Diuretics

Definitions

Diuretic: substance that promotes the excretion of urine

Caffeine, nettles, cranberry juice, alcohol

Natriuretic: substance that promotes the renal excretion of Na+

Diuretics

- Mainly promotes the excretion of the Na^+, Cl^- or HCO_3^- and water,
- The net result being:
  - Increase the urine flow,
  - Change urine pH
  - Change the ionic composition of the urine and blood.

Diuretics:

Diuretics are very effective in the treatment of:

- Edema: CHF, pregnancy, & nutritional
- Nephrotic syndrome
- Diabetes insipidus
- Hypertension
- Cirrhosis of liver
- and also lower the intracellular and CSF pressure.

NORMAL PHYSIOLOGY OF URINE FORMATION

Two important functions of the kidney are:-

- ❖ To maintain a **homeostatis balance of electrolytes and water**.
- ❖ To **excrete water soluble end products of metabolites**.

Each kidney contains approximately one million nephrons and is capable of forming urine independently.

The nephrons are composed of glomerulus, proximal tubule, loop of henle, distal tubule.

- Approximately **1200 ml of blood per minute** flows through both kidneys.
- Ions such as **sodium, chloride,calcium** are reabsorbed.
- Total amount of **glucose, amino acids, vitamins, proteins** are reabsorbed.
- If the presence of this molecule in urine is represent the disorders.

  For example proteins such as albumin in higher amounts causes **albuminaria**.

Renal Physiology

Renal epithelial transport

Tubular reabsorption

Proximal tubule

Loop of Henle

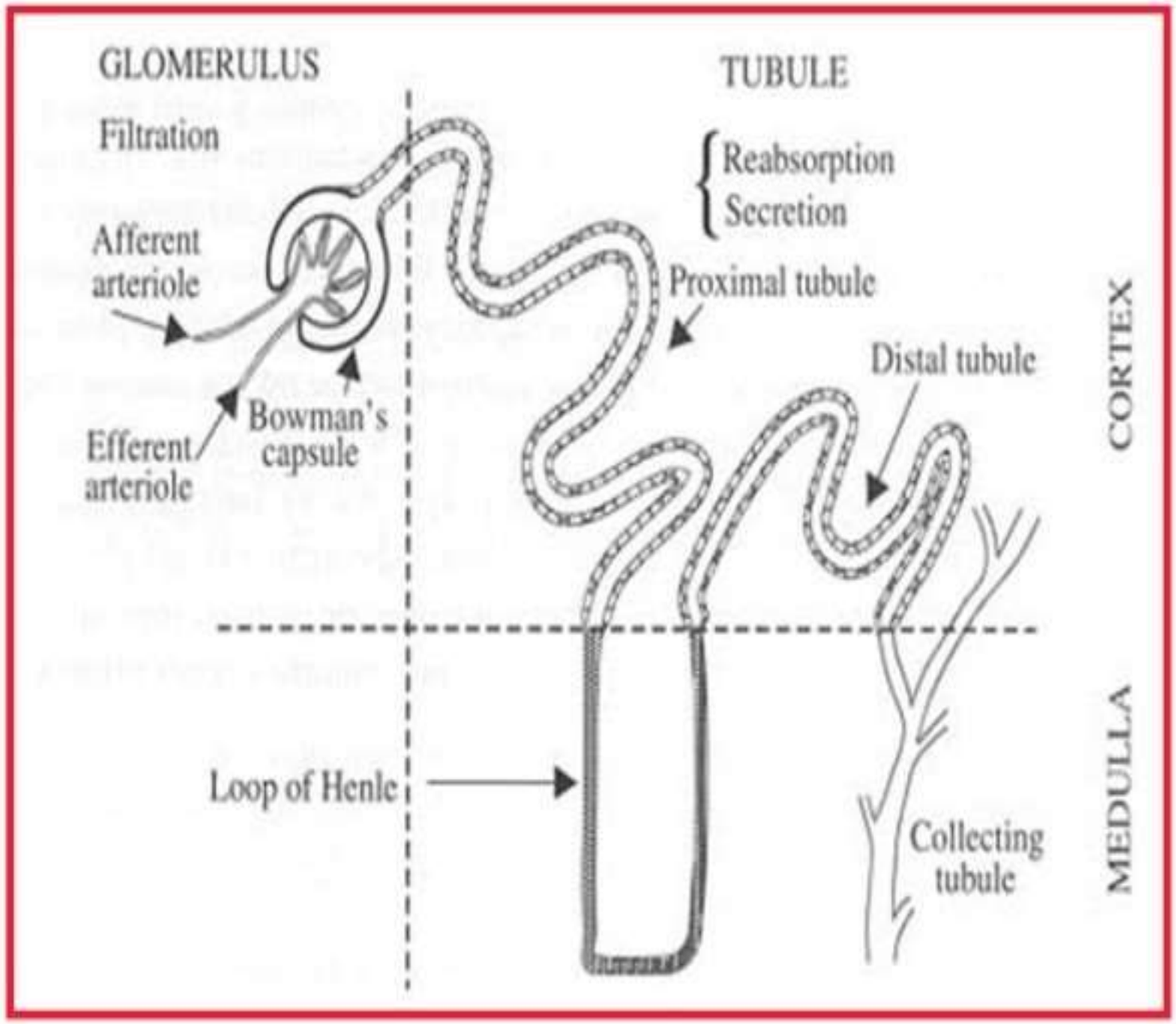
Thick ascending limb

Distal convoluted tubule

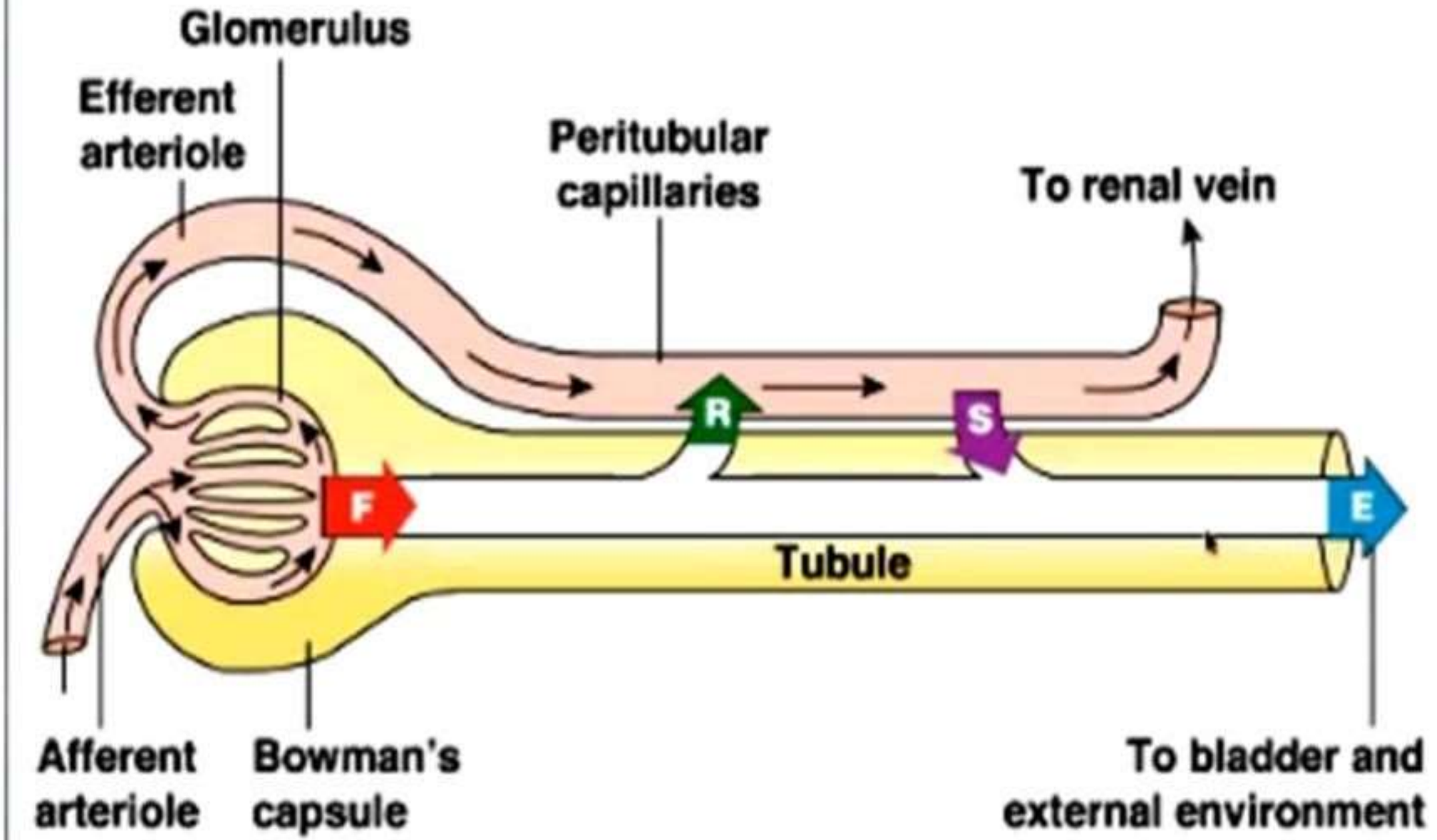
Collecting tubule

Tubular secretion

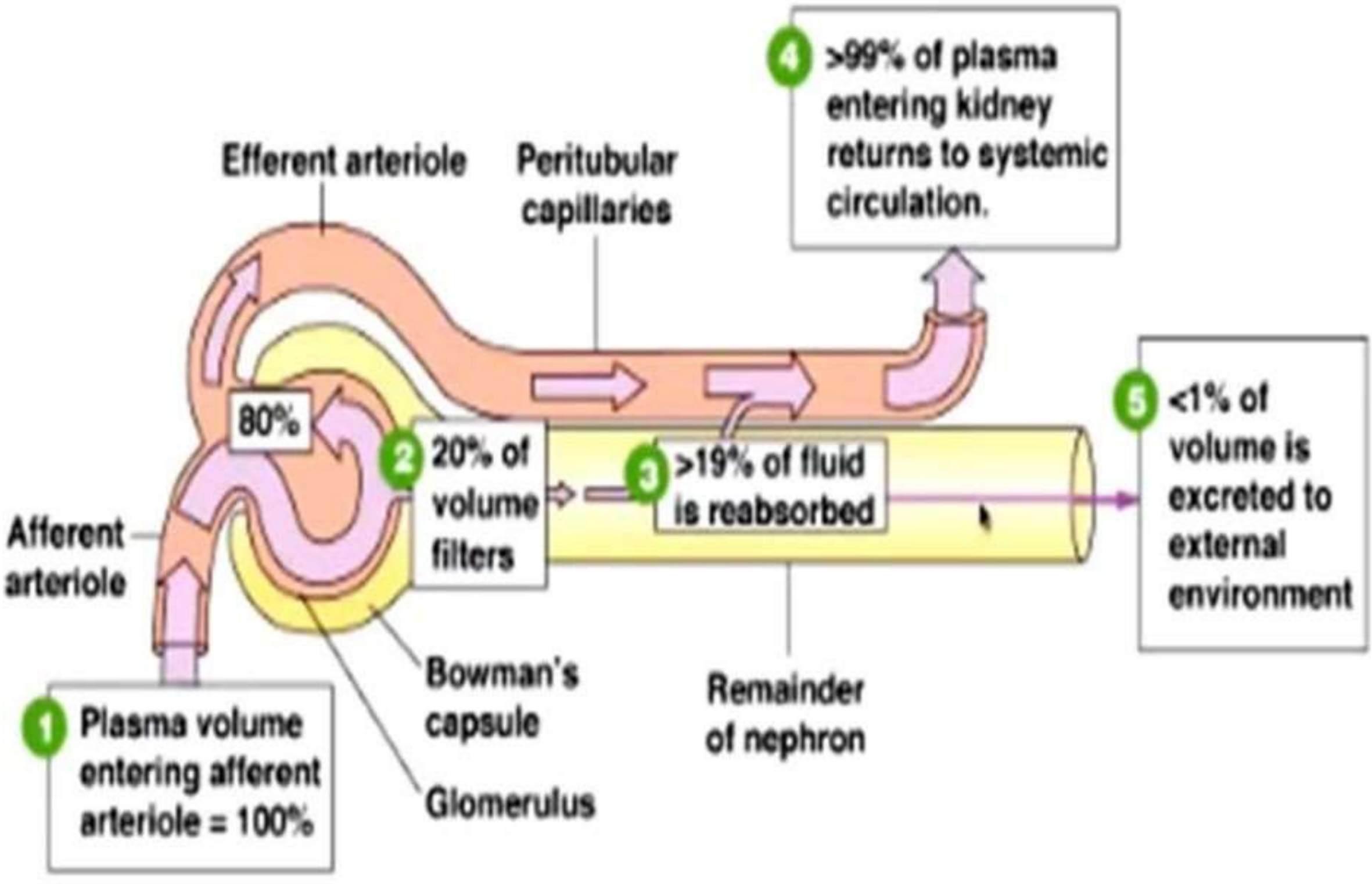
Collecting tubules



The excretion by kidney is dependent on: glomerular filtration, tubular reabsorption and tubular secretion.



Amount filtered	–	amount reabsorbed	+	amount secreted	=	Amount of solute excreted
F		R		S		E


Efferent arteriole
Peritubular capillaries
4 >99% of plasma entering kidney returns to systemic circulation.
80%
2 20% of volume filters
3 >19% of fluid is reabsorbed
5 <1% of volume is excreted to external environment
Afferent arteriole
Bowman's capsule
Remainder of nephron
1 Plasma volume entering afferent arteriole = 100%
Glomerulus

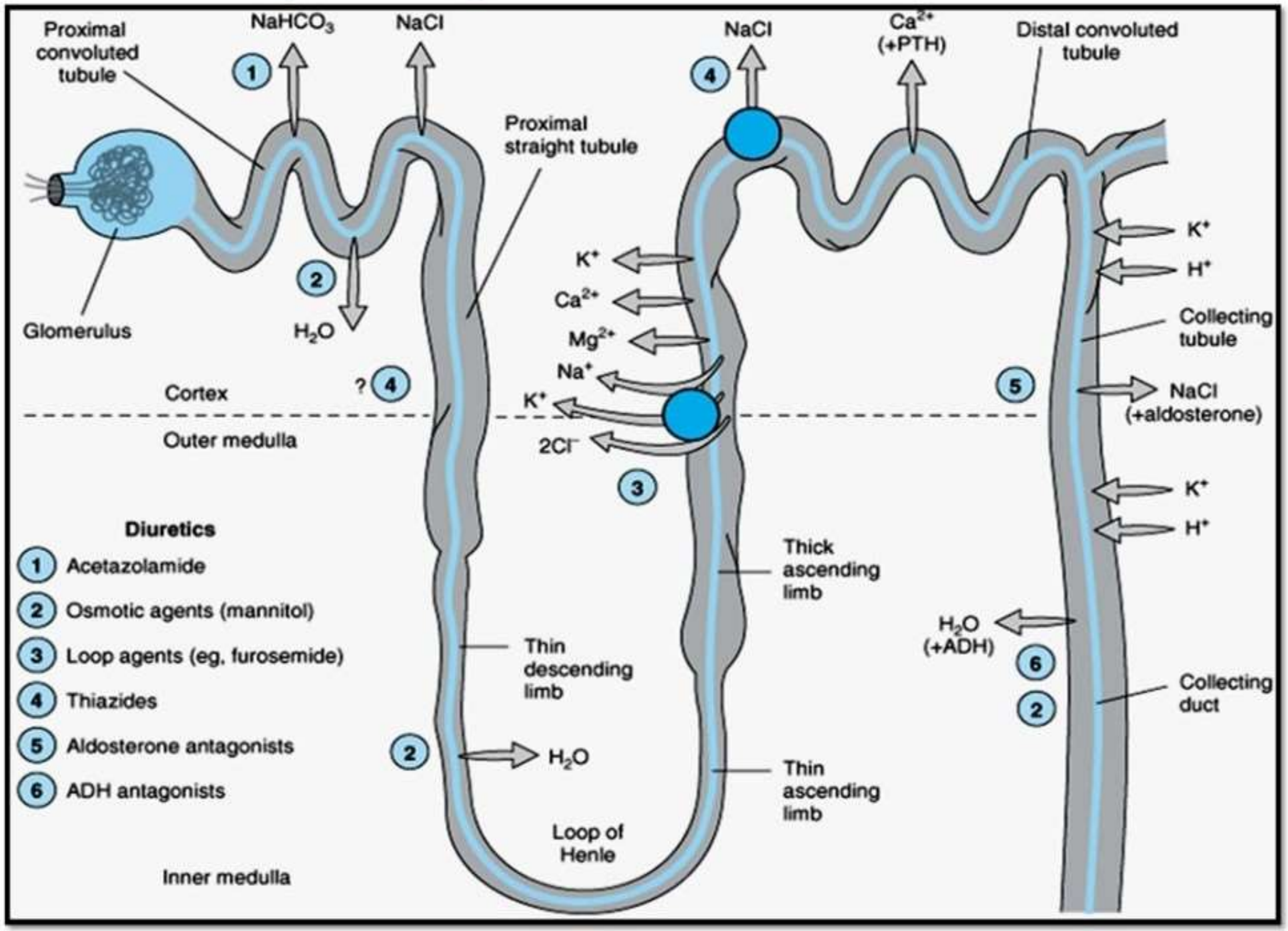
Oliguria

Types of urine

Normal

Polyuria

Electrolyte Transport and Site of Action of Diuretics



Classifications of Diuretics

- **Thiazide Diuretics:**

  a) Thiazides: Hydrochlorothiazide, Benzthiazide

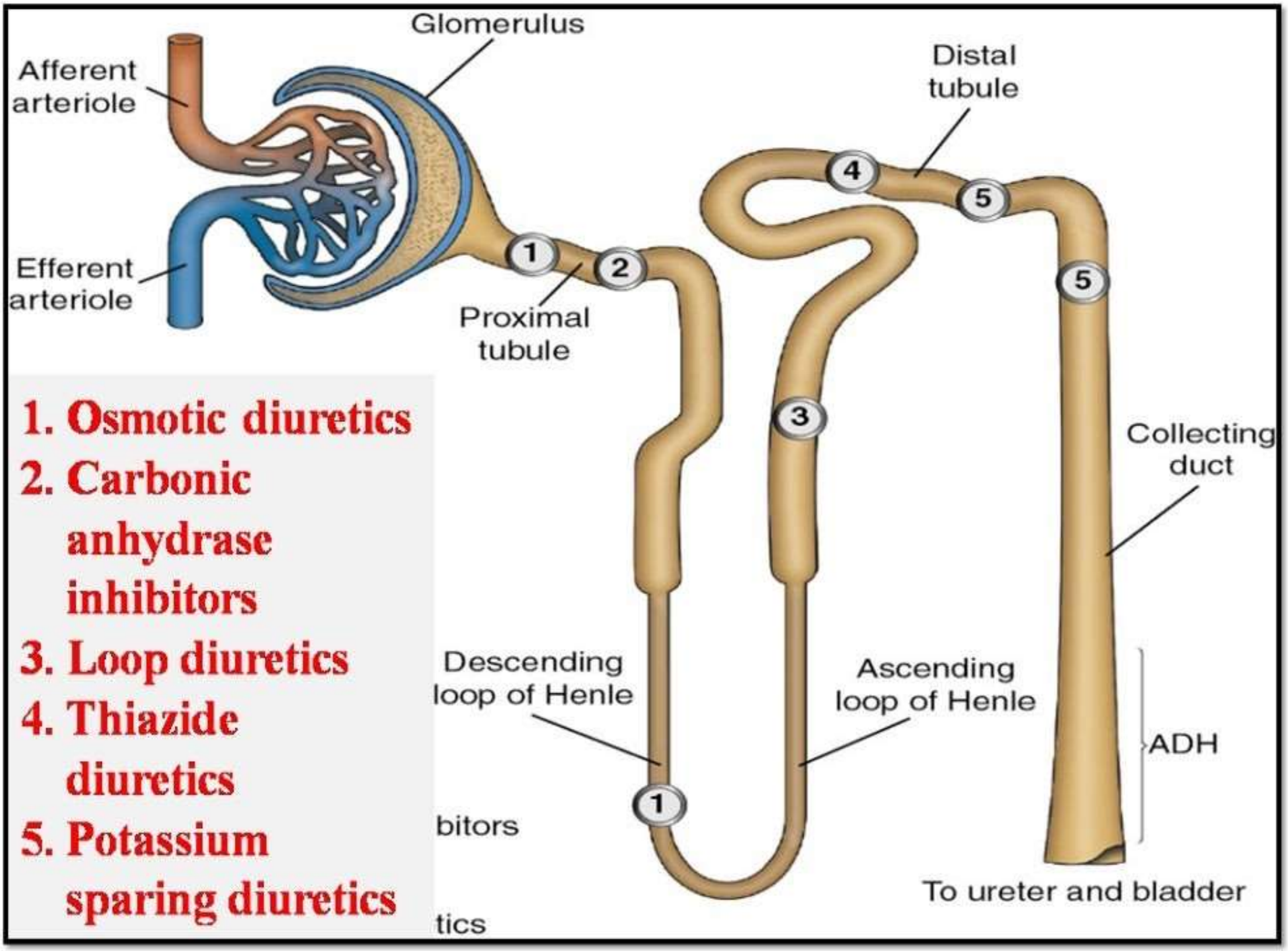
  b) Thiazide like: Chlorthalidone, Metolazone, Xipamide, Indapamide, Clopamide

- **Loop Diuretics :** *Frusemide, Bumetanide, Torasemide, Ethacrynic acid*
- **Potassium Sparing Diuretics :**

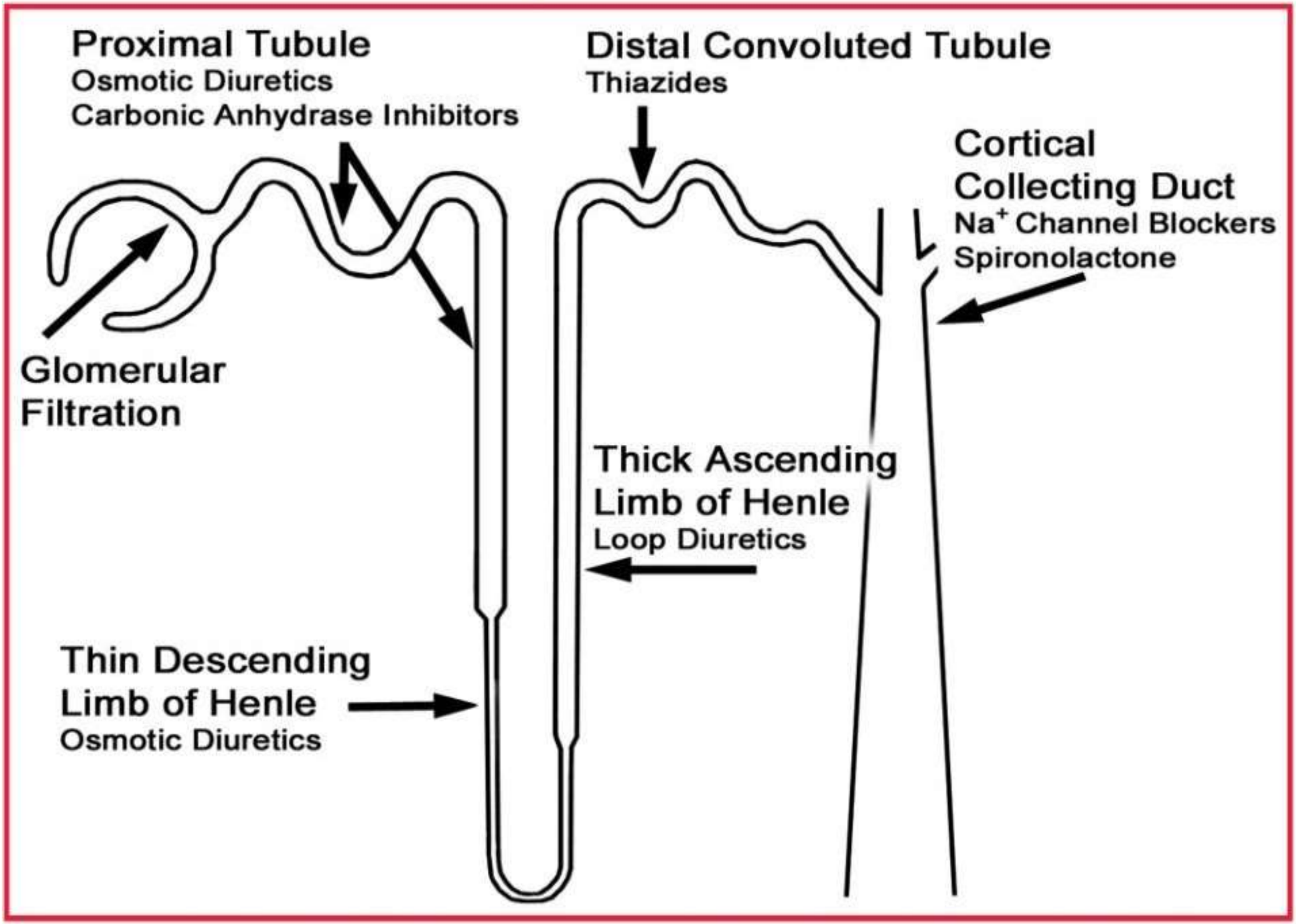
  – **Aldosterone Antagonist:** *Spironolactone, Canrenone, Eplerenone*

  – **Directly Acting (Inhibition of Na^+ channel):** *Triamterene, Amiloride*
- **Carbonic anhydrase inhibitors :** *Acetazolamide, Brinzolamide, Dorzolamide*
- **Osmotic Diuretics :** *Mannitol, Glycerine, Urea, Isosorbide*

1. Osmotic diuretics
2. Carbonic anhydrase inhibitors
3. Loop diuretics
4. Thiazide diuretics
5. Potassium sparing diuretics



Summary: Sites of Action



Site and Mechanisms of Actions of Diuretics

Diuretics	Site of Action	Mechanism
Osmotic Diuretic	1. Proximal tubules 2. Loop of Henle 3. Collecting duct	Inhibition of water and Na+ reabsorption
Carbonic Anhydrase Inhibitor (CA-I)	Proximal tubules	Inhibition of bicarbonate reabsorption
Loop Diuretic	Loop of Henle (*thick ascending limb*)	Inhibition of Na^+, K^+, Cl^- cotransport
Thiazide	Early distal tubule	Inhibition of Na^+, Cl^- cotransport
K^+ sparing diuretics	Late distal tubule Collecting duct	Inhibition of Na+ reabsorption and K^+ secretion

Osmotic Diuretics

Do not interact with receptors or directly block renal transport

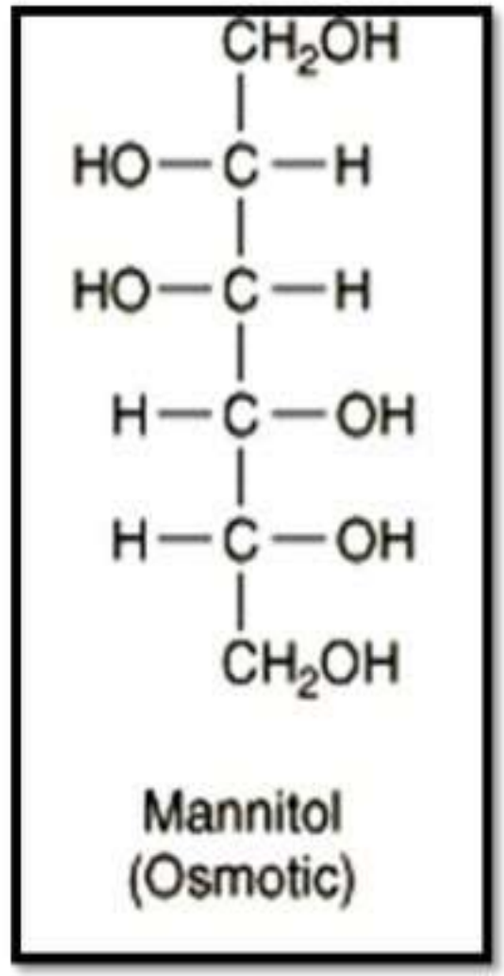
Activity dependent on development of **osmotic pressure**

Mannitol (prototype)

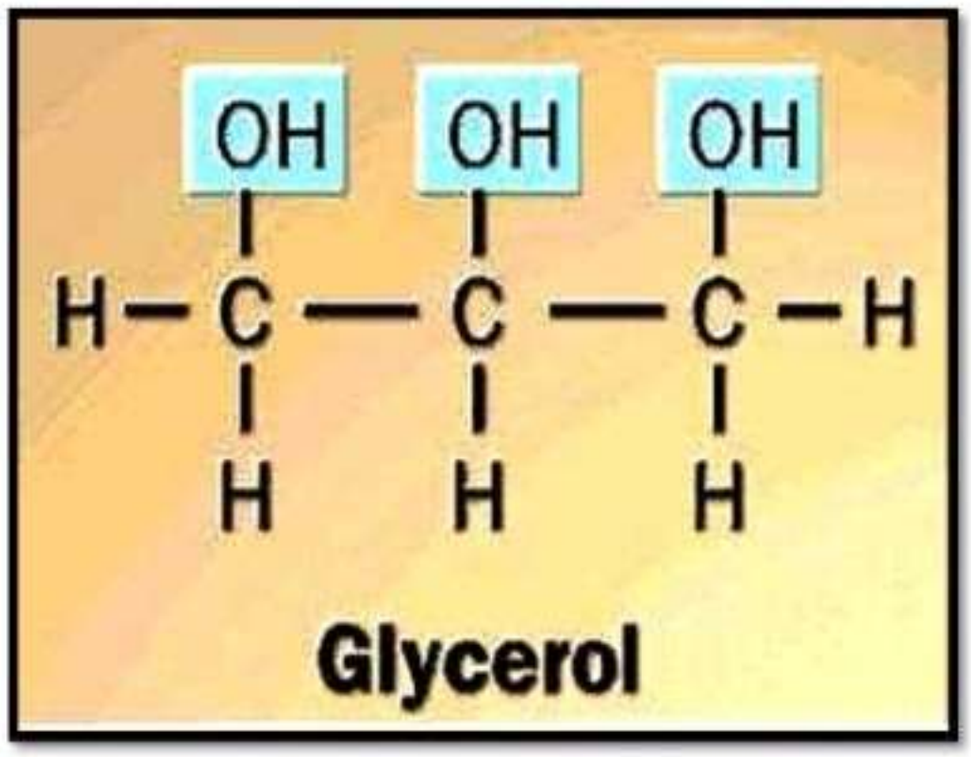
Urea

Glycerol

Isosorbide



Mannitol
(Osmotic)



Glycerol

Mechanism of Action

Osmotic diuretics are **not** **reabsorbed**

Increases **osmotic pressure** specifically in the **proximal tubule** and **loop of Henle**

Prevents passive reabsorption of H2O

Osmotic force solute in lumen > osmotic force of reabsorbed Na+

Increased H_2O and Na^+ excretion

Therapeutic Uses

Mannitol

- **Drug of choice:** non-toxic, freely filtered, non-reabsorbable and non-metabolized
- Administered **prophylatically** for acute renal failure secondary to trauma, CVS disease, surgery or nephrotoxic drugs
- **Short-term treatment of acute glaucoma**
- **Infused to lower intracranial pressure**
- Urea, glycerol and isosorbide are less efficient

Side Effects

Increased extracellular fluid volume

Cardiac failure

Pulmonary edema

Hypernatremia

Hyperkalemia secondary to diabetes or impaired renal function

Headache, nausea, vomiting

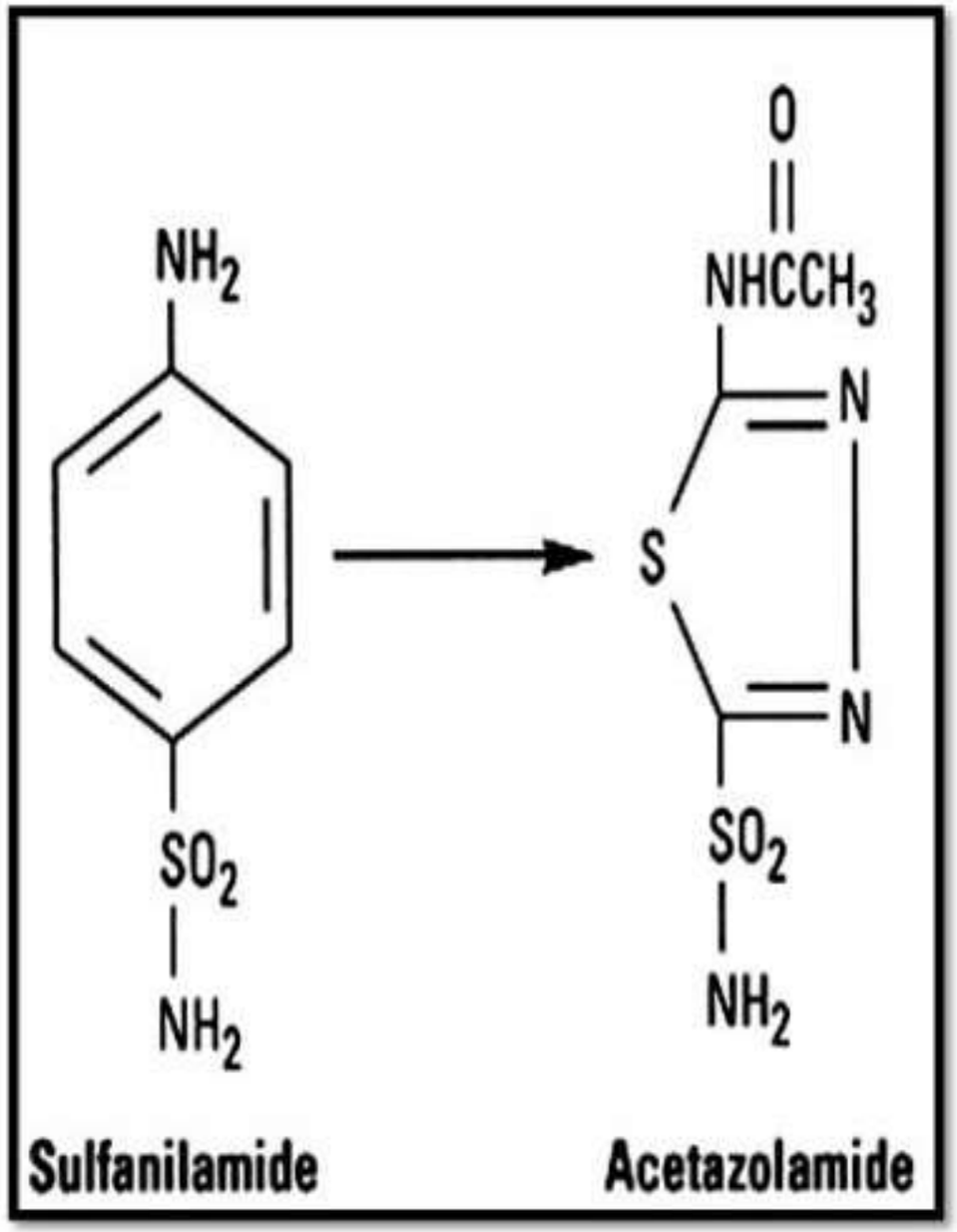
Carbonic Anhydrase Inhibitors

limited uses as diuretics

Acetazolamide

Prototype carbonic anhydrase inhibitor

Developed from sulfanilamide (caused metabolic acidosis and alkaline urine)



Mechanism of Action

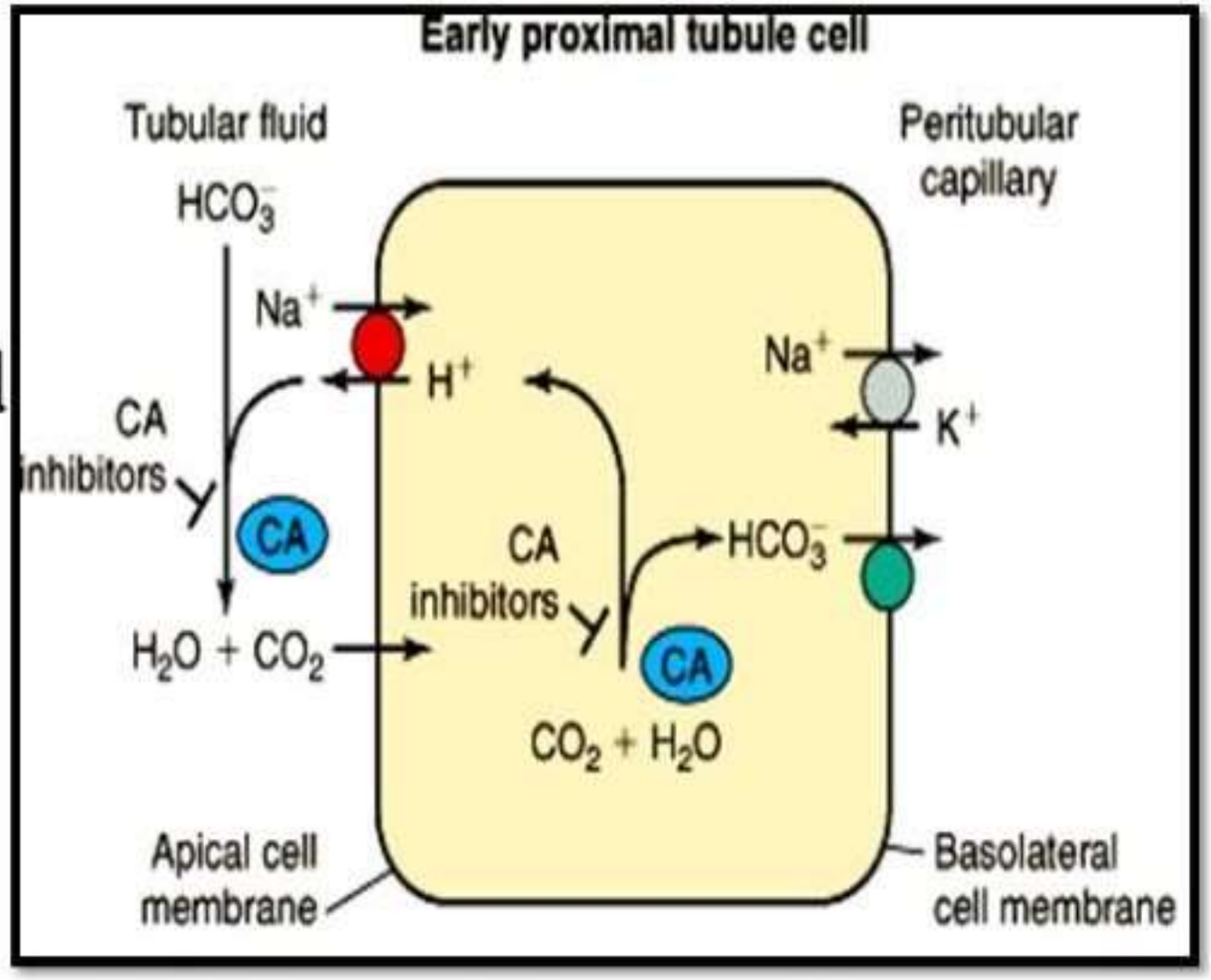
Inhibits carbonic anhydrase in renal proximal tubule cells

Carbonic anhydrase catalyzes **formation of HCO_3- and H_+ from H_2O and CO_2**

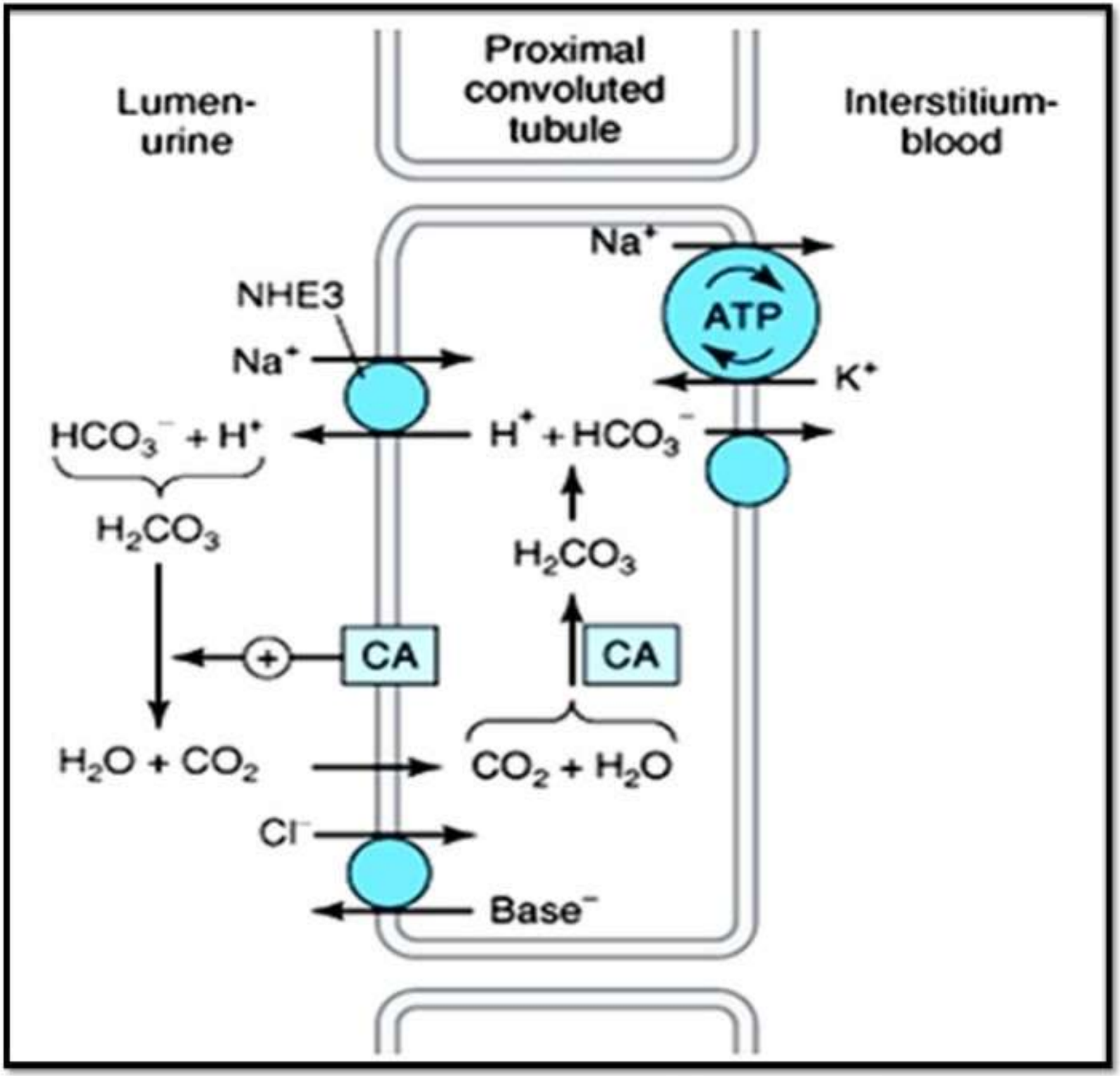
Inhibition of carbonic anhydrase **decreases $[H^+]$ in tubule lumen**

Less H+ for Na+/H+ exchange

Increased lumen Na+, increased H_2O excretion



Mechanism of Action of CA-I



Therapeutic Uses

Used to treat **chronic open-angle glaucoma**

High **aqueous humor [HCO3-]** acute **mountain sickness**

Prevention and treatment metabolic alkalosis

Mostly used in **combination with other diuretics** in resistant patients

Side Effects

Rapid tolerance

Increased HCO3- excretion causes **metabolic acidosis**

Drowsiness

Fatigue

CNS depression

Paresthesia (pins and needles under skin)

Nephrolithiasis (renal stones)

K^+ wasting

Thiazide Diuretics

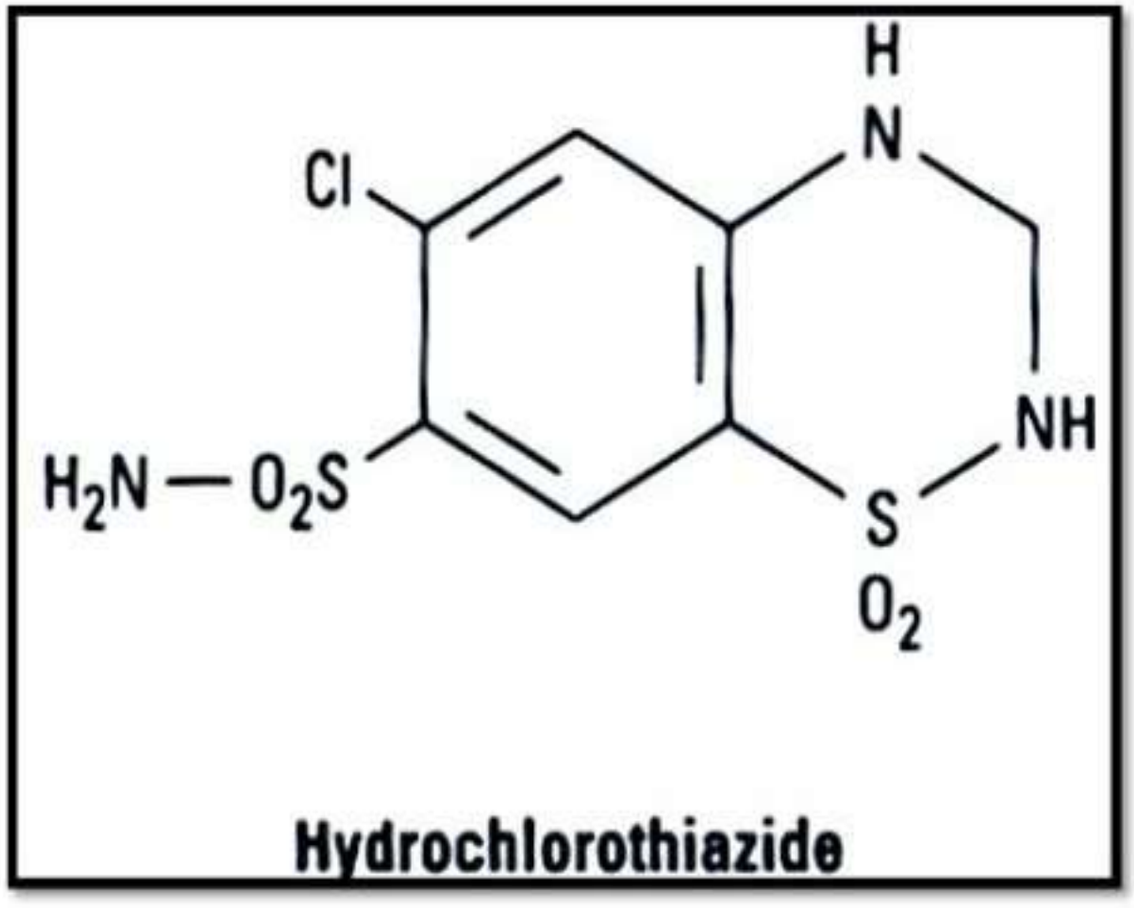
Active in distal convoluted tubule

Chlorothiazide (prototype)

Hydrochlorothiazide

Chlorthalidone

Metolazone



Hydrochlorothiazide

Mechanism of Action

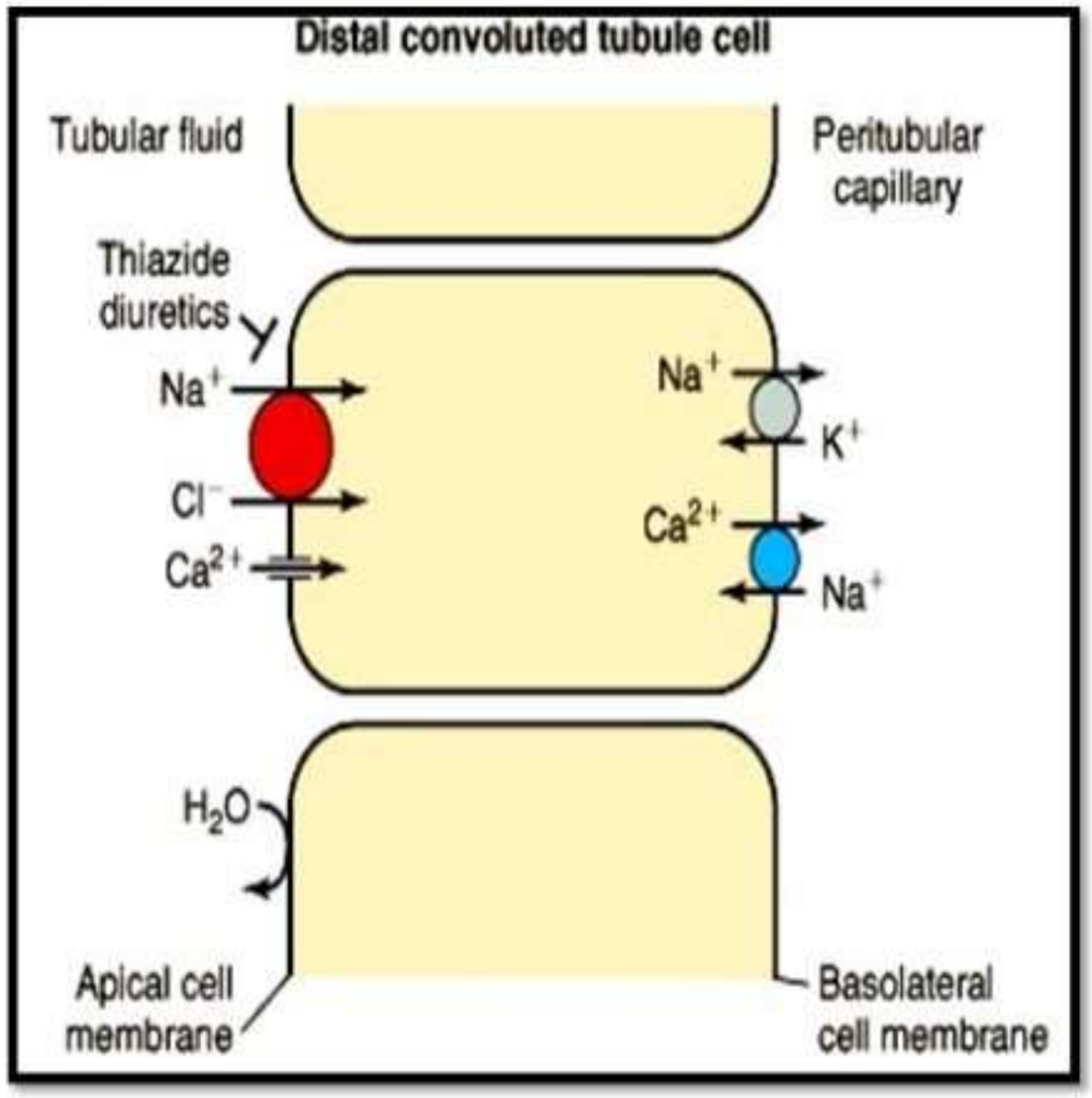
Inhibit Na+ and Cl- transporter in distal convoluted tubules

Increased Na+ and Cl- excretion

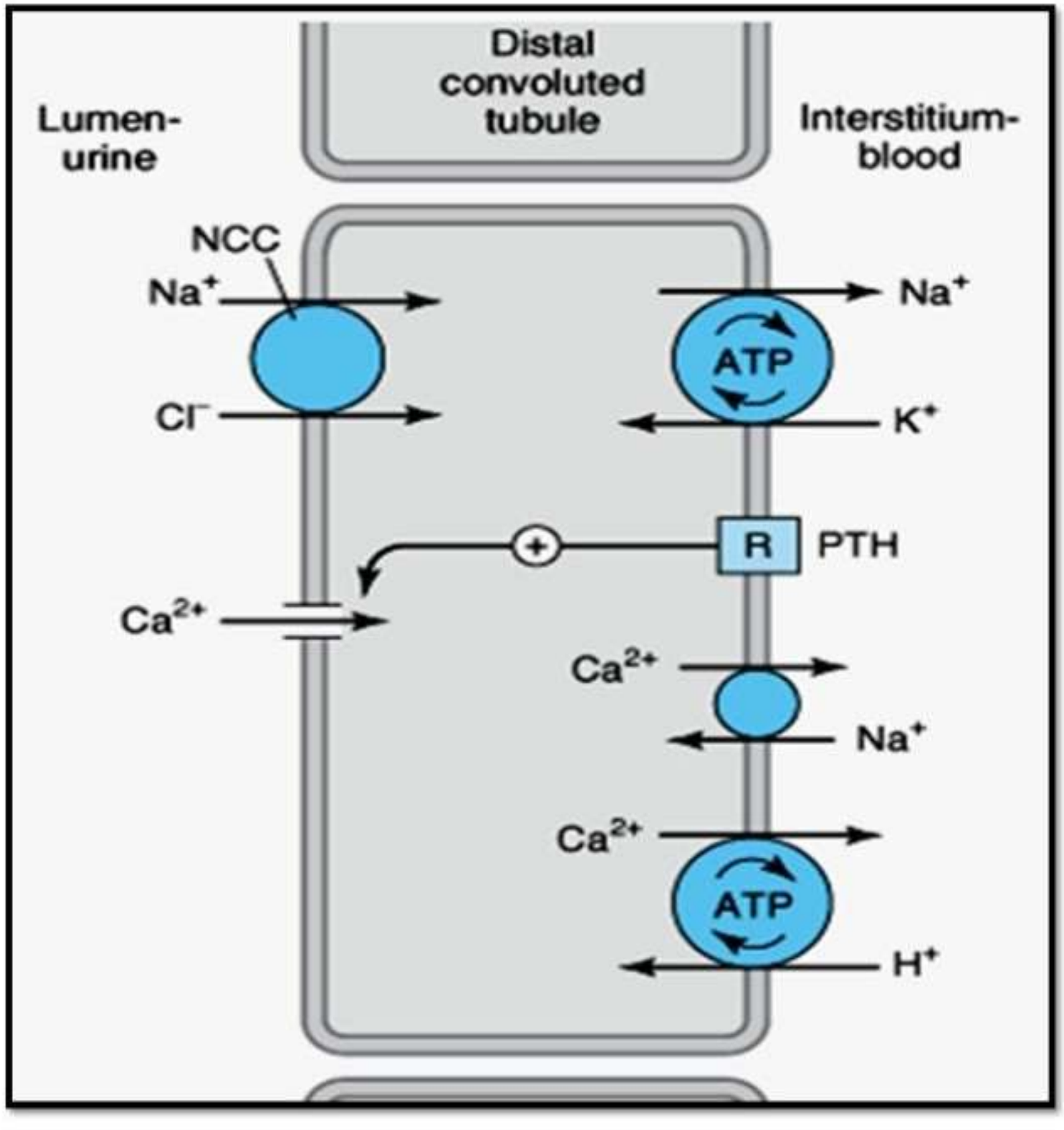
Weak inhibitors of carbonic anhydrase, increased HCO3- excretion

Increased K+/ Mg2+ excretion

Decrease Ca2+ excretion



Mechanism of Action of Thiazide



Therapeutic Uses

Hypertension

Congestive heart failure

Hypercalciuria: prevent excess Ca2+ excretion to form stones in ducts

Osteoperosis

Nephrogenic diabetes insipidus

Treatment of **Li+ toxicity**

Pharmacokinetics

Orally administered

Poor absorption

Onset of action in ~ 1 hour

Wide **range of T 1/2 amongst different thiazides, longer then loop diuretics**

Free drug enters tubules by filtration and by organic acid secretion

Side Effects

Hypokalemia

Increased Na+ exchange in CCD

Volume-contraction induced aldosterone release

Hyponatremia

Hyperglycemia

Diminished insulin secretion

Elevated plasma lipids

Hyperuricemia

Hypercalcemia

Loop Diuretics

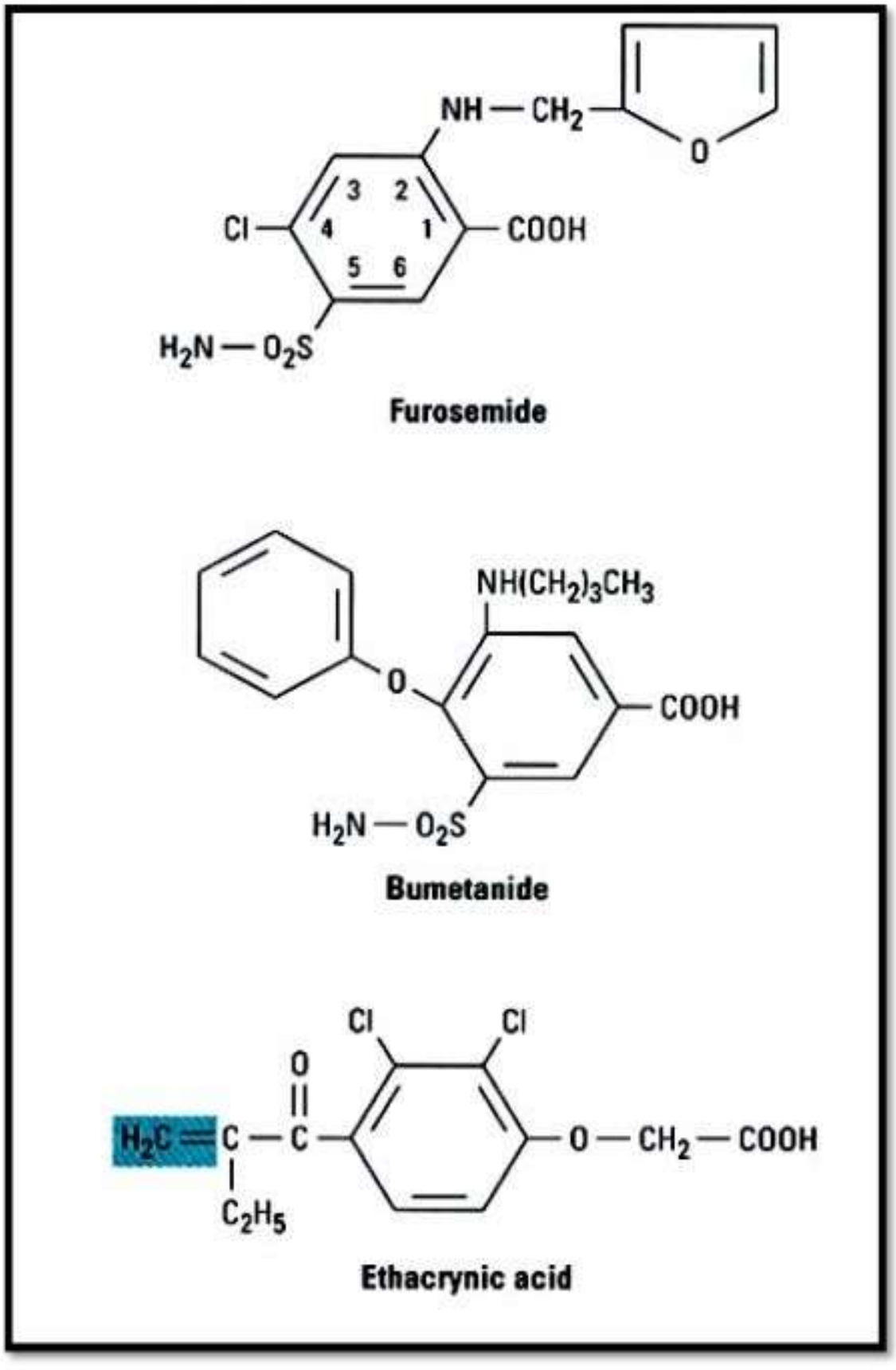
Active in "loop" of Henle

Furosemide (prototype)

Bumetanide

Torsemide

Ethacrynic acid



Furosemide

Bumetanide

Ethacrynic acid

Mechanism of Action

Enter proximal tubule via organic acid transporter

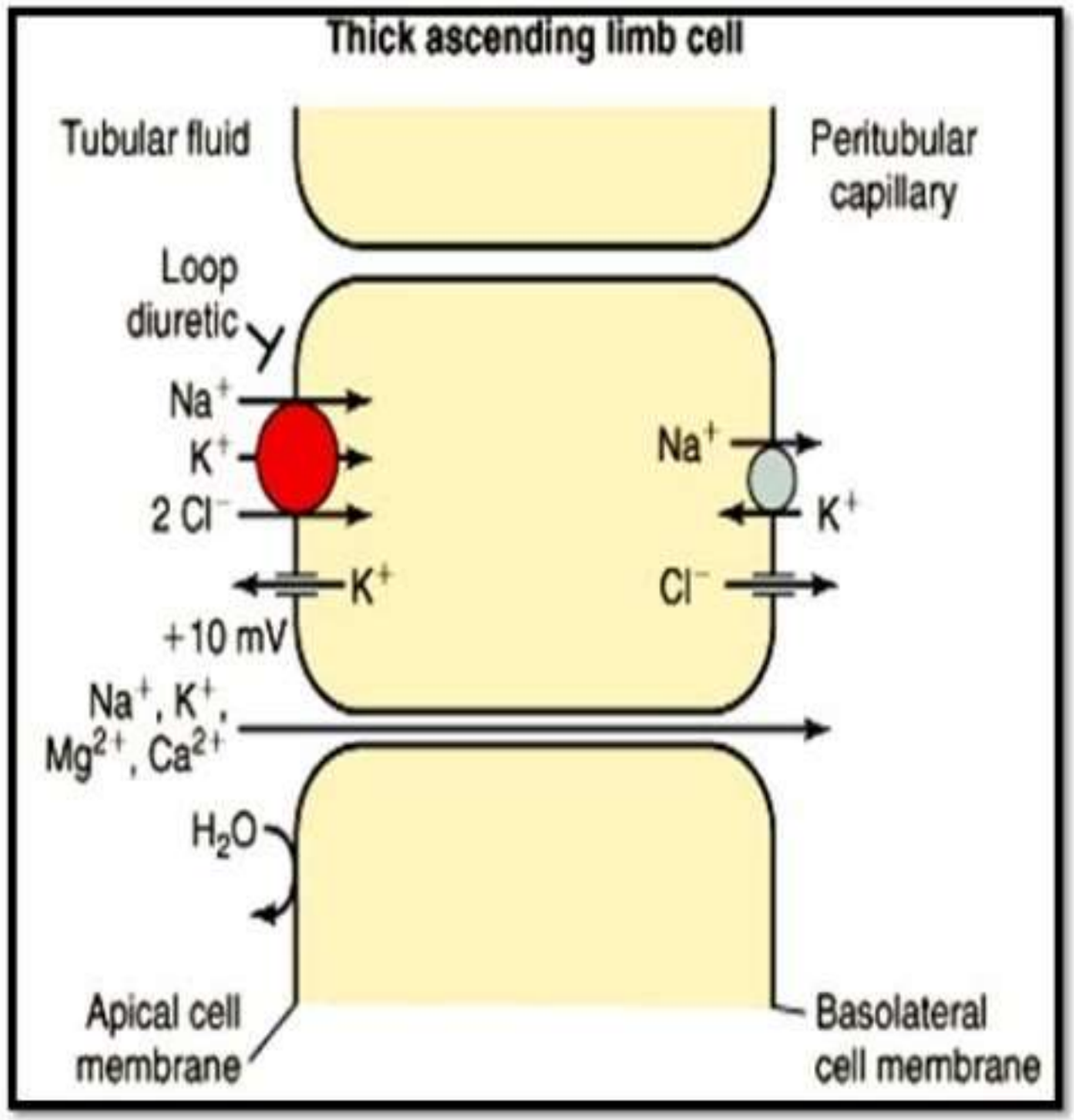
Inhibits apical Na-K-2Cl transporter in thick ascending loop of Henle

Competes with Cl- binding site

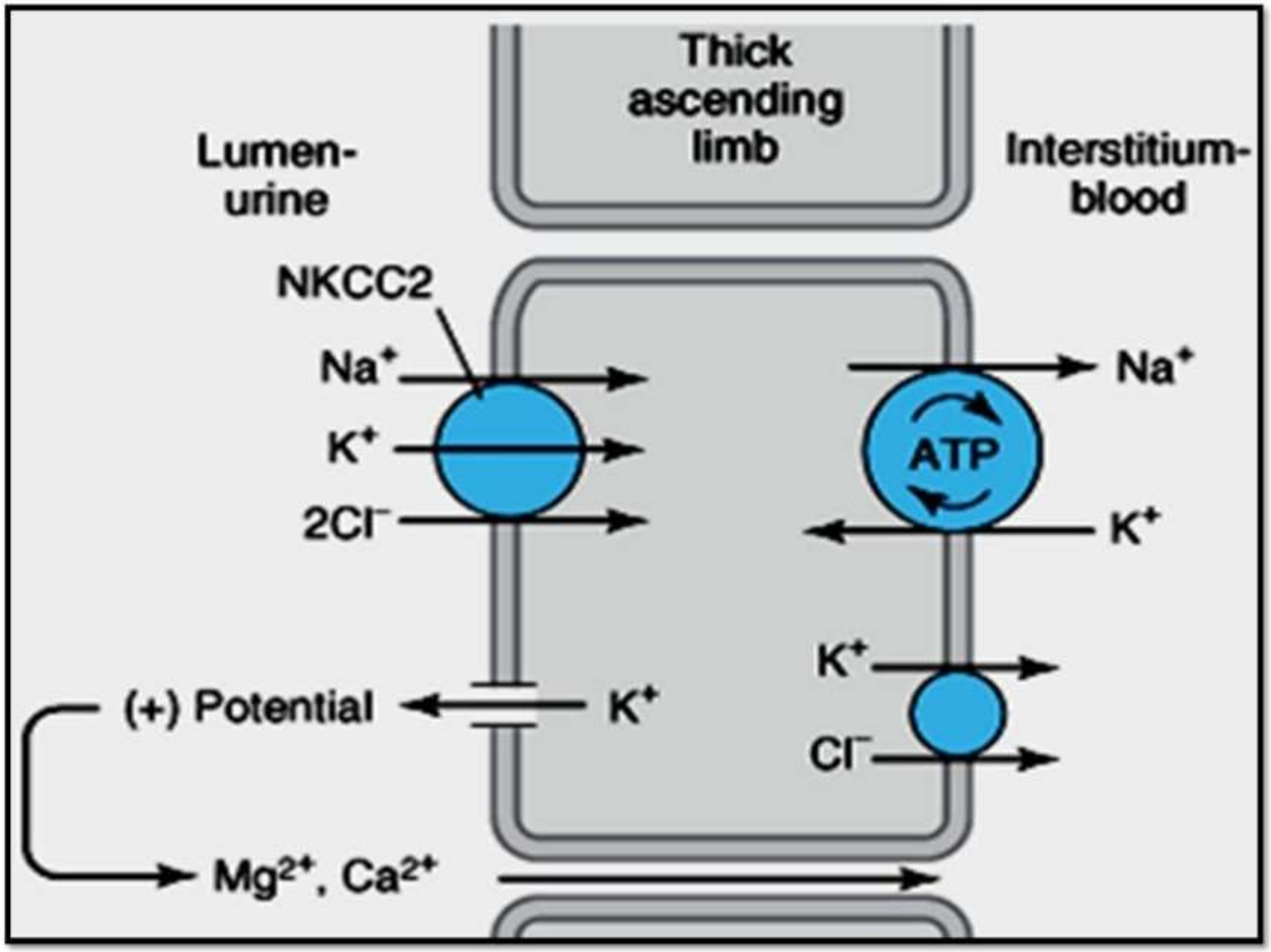
Enhances passive Mg^{2+} and Ca^{2+} excretion

Increased K+ and H+ excretion in CCD

Inhibits reabsorption of ~25% of glomerular filtrate



Mechanism of Action of Loop Diuretic



Therapeutic Uses

Edema: cardiac, pulmonary or renal

Chronic renal failure or nephrosis

Hypertension

Hypercalcemia

Acute and chronic hyperkalemia

Pharmacokinetics

Orally administered, rapid absorption

Rapid onset of action

Bound to plasma proteins: displaced by warfarin, and clofibrate

Increase toxicity of cephalosporin antibiotics and lithium

additive toxicity with other ototoxic drugs

Inhibitors of organic acid ion transport decrease potency

(i.e. probenecid, NSAID's)

Side Effects

Hypokalemia

Hyperuricemia

Metabolic alkalosis

Hyponatremia

Ototoxicity

Mg2+ depletion

K+ sparing diuretics

Three groups

- **Steroid aldosterone antagonists**

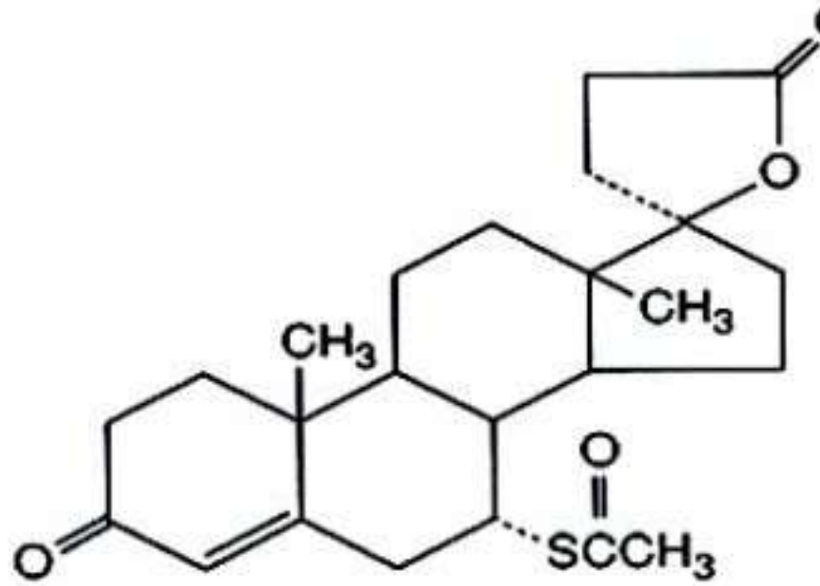
  Spironolactone, eplerenone

- **Pteridines**

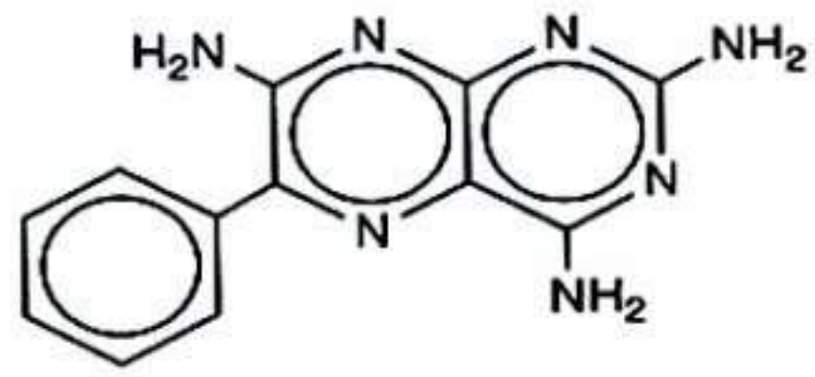
  Triamterene

- **Pyrazinoylguanidines**

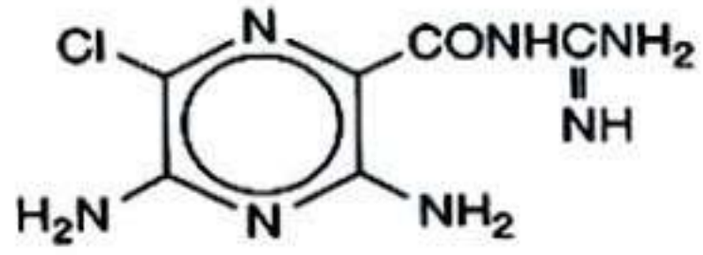
  Amiloride



Spironolactone



Triamterene



Amiloride

Mechanism of Action

K+ sparing diuretics function in CCD; decrease Na+ transport in collecting tubule

Spironolactone

competitive antagonist for mineralocorticoid receptor

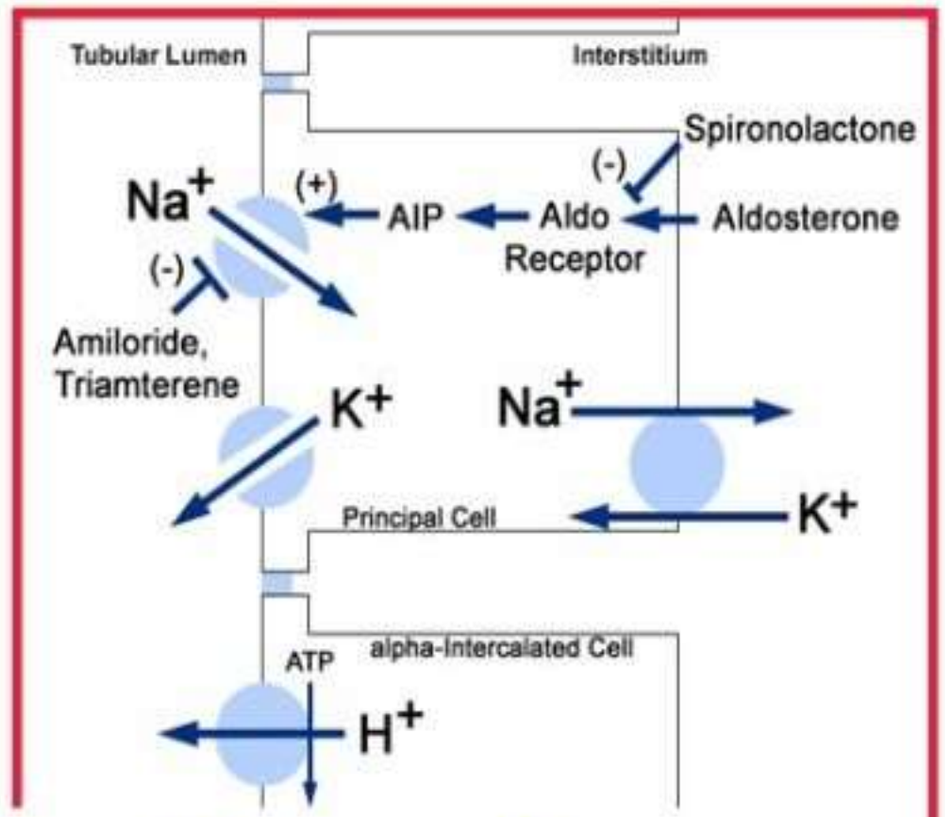
prevents aldosterone stimulated increases in Na+ transporter expression

Triamterene/Amiloride

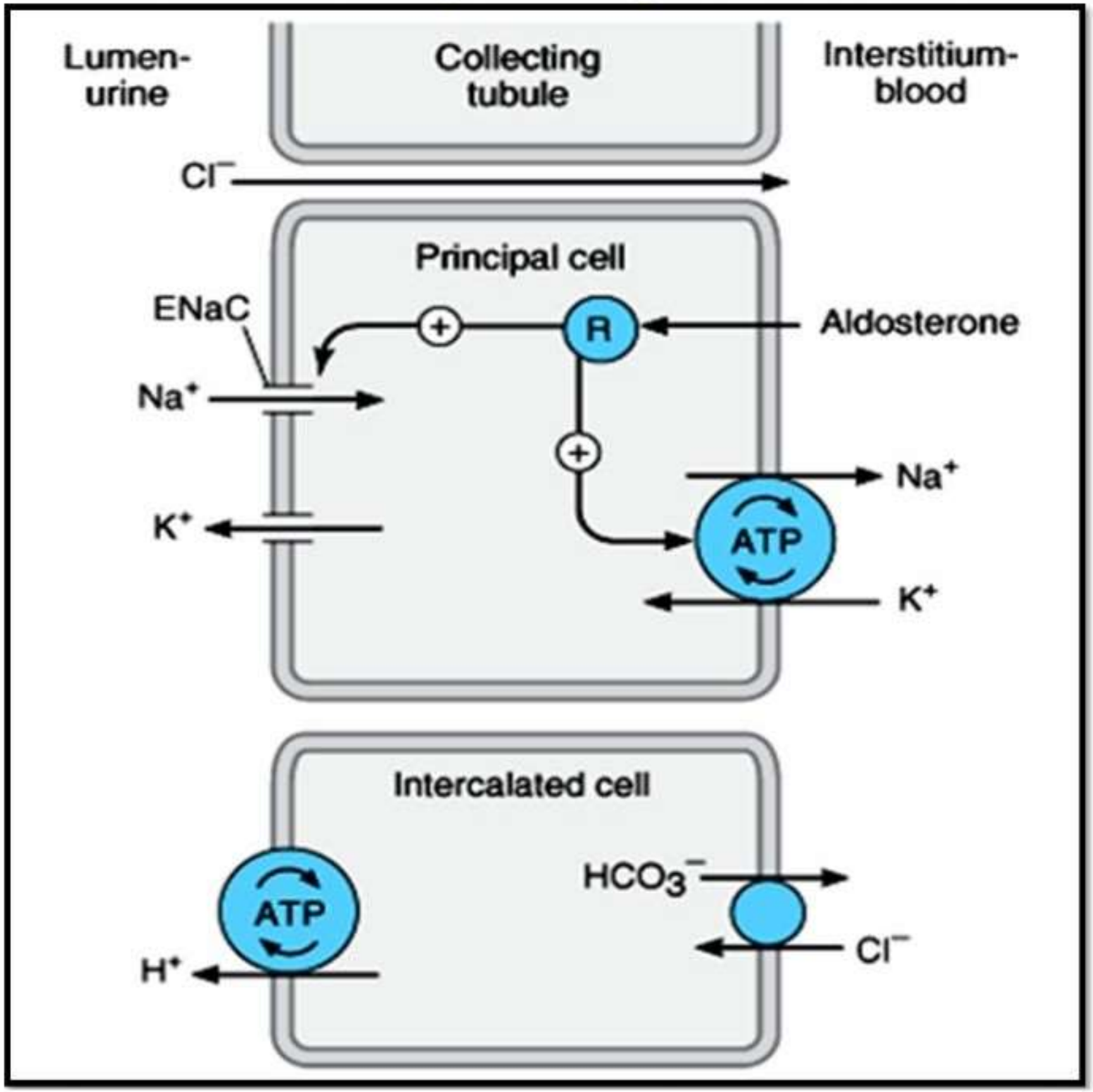
organic bases

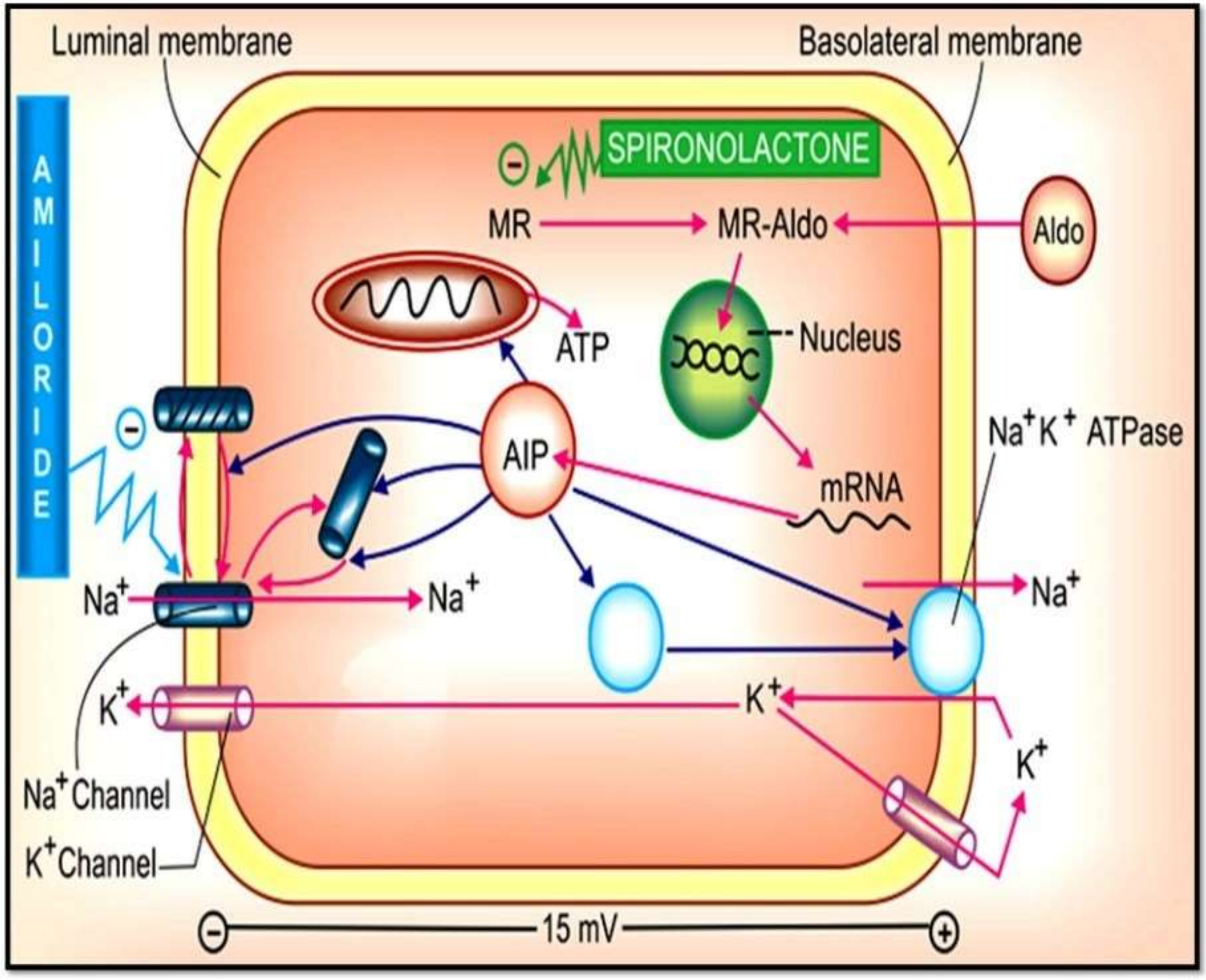
secreted into lumen by proximal tubule cells

inhibit apical Na+ channel



Potassium Sparing Diuretics




Luminal membrane
Basolateral membrane
AMILORIDE
SPIRONOLACTONE
MR
MR-Aldo
Aldo
ATP
Nucleus
AIP
mRNA
Na+K+ ATPase
Na+
Na+
Na+
K+
K+
K+
Na+Channel
K+Channel
15 mV

Therapeutic Uses

Primary hyperaldosteronism

adrenal adenoma, bilateral adrenal hyperplasia.

Congestive heart failure

Cirrhosis

Nephrotic syndrome in conjunction with K+ wasting diuretics

Pharmacokinetics

Spironolactone

Orally administered

Aldactazide: spironolactone/thiazide combo

Amiloride

- Oral administration, 50% effective
- Not metabolized
- Not bound to plasma proteins

Triamterine

- Oral administration, 50% effective
- 60% bound to plasma proteins
- Liver metabolism, active metabolites

Side Effects

Hyperkalemia: Monitor plasma [K+]

Spironolactone: Gynecomastia

Triamterene: Megaloblastic anemia in cirrhosis patients

Amiloride: Increase in blood urea nitrogen, glucose intolerance in diabetes mellitus

Furosemide is preferred usually to ethacrynic acid for a number of reasons:

- ❖ It is **less ototoxic.**
- ❖ It has **broader dose response curve**.
- ❖ It is **more convenient for i.v. use.**
- ❖ It **causes fewer gait side effects.**

Loop diuretics

- ✓ They inhibit Na/K/2Cl symporetr.
- ✓ Acts at thick ascending loop of henle.
- ✓ These are Ca wasting drugs.
- ✓ They cause heavy diuresis.
- ✓ Para thyroid hormone independent Ca absorption.
- ✓ It can reabsorb 25%to 30% of Na.

Thiazide diuretics

- ✓ They act by inhibiting Na/Cl symporter.
- ✓ Acts at distal convoluted tubule.
- ✓ These are Ca retaining drugs.
- ✓ They cause mild diuresis.
- ✓ Para thyroid hormone dependent Ca absorption.
- ✓ It can reabsorb 8% of Na.

Drugs used in renal disorders

I. Drugs that modify salt excretion:

A. PCT: Carbonic anhydrase inhibitors
B. TAL: Loop diuretics
C. DCT: Thiazides
D. CCT; K-spairing diuretics
E. Osmotic diuretics; manitol

II. Drugs that modify water excretion

A. Osmotic diuretics: Manitol
B. ADH agonists: Desmopressin
C. ADH antagonists: Conivaptan, demeclocycline, lithium

Diuretic	Site of Action	Adverse Effects	Special points
Loop Diuretics	Thick Ascending Limb of Henle (NaK2Cl inhibition) Weak CAI action	Hyponatremia Hypomagnesaemia Hypocalcaemia Hyperuricemia Hyperglycemia Hyperlipidemia Hyperuricemia Ototoxic (ECA)	Most potent, Most Potent is Bumetanide, Effective even in low GFR, All except Ethacrynic acid are sulphonamide related, Used in Acute LVF, Pulmonary Edema, Nephrotic syndrome, ARF NSAIDS blunt effect
Thiazide Diuretics	DCT (NaCl)	Hypokalemic metabolic alkalosis (Gitelman's Syndrome) Hypercalcemia	Moderate, Chlorthalidone is Longest acting, Paradoxical effect in Diabetes Insipidus First line in Hypertension,

Diuretic	Site of Action	Adverse Effects	Special points
Carbonic anhydrase inhibitors	PTC (inhibition of CAE)	Metabolic Acidosis	Weak, Used in Glaucoma, Petit mal epilepsy, Acute mountain sickness, to alkaline the urine
Osmotic Diuretics	PTC, LOH, DCT	Shifting of fluid from intracellular to extracellular, Hyponatremia, Pulmonary edema	Used in Glaucoma, Poisoning, Increased ICT, impending ARF
Potassium Sparing Diuretics	CD	Hyperkalemia Antiandrogenic effect	Weak, As supplement to other to counter the hypokalemia, Canrenone is active metabolite, used in Conn's syndrome (Primary Hyperaldosteronism), cirrhotic edema

Antidiuretic Hormone (ADH)

Agonists and Antagonists

Antidiuretic Hormone (ADH) Agonists and Antagonists

- ADH & Desmopressin are ADH Agonists
- Peptides must be given parenterally **(rapid degradation by trypsin)**
- Secretion of ADH increase in response to:
  - ↑ Plasma osmolarity
  - Hypovolemia, hypotension (bleeding, dehydration)

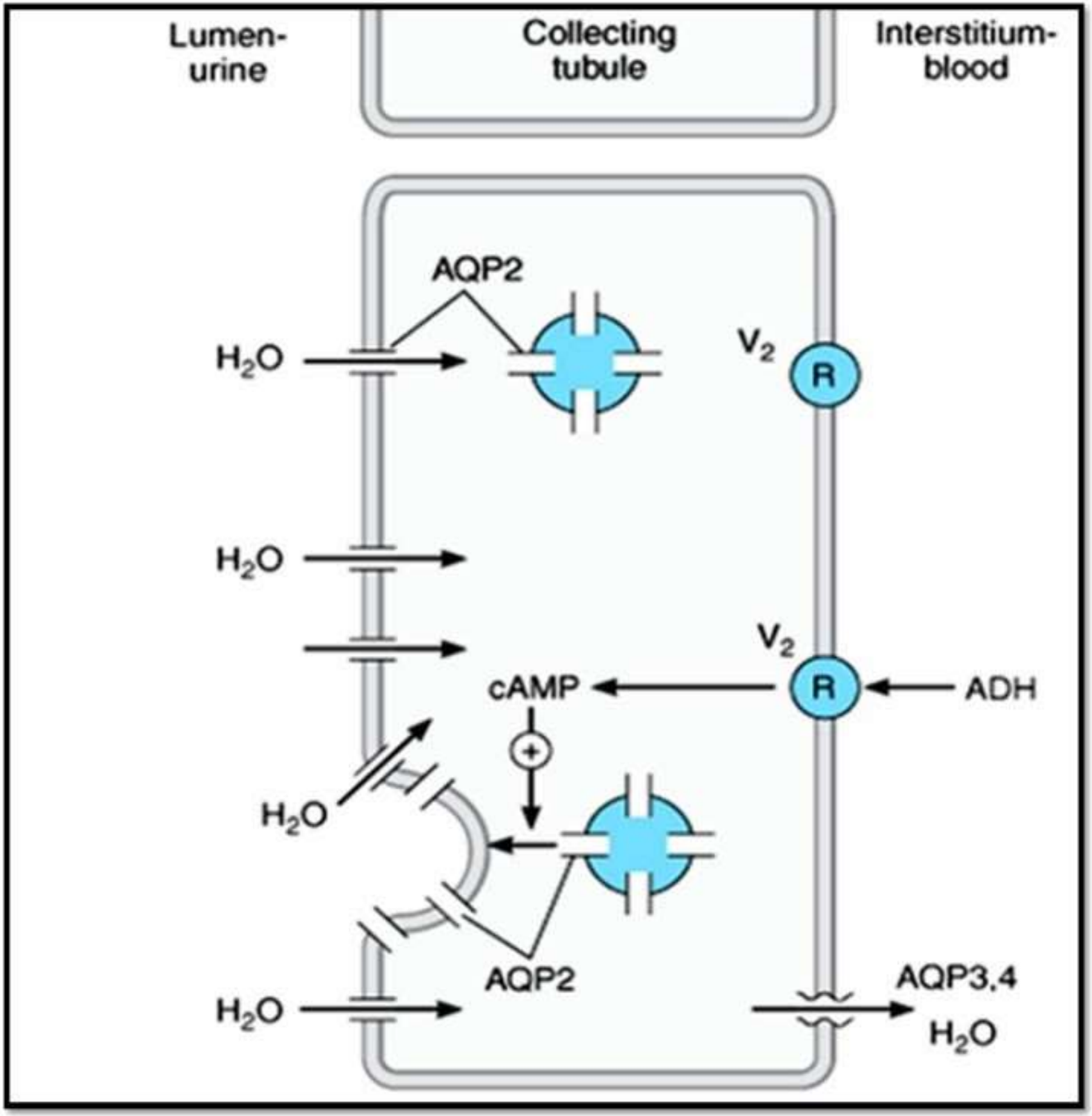
- Demeclocycline and conivaptan are ADH antagonists
- Lithium has ADH antagonist effect but never used for this purpose

Mechanism of Action

- Works in ascending limb of Henle's loop and collecting ducts
- **Two kind of receptors:**
  - V1: vascular smooth muscle→ vasoconstriction
  - V2: kidney → increase water permeability of tubular epithelium → water reabsorption

ADH

- ADH facilitates **water reabsorption** from the collecting tubule by:
- **Activation of V_2 receptors** (coupled to GS, **stimulate AC) increase cAMP** ⟶
- Cause **insertion of additional aquaporin AQP2 water channels** into the luminal membrane in this part of the tubule


Lumen-
urine
Collecting
tubule
Interstitium-
blood
AQP2
H_2O
V_2
R
H_2O
H_2O
V_2
cAMP
R
ADH
H_2O
AQP2
H_2O
AQP3,4
H_2O

ADH antagonists

- **Conivaptan** is an ADH inhibitor at V_{1a} and V_2 receptors
- **Demeclocycline and Li** inhibit the action of ADH at some point distal to the generation of cAMP and presumably the insertion of water channels into the membrane.

Clinical uses of ADH Agonists

- ADH and desmopressin reduce urine volume and concentrate it, are useful in **Pitutary Diabetes Insipidus** (**<u>not for</u> nephrogenic DI** Rx by salt restriction, thizides and loop diuretics)
- **DI due to head trauma or brain surgery**
- **Gastrointestinal bleeding due to portal hypertension** (by reducing mesenteric blood flow)

Clinical uses of ADH Antagonists

- Oppose the actions of ADH and other naturally occurring peptides (certain tumors; small cell carcinoma of the lung) that act on the same V_2 receptors, ➡ significant water retention and dangerous hyponatremia.
- Syndrome of inappropriate ADH secretion (SIADH) can be treated with demeclocycline and conivaptan

Adverse effects

- **ADH, Desmopressin,** water overload, hyponatremia
- **Demeclocycline:** bone and teeth abnormalities
- **Li:** nephrogenic DI