

# **Diuretic Agents**

**2020**

- A "diuretic" is an agent that increases urine volume.
- They decrease extracellular fluid (ECF) and effective circulating volume.
- A Natriuretic causes an increase in renal sodium excretion.
- Because natriuretics also increase water excretion, they are usually called diuretics.
- Osmotic diuretics are diuretics that are not directly natriuretic.

Diuretics increase urine excretion mainly by ↓ reabsorption of salts and water from kidney tubules

These agents are **ion transport inhibitors** that decrease the reabsorption of  $\text{Na}^+$  at different sites in the nephron, thus increasing the volume of the urine and often change its pH as well as the ionic composition of the urine and blood.

Water, digitalis, caffeine and theophylline have diuretic activity, but are not diuretics.

## General consideration

- Diuretics are widely used in the management of any condition associated with salt and water retention.
- Diuretics act at different sites of the nephron (the basic unit of the kidney).
- Diuretics are highly effective, relatively safe and cheap.
- Diuretics, especially thiazides, are considered first-line therapy for most hypertensive pts.
- Accumulating evidence proves that in hypertensive patients, diuretics, particularly thiazides decrease the risk of cardiovascular disease, fatal and nonfatal MI and stroke.

# Mechanism of Diuretics Antihypertensive action

- By increasing urine output  $\rightarrow$   $\downarrow$  plasma and stroke volume  $\rightarrow$   $\downarrow$  CO  $\rightarrow$   $\downarrow$  BP

The initial  $\downarrow$  in CO leads to  $\uparrow$  peripheral resistance, but with chronic use extracellular fluid and plasma volume return to normal and peripheral resistance  $\downarrow$  to values lower than those observed before diuretic therapy

- Thiazides also have direct vasodilating effect.

## Diuretic therapy cautions

Excessive diuretic usage may lead to a decrease in the effective arterial blood volume which causes a reduction in the perfusion of vital organs.

Therefore, the use of diuretics to treat edema requires careful monitoring of the patient's hemodynamic status and an understanding of the pathophysiology of the underlying condition.

The decrease in blood volume can lead to hypotension and collapse

Blood viscosity rises due to an increase in erythro- and thrombocyte concentration, which could lead to an increased risk of intravascular coagulation or thrombosis

- Many diuretics (loop diuretics, thiazides, amiloride, and triamterene) exert their effects on specific membrane transport proteins in renal tubular epithelial cells,
- Other diuretics exert osmotic effects that prevent water reabsorption (mannitol),
- Still others inhibit enzymes (acetazolamide),
- Some others block hormone receptors in renal epithelial cells (spironolactone).

## **Classification of diuretics**

Diuretics are usually classified according to their site of action in the kidney; their mode of action and to a lesser extent by their potency

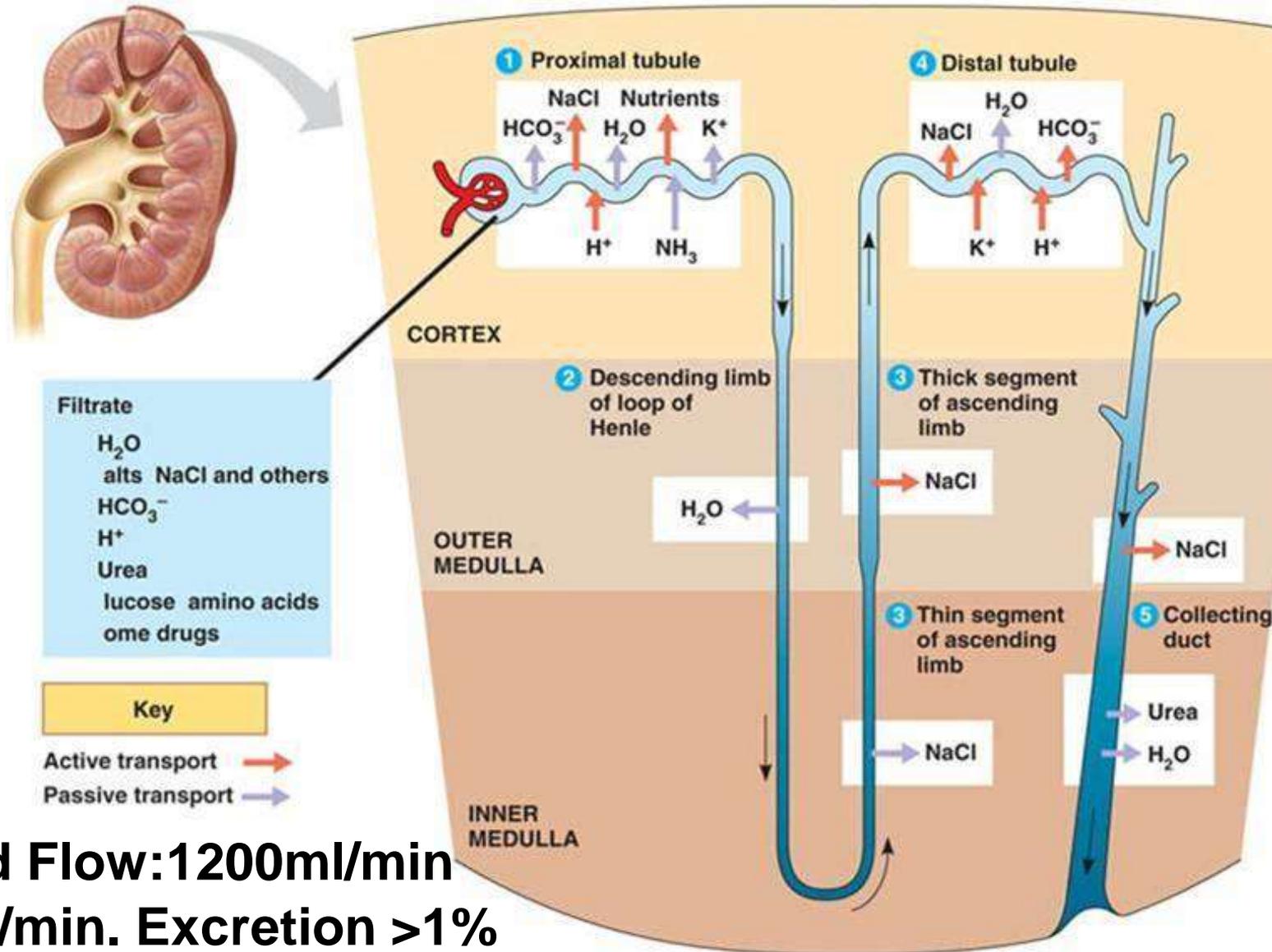
## **Diuretic resistance (Therapeutic Failure)**

- Continued ingestion of salt
- Impairment of organic acid secretion mechanisms in the proximal tubules due to diseases or drugs
- Secondary hyperaldosteronism
- Lowered renal blood flow  $\rightarrow$   $\uparrow$   $\text{Na}^+$  reabsorption (post-diuretic salt retention).
- Lowered bioavailability of the drug.

## **Management of diuretic resistance**

Restriction of sodium intake, changes in dose, changes in timing, and combination of diuretic therapy

# Permeability of the segments



**Renal Blood Flow: 1200ml/min**

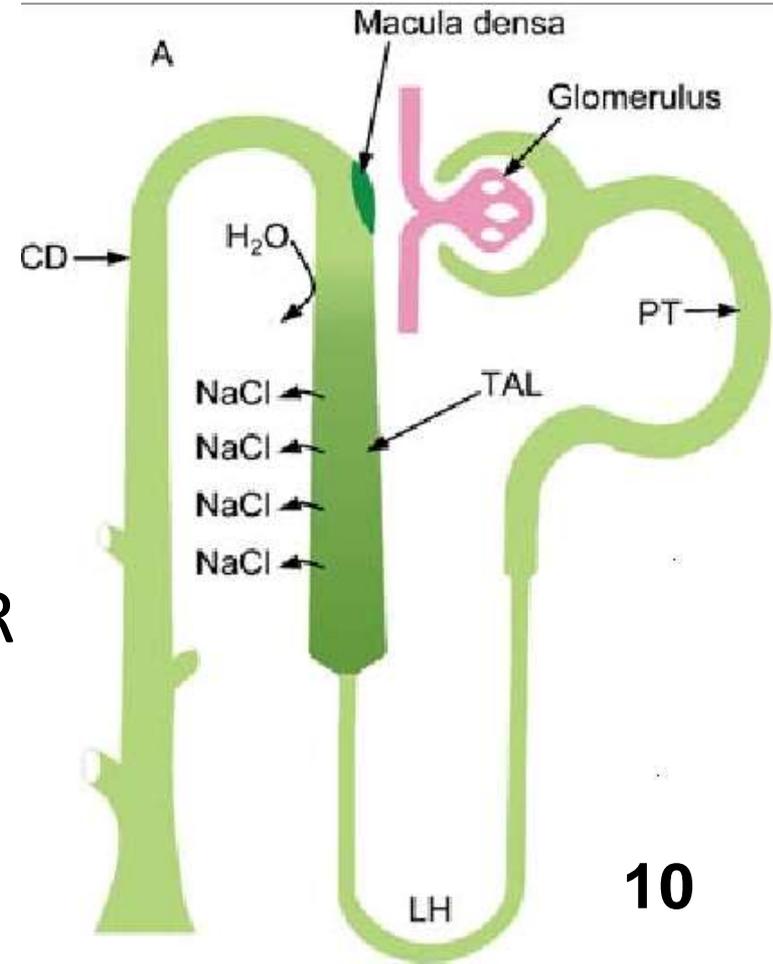
**GFR: 120 ml/min. Excretion >1%**

**Reabsorb  $\text{Na}^+$ ,  $\text{Cl}^-$ , &  $\text{HCO}_3^-$  99% while  $\text{K}^+$  about 85%**

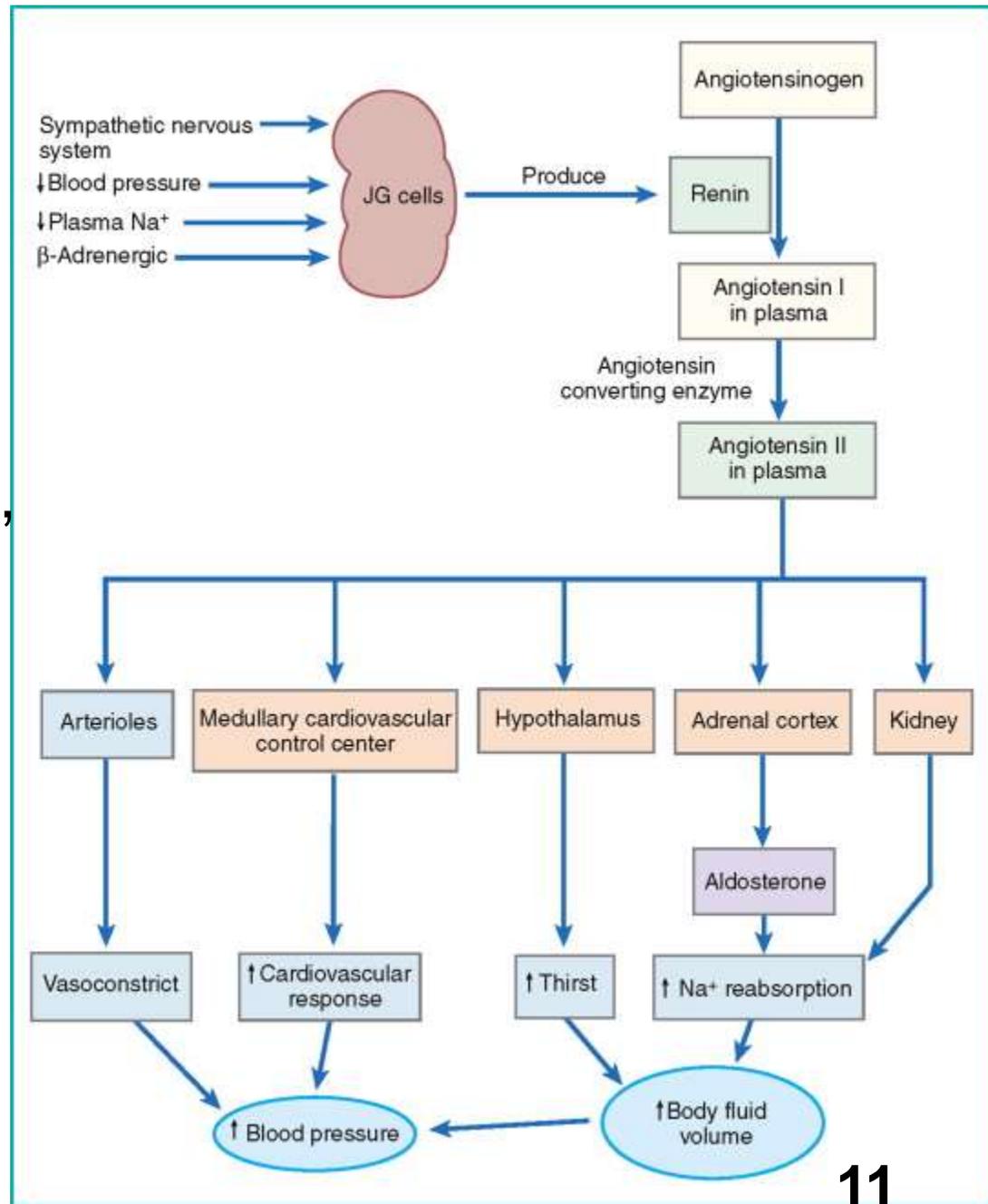
# Macula Densa

The macula densa is strategically located to sense concentrations of NaCl leaving the loop of Henle to protect from salt and volume wasting.

If the conc. of NaCl is too high, it sends a chemical signal to the afferent arteriole of the same nephron, causing it to constrict. This, in turn, causes a decrease in Glomerular filtration rate GFR



If the conc. of NaCl is too low, it send signal to **juxtaglomerular cells** in the wall of the afferent arteriole to release renin, thus activating the **Renin angiotensin Aldosterone** system which causes vasoconstriction and Na<sup>+</sup> retention.

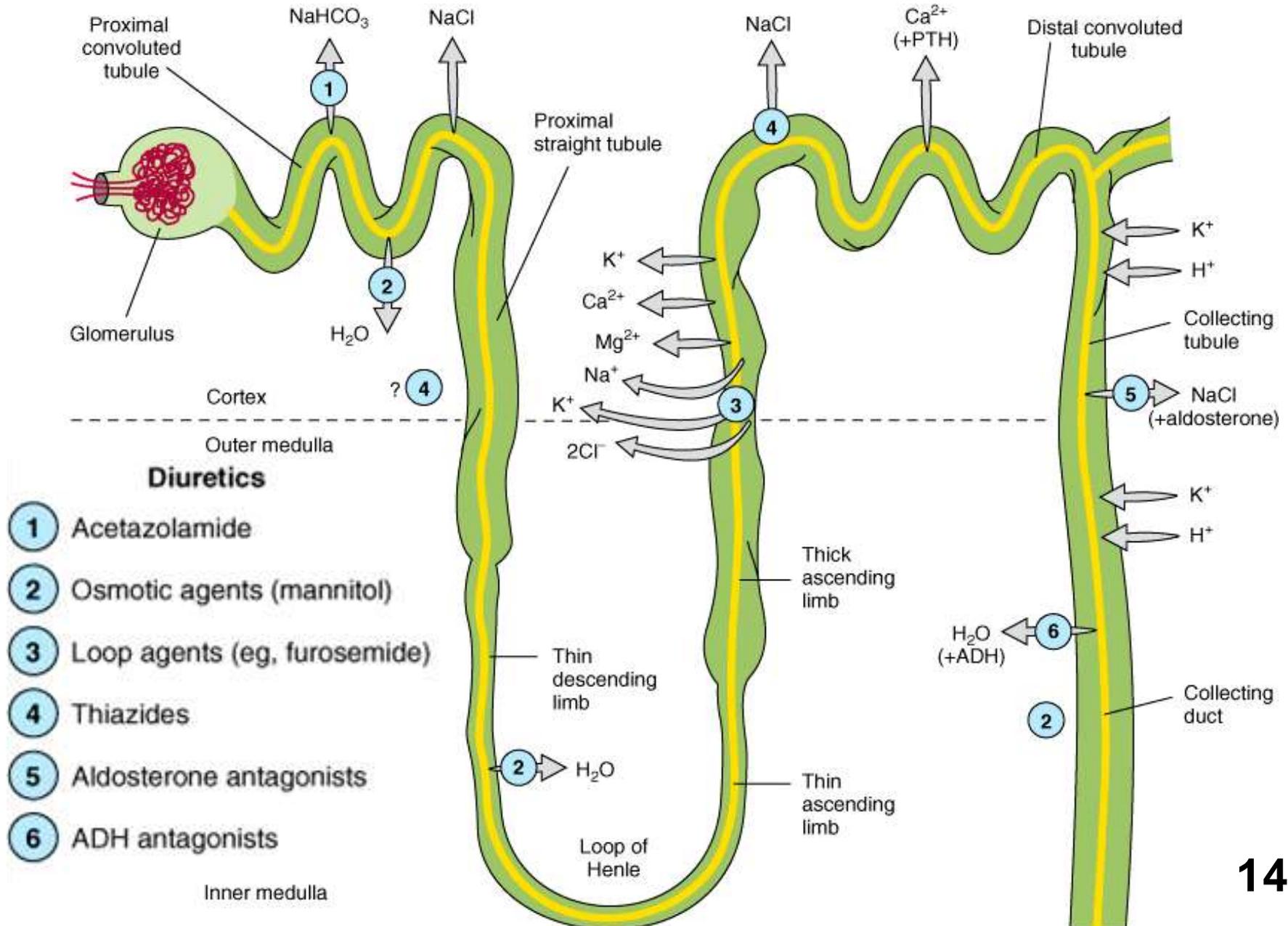


- **Caffeine** is a weak diuretic because it nonspecifically and weakly blocks adenosine receptors that participate in the control of proximal tubule  $\text{Na}^+$  reabsorption in the kidney.
- **Rolofylline**, an adenosine A1 receptor antagonists (A new class of drugs), have potent vasomotor effects in the renal microvasculature and blunts both proximal tubule and collecting duct  $\text{NaCl}$  reabsorption.

# Prostaglandins

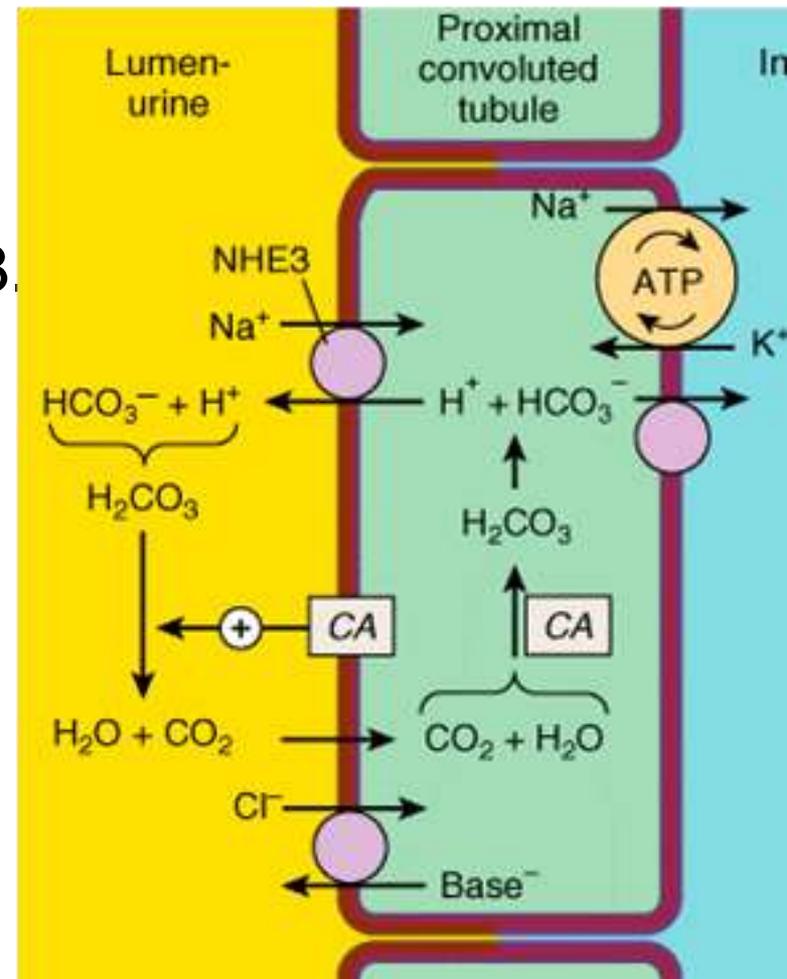
- Five subtypes (PGE, PGI, PGD, PGF, and thromboxanes) are synthesized in the kidney.
- The **PGE** participate in the regulation of salt reabsorption and play a role in the activity of certain diuretics.
- **PGE2** decreases both Na<sup>+</sup> reabsorption in the **TAL of Henle's** loop and **ADH**-mediated water transport in collecting tubules.
- These actions of PGE2 contribute to the diuretic efficacy of loop diuretics.
- Blockade of prostaglandin synthesis can therefore interfere with loop diuretic activity.

# Pharmacology of Diuretic Agents



# Carbonic Anhydrase Inhibitors

- Carbonic anhydrase is responsible for reabsorption of  $\text{Na}^+\text{HCO}_3^-$  from proximal convoluted tubules and for formation of aqueous humor (fluid of the eye)
- Carbonic anhydrase (CA) predominant location is the luminal membrane of the PCT where it catalyzes the dehydration of  $\text{H}_2\text{CO}_3$ .
- CA inhibitors block  $\text{NaHCO}_3$  reabsorption & decrease  $\text{Na}^+/\text{H}^+$  transporter activity
- Only mild natriuresis (1-3%)
- Increased bicarbonate in urine



- **CA** inhibitors are now rarely used as diuretics, their major clinical use: glaucoma

## **Acetazolamide (prototype)**

### **Pharmacokinetics:**

- Well absorbed after oral administration.
- An increase in urine pH from the  $\text{HCO}_3^-$  diuresis is apparent within 30 minutes, is maximal at 2 hours, and persists for 12 hours after a single dose.
- Excretion of the drug is by secretion in the proximal tubule.

# Pharmacodynamics

- 85% of the  $\text{HCO}_3^-$  reabsorption in the PCT is inhibited.
- Some  $\text{HCO}_3^-$  can still be absorbed at other nephron sites by CA-independent mechanisms, so the overall effect is only about 45% inhibition
- CA inhibition causes significant  $\text{HCO}_3^-$  losses & hyperchloremic metabolic acidosis.
- $\text{HCO}_3^-$  depletion leads to enhanced NaCl reabsorption, so, the diuretic efficacy of acetazolamide decreases significantly with use over 2 or 3 days.
- The ciliary body of the eye secretes  $\text{HCO}_3^-$  from the blood into the aqueous humor.
- Formation of cerebrospinal fluid by the choroid plexus involves  $\text{HCO}_3^-$  secretion.

# Clinical Indications

**Glaucoma:** used to control intraocular pressure during **acute attacks of glaucoma** and for **short-term reductions in intraocular pressure** both preoperatively and postoperatively in patients who require ocular surgery, Acetazolamide is effective orally & topically.

- Topically, **dorzolamide**, **brinzolamide** reduce intraocular pressure without systemic effects.
- **Urinary alkalization** : to increase renal excretion of weak acids e.g. cystin and uric acid.

**Metabolic Alkalosis**, acetazolamide produces metabolic acidosis so it is useful in correcting the alkalosis.

## **Acute Mountain Sickness**

- Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers who rapidly ascend above 3000 m.
- By decreasing cerebrospinal fluid formation and by decreasing the pH of the cerebrospinal fluid and brain, acetazolamide can increase ventilation and diminish symptoms of mountain sickness.

**Epilepsy** : because acidosis results in ↓seizures.

**To increase urinary phosphate excretion** during severe hyperphosphatemia.

# Toxicity

- **Hyperchloremic metabolic acidosis**

Acidosis results from chronic reduction of body bicarbonate stores.

This limits the diuretic efficacy of these drugs to 2 or 3 days but acidosis persists as long as the drug is continued.

- **Renal Stones** Calcium salts & phosphate salts are relatively insoluble at alkaline pH, thus, renal stone formation from these salts is enhanced.

- **Renal Potassium Wasting**

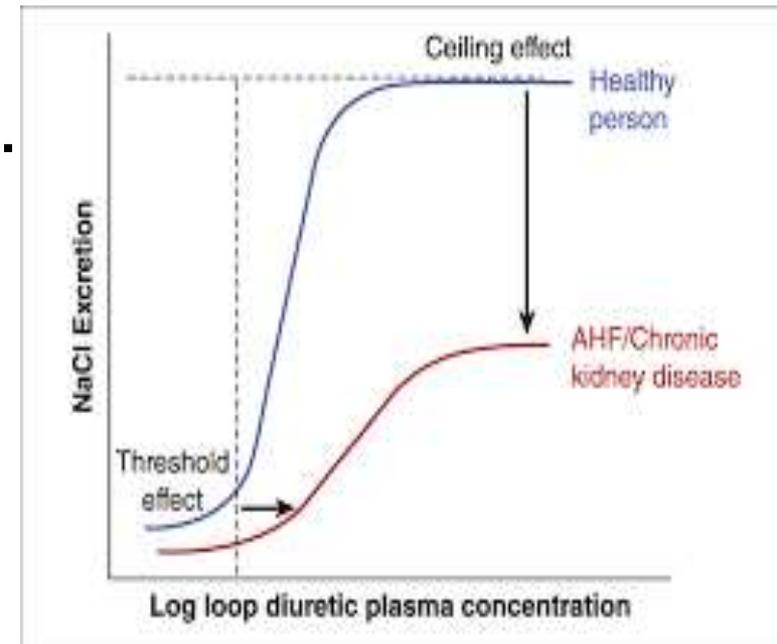
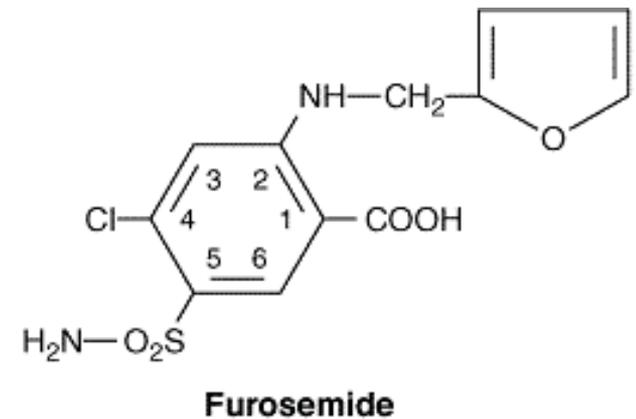
## Other Toxicities

- Drowsiness and paresthesias (an abnormal sensation, typically tingling or pricking).

- Hypersensitivity reactions may also occur.

# Loop Diuretics

- Loop diuretics selectively inhibit NaCl reabsorption in the **TAL**.
- Because of the large NaCl absorptive capacity of **TAL**, loop diuretics are the most efficacious diuretic agents currently available.
- They are high ceiling diuretics.
- **Furosemide (Frusemide)**, **Bumetanide** and **Torseamide** are sulfonamide loop diuretics but **Ethacrynic acid** is not a sulfonamide.



# Pharmacokinetics

Absorption of oral **torseamide** in 1 hour, duration 4–6 hours, **furosemide** 2–3 hours, duration 2–3 hours .

Elimination by the glomerular filtration and tubular secretion.

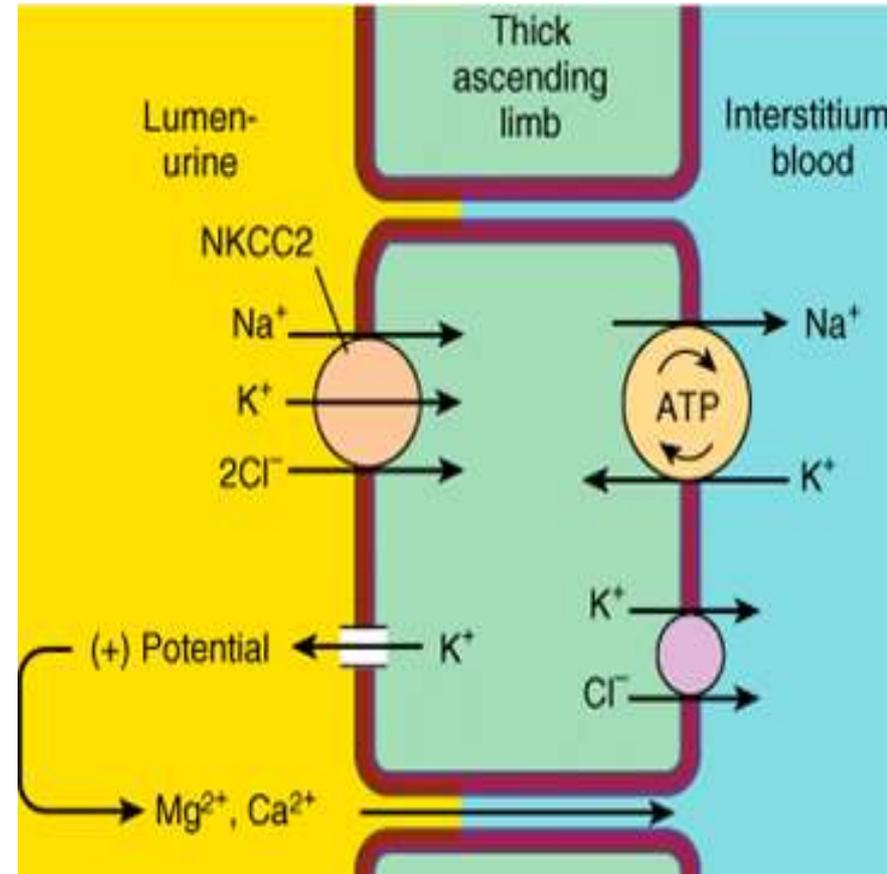
They cause 10-25% loss of filtered  $\text{Na}^+$

↑ dose → ↑ diuretic effect; over-treatment causes dehydration.

Effective even at GFR below 10 ml/min (loop diuretics are most effective in patients with renal insufficiency).

# Pharmacodynamics

- Loop diuretics inhibit **NKCC2**, the luminal  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  transporter in the **TAL** of Henle's loop.
- Loop diuretics reduce the reabsorption of  $\text{NaCl}$  and also diminish the lumen-positive potential which drives divalent cation reabsorption causing an increase in  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  excretion.
- Since  $\text{Ca}^{2+}$  is actively reabsorbed in the DCT, loop diuretics do not generally cause hypocalcemia.



- Loop diuretics induce expression cyclooxygenase 2 (COX-2), which synthesizes prostaglandins from arachidonic acid.
- PGE<sub>2</sub> , inhibits salt transport in the TAL and thus participates in the renal actions of loop diuretics.
- **NSAIDs** interfere with the actions of loop diuretics by reducing prostaglandin synthesis in the kidney and by reducing the secretion of loop diuretics due to competition for secretion in the proximal tubule.
- Loop agents increases renal blood flow.
- Both furosemide and ethacrynic reduce pulmonary congestion and left ventricular filling pressures in heart failure before a measurable increase in urinary output occurs. These effects on peripheral vascular tone may be due to release of prostaglandins.

# **Clinical Indications**

## **Acute pulmonary edema**

Decreasing blood volume reduces left ventricular filling pressures and rapidly relieves pulmonary edema.

## **Other edematous conditions.**

## **Hyperkalemia**

loop diuretics enhance urinary excretion of  $K^+$ .

## **Acute Renal Failure**

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

## **Anion Overdose**

Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the TAL

# Toxicity

**Hypokalemic Metabolic Alkalosis:** due to increased  $K^+$  and  $H^+$  secretion

**Ototoxicity:** Dose-related hearing loss, usually reversible.

**Hyperuricemia:** common, but painful episodes of gout are rarely reported.

**Hypomagnesemia:** Occurs in patients with dietary magnesium deficiency.

**Allergic Reactions:** less common with ethacrynic acid.  
**severe dehydration.**

**Hyponatremia** is less common than with the thiazides

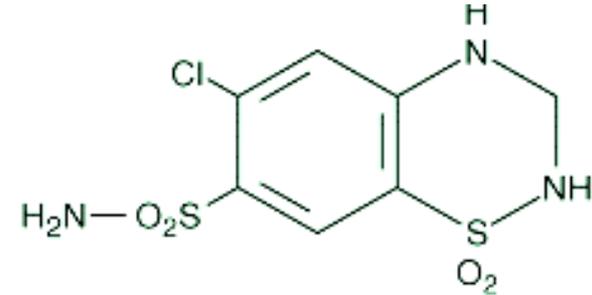
**hypercalcemia** can occur in volume-depleted patients

# Thiazides

The thiazide diuretics emerged from efforts to synthesize more potent carbonic anhydrase inhibitors.

Some members of this group retain significant carbonic anhydrase inhibitory activity.

The prototypical is **hydrochlorothiazide**.



Hydrochlorothiazide

## Pharmacokinetics

- 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.

- **Chlorthalidone** is slowly absorbed and has a longer duration of action.
- **Indapamide** is excreted primarily by the biliary system, but enough of the active form is cleared by the kidney to exert its diuretic effect in the DCT.
- All thiazides are secreted by the organic acid secretory system in the proximal tubule and compete with the secretion of uric acid by that system.
- As a result, thiazide use may blunt uric acid secretion and elevate serum uric acid level.

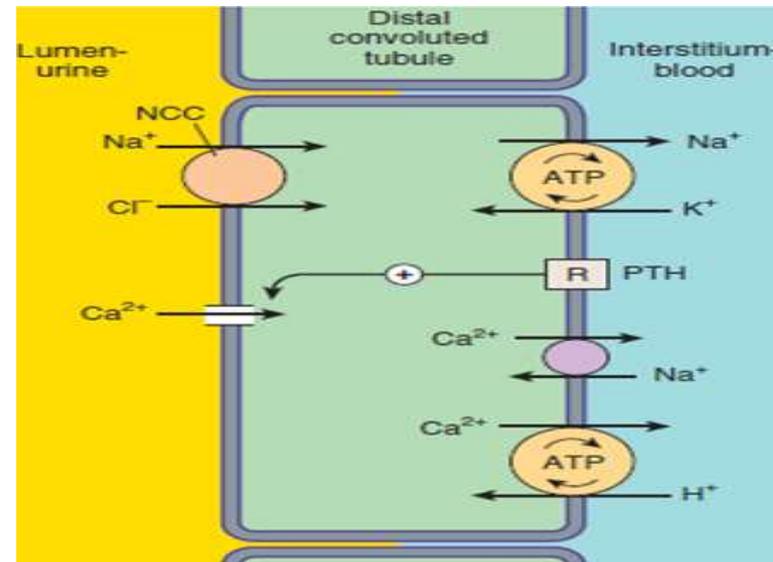
# Pharmacodynamics

- Thiazides inhibit NaCl reabsorption in the **DCT** by blocking the Na<sup>+</sup>/Cl<sup>-</sup> transporter (**NCC**).
- Inhibition of Na<sup>+</sup> reabsorption → ↑Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup> and H<sub>2</sub>O excretion
- Thiazides enhance Ca<sup>2+</sup> reabsorption but rarely cause hypercalcemia

Have Little carbonic anhydrase inhibitory effect.

They are number one drugs in treating hypertension. Their early hypotensive effect is related to a

reduction in blood volume, their long-term effect is related to a reduction in peripheral vascular resistance (direct vasodilating effect, **Indapamide**)



Thiazides are the most frequently used diuretics and the least expensive.

The action of thiazides depends in part on renal prostaglandin & can also be inhibited by NSAIDs under certain conditions.

Thiazides lead to  $\approx$  5-10% loss of filtered  $\text{Na}^+$

High doses will not lead to further increase in their diuretic effect (low ceiling)

They are ineffective in pts with impaired renal function or pts with  $\text{GFR} < 20 \text{ ml/min}$

They are highly effective in lowering BP when combined with other antihypertensive drugs (synergistic effect)

# Clinical Indications

- (1) hypertension.
- (2) Edema of heart failure ; liver cirrhosis...etc
- (3) Nephrolithiasis (renal stones) due to idiopathic hypercalciuria.
- (4) Nephrogenic diabetes insipidus (inability to concentrate urine due to impaired renal tubule response to vasopressin which leads to excretion of large amounts of dilute urine.)

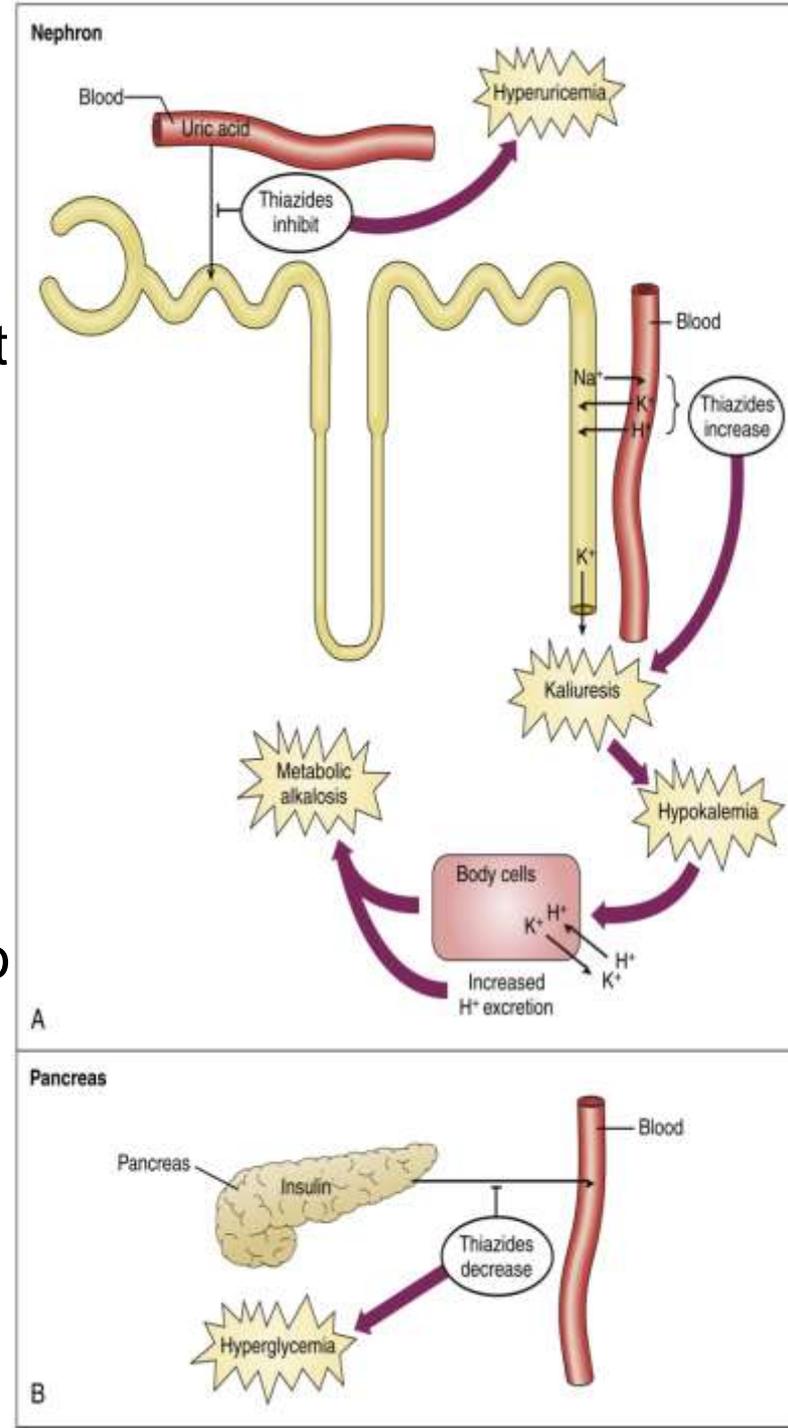
Thiazide diuretics allow increased excretion of  $\text{Na}^+$  and water, thereby reducing the serum osmolarity and eliminating volume excess. Thiazides allow increased solute excretion in the urine, breaking the polydipsia-polyuria cycle (polydipsia: thirst).

# Toxicity

- **Hypokalemic Metabolic Alkalosis**
- **Hyperuricemia** could precipitate gout
- **Hyperglycemia** due to both impaired release of insulin and decrease tissue utilization of glucose. Hyperglycemia is partially reversible with correction of hypokalemia.
- **Hyperlipidemia**  
5–15% increase in total serum cholesterol and low-density lipoproteins (LDL). These levels may return to baseline after prolonged use.

- **Hyponatremia**

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- **Allergic Reactions**

The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group. Photosensitivity or generalized dermatitis occurs rarely.

- **Other Toxicities**

- Weakness, fatigability, and paresthesias may occur.

- Impotence

- **Contraindications**

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

# Potassium-Sparing Diuretics

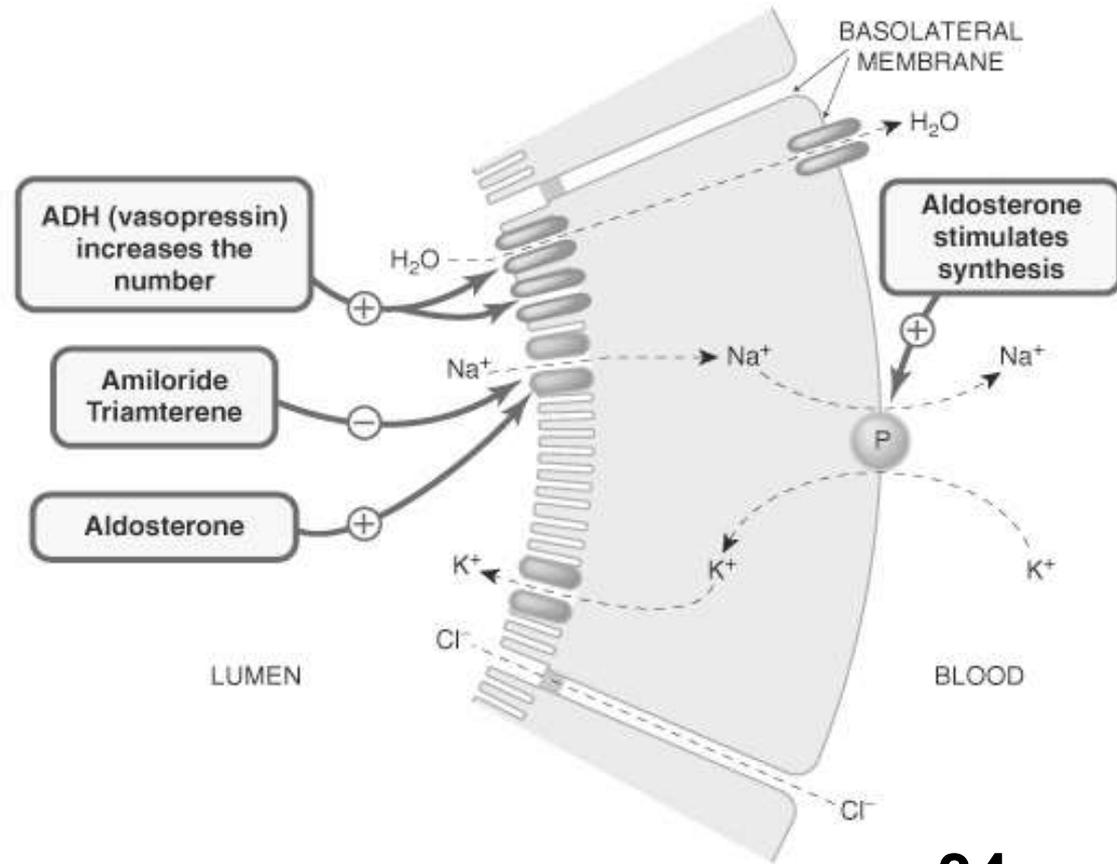
## low efficacy diuretics

Act on the distal portion of the distal tubule & the cortical collecting tubule (CCT).

(where  $\text{Na}^+$  is exchanged for  $\text{K}^+$ )

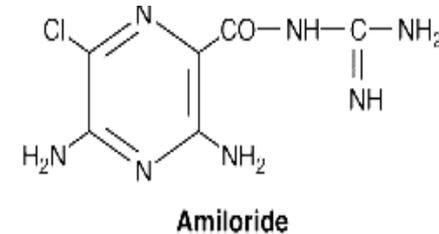
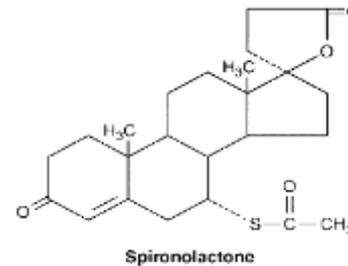
Aldosterone promotes reabsorption of  $\text{Na}^+$  in exchange for  $\text{K}^+$  upregulates the  $\text{Na}^+/\text{K}^+$  pump and sodium channels)

$\uparrow$   $\text{Na}^+$  reabsorption,  
 $\downarrow$  reabsorption of  $\text{K}^+$   
( $\uparrow$  excretion of  $\text{K}^+$  &  $\text{H}^+$ )



Aldosterone antagonists → ↑ Na<sup>+</sup> excretion & ↓ K<sup>+</sup> & H<sup>+</sup> excretion

## Spironolactone; Eplerenone



Only effective in presence of aldosterone (competitive antagonists)

Given orally; have delayed onset of action requires several days

Weak diuretics, usually combined with other diuretics

Have great benefit in improving myocardial function in patients with heart failure

Eplerenone is more potent than Spironolactone

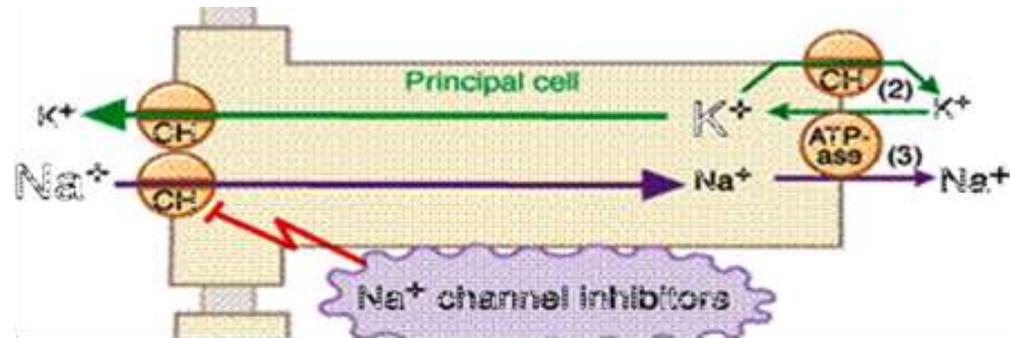
**Eplerenone** is a spironolactone analog with much greater selectivity and potency for the mineralocorticoid receptor.

It is several hundred-fold less active on androgen and progesterone receptors than spironolactone, and therefore has fewer adverse effects.

# Amiloride and triamterene

Are **none steroidal potassium sparing diuretics**.

They do not block aldosterone receptors, but instead directly interfere with  $\text{Na}^+$  entry through the epithelial  $\text{Na}^+$  channels (ENaC) in the apical membrane of the collecting tubule.



**Triamterene** is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites.

it has a shorter half-life and must be given more frequently than **amiloride** (not metabolized).

They are available alone or combined with thiazides

- The actions of the aldosterone antagonists depend on renal prostaglandin production.
- The action of K<sup>+</sup>-sparing diuretics can be inhibited by NSAIDs under certain conditions.

## **Clinical uses of potassium sparing diuretics**

- Spironolactone is particularly useful in the treatment of resistant hypertension due to primary hyperaldosteronism and of refractory edema associated with secondary aldosteronism (cardiac failure, hepatic cirrhosis, nephrotic syndrome and severe ascities)
- Hypokalemia
- Hirsutism (antiandrogenic effect).

# Toxicity

## Hyperkalemia

Can cause mild, moderate, or even life-threatening hyperkalemia. → cardiac arrhythmias.

More severe with eplerenone.

More common in patients with diabetes, chronic renal disease or patients on ACE inhibitors

Combinations of  $K^+$ -sparing and thiazide diuretics, the thiazide-induced hypokalemia and metabolic alkalosis are ameliorated.

## Hyperchloremic Metabolic Acidosis

By inhibiting  $H^+$  secretion in parallel with  $K^+$  secretion, the  $K^+$ -sparing diuretics can cause acidosis. 39

## **Gynecomastia**

Spironolactone may cause Gynecomastia, impotence, benign prostatic hyperplasia in males and breast tenderness in females (rare with Eplerenone)

## **Acute Renal Failure**

The combination of **triamterene** with **indomethacin** may cause acute renal failure. This has not been reported with other K<sup>+</sup>-sparing diuretics.

## **Kidney Stones**

Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.

# Contraindications

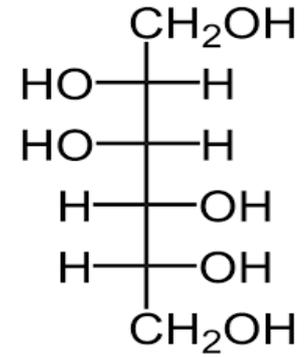
- Oral K<sup>+</sup> administration should be discontinued if K<sup>+</sup>-sparing diuretics are administered.
- Concomitant use of other agents that blunt the renin-angiotensin system (  $\beta$  blockers or ACE inhibitors) increases the likelihood of hyperkalemia.
- Patients with liver disease may have impaired metabolism of triamterene and spironolactone, so dosing must be carefully adjusted.
- Strong CYP3A4 inhibitors (e.g., **ketoconazole**) can markedly increase blood levels of eplerenone.

# Agents That Alter Water Excretion

## Osmotic diuretics

### Mannitol, urea, glycerole

The proximal tubule and descending limb of Henle's loop are freely permeable to water.



Any osmotically active agent that is filtered by the glomerulus but not reabsorbed promotes a water diuresis.

**Mannitol** is a sugar, not absorbed by kidney tubules, has no systemic effects and not metabolized

### Pharmacokinetics

Not absorbed by the GI tract, & must be given parenterally.

Mannitol is not metabolized and is excreted by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion.

# Pharmacodynamics

Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop.

Through osmotic effects, they also oppose the action of ADH in the collecting tubule.

As a result, urine volume increases.

The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing  $\text{Na}^+$  as well as water reabsorption.

The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

# **Clinical Indications & Dosage**

## **Increase of Urine Volume**

used to maintain urine volume and to prevent anuria when using a large pigment loads to the kidney.

## **Reduction of Intracranial and Intraocular Pressure**

Osmotic diuretics are used to reduce intracranial pressure , cerebral edema and brain mass before and after neurosurgery. and to reduce intraocular pressure in glaucoma before ophthalmologic procedures.

The above therapeutic uses are based on the fact that osmotic diuretics increase the osmotic pressure of plasma thus extract water from the eye and brain.

# **Toxicity**

## **Extracellular Volume Expansion**

Mannitol extracts water from cells prior to the diuresis. This leads to expansion of the extracellular volume and hyponatremia.

**Headache, nausea, and vomiting.**

## **Dehydration, Hyperkalemia, and Hypernatremia**

As water is extracted from cells, intracellular K<sup>+</sup> concentration rises, leading to cellular losses and hyperkalemia.

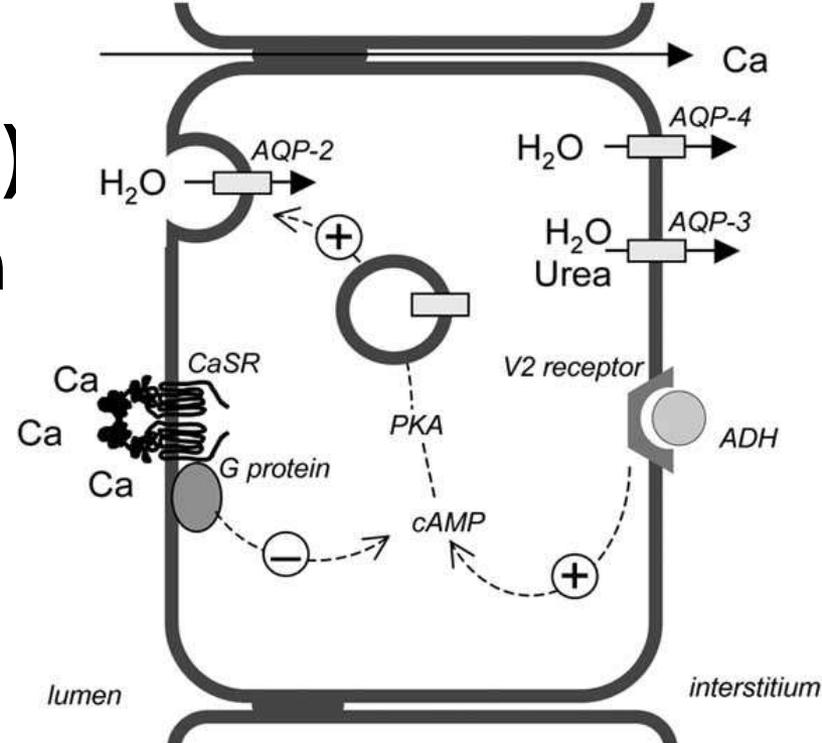
## **Hyponatremia**

In patients with diminished renal function, mannitol is retained intravenously and causes osmotic extraction of water from cells, leading to hyponatremia. **45**

# Antidiuretic Hormone (ADH) Vasopressin & desmopressin

Are used in the treatment of central diabetes insipidus. Their renal action is mediated primarily via V2 receptors

**Antidiuretic hormone** stimulates water reabsorption by stimulating insertion of "water channels" or **aquaporins** into the membranes of kidney tubules. These channels transport solute-free water through tubular cells and back into blood, leading to a decrease in plasma osmolarity and an increase osmolarity of urine.



# Antidiuretic Hormone (ADH) Antagonists

Congestive heart failure and syndrome of inappropriate ADH secretion (SIADH), cause water retention as the result of ADH excess.

- Dangerous hyponatremia can result
- **Conivaptan** (available only for IV use) Antagonist to both V1a and V2 receptors .
- Two nonselective agents, **lithium** and **demeclocycline** (a tetracycline antimicrobial drug have anti-ADH effects).
- Both lithium and demeclocycline reduce the formation of cAMP in response to ADH.

Conivaptan and demeclocycline have half-lives of 5–10 hours.

## **Pharmacodynamics**

- Antidiuretic hormone antagonists inhibit the effects of ADH in the collecting tubule.  
**Conivaptan** is a pharmacologic antagonist at V1a and V2 receptors.

# Clinical Indications

- Syndrome of Inappropriate ADH Secretion (excessive unsuppressible release of ADH)  
Lithium carbonate used to treat this syndrome, but the response is unpredictable.
- Demeclocycline yields a more predictable result and is less toxic.
- Conivaptan is administered by IV injection, so it is not suitable for chronic use in outpatients.
- water restriction is often the treatment of choice.

- Antidiuretic hormone is also elevated in response to diminished effective circulating blood volume, as often occurs in congestive heart failure.
- When treatment by volume replacement is not desirable, hyponatremia may result.
- **Conivaptan** may be particularly useful because blockade of V1a receptors by this drug leads to decreased peripheral vascular resistance and increased cardiac output.

# Toxicity

- **Nephrogenic Diabetes Insipidus**

ADH antagonists can cause severe hypernatremia and nephrogenic diabetes insipidus (disorder caused by complete or partial resistance of the kidneys to vasopressin). Nephrogenic diabetes insipidus can be treated with a thiazide diuretic.

- **Renal Failure**

Both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis.

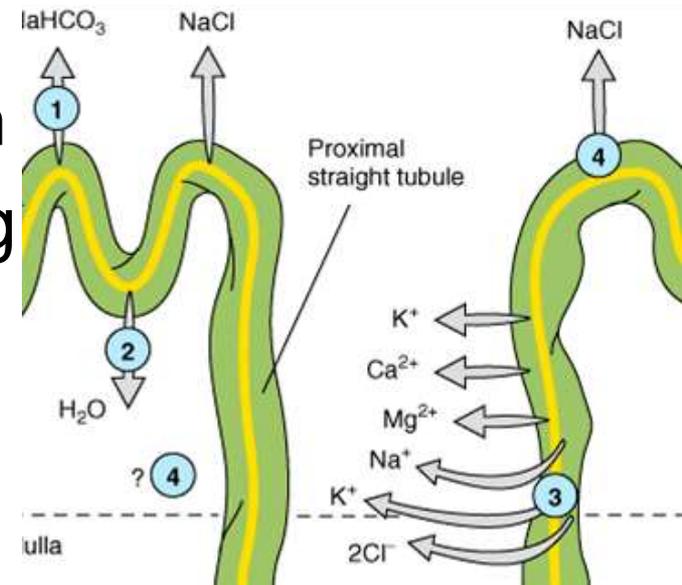
- **Other**

- Demeclocycline should be avoided in liver disease and in children younger than 12 years.

# Diuretic Combinations

## Loop Agents & Thiazides

- The combination of loop diuretics and thiazides can mobilize large amounts of fluid, even in patients who have not responded to single agents.
- salt reabsorption in either the TAL or the DCT can increase when the other is blocked. Inhibition of both produces more than an additive diuretic response.
- $K^+$ -wasting is extremely common & may require parenteral potassium administration with careful monitoring of fluid and electrolyte status.



# Potassium-Sparing Diuretics & Loop Agents or Thiazides

Hypokalemia develops in many patients taking loop diuretics or thiazides.

This can usually be managed by taking dietary KCl supplements. When hypokalemia cannot be managed in this way, the addition of a K<sup>+</sup>-sparing diuretic can significantly lower K<sup>+</sup> excretion.

it should be avoided in patients with renal insufficiency and in those receiving ACE inhibitors, in whom life-threatening hyperkalemia can develop in response to K<sup>+</sup>-sparing diuretics.