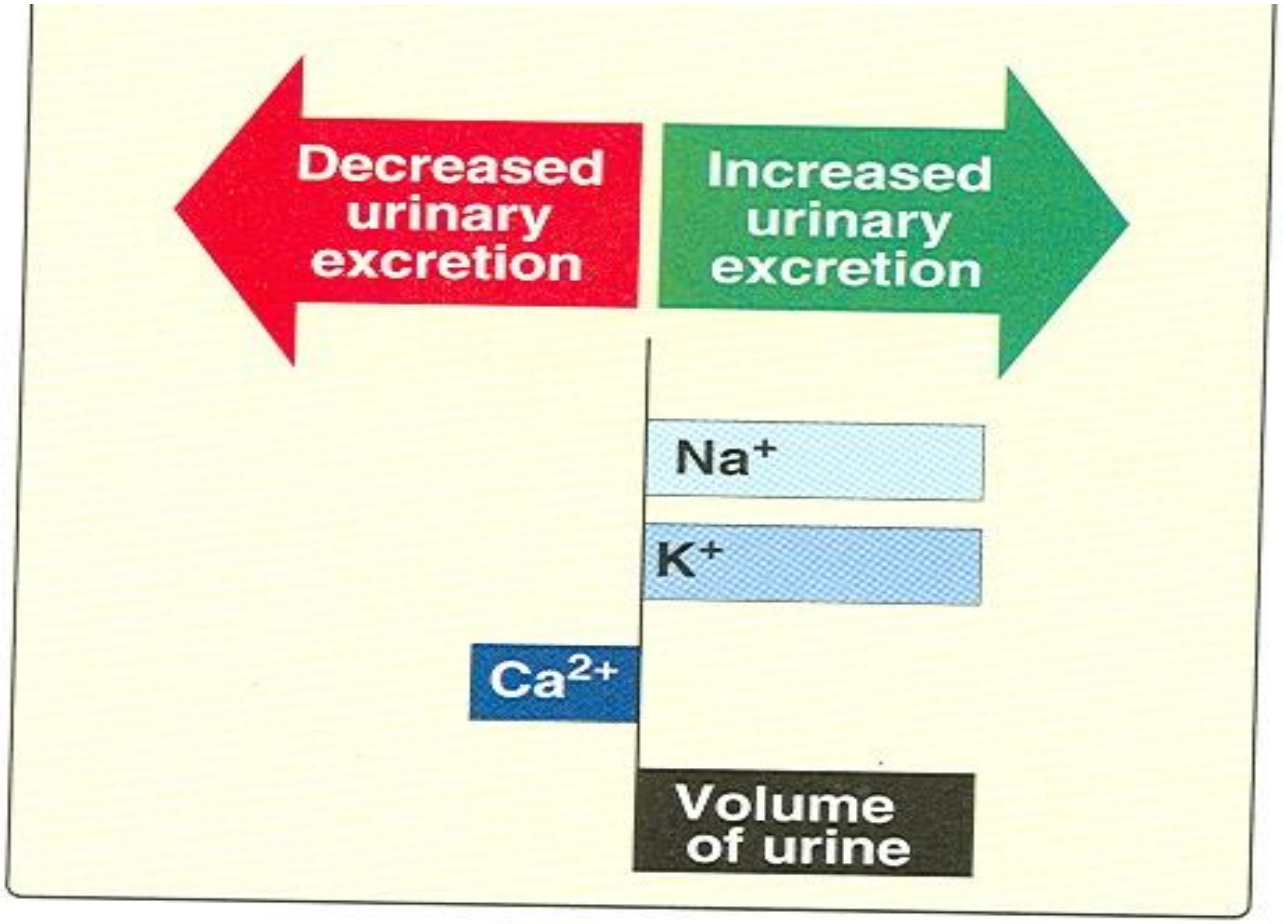
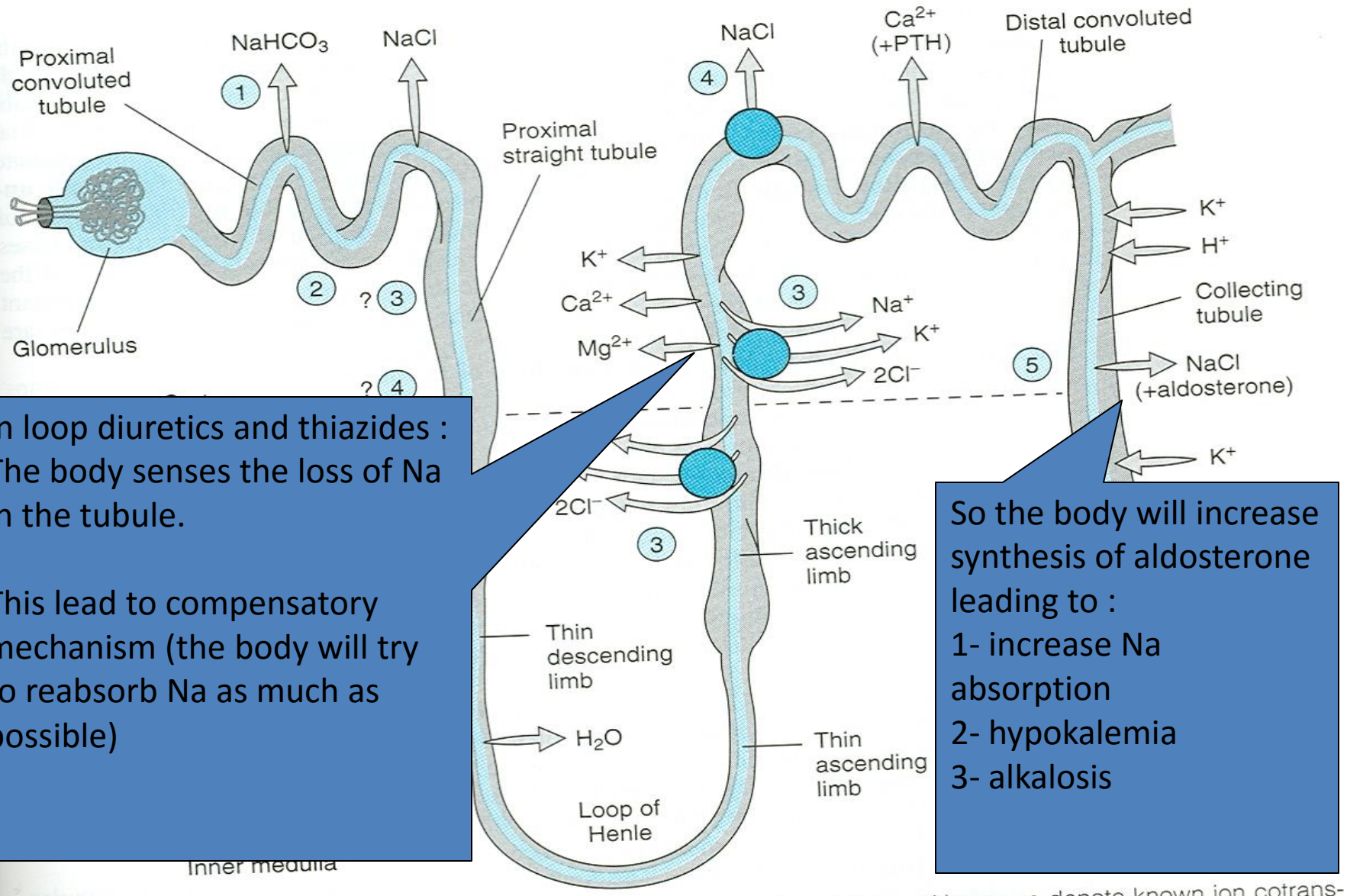


Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.



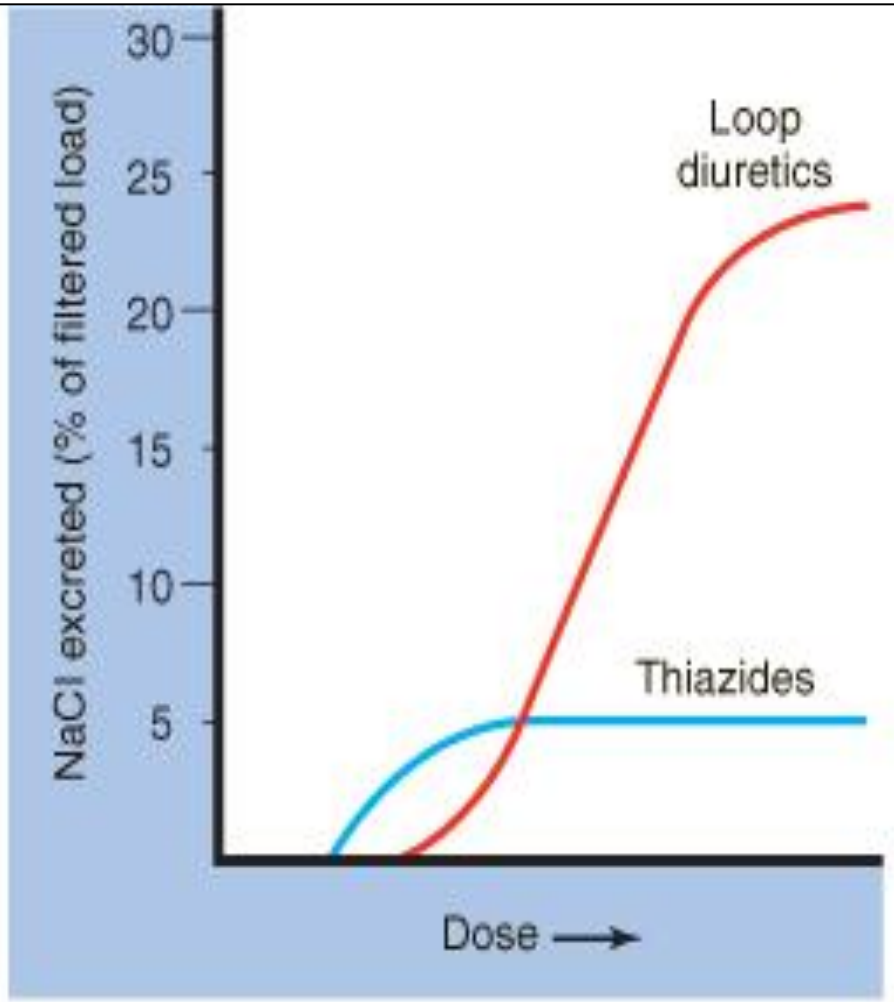
In loop diuretics and thiazides :
The body senses the loss of Na in the tubule.

This lead to compensatory mechanism (the body will try to reabsorb Na as much as possible)

So the body will increase synthesis of aldosterone leading to :
1- increase Na absorption
2- hypokalemia
3- alkalosis

Figure 15–2. Tubule transport systems and sites of action of diuretics. Circles with arrows denote known ion cotransporters that are targets of the diuretics indicated by the numerals. Question marks denote preliminary or incompletely documented suggestions for the location of certain drug effects. (Reproduced, with permission, from Katzung BG [editor]: *Basic & Clinical Pharmacology*, 8th ed. McGraw-Hill, 2001.)

Comparison of loop and thiazide diuretics



►D. Diuretics that inhibit transport in the Cortical Collecting Tubule (e.g. potassium sparing diuretics).

Classification of Potassium Sparing Diuretics:

A) Direct antagonist of mineralocorticoid receptors (Aldosterone Antagonists e.g spironolactone (Aldactone^{R}) or

B) Indirect via inhibition of Na^{+} influx in the luminal membrane (e.g. Amiloride, Triametrene)

THEY ARE VERY IMPORTANT TO BALANCE K^{+} IN THE BODY

Spironolactone (Aldactone^{R})

- **Synthetic steroid acts as a competitive antagonist of aldosterone with a slow onset of action.**
- **Mechanism of action: Aldosterone cause ↑K and H^{+} secretion and ↑Na reabsorption.**
- **The action of spironolactone is the opposite**

Clinical Uses of K^+ sparing Diuretics:

- In states of primary aldosteronism (e.g. Conn's syndrome, ectopic ACTH production) and secondary aldosteronism (e.g. heart failure, hepatic cirrhosis, nephrotic syndrome)
- To overcome the hypokalemic action of diuretics
- Hirsutism (the condensation and elongation of female facial hair) because it is an antiandrogenic drug.

Side effects:

- Hyperkalemia (some times it's useful other wise it's a side effect).
- Hyperchloremic (it has nothing to do with Cl) metabolic acidosis
- Antiandrogenic effects (e.g. gynecomastia: breast enlargement in males, impotence) by spironolactone.
- Triametrene causes kidney stones.

- **Diuretics Combination preparations**
  these are anti-hypertensive drugs:
  Dyazide^{R} = Triametrene 50 mg + Hydrochlorothiazide HCT 25 mg
  Aldactazide^{R}= Spironolactone 25 mg + HCT 25 mg
  Moduretic^{R} = Amiloride 5 mg + HCT 50 mg

- Note : HCT to decrease hypertension and K sparing diuretics to overcome the hypokalemic effect of HCT

- Contraindications: Oral K administration and using of ACE inhibitors

Types and Names of Diuretics

Type	Example	Sites of Action
Osmotic agents	Mannitol	Proximal tubule Descending loop Collecting duct
Carbonic anydrase inhib.	Acetazolamide	Proximal tubule
Thiazides	Hydrochlorothiazide	Distal convoluted tubule
Loop diuretic	Ethacrynic acid Furosemide	Loop of Henle
K^+ - sparing	Spironolactone Amiloride	Collecting tubule

Table 15–2. Electrolyte changes produced by diuretic drugs.

Drug Group	Urine			Body pH
	NaCl	$NaHCO_3$	K^+	
Carbonic anhydrase inhibitors	↑	↑↑↑	↑	Acidosis
Loop diuretics	↑↑↑↑	—	↑	Alkalosis
Thiazides	↑↑	—	↑	Alkalosis
Potassium-sparing diuretics	↑	—	↓	Acidosis

References

- **Prof. A. Alhaider, lecture notes**
- **Lipincott's Pharmacology 5th edition**