Diuretic Agents Part-1

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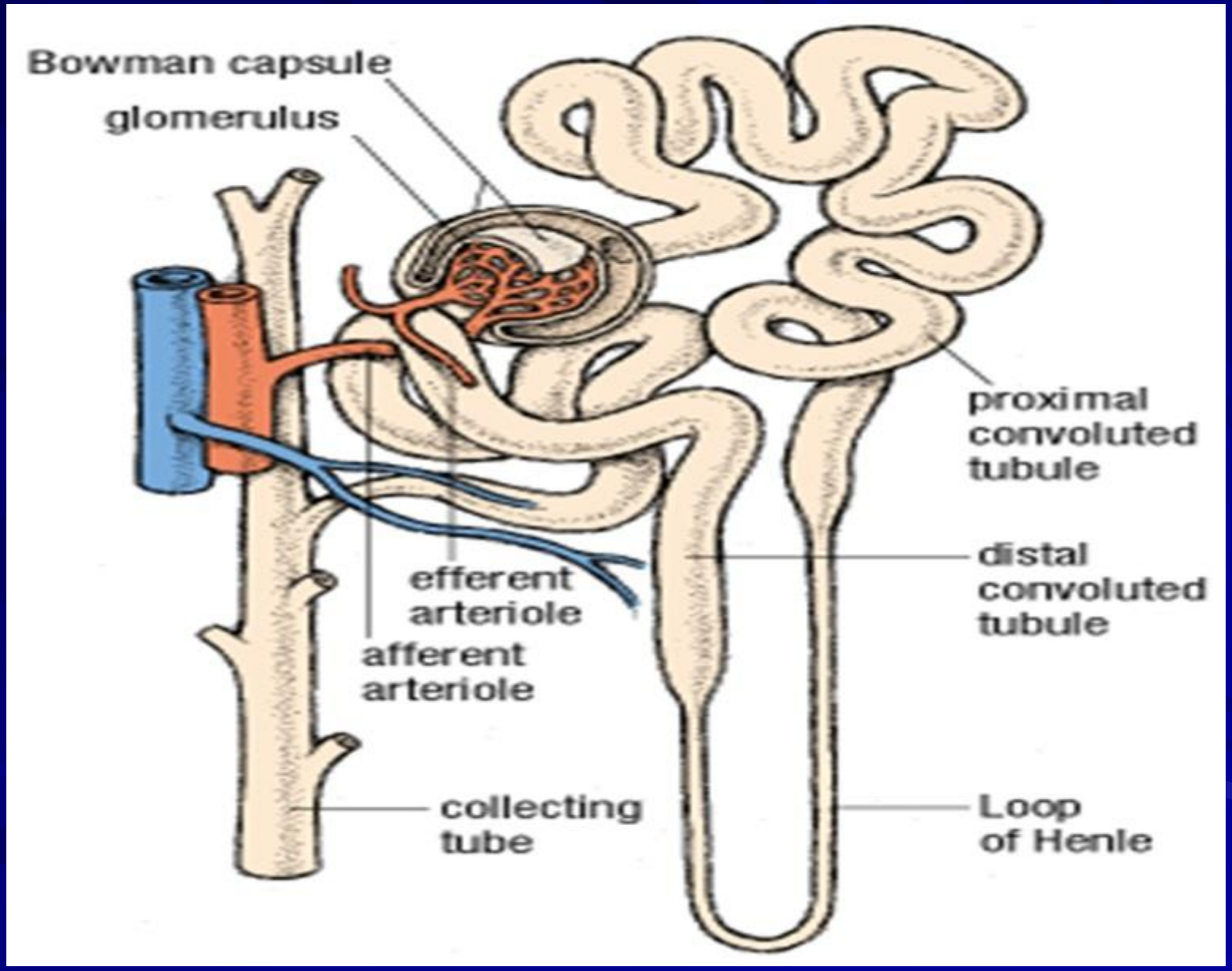
- Kidneys eliminates waste products and regulates the volume, electrolyte and pH of the extracellular fluid
- Approximately 16-20% of the blood plasma entering kidneys is filtered from glomerular capillaries into Bowman capsule.
- The filtrate normally free from proteins and blood cells, it contain most low-molecular-weight plasma components in approximately same concentrations as are found in plasma.

- These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na+, K+, and Cl-.
- The kidney regulates ionic composition and volume of urine by the active reabsorption or secretion of ions and/or the passive reabsorption of water at five functional zones along the nephron
- Kidney is main organ by which drugs are eliminated.
- In the presence of renal failure dose must be adjusted

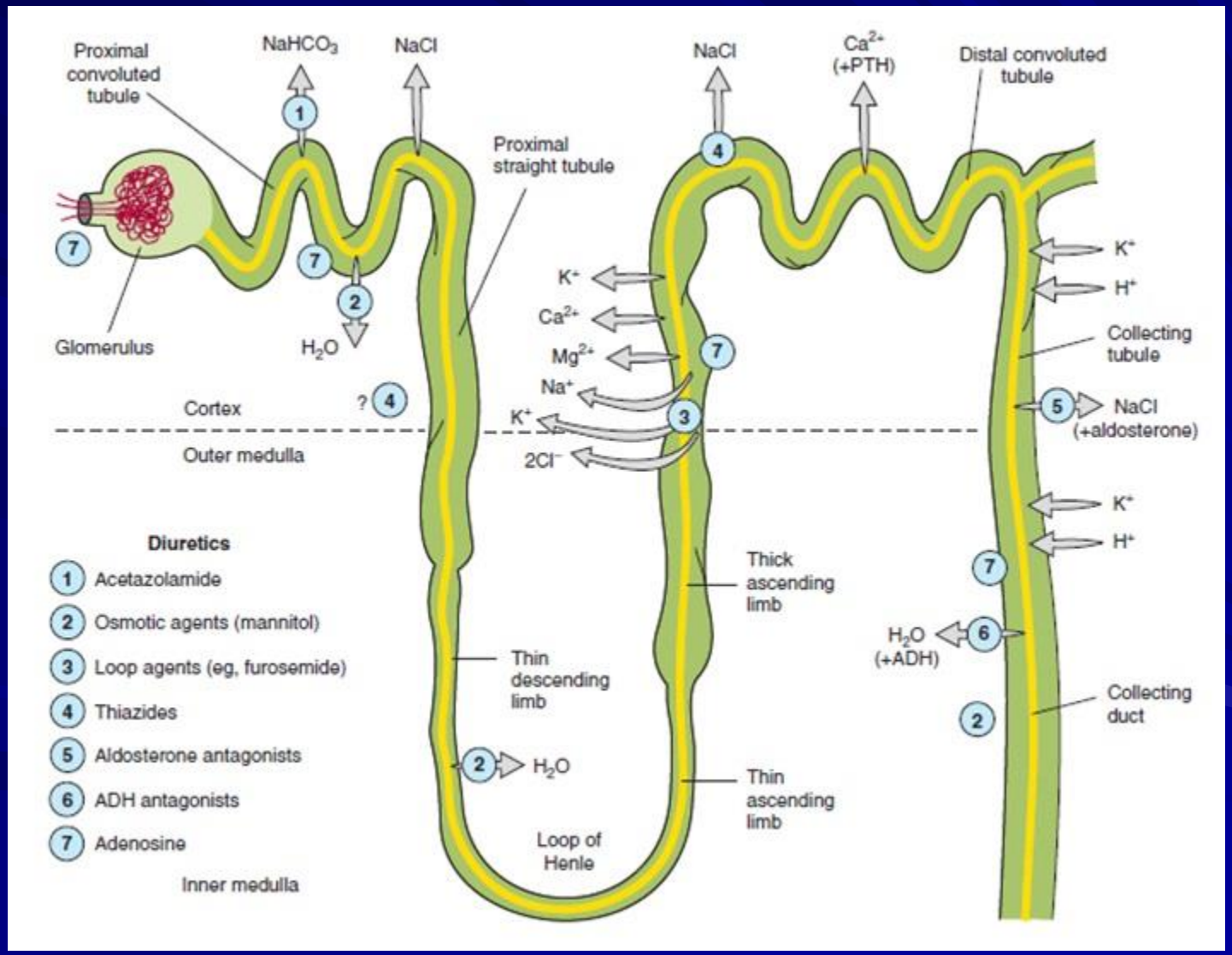

Bowman capsule
glomerulus
proximal convoluted tubule
distal convoluted tubule
efferent arteriole
afferent arteriole
collecting tube
Loop of Henle

- Diuretic is an agent that increases urine volume
- Natriuretic is an agent that causes an increase in renal sodium excretion , they called diuretic (increase water excretion)

Diuretic Drugs

Thiazide Diuretics	Chlorothiazide ,Chlorthalidone Hydrochlorothiazid, Indapamide, Metolazone
Loop Diuretics	Bumetanide ,Ethacrynic Acid Furosemide, Torsemide
Potassium-Sparing Diuretics	Amiloride ,Spironolactone, Triamterene
Carbonic Anhydrase Inhibitors	Acetazolamide
Osmotic Diuretics	Mannitol

Tubule transport systems and sites of action of diuretics ADH, antidiuretic hormone; PTH, parathyroid hormone.



Carbonic Anhydrase Inhibitors

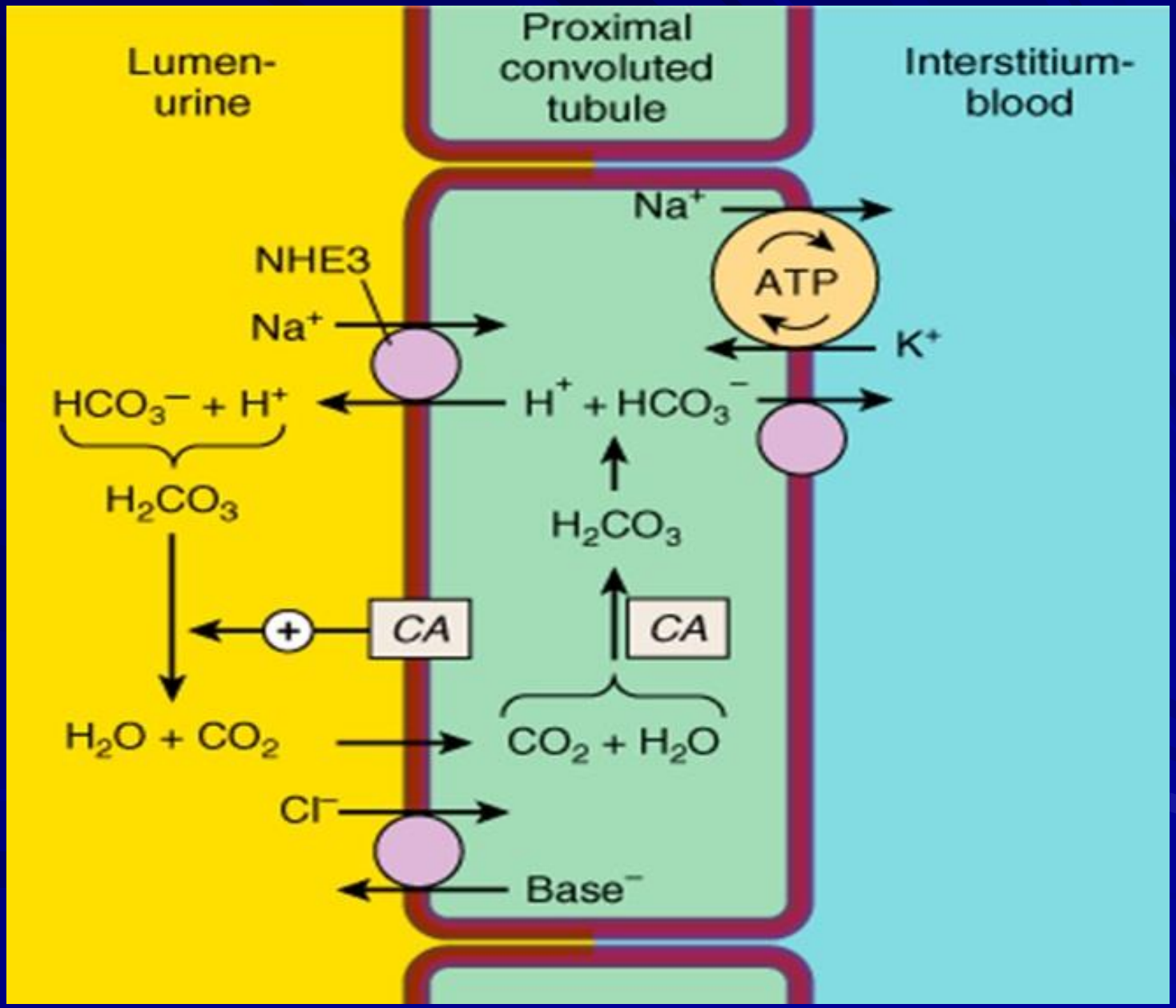
Acetazolamide

- They are now rarely used as diuretics because they are much less efficacious than the thiazides or loop diuretics
- Carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect
- Acetazolamide inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells.

Mechanism of Action

- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- Carbonic anhydrase catalyzes the reaction of CO_2 (carbon dioxide) and H_2O, leading to H_2CO_3 (carbonic acid). which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate)

- The decreased ability to exchange Na+ for H+ in the presence of acetazolamide results in a mild diuresis. Additionally, $HCO3^-$ is retained in the lumen, with marked elevation in urinary pH.
- The loss of HCO3- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy


Lumen-
urine
Proximal
convoluted
tubule
Interstitium-
blood
Na+
NHE3
Na+
ATP
K+
HCO3− + H+
H+ + HCO3−
H2CO3
H2CO3
CA
CA
H2O + CO2
CO2 + H2O
Cl−
Base−

Pharmacokinetics

- Acetazolamide is given orally once a day.
- An increase in urine pH from the HCO_3^- diuresis is apparent within 30 minutes, is maximal at 2 hours, and persists for 12 hours after a single dose
- The drug excretion is by secretion in the proximal tubule
- Dosing must be reduced in renal insufficiency

Clinical Uses

- Treatment of glaucoma
- Enhancement renal excretion of weak acids by urine alkalinization
- Metabolic Alkalosis
- Mountain sickness

Treatment of Glaucoma

- Acetazolamide decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary body of the eye (reducing elevated intraocular pressure).
- It is useful in the chronic treatment of glaucoma but should not be used for an acute attack; pilocarpine is preferred for an acute attack because of its immediate action.
- Topical carbonic anhydrase inhibitors, such as dorzolamide and brinzolamide, have the advantage of not causing any systemic effects

Enhancement renal excretion of weak acids by urine alkalinization

- Uric acid, cystine, and other weak acids are most easily reabsorbed from acidic urine. Therefore, renal excretion of weak acids can be enhanced by increasing urinary pH with carbonic anhydrase inhibitors

Mountain Sickness

- Acetazolamide can be used in the prophylaxis of acute mountain sickness among healthy individuals who ascend above 10,000 feet.
- Acetazolamide given nightly for five days before the ascent
- It prevents the weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema
- By decreasing cerebrospinal fluid (CSF) formation &by decreasing the pH of the cerebrospinal fluid
- Acetazolamide can increase ventilation and diminish symptoms of mountain sickness

Adverse Effects

1. Metabolic acidosis (mild) , (results from chronic reduction of body HCO_3^- stores)
2. Renal potassium depletion (hypokalemia) Because the increased Na^+ presented to the collecting tubule (with HCO_3^-) is partially reabsorbed, increasing the lumen-negative electrical potential in that segment and enhancing K^+ secretion, this effect can be counteracted by simultaneous administration of potassium chloride
3. Renal stone formation (calcium salts are relatively insoluble at alkaline pH)

4. Drowsiness and paresthesia.
5. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+
6. Fever, rashes, bone marrow suppression, and interstitial nephritis (these drugs are sulfonamide derivatives)

Contraindications Of Carbonic Anhydrase Inhibitor

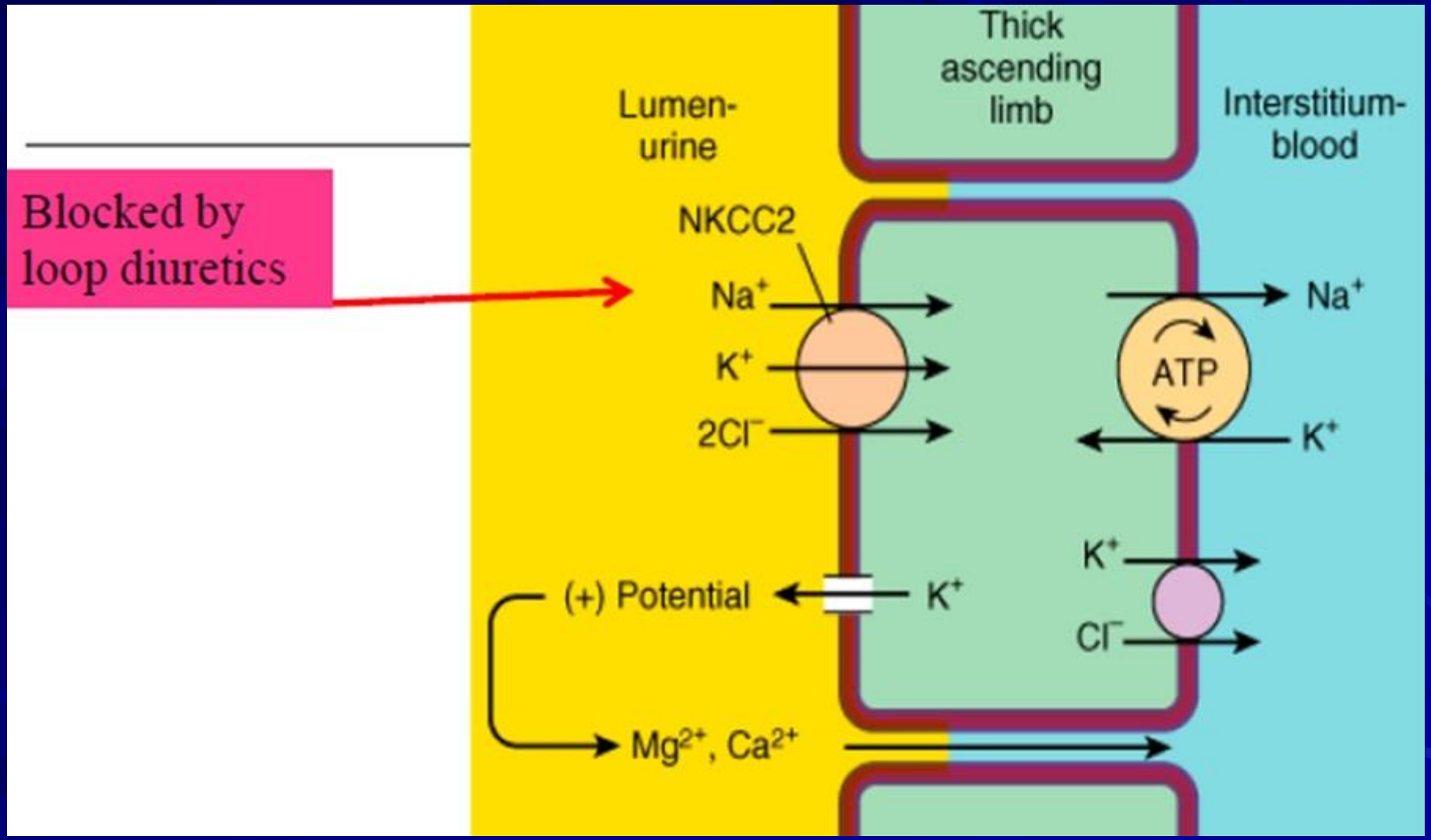
- Patients with cirrhosis

  Carbonic anhydrase inhibitor cause alkalinization of the urine which decreases urinary excretion of NH_4^+ (by converting it to rapidly reabsorbed NH_3) and development of hyperammonemia and hepatic encephalopathy

Loop Diuretics

Bumetanide, Furosemide, Torsemide And Ethacrynic Acid

- They are the most efficacious diuretic drugs
- Furosemide is the most commonly used of these drugs
- Have their major action on the ascending limb of loop of Henle.


Blocked by loop diuretics
Lumen- urine
Thick ascending limb
Interstitium- blood
NKCC2
Na+
K+
2Cl−
ATP
Na+
K+
K+
Cl−
(+) Potential
K+
Mg2+, Ca2+

- Ethacrynic acid shows greater side effects than other loop diuretics, and its use is therefore limited.
- Bumetanide is much more potent than furosemide
- Bumetanide and furosemide are sulfonamide derivatives.

Mechanism of Action of Loop Diuretics

- Inhibit cotransport of Na+/K+/ +/2Cl– by inhibiting the luminal Na+/K+/2Cl– transporter in the thick ascending limb of Henle's loop and the reabsorption of these ions is decreased

The loop diuretics act, even among patients who have poor renal function or have not responded to thiazides or other diuretics.
Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease the Ca^{2+} concentration of the urine.

- Hypocalcemia does not result in patients with normal serum Ca^{2+} concentrations because Ca^{2+} is reabsorbed in the distal convoluted tubule.
- Hypomagnesemia can occur due to loss of Mg^{2+}.

- The loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
- Loop diuretics increase prostaglandin synthesis,the PGs have a role in their diuretic action, indomethacin reduce their diuretic action

Therapeutic Uses of Loop Diuretics

1. Acute Pulmonary Edema

- The loop diuretics are the drugs of choice for reducing the acute pulmonary edema of heart failure Because of their rapid onset of action, particularly when given intravenously
- The loop diuretics cause rapid, intense diuresis.

2. **Acute Renal Failure**

   Loop agents can increase the rate of urine flow and enhance K+ excretion in acute renal failure

3. **Toxicity by Anion Overdose**

   useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the thick ascending limb of Henle's loop avoid extracellular fluid volume depletion therefore Saline solution must be administered to replace urinary losses of Na+ and Cl–

4. Hypercalcemia

- Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca2+ excretion.

5. Hyperkalemia

Pharmacokinetics of Loop Diuretics

- Administered orally or parenterally
- Their duration of action is 2-4 hours
- They are secreted into the urine.

Adverse Effects of Loop Diuretics

1. **Ototoxicity**
   - Deafness –Particularly when concomitantly with the aminoglycoside antibiotics. Ethacrynic acid is the most likely to cause deafness
   - Disturbance of Vestibular function

2. **Hyperuricemia**

Furosemide and ethacrynic acid may cause gouty attacks because they compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion .

3. Acute Hypovolemia

Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

4. Potassium Depletion

5. Hypomagnesemia

- Chronic use of loop diuretics and low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly.
- Hypomagnesemia corrected by oral supplementation.

Contraindication*:*

- Furosemide, bumetanide, and torsemide may exhibit allergic cross-reactivity in patients who are sensitive to other sulfonamides
- Overzealous use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure.

Thiazides & Related Compounds

Chlorothiazide and hydrochlorothiazide

- The thiazides are most widely used of diuretic drugs. They are sulfonamide derivatives.
- Chlorothiazide was active orally, and was capable of affecting the severe edema of cirrhosis and heart failure with a minimum of side effects.
- Hydrochlorothiazide is more potent than chlorothiazide, required lower dose

Thiazides

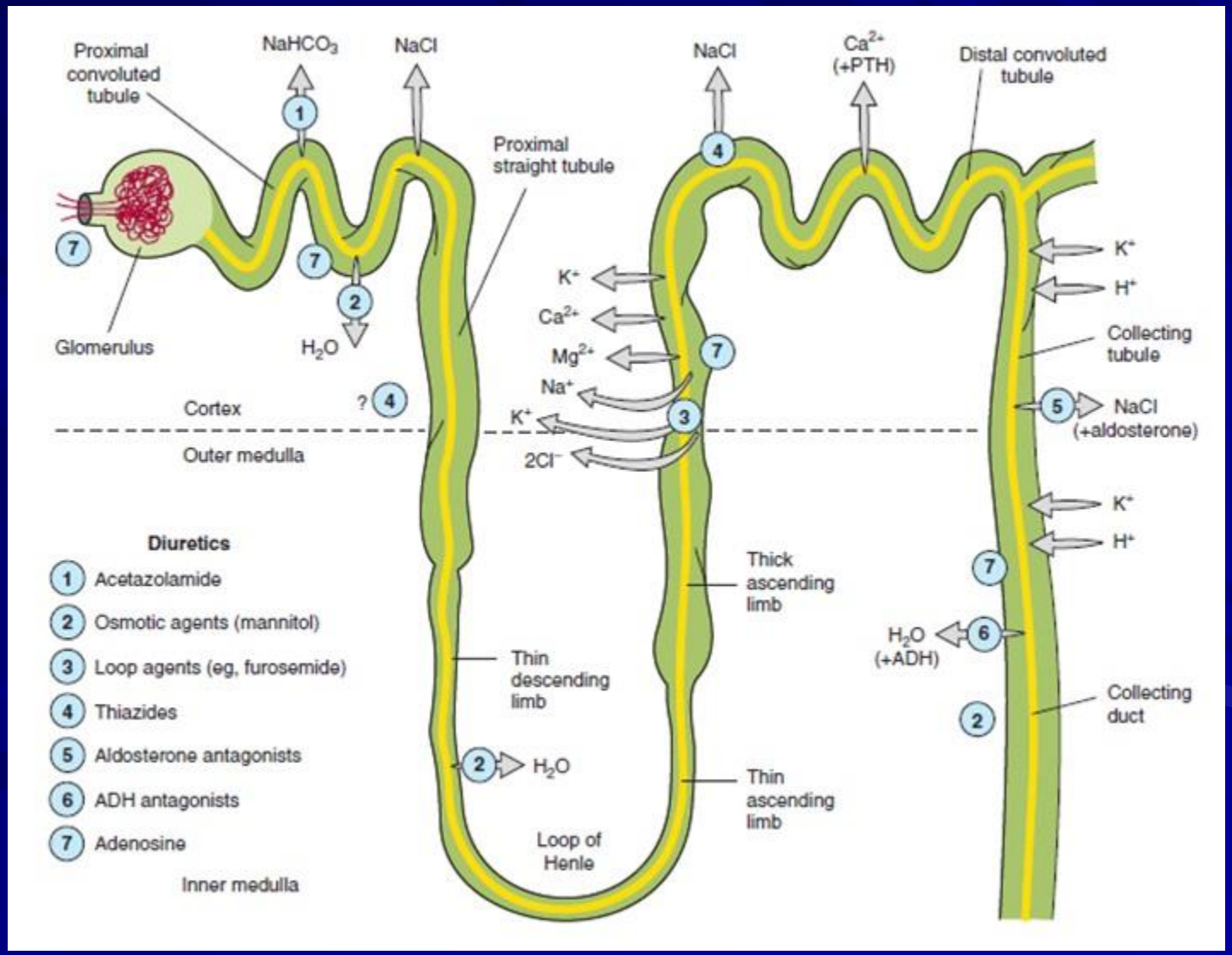
- The thiazide diuretics were discovered in 1957, as a result of efforts to synthesize more potent carbonic anhydrase inhibitors. It subsequently became clear that the thiazides inhibit NaCl, rather than $NaHCO_3$ – transport
- Their action was predominantly in the DCT, rather than the PCT.
- CHlorthalidone have significant carbonic anhydrase inhibitory activity .

Mechanism of Action

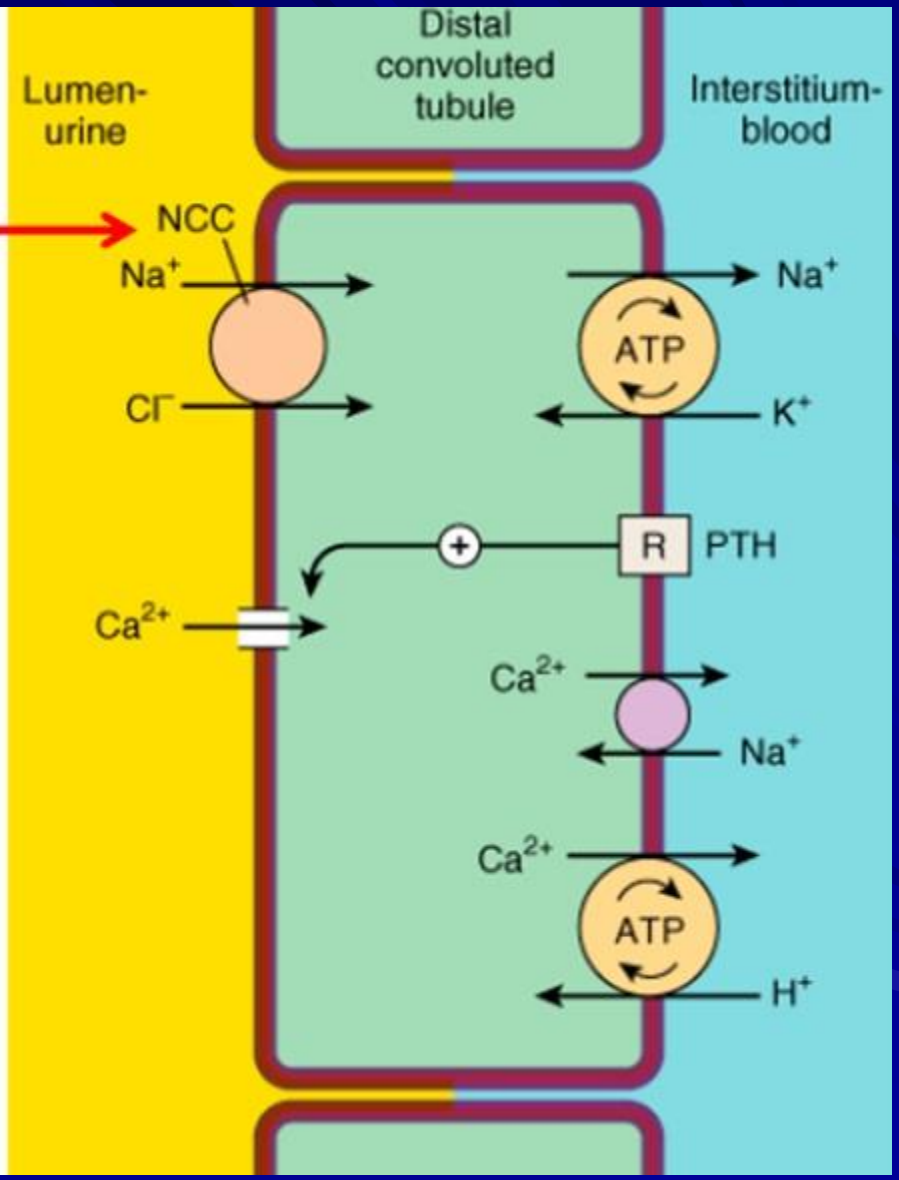
- Thiazides inhibit NaCl reabsorption from the luminal side of epithelial cells in the DCT by blocking the Na+/Cl – transporter
- Thiazides actually enhance Ca 2+ reabsorption. This enhancement result from effects in both the proximal and distal convoluted tubules.
  - In the proximal tubule, thiazide-induced volume depletion leads to enhanced Na + & passive Ca 2+ reabsorption.
  - In the DCT, lowering of intracellular Na + by thiazide-induced blockade of Na + entry enhances Na + /Ca 2+ exchange in the basolateral membrane and increases overall reabsorption of Ca 2+ .

- Thiazides rarely cause hypercalcemia as the result of this enhanced reabsorption but they can unmask hypercalcemia due to other causes (eg, hyperparathyroidism, carcinoma).
- Thiazides are useful in the treatment of kidney stones caused by hypercalciuria.
- The action of thiazides depends in part on renal prostaglandin production, thiazides can also be inhibited by NSAIDs

Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.



Blocked by thiazide diuretics



Pharmacokinetics

- Thiazides have an unsubstituted sulfonamide group
- All thiazides can be administered orally, but there are differences in their metabolism
- Chlorothiazide, the parent of the group, is not very lipid-soluble and must be given in relatively large doses. It is the only thiazide available for parenteral administration
- HCTZ is more potent and should be used in much lower doses
- Chlorthalidone is slowly absorbed and has a longer duration of action.

- Indapamide is excreted primarily by the biliary system and enough of the active form is cleared by the kidney to exert its diuretic effect in the DCT. It is therefore less likely to accumulate in patients with renal failure, and may be useful in their treatment.
- All thiazides compete with the secretion of uric acid in the proximal tubule

Clinical Indications

The major indications for thiazide diuretics are

1. Hypertension
2. Heart failure
3. Nephrolithiasis due to idiopathic hypercalciuria
4. Nephrogenic diabetes insipidus.

1. **Hypertension:**

   Thiazides are effective in reducing systolic and diastolic blood pressure for extended periods in patients with mild to moderate essential hypertension

   patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as beta-adrenergic blockers.

2. Heart Failure

Thiazide diuretics are used for the treatment of the edema associated with congestive heart failure

Note: Thiazide used for the treatment of the edema associated with hepatic cirrhosis nephrotic syndrome, chronic renal failure, and acute glomerulonephritis

3. Nephrolithiasis Due to Idiopathic Hypercalciuria

- Thiazide reduce the urinary excretion of Ca^{2+} by increase Ca^{2+} reabsorption in the distal convoluted tubule
- Used in patients with kidney stones that contain Ca^{2+} phosphate or Ca^{2+} oxalate and exhibit a defect in proximal tubular Ca^{2+} reabsorption that causes hypercalciuria

4. Nephrogenic diabetes insipidus

- Diabetes insipidus is due to either deficient production of ADH (neurogenic or central diabetes insipidus) or inadequate responsiveness to ADH (nephrogenic diabetes insipidus [NDI]).
- Administration of supplementary ADH is effective only in central diabetes insipidus.
- Thiazide diuretics can reduce polyuria and polydipsia in nephrogenic diabetes insipidus, which is not responsive to ADH supplementation.
- Lithium, used in the treatment of manic depressive disorder, is a common cause of NDI, and thiazide diuretics have been found to be very helpful in treating it

Adverse Effects

1. Hypokalemic Metabolic Alkalosis and Hyperuricemia (similar to loop diuretics)
2. Impaired Carbohydrate Tolerance
   - Hyperglycemia may occur in patients who are diabetic or have abnormal glucose tolerance tests. The effect is due to both
     - Impaired pancreatic release of insulin
     - Diminished tissue utilization of glucose.

Hyperlipidemia

- Thiazides cause a 5–15% increase in total serum cholesterol and low-density lipoproteins (LDLs).
- These levels may return toward baseline after prolonged use.

Hyponatremia

- It is caused by a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst.
- It can be prevented by reducing the dose of the drug or limiting water intake

Other Toxicities

- The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group.
- Photosensitivity, dermatitis , acute necrotizing pancreatitis.
- Hemolytic anemia, thrombocytopenia
- Weakness, fatigability, and paresthesias similar to those of carbonic anhydrase inhibitors may occur.
- Impotence related to volume depletion.

Contraindications

Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure