DIURETICS
Part 1

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KIDNEY

- Nephron is the unit of the kidney
- It is classified structurally and functionally into different zones
  - Glomerulus
  - Proximal convoluted tubule
  - Descending loop of Henle
  - Ascending loop of Henle
  - Distal convoluted tubule
  - Collecting duct

REGULATION OF FLUIDS AND ELECTROLYTES

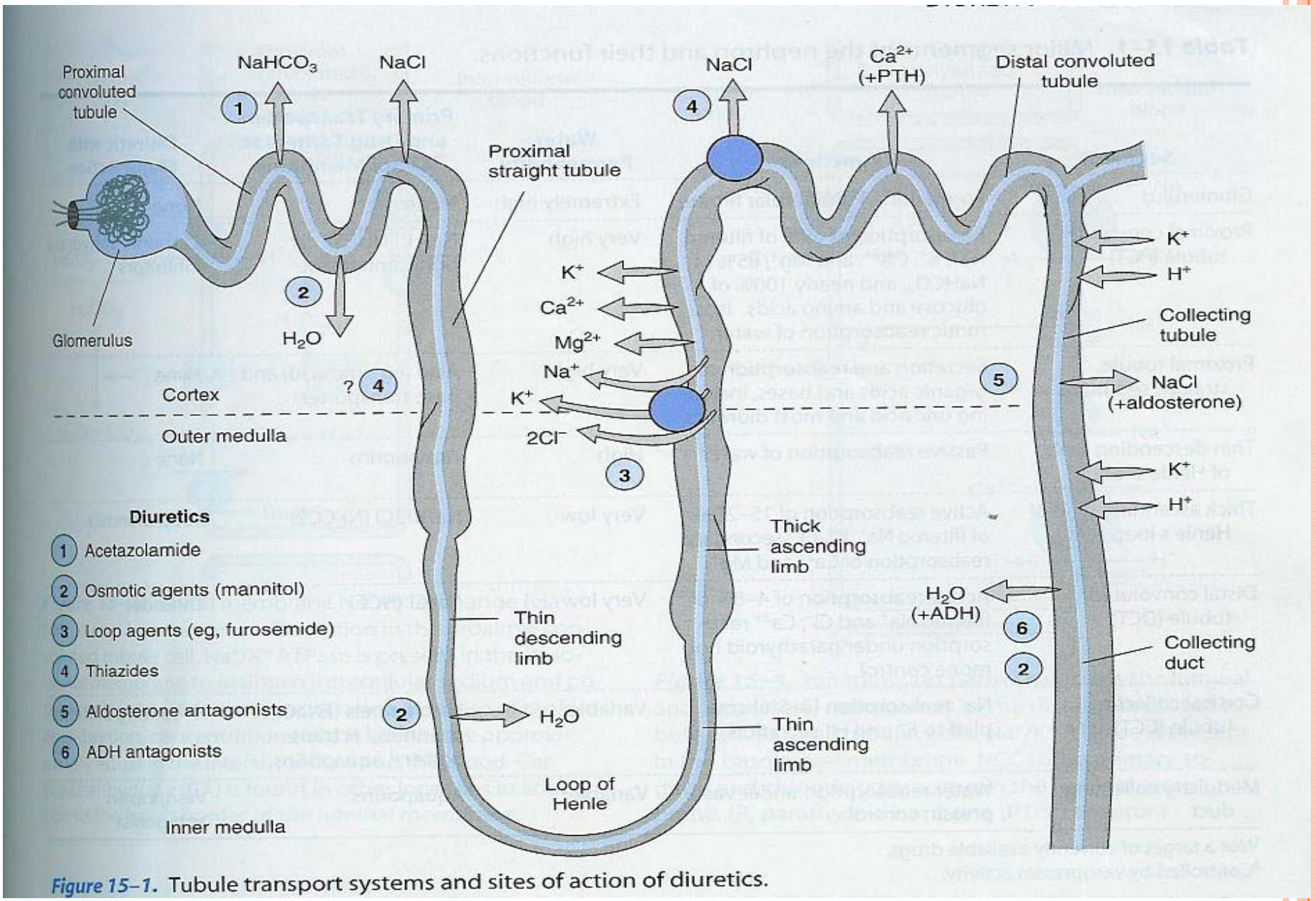
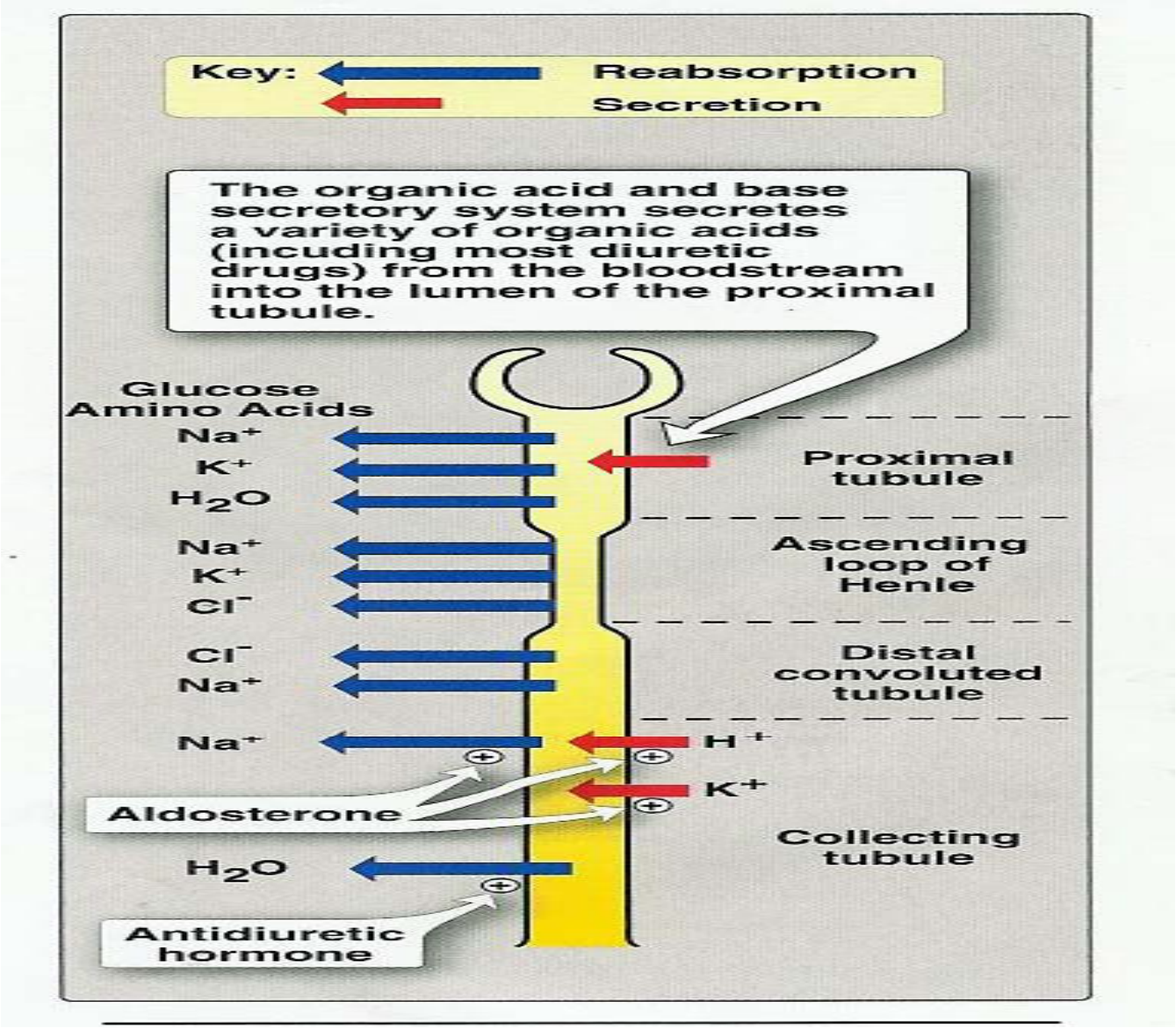


Figure 15–1. Tubule transport systems and sites of action of diuretics.

SITES FOR SOLUTES AND WATER TRANSPORT ALONG THE NEPHRON



FUNCTION OF THE KIDNEY

- **Kidney is responsible for regulation of fluids and electrolytes**
- **It controls:**
  - **volume of the urine**
  - **ionic composition of the urine**

- **Kidney do its function through three processes**
  - **Glomerular filtration**
  - **Passive tubular reabsorption**
  - **Active tubular secretion**

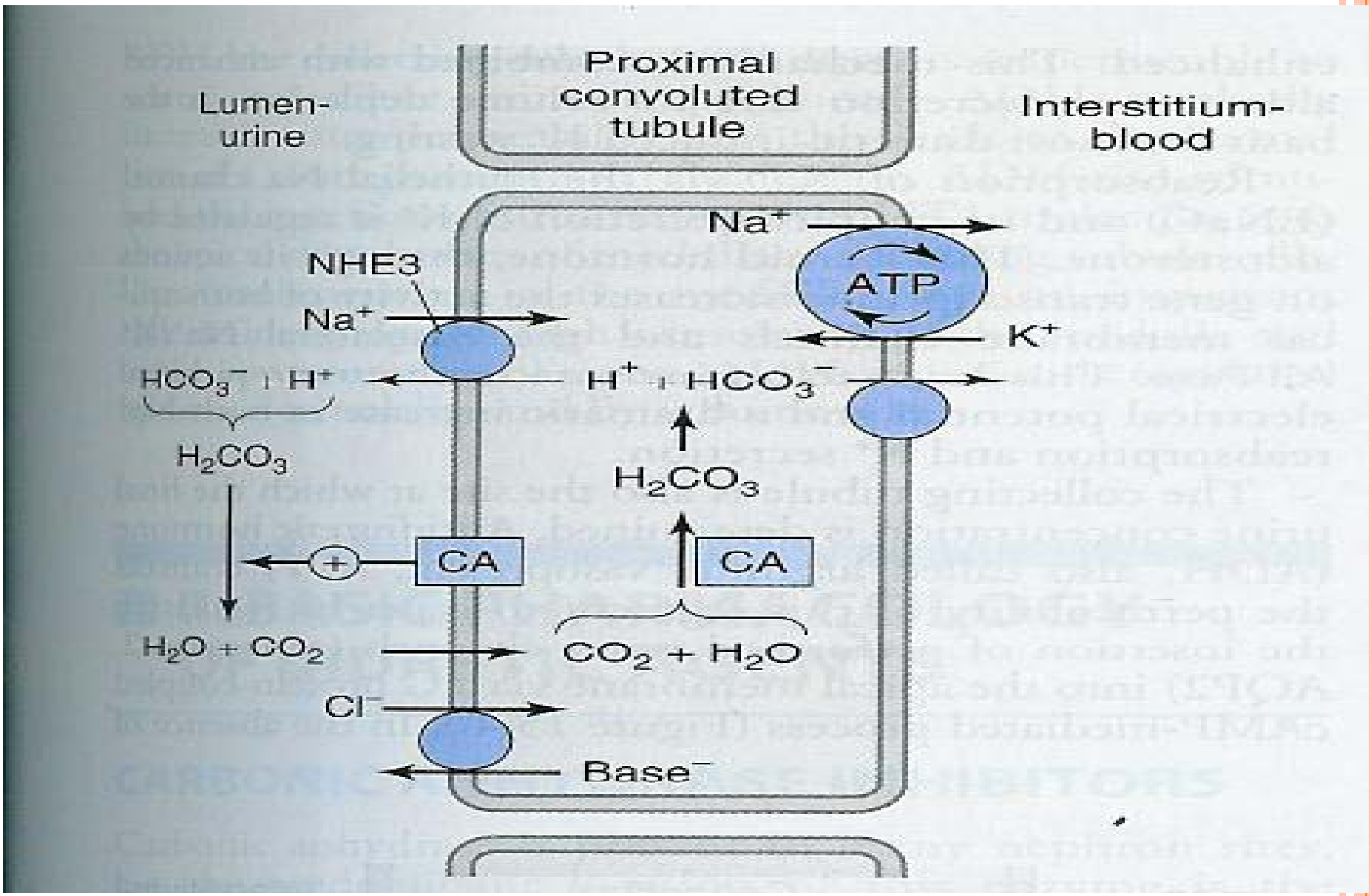
- **Glomerular filtration:**
  - **16-20 % of blood entering the kidney is filtered**
  - **Filtrate contains glucose, amino acids, sodium bicarbonates, organic solutes and electrolytes as sodium, potassium, chloride**

- **Proximal convoluted tubule:**
  - **Located in the cortex**
  - **Responsible for reabsorption of**
    - **all glucose, amino acids,**
    - **organic solutes**
    - **electrolytes as**
      - **sodium chloride (NaCl)(66% of Na)**
      - **Potassium (K^+ , 66 %)**
      - **sodium bicarbonate (NaHCO3, 85%)**

Proximal convoluted tubule:

- **$NaHCO_3$ is reabsorbed by action of enzyme carbonic anhydrase (*luminal membrane of proximal tubular cells*).**
- **water is absorbed passively following salts to maintain osmolarity in tubular fluids (60%).**
- **PCT is the site of organic acids or bases secretory systems**

CARBONIC ANHYDRASE

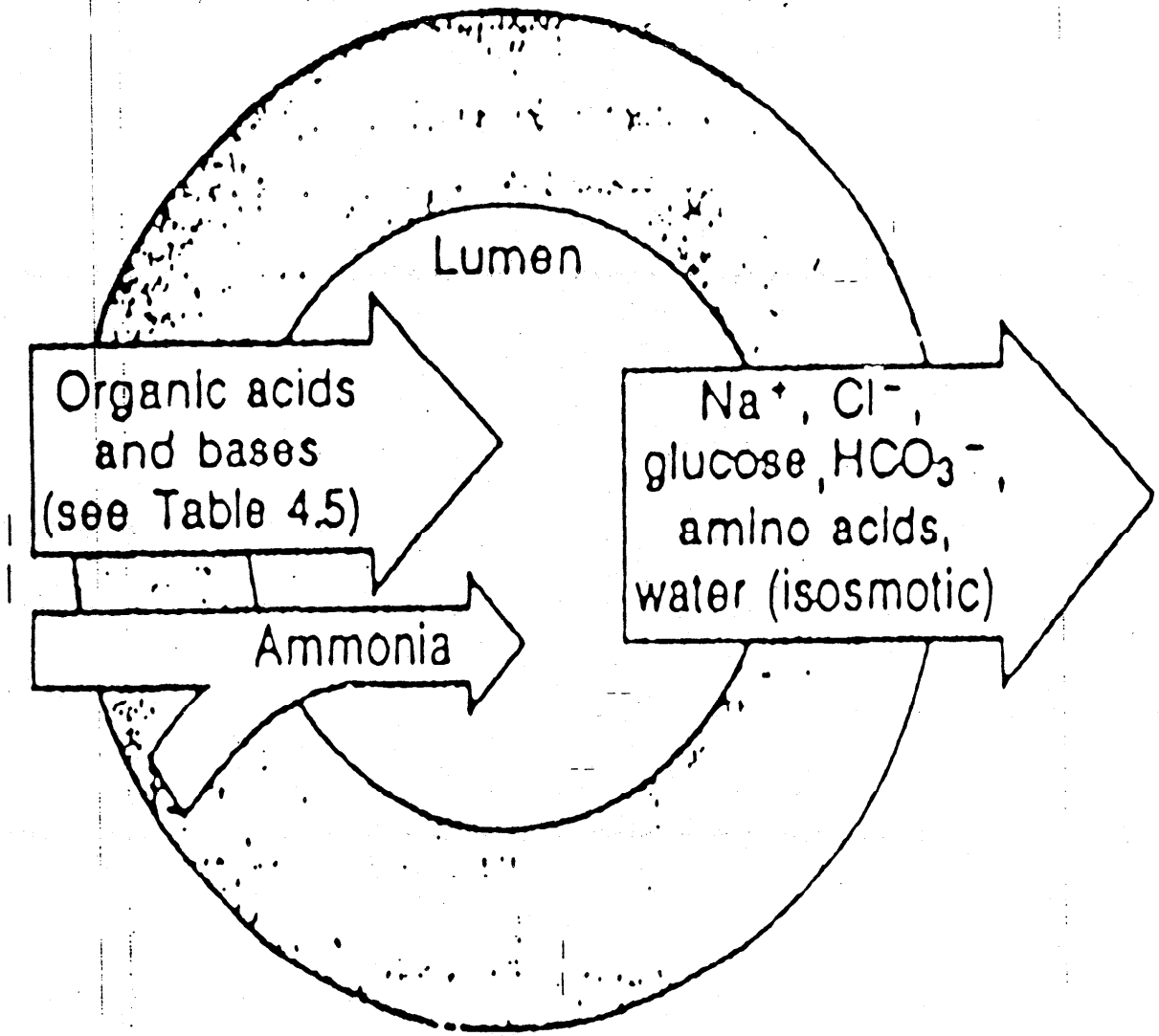


organic acids or bases secretory systems

- **Organic base secretory system**
  responsible for secretion of bases into luminal fluid e.g. choline and creatinine

- **Organic acid secretory system**
  responsible for secretion of acids into luminal tubular fluid e.g. uric acid, NSAIDs, antibiotics and diuretics.

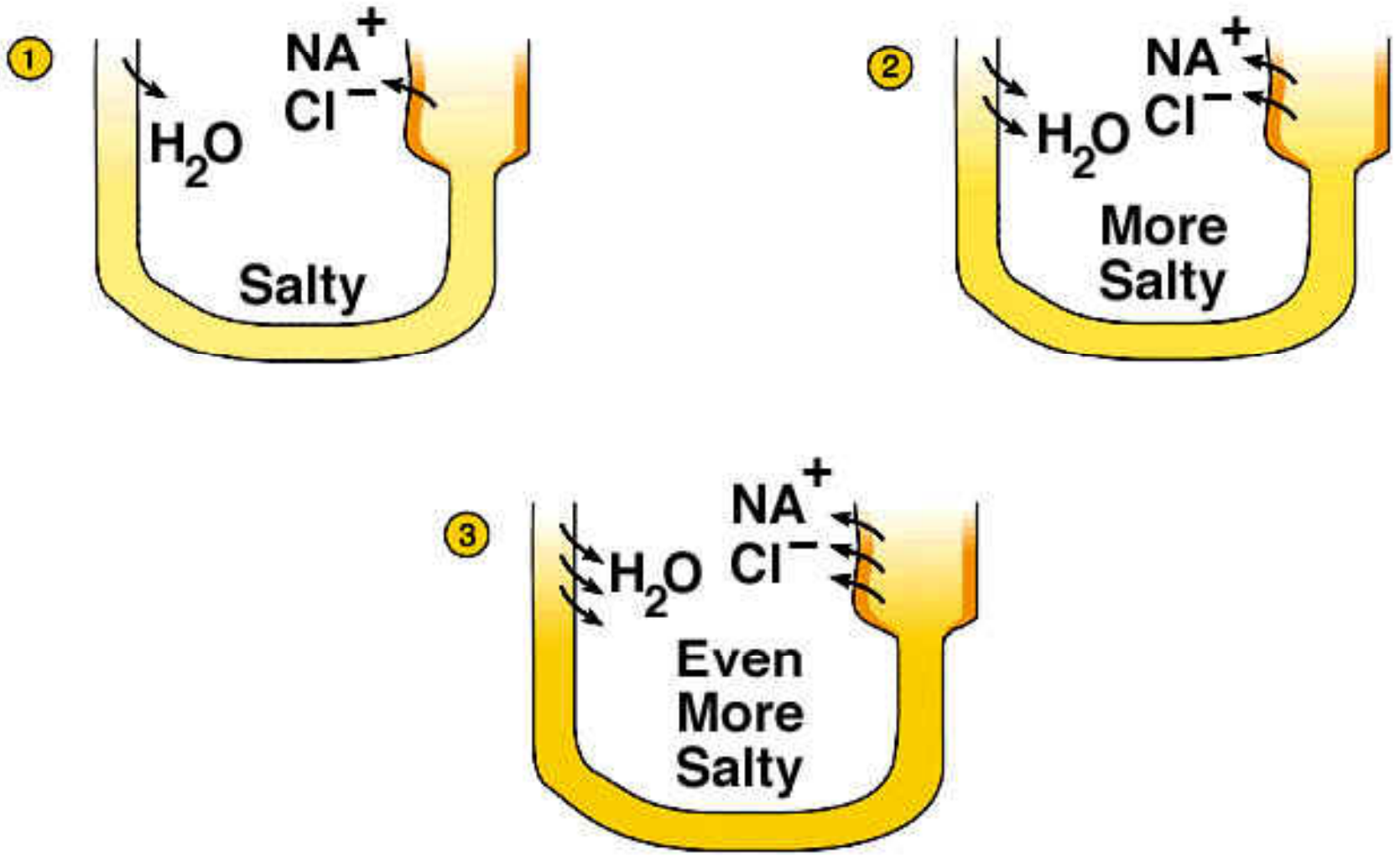
- **are saturable**


Lumen
Organic acids
and bases
(see Table 4.5)
Ammonia
Na+, Cl−,
glucose, HCO3−,
amino acids,
water (isosmotic)

Descending loop of Henle

- **Located in the medulla**
- ***In thin descending loop of Henle* : water is reabsorped by osmotic forces in hypertonic medullary interstitium (*counter current mechanism*)**
- **The filtrate (isotonic) becomes concentrated along this descending loop due to water reabsorption**
- **Diuretics *(impermeant mannitol)***

Countercurrent Mechanism



Ascending loop of Henle

- **Is impermeable to water**

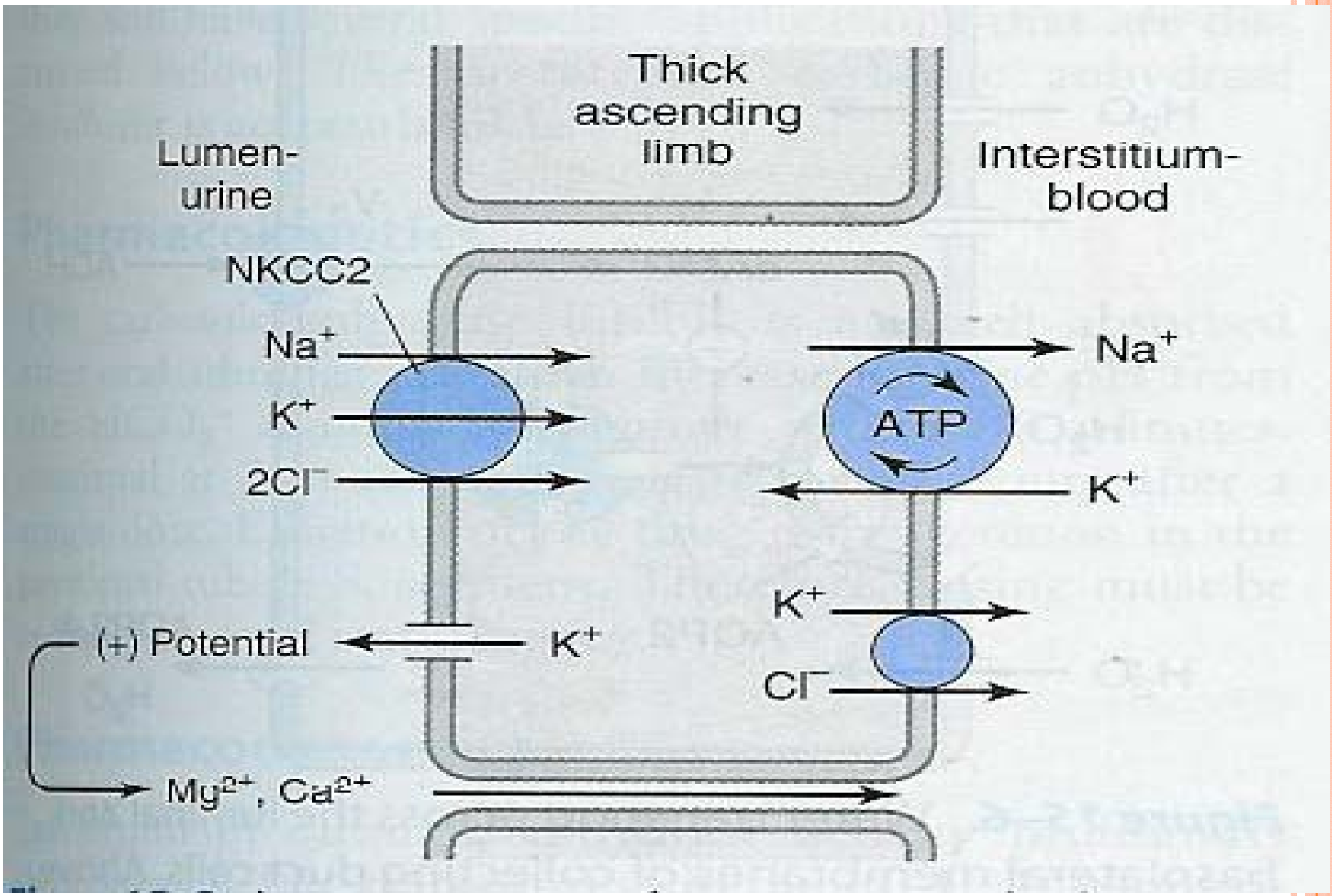
- ***In Thick ascending loop of Henle (TAL)*** **is responsible for active reabsorption of Na, K and Cl (25% of Na) via transport system in luminal membrane called Na^+/ K^+ / $2Cl^-$ co-transporter**

- **TAL is called the diluting segment**

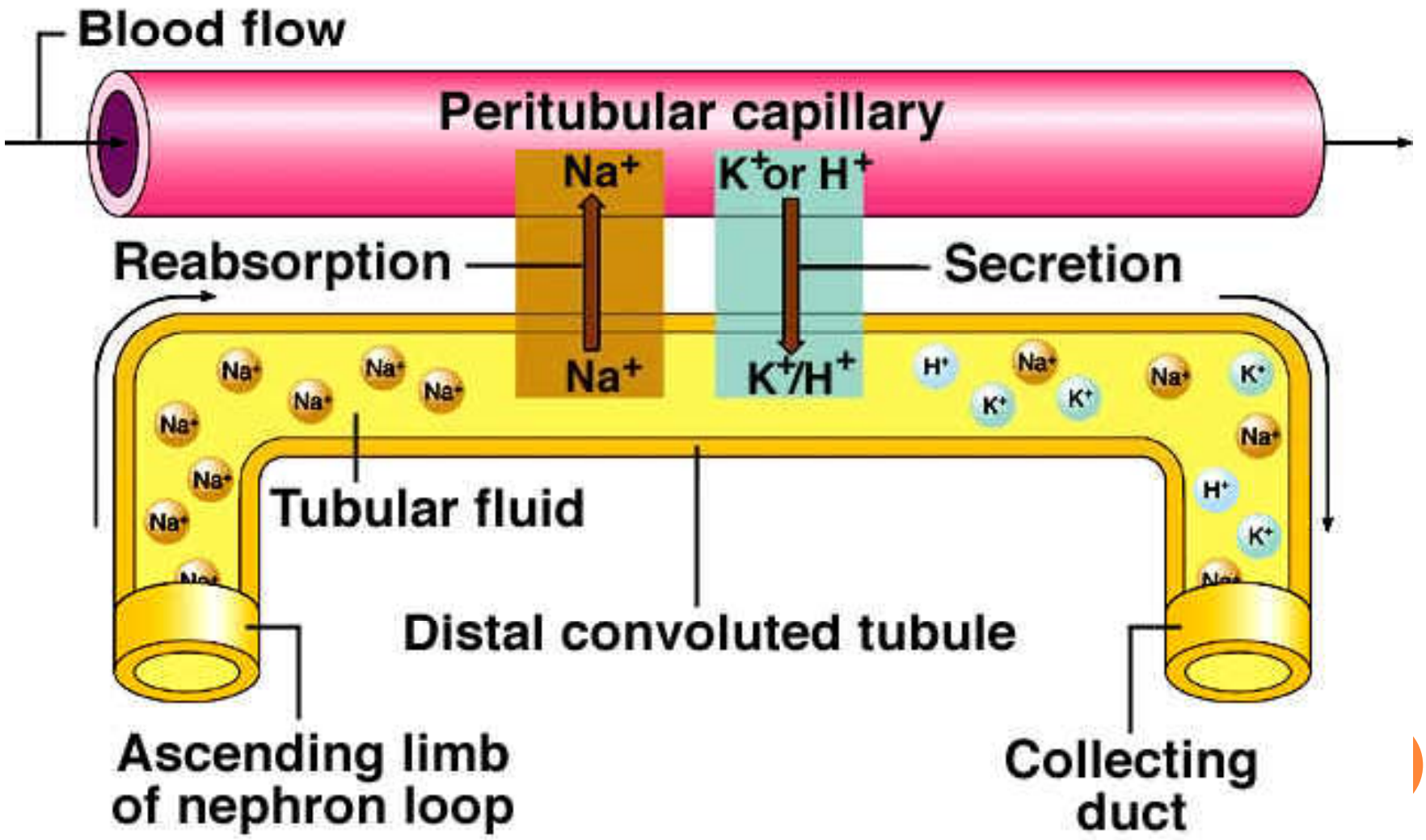
Ascending loop of Henle

- **Ca and Mg enter the interstitial fluid via paracellular pathway**
- **Loop diuretics act on this segment to inhibit NaCl, Ca, Mg reabsorption**

ASCENDING LOOP OF HENLE

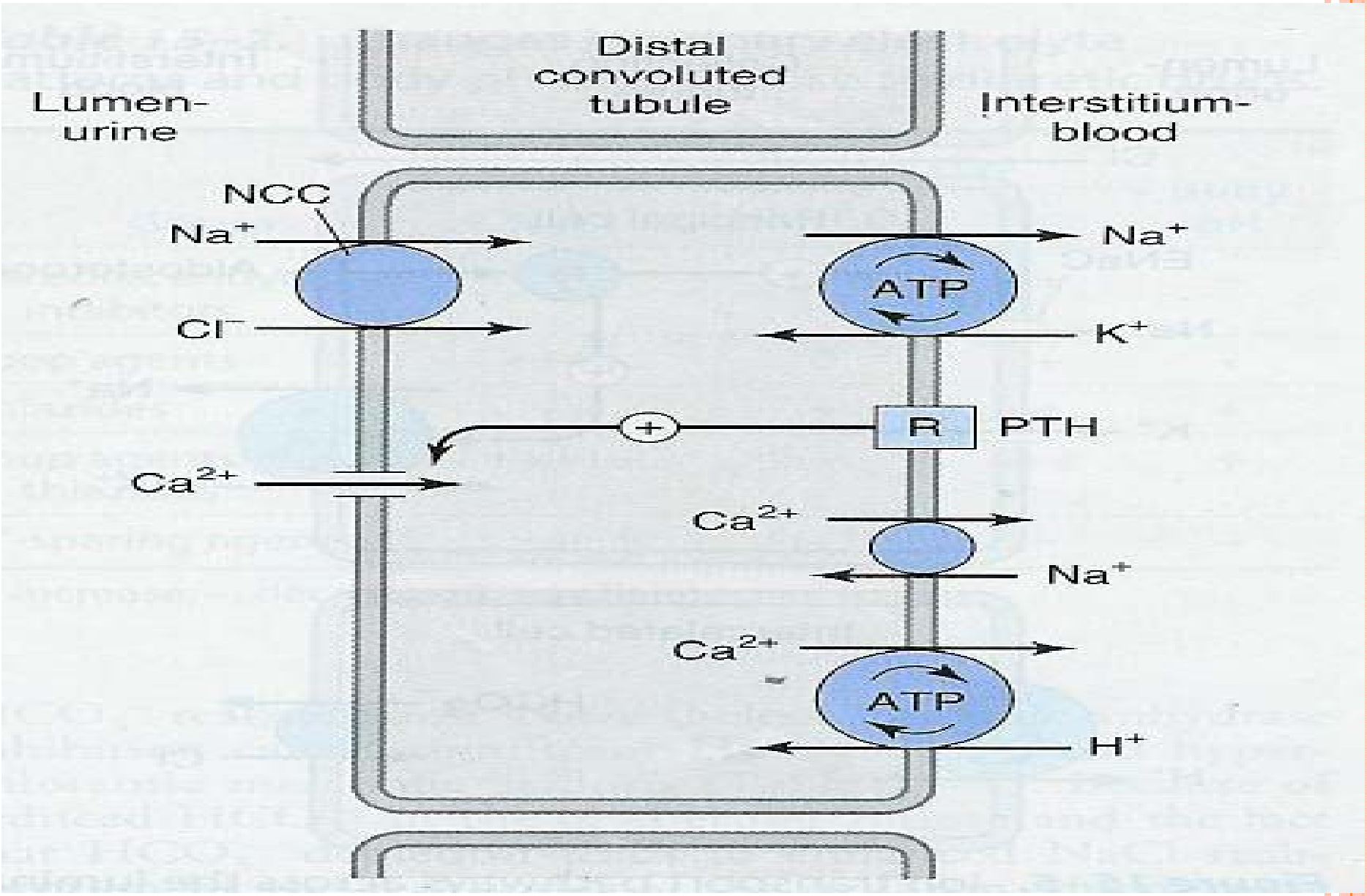


Tubular Reabsorption and Secretion



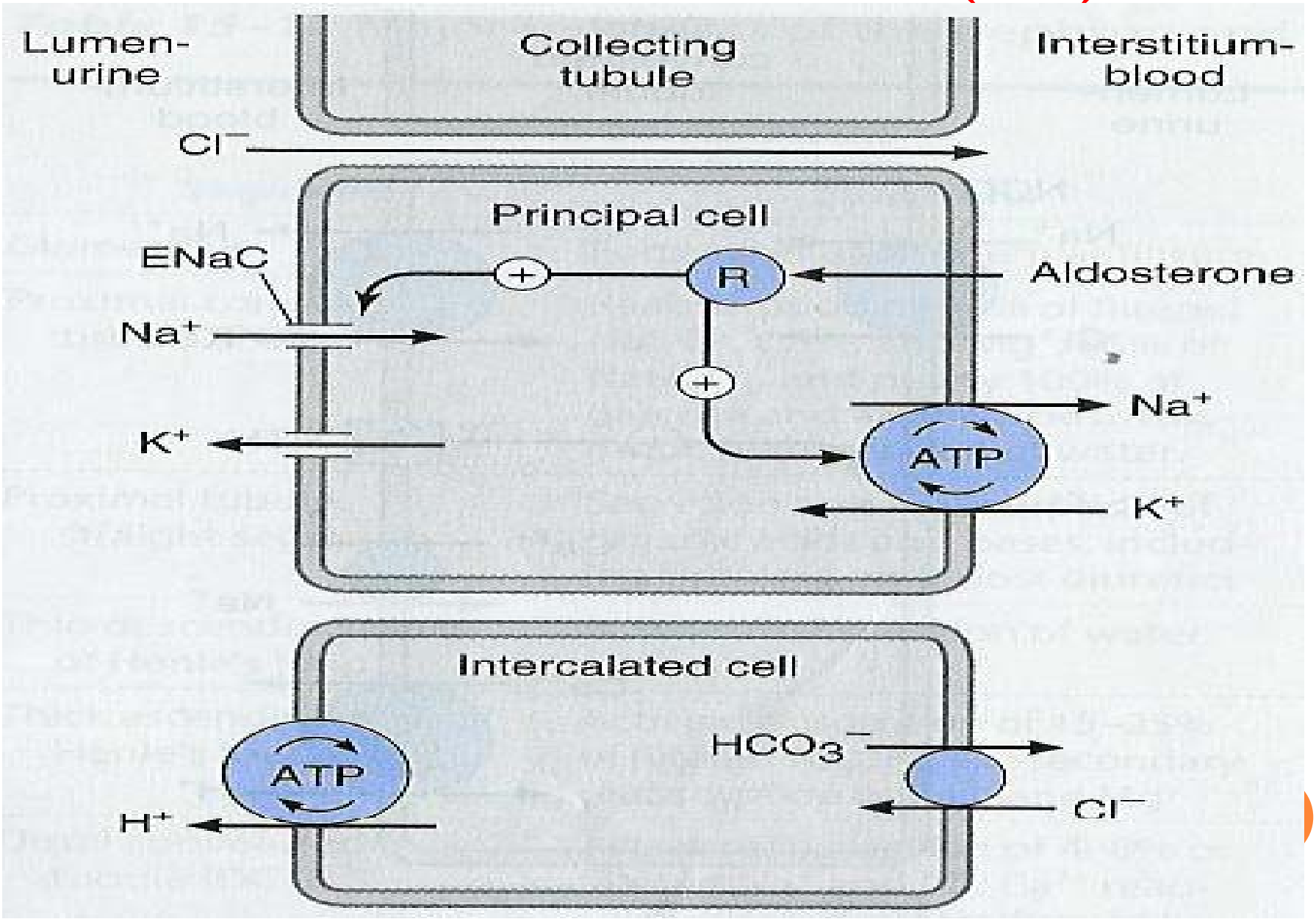
- **Distal convoluted tubule (DCT)**
  - **Is impermeable to water**
  - **Responsible for active reabsorption of NaCl (10%) via transport system Na/Cl transporter in luminal membrane of**
  - **Ca^{2+} actively reabsorbed via Ca channel and Na^{+}/Ca^{2+} exchanger in basolateral membrane**

DISTAL CONVOLUTED TUBULES (DCT)

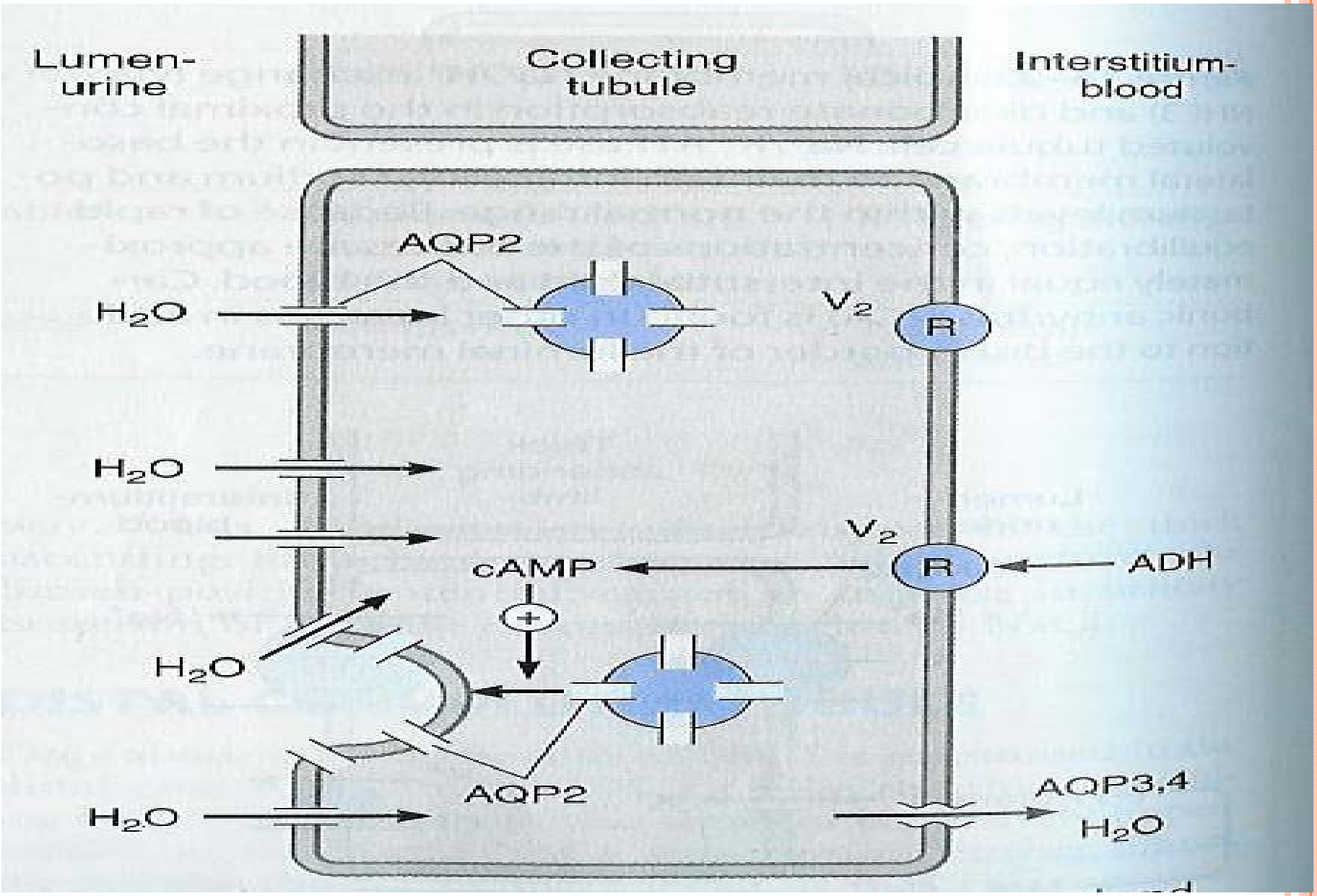


- **Collecting tubule**
  - **Principal cells are responsible for reabsorption of Na (in exchange for K via Na/K-ATPase) and water**
  - **Intercalated cells affect H secretion**
  - **Aldosterone receptors located in the principle cells infleunce Na reabsorption and K secretion**
  - **Antidiuretic hormone (ADH) promotes reabsorption of water.**

COLLECTED TUBULES (CT)



COLLECTED TUBULES (CT)



FUNCTION OF DIFFERENT PARTS OF NEPHRON

segment	Function	transporter	Diuretic drug
PCT	Reabsorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% $NaHCO_3$	Na/H transporter, Carbonic anhydrase enzyme	Carbonic anhydrase inhibitors
PST	Secretion snd reabsorption of organic acids and bases	Acid & base transporter	None
TAL	Active reabsorption 25% Na, K, Cl Secondary reabsorption Ca, Mg	Na/K/2Cl transporter	Loop diuretics
DCT	Active tubular reabsorption of 5%Na, Cl, Ca	Na and Cl cotransporter	Thiazide diuretics
CCT	Na reabsorption K & H secretion	Na channels K & H transporter	K-sparing diuretics

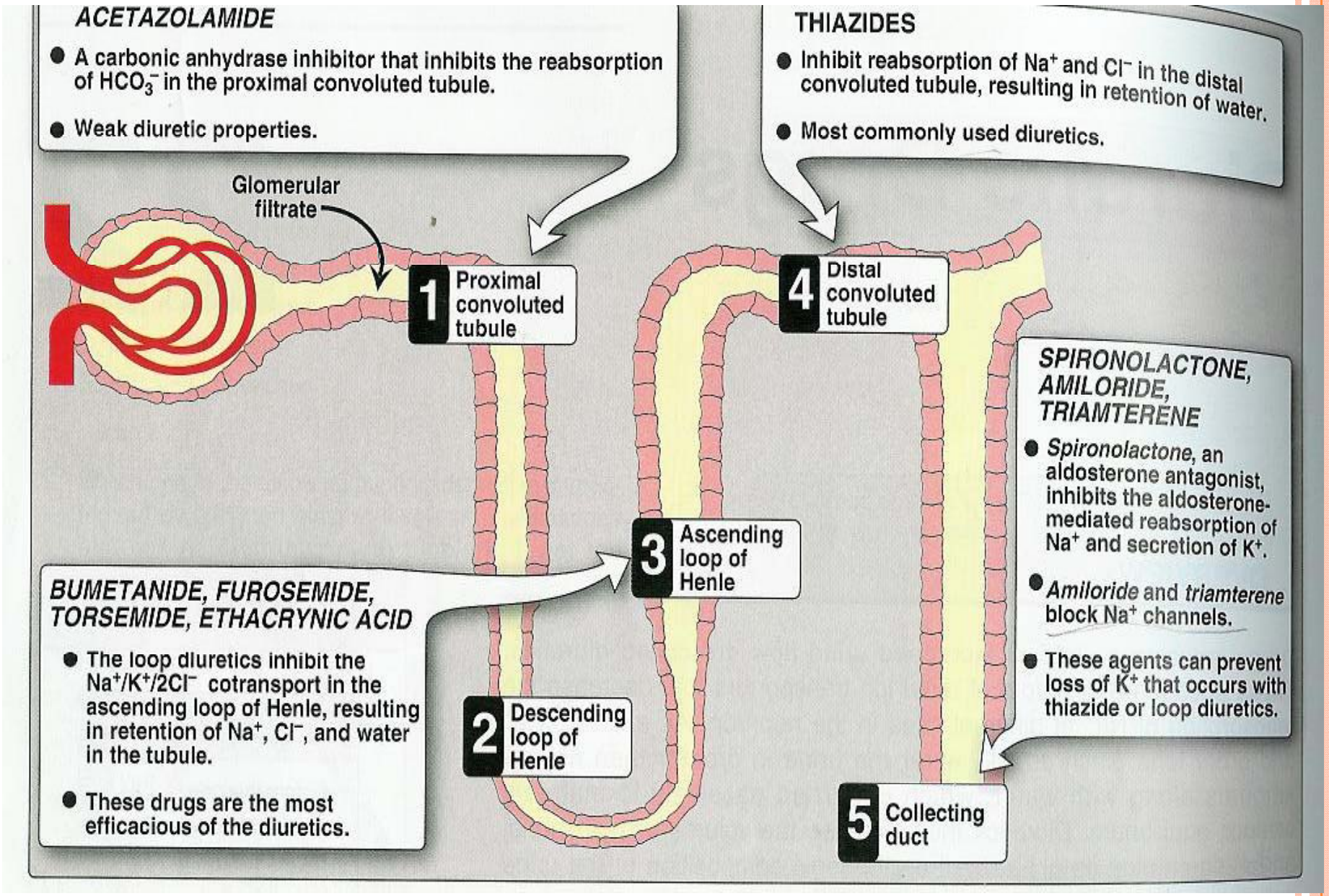
- **Diuretics :** drugs that increase urine volume.
- **Natriuretics:** drugs that increase urinary excretion of sodium.
- Increased urinary sodium excretion result in increased water excretion.

DIURETICS

are classified into

- **Carbonic Anhydrase Inhibitors**
- **Loop Diuretics**
- **Thiazides**
- **Potassium-Sparing Diuretics**
- **Osmotic Diuretics**

SITES OF ACTION OF DIURETICS



CARBONIC ANHYDRASE INHIBITORS

ACETAZOLAMIDE

Chemistry: Sulphonamide derivative

Mechanism of action:

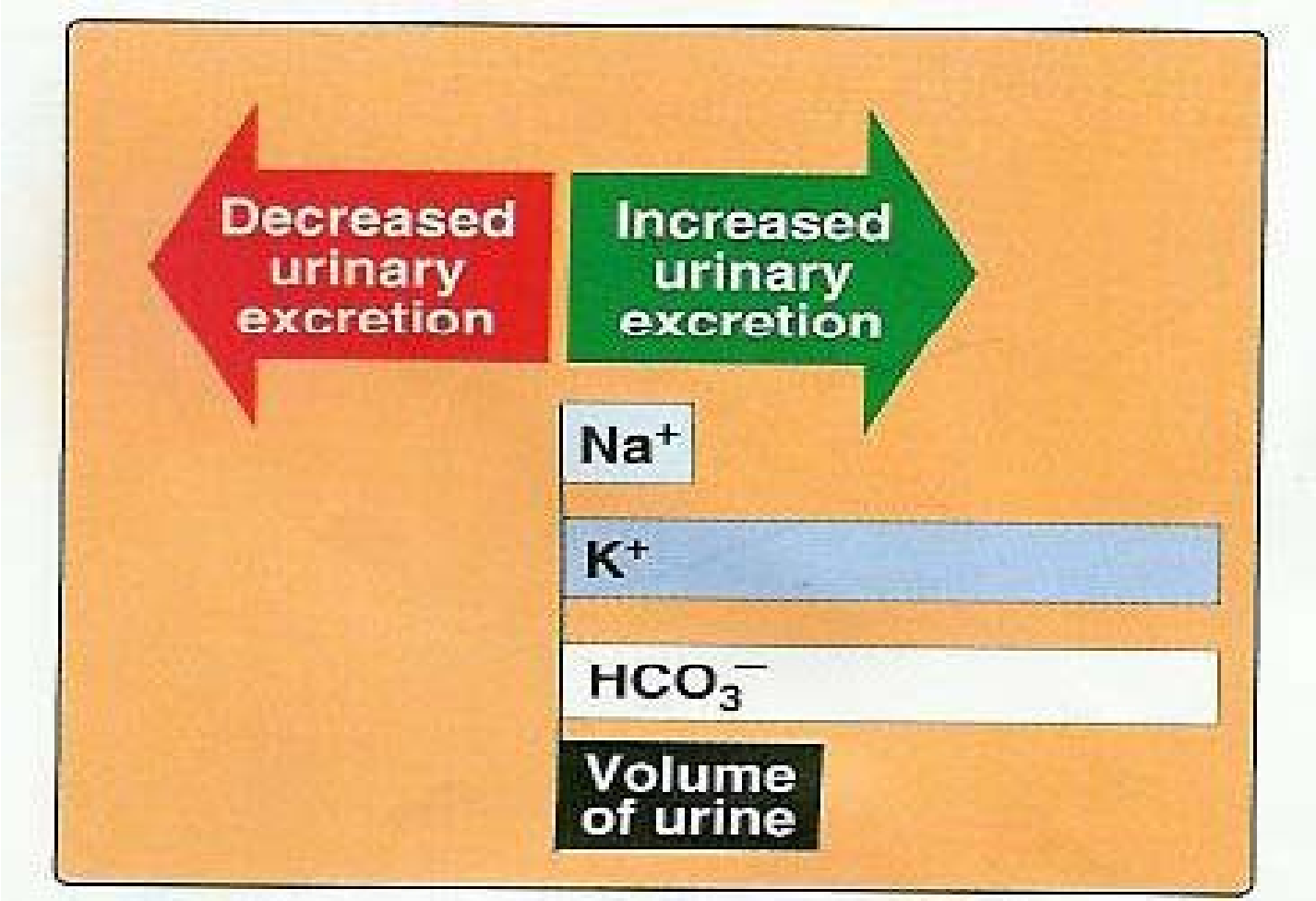
Inhibits carbonic anhydrase enzyme in PCT thus interferes with $NaHCO_3$ reabsorption.

Pharmacodynamics:

- **Increase excretion of bicarbonate, sodium, potassium "alkaline diuresis"**
- **Metabolic acidosis.**
- **Phosphate excretion is increased**
- **Weak diuretics.**
- **Decreases after several days**

(*self-limiting as the blood bicarbonate falls*).

PHARMACODYNAMICS OF CA INHIBITORS:



- **Pharmacokinetics:**

- **given orally or parenterally.**
- **Onset of action is rapid (30 min).**
- **Duration of action12 h.**
- **Excreted by active secreted in proximal convoluted tubules**
- ***(dose should be reduced in renal insufficiency)***

Therapeutic uses:

- **Open angle glaucoma (*reduce formation of aqueous humor by blocking carbonic anhydrase in ciliary body of eye*).**

- **Epilepsy *(decrease cerebrospinal fluid -CSF).***

- **Urinary alkalinization to enhance excretion of uric acid and cystine which are soluble in alkaline urine**

Therapeutic uses:

- **In prophylaxis of acute mountain sickness (*to decrease CSF and pH of brain).* Given five days before the ascent .**

- **Acute mountain sickness is characterized by nausea, headache, weakness, pulmonary and cerebral edema**
- **Hyperphosphatemia**
- **Metabolic alkalosis**

Adverse effects:

- **Metabolic acidosis.**
- **Renal stones (calcium phosphate)**
- **Hypokalemia (potassium loss).**
- **Drowsiness, Paresthesia.**

Contraindication

- **liver cirrhosis: it decrease NH_4 excretion & hepatic encephalopathy**

- **Renal failure: it accumulates to produce nervous system toxicity**

NEW CARBONIC ANHYDRASE INHIBITORS

- **Dorzolamide**
  - **Topically active.**
  - **Reduce introcular pressure equal to oral agents.**
  - **Have no diuretic or systemic metabolic effects.**

THIAZIDES DIURETICS

- **Chemistry:**
  - **are sulphonamide derivatives.**
  - **Chlorothiazide, hydrochlorothiazide**
  - **Chlorthalidone, indapamide are *thiazide-like diuretics.***

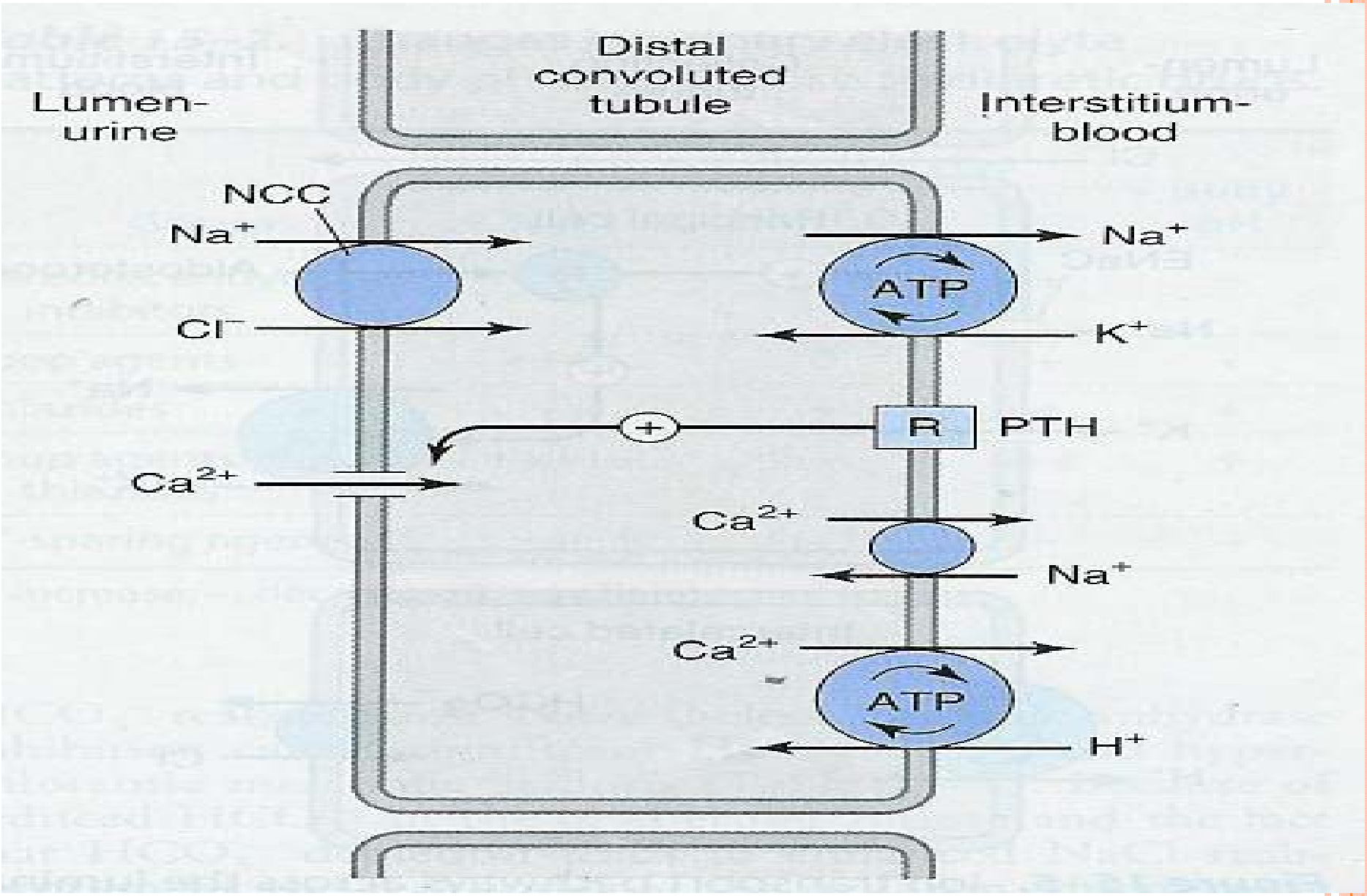
Pharmacokinetics:

- given orally.
- Chlorothiazide- injection available.
- Chlorothiazide is the least potent
- All have slow of onset
- All have long duration of action (40 h)
- All are secreted by active tubular secretion (organic acid secretory system) ***may interfere with uric acid secretion and cause hyperuricemia***

MECHANISM OF ACTION

- **Affect distal convoluted tubules (DCT)**
- **Decreases NaCl reabsorption via inhibition of Na/Cl cotransporter on the luminal membrane of DCT**

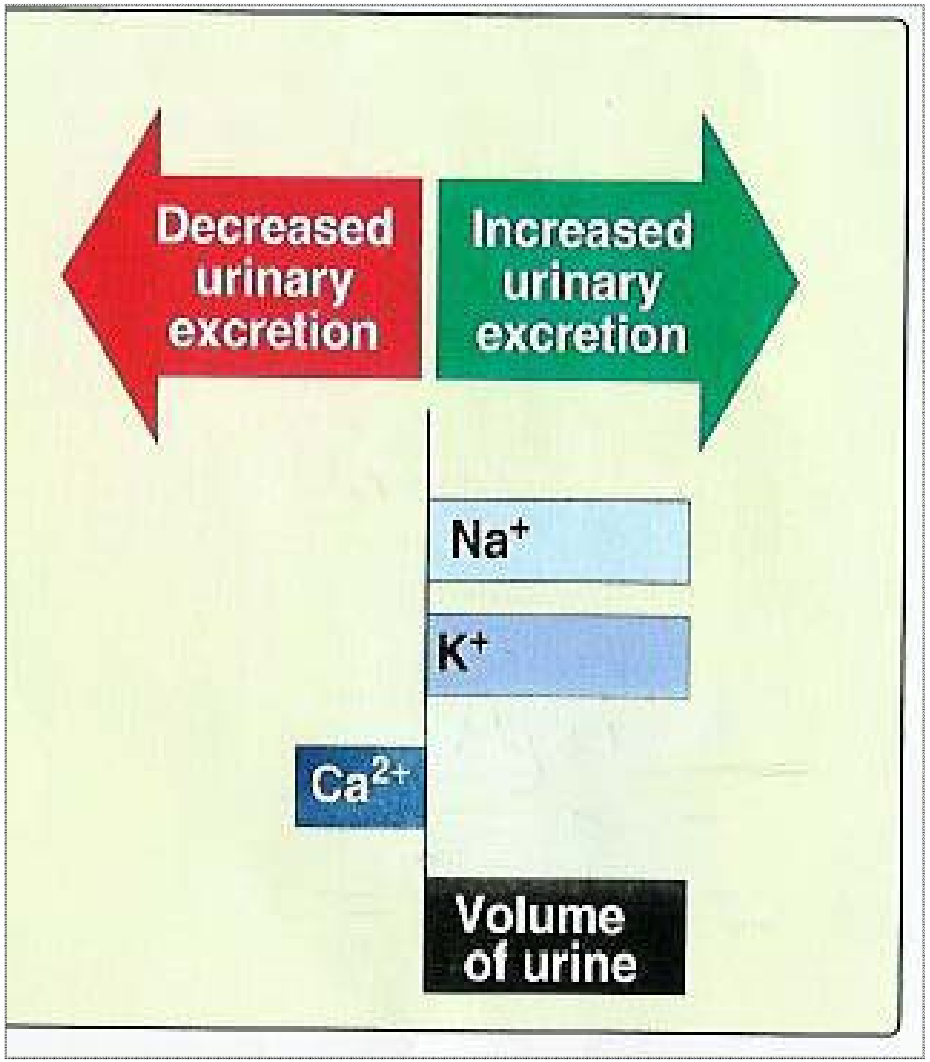
MECHANISM OF ACTION OF THIAZIDE DIURETICS



PHARMACODYNAMICS:

- **Increased NaCl excretion in urine**
- **loss of K in urine (Hypokalemia)**
- **loss of magnesium in urine**
- **Increase calcium reabsorption**
- **Mild vasodilator action.**
- **Hyperglycemia: impaired release of insulin, decreased tissue utilization of glucose.**

EFFECTS OF THIAZIDE DIURETICS



THERAPEUTIC USES:

- **most widely used**
  - **Essential hypertension *(cheap-well tolerated)***
  - **Heart Failure *(to reduce extracellular volume)***
  - **Severe edema of cirrhosis.**
  - **Nephrolithiasis or hypercalciuria *(to prevent kidney stone formation of calcium)***
  - **Nephrogenic diabetes insipidus *(decrease blood volume and GFR)***

Adverse Effects:

- Fluid and electrolyte imbalance
- Hypokalemic (Potassium depletion)
- Hyponatremia
- Hypovolemia (volume depletion)
- Metabolic alkalosis.
- Hyperuricaemia (gout)
- Hypercalcemia
- Hyperglycaemia:
- Hyperlipidemia: increased plasma cholesterol.
- Hypersensitivity

Contraindications:

- **Liver cirrhosis → encephalopathy.**
- **Borderline renal failure.**

LOOP DIURETICS
HIGH CEILING DIURETICS

- **Furosemide**
- **Torsemide**
- **Bumetanide**
- **Ethcrynic acid**

- **Chemistry:**
  - **Sulphonamide derivatives.**

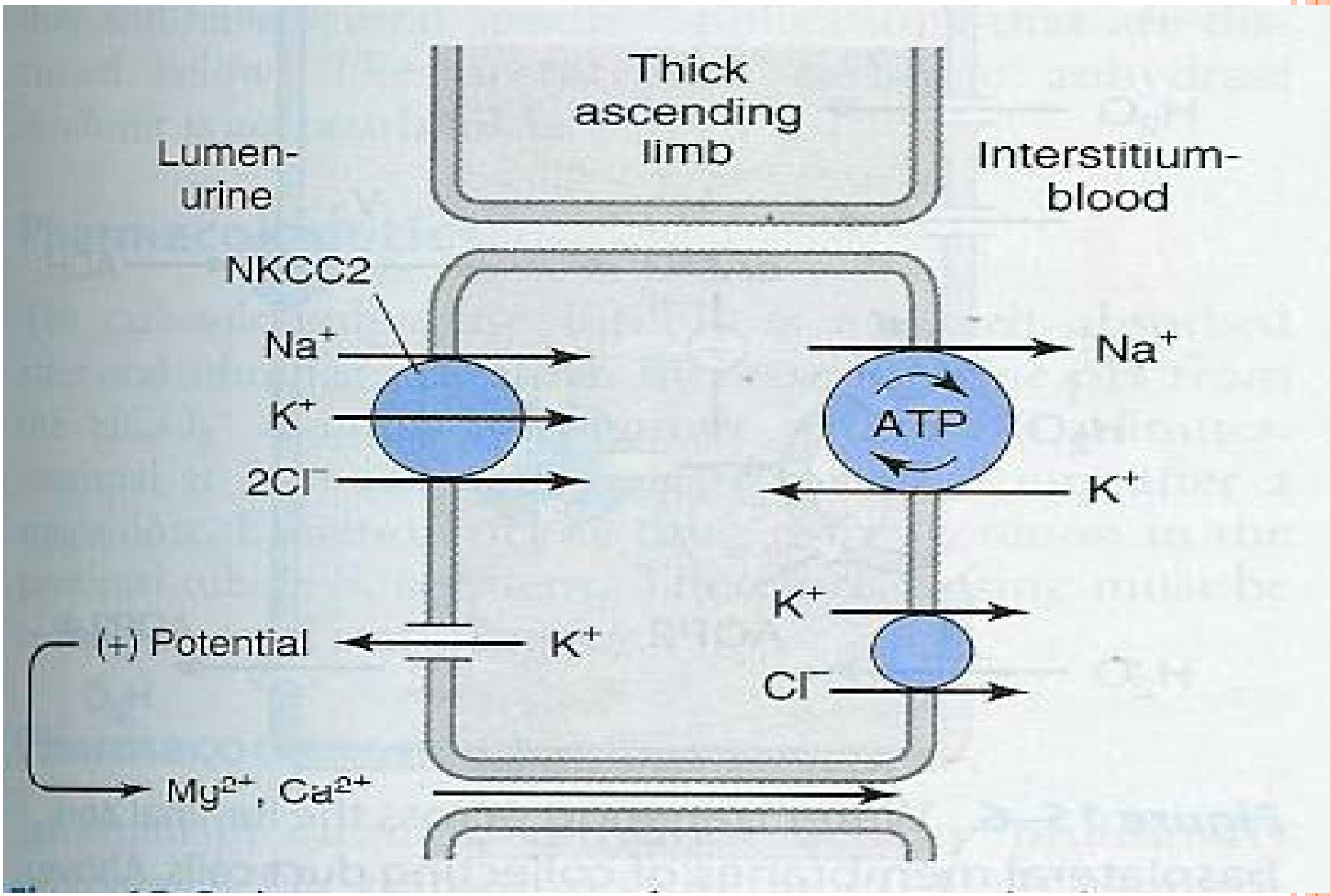
PHARMACOKINETICS OF LOOP DIURETICS

- **Given orally or I. V.**
- **Has fast onset of action (suitable for emergency)**
- **Onset of action is more rapid after I.V. route.**
- **Have short duration of action (2-4 h)**
- **Excreted by active tubular secretion of weak acids into urine (*compete with uric acid for renal secretory system)* .**

MECHANISM OF ACTION OF LOOP DIURETICS

- **Act on Thick ascending loop of Henle (TAL).**
- **Inhibit Na^+ / K^+ / 2 Cl^- transport system reducing NaCl reabsorption (25-30%).**
- **The most efficacious diuretics**
- **Inhibit Ca^{++} and Mg $^{++}$ reabsorption.**

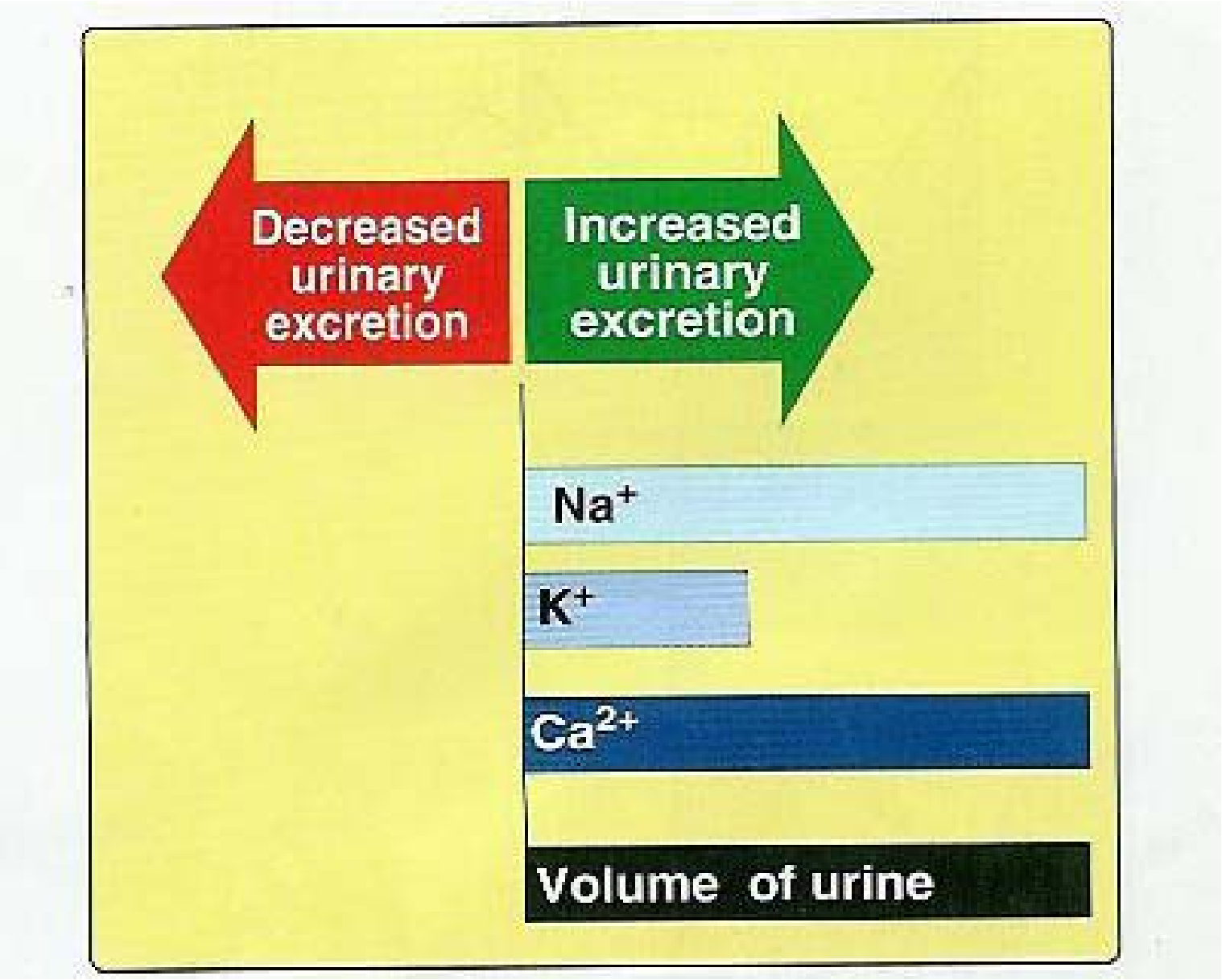
ASCENDING LOOP OF HENLE



Pharmacodynamics of loop diuretics:

- ↑ urinary excretion of Na^{+} , $K,^{+}$ Ca^{++} and Mg^{++}
- ↑ urine volume
- Haemodynamic effects:
  - Increase renal blood flow.
  - Decrease renal vascular resistance
  - Increase prostaglandin synthesis

Effects of loop diuretics:



THERAPEUTIC USES OF LOOP DIURETICS

- **Are widely used drugs (drug of choice) for emergency :**

- **Acute pulmonary edema of heart failure .**
- **Acute hyperkalaemia.**
- **Acute hypercalcemia**
- **Congestive heart failure**

Adverse effects of loop diuretics:

- **Metabolic alkalosis.**
- **Acute Hypovolemia**
- **Hyponatraemia.**
- **Hypokalemia**

  (dietary K supplementation or K-sparing diuretics).

Adverse effects of loop diuretics:

- **Hypomagnesaemia (oral supplementation)**
- **Hyperuricemia *(increase gouty attack).***
- **Ototoxicity**
- **Allergic reactions.**

POTASSIUM-SPARING DIURETICS

Drugs:

- **Spironolactone.**
- **Triamterene.**
- **Amiloride.**

PHARMACOKINETICS:

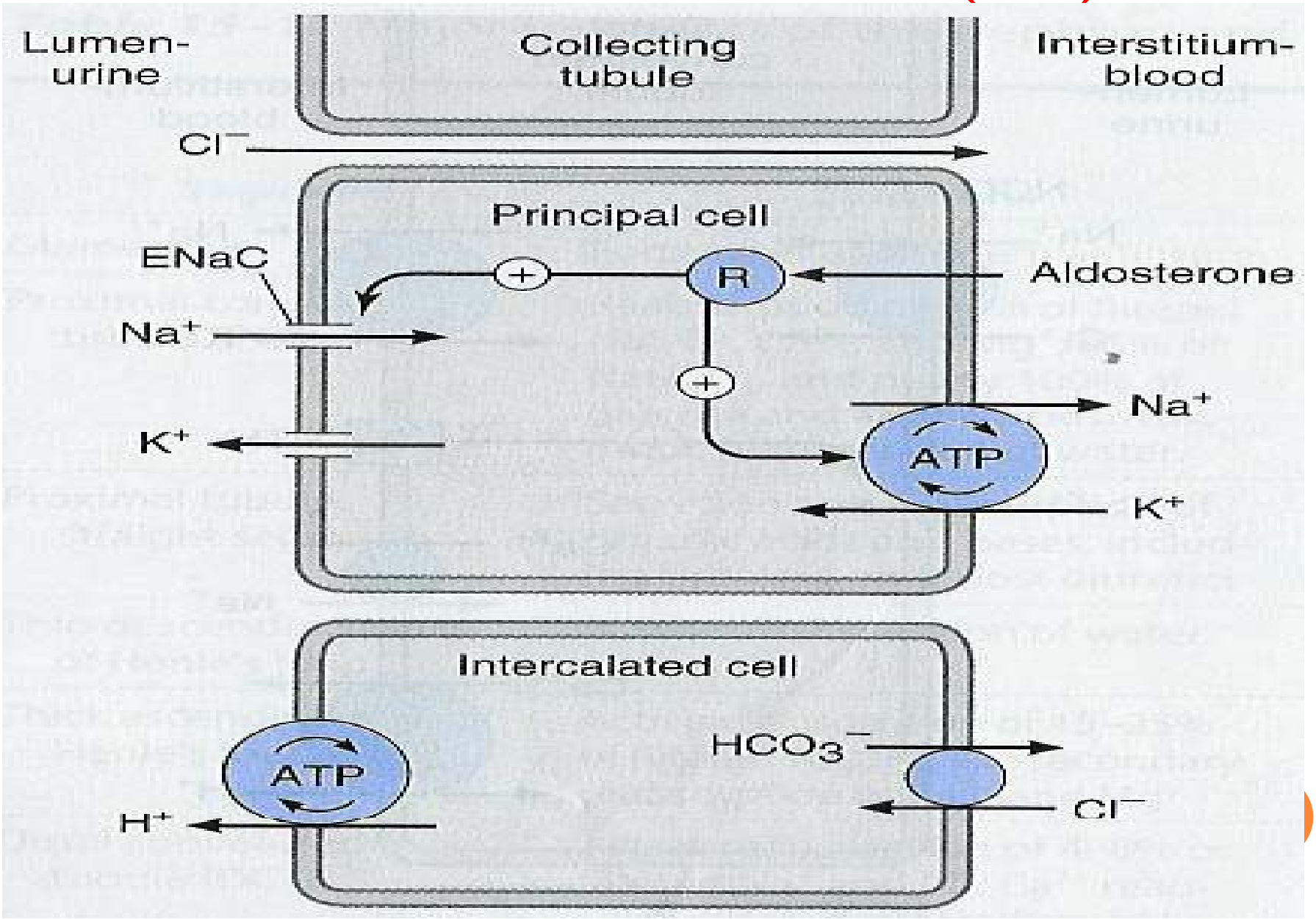
- **Spironolactone**
- **Rapidly absorbed orally**
- **Has slow onset of action, takes several days**
- **Converted into active metabolite**
- **Induces CYT P450**

Mechanism of action of k-sparing diuretics

- **Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone at its cytoplasmic receptors**

- **Act in collecting tubules and ducts by inhibiting Na reabsorption and K & H secretion (*K-sparing effect*).**

COLLECTED TUBULES (CT)



Pharmacodynamics of K-sparing diuretics

Increase urinary Na excretion

Decrease urinary K excretion (Hyperkalemia)

Decrease H secretion (acidosis)

THERAPEUTIC USES:

- **Drug of choice for patients with hepatic cirrhosis**
- **In mineralocorticoid hypersecretion e.g. Conn's syndrome**
- **Secondary hyperaldosteronism: CHF, hepatic cirrhosis, nephrotic syndrome.**
- **Diuretics in combination with thiazide or loop diuretics (to correct for hypokalemia).**

Adverse Effects

- Gynaecomastia
- Hyperkalaemia.
- Metabolic acidosis.
- GIT upset and peptic ulcer

Contraindications:

- **Hyperkalaemia: as in chronic renal failure, K+ supplementation, β-blockers or ACE inhibitors.**

- **Patients with liver disease, dose adjustment is needed.**

OSMOTIC DIURETICS

Mannitol

- Poorly absorbed
- Given intravenously.
- Distributed in extracellular compartments
- Not metabolized

Mannitol

- Undergoes glomerular filtration **BUT not reabsorbed or secreted.**
- Acts in proximal tubules & descending loop of Henle by **osmotic effect.**
- Retains water within the tubules (diuresis).
- Has a secondary effect on reducing sodium reabsorption.

Therapeutic Uses:

- **Cerebral edema (increased intracranial pressure).**
- **Acute renal failure due to shock, trauma, drug toxicities (maintain urine flow- preserve kidney function).**
- **Glaucoma.**

Adverse Effects:

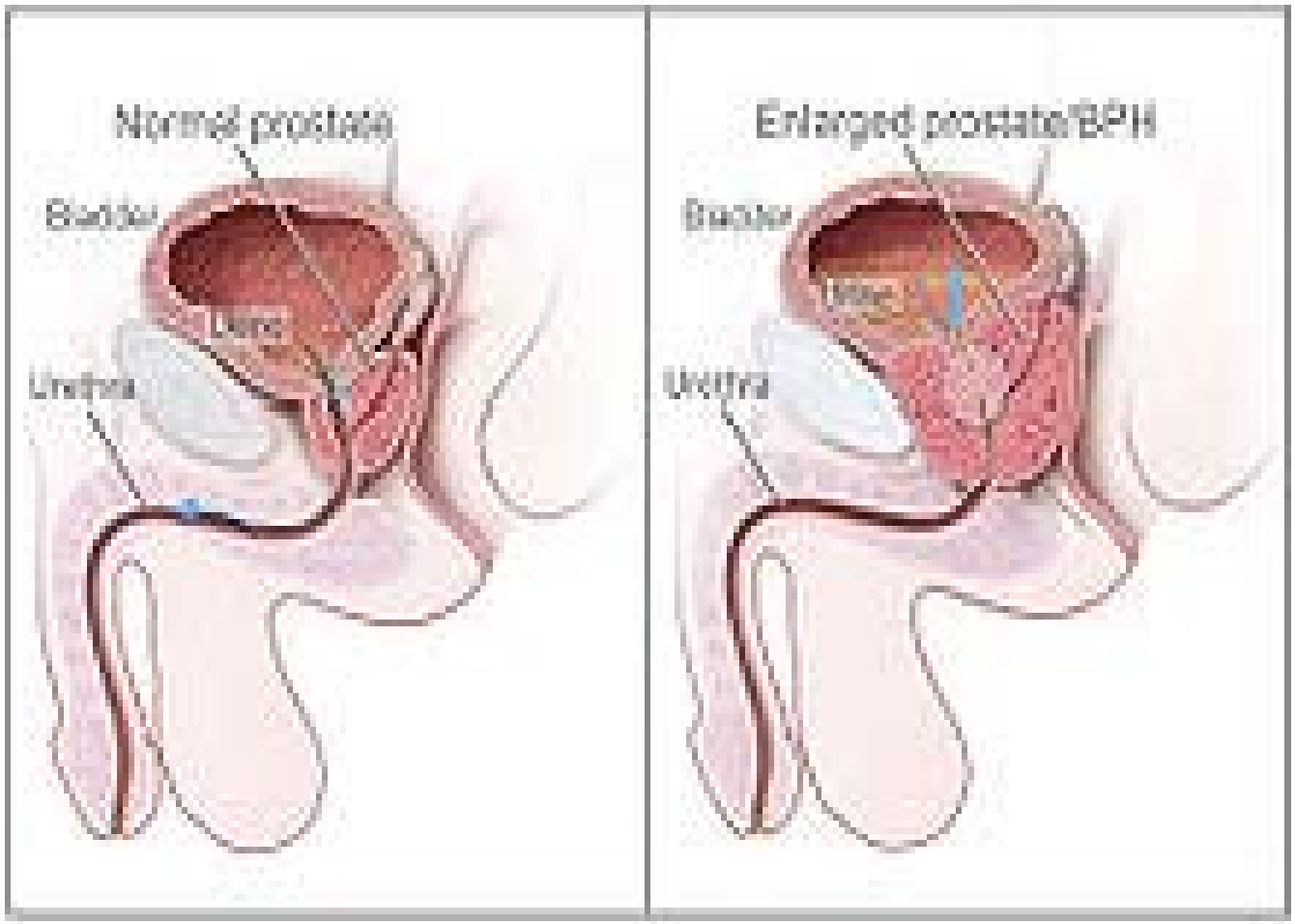
- **Extracellular water expansion *(extracts water from cells)***
- **Dehydration**
- **Hypernatremia**
- **Headache, Nausea, Vomiting**
- **Adequate water replacement is required.**

Diuretics	Mechanism of action	Effects
CA inhibitors Acetohexamide Dorzolamide	Inhibition of NaHCO3 reabsorption in PCT	↑ Urinary Na HCO3, K Urinary alkalosis Metabolic acidosis
Osmotic diuretic Mannitol	Osmotic effect in PCT & DLH	↑Urine excretion ↑ Little Na
Loop diuretics Furosemide	Na/K/2Cl transporter in TAL the most effective	↑Urinary Na, K, Ca, Mg
Thiazide diuretics Chlorothiazide hydrochlorothiazide	Na and Cl cotransporter in DCT	↑Urinary Na, K, Mg BUT↓ urinary Ca (hypercalcemia) Metabolic alkalosis
K-sparing diuretic Spironolactone.	competitive antagonist of aldosterone in CCT	↑ Urinary Na ↓ K, H secretion Metabolic acidosis

Diuretics	Uses
CA inhibitors Acetohexamide Dorzolamide (topically) for glaucoma	Glaucoma, epilepsy Mountain sickness
Osmotic diuretic Mannitol	•Cerebral edema •Acute renal failure
Loop diuretics Furosemide	Pulmonary fibrosis (Drug of choice) Heart failure Hyperkalemia, Hypercalcemia
Thiazide diuretics Chlorothiazide hydrochlorothiazide	Commonly used Hypertension, heart failure, hypercalciuria, kidney stones, diabetes inspidus
K-sparing diuretic Spironolactone.	Hepatic cirrhosis (Drug of choice)

Diuretics	Side effects
CA inhibitors **Acetohexamide** **Dorzolamide**	**Metabolic acidosis , Urinary alkalosis** **Hypokalemia**
Osmotic diuretic **Mannitol**	**Extracellular water expansion** **Dehydration** **Hypernatremia**
Loop diuretics **Furosemide**	**Hypokalemia,** **hypovolemia, hyponatremia,** **hypomagnesemia, hypocalcemia** **Precipitate gout, alkalosis**
Thiazide diuretics **Chlorothiazide** **hydrochlorothiazide**	**Hypokalemia, hyponatremia, hypovolemia,** **hypomagnesemia, hypercalcemia** **Alkalosis, precipitate gout** **Hyperlipidemia, hyperglycemia**
K-sparing diuretic **Spironolactone.**	**Gynaecomastia** **Hyperkalaemia, Metabolic acidosis.** **GIT upset and peptic ulcer**

PROSTATIC HYPERTROPHY



PROSTATIC HYPERTROPHY

- **is a benign enlargement of the prostate an increase in size of the prostate in middle-aged and elderly men.**
- **occurs by some drugs as alpha agonists *(contraction of smooth muscles)* and antimuscrinics *(urinary retention).***

BPH is characterized by:

- Hyperplasia of prostatic cells
- Partial or complete obstruction of the urethra, which interferes with the normal flow of urine.
- dysuria (painful urination), increased risk of urinary tract infections, and urinary retention.

Treatments of BPH

- Alpha blockers (α_1-adrenergic receptor antagonists) are the most common choice as tamsulosin, and alfuzosin

- act by relaxing smooth muscle in the prostate and the bladder neck, thus decreasing the blockage of urine flow.

- **5α-reductase inhibitors**
  - **finasteride**
  - **Inhibits 5α-reductase, which in turn inhibits production of DHT, a hormone responsible for enlarging the prostate.**
  - **Effects may take longer to appear than alpha blockers, but they persist for many years.**

Side effects:

erectile dysfunction