Diuretic Agents Part-2

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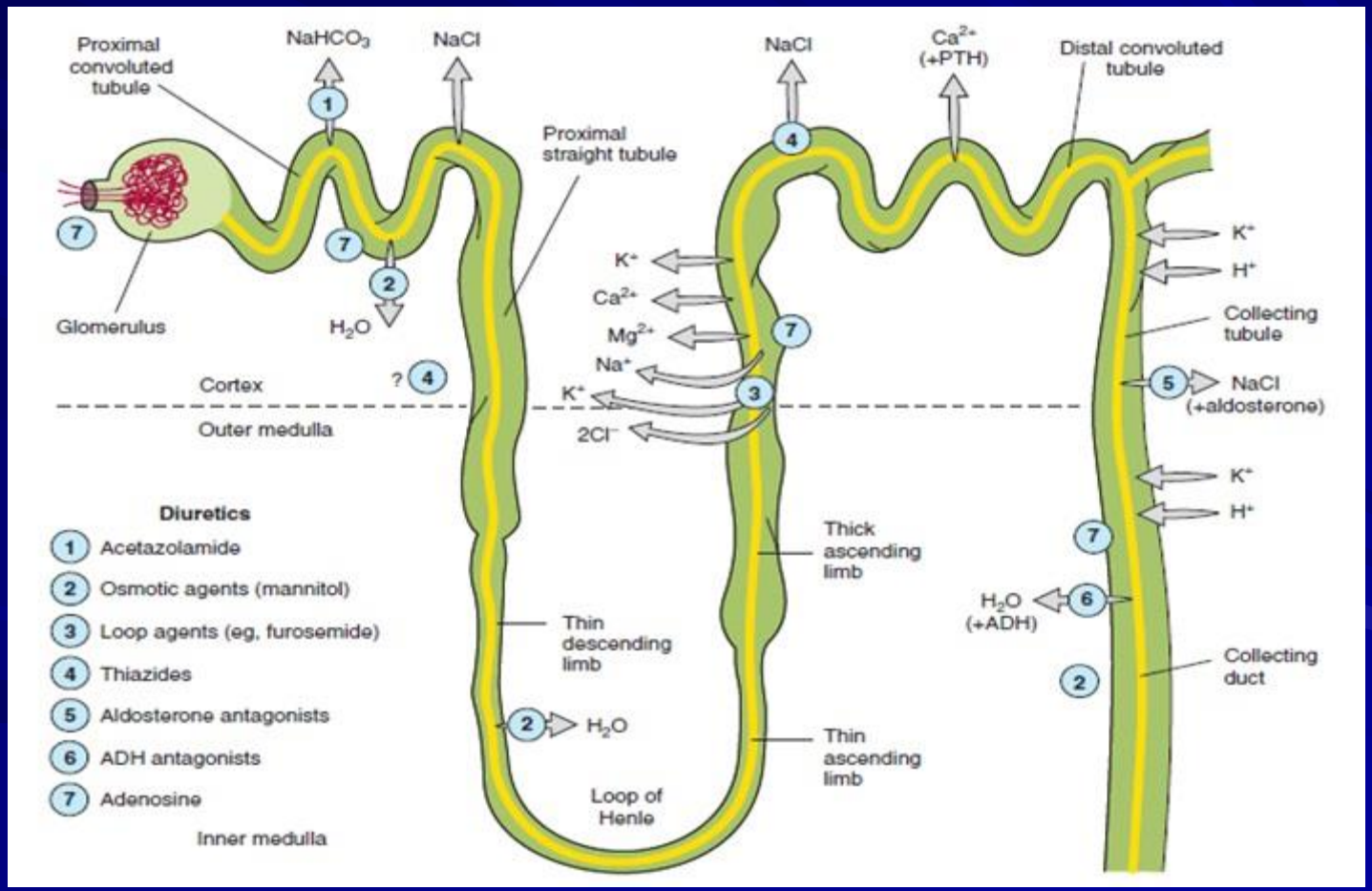
Potassium-sparing diuretics

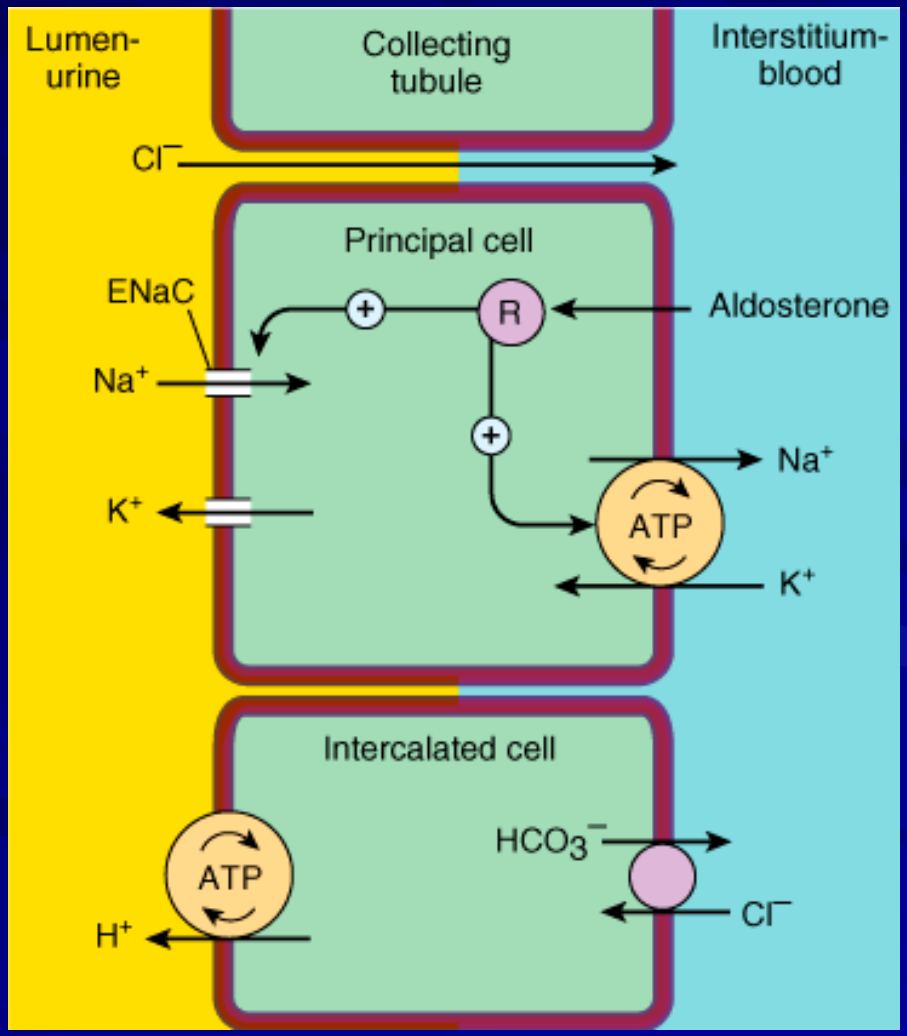
The Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells occurs by:

- Inward diffusion of Na + via the epithelial sodium channel leaves a lumen-negative potential, which drives reabsorption of Cl – and efflux of K + .

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

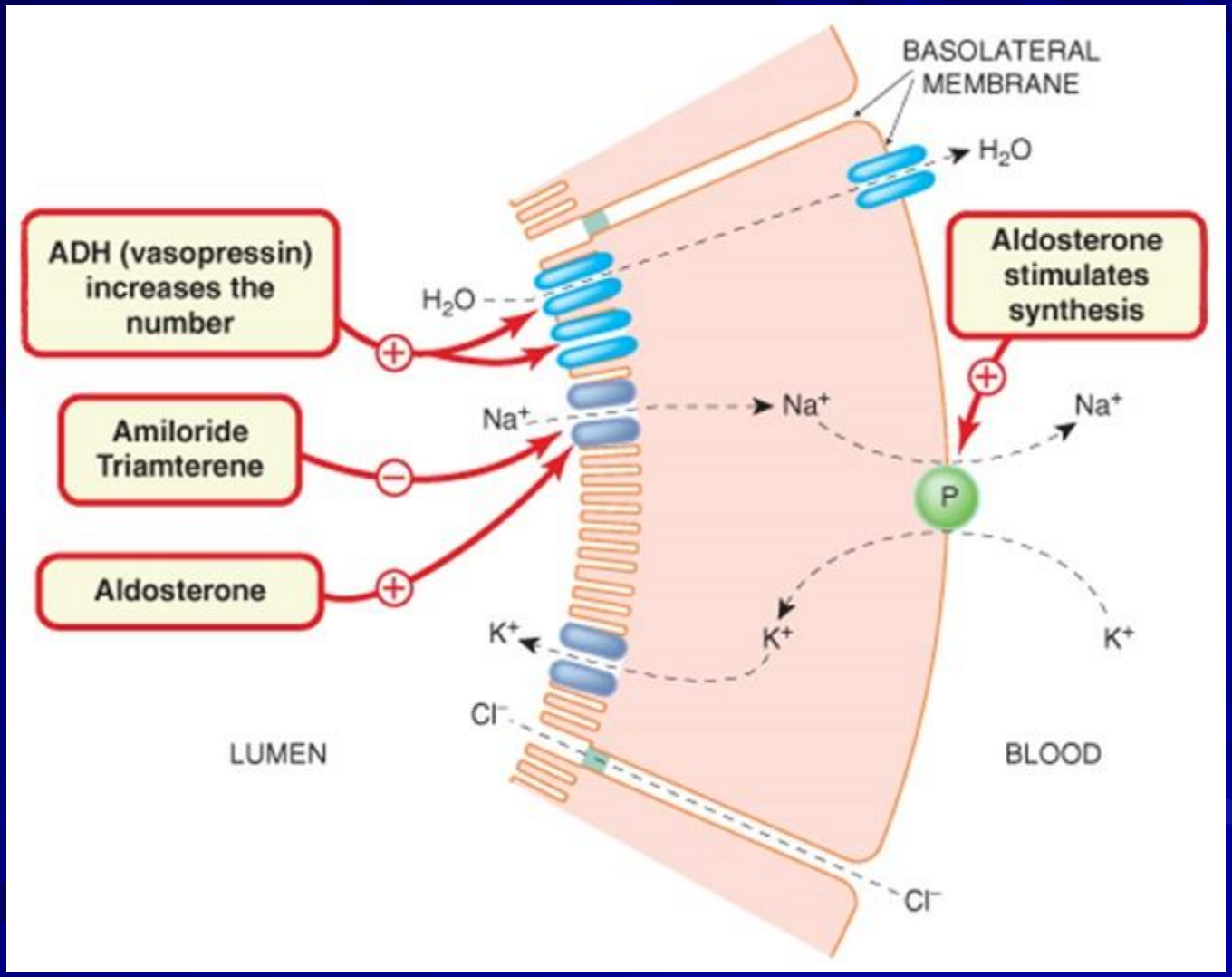


The Ion transport pathways in the collecting duct, R, aldosterone receptor



Potassium-sparing diuretics

- Prevent K + secretion by antagonizing the effects of aldosterone in collecting tubules.
- Inhibition may occur by
  - Direct pharmacologic antagonism of mineralocorticoid receptors **(spironolactone, eplerenone),** Reduce the expression of genes controlling synthesis of epithelial sodium ion channel &Na+/K+ATPase , ↓Na+ reabsorption & ↓ K+ , H+ secretion
  - Inhibition of Na + influx through ion channels in the luminal membrane **(amiloride, triamterene).** This property appears to be shared by adenosine antagonists, which primarily blunt Na + reabsorption in the PCT, but also blunt Na + reabsorption and K + secretion in collecting tubules.


BASOLATERAL MEMBRANE
H_2O
ADH (vasopressin) increases the number
H_2O
Aldosterone stimulates synthesis
Amiloride Triamterene
Na^+
Na^+
Na^+
P
Aldosterone
K^+
K^+
K^+
Cl^-
LUMEN
BLOOD
Cl^-

Pharmacokinetics

Spironolactone

- Acts as a competitive antagonist to aldosterone.
- Has slow onset of action, requiring days before full therapeutic effect is achieved.
- Inactivation of spironolactone occurs in the liver.

Eplerenone

- It is a spironolactone analog with much greater selectivity for the mineralocorticoid receptor (fewer adverse effects)

Amiloride and Triamterene

- Direct inhibitors of Na + influx in the CCT (cortical collecting tubule).
- Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites.
- Triamterene has a shorter half-life and must be given more frequently than Amiloride (which is not metabolized).

Mechanism of Action

Spironolactone and Eplerenone

- Bind to mineralocorticoid receptors and blunt aldosterone activity.

Amiloride and Triamterene

- They do not block aldosterone, but directly interfere with Na + entry through the epithelial Na + channels in the apical membrane of the collecting tubule. Since K + secretion is coupled with Na + entry in this segment, these agents are K + -sparing diuretics.

Note: The actions of the aldosterone antagonists depend on renal prostaglandin production& The actions of K + -sparing diuretics can be inhibited by NSAIDs

Clinical Indications

- Hyperaldosteronism (aldosteronism)
- Hepatic cirrhosis
- Nephrotic syndrome

Note: low doses of Eplerenone may interfere with effects of aldosterone. And slow the progression of albuminuria in diabetic patients.

- It reduce myocardial perfusion defects after myocardial infarction.

Adverse Effects

1. **Hyperkalemia**

   K+ -sparing diuretics reduce urinary excretion of K+. This side effect ↑ by:

   - Renal disease (in which K + excretion reduced)
   - The use of other drugs that reduce or inhibit renin (β blockers, NSAIDs and Aliskiren)
   - The use of other drugs that reduce or inhibit angiotensin II activity (angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors).

Combinations of K + -sparing and thiazide diuretics

- Hypokalemia and metabolic alkalosis associated with Thiazide side effects are improved
- It is impotant to adjust the doses of the two drugs separately.

2. **Hyperchloremic Metabolic Acidosis**
   - By inhibiting H + secretion in parallel with K + secretion
3. **Endocrine abnormalities**

   Spironolactone may cause endocrine abnormalities by actions on other steroid receptors and causes Gynecomastia, impotence, and benign prostatic hyperplasia (very rare)
   - Eplerenone not cause endocrine abnormalities

4. **Acute Renal Failure**
   The combination of Triamterene with Indomethacin has been reported to cause acute renal failure.
5. **Kidney Stones**
   Triamterene is slightly soluble and may precipitate in the urine, causing kidney stones.

Contraindications

- Chronic renal insufficiency
- Patient who take Oral K + administration
- Patient withConcomitant use of agents that blunt the renin-angiotensin system (β blockers, ACE)

Osmotic Diuretics

- Mannitol is poorly absorbed by the GI tract
- when administered orally causes osmotic diarrhea rather than diuresis.
- For systemic effect, mannitol must be given intravenously.
- Mannitol is not metabolized and is excreted by glomerular filtration within 30-60 minutes,
- It must be used cautiously in patients with even mild renal

Mechanism of Action

- Mannitol (non reabsorbable solute), through osmotic effects prevents the normal absorption of water on parts of the nephron that are freely permeable to water: the proximal tubule and descending limb of the loop (urine volume increases).
- They also oppose the action of ADH in the collecting tubule
- The natriuresis is less than the water diuresis, leading to excessive water loss & hypernatremia.

Clinical Indications

1. Increase of Urine Volume

Osmotic diuretics are used to increase water excretion in preference to sodium excretion. It can be used to maintain urine volume and to prevent anuria that result from presentation of large pigment loads to the kidney (eg, from hemolysis or rhabdomyolysis).

2. Reduction of Intracranial and Intraocular Pressure

- Water leaves cells and intracellular volume reduces by the effect of Osmotic diuretics.
- This effect is used to reduce intracranial pressure in neurologic conditions &to reduce intraocular pressure before ophthalmologic procedures.
- Mannitol is administered intravenously. Intracranial pressure, should fall in 60–90 minutes.

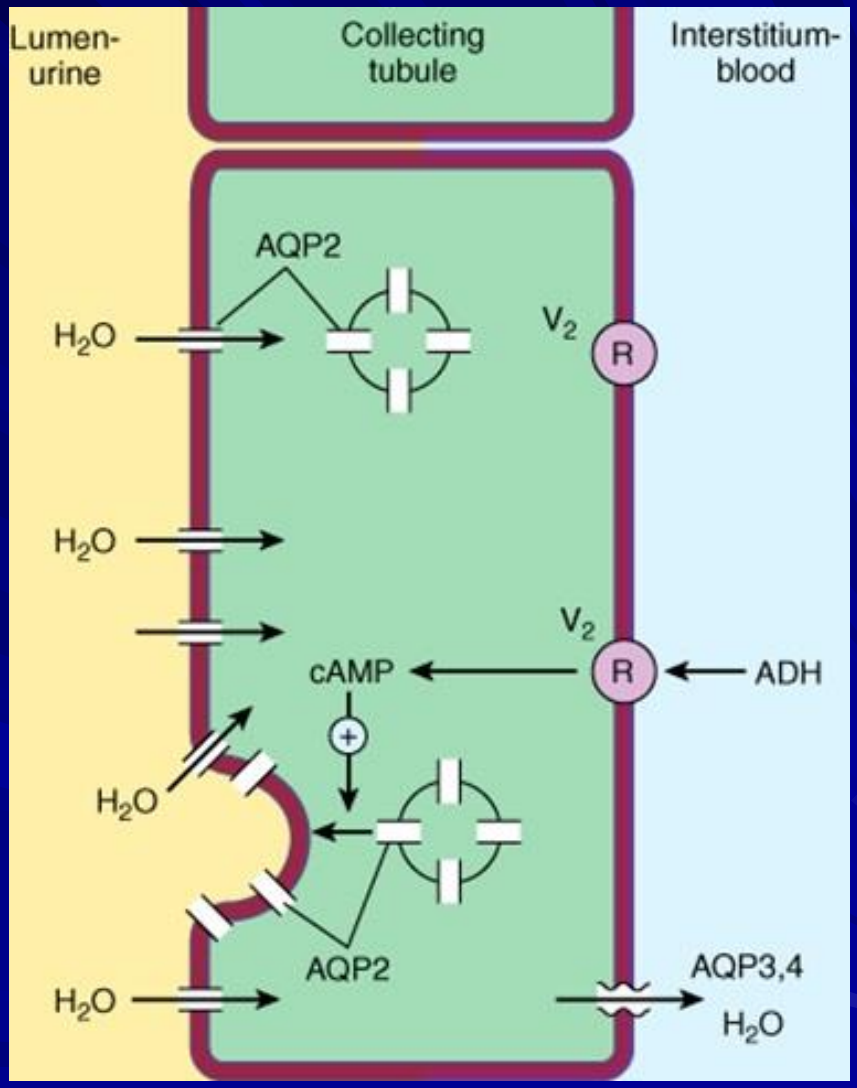
Osmotic Diuretics Adverse Effects

1. **Extracellular Volume Expansion**
   Mannitol is rapidly distributed in the extracellular compartment , extracts water from the cells and causes hyponatremia until diuresis occurs
2. **Dehydration, Hyperkalemia and Hypernatremia**
   water is extracted from cells, intracellular K+ concentration rises, leading to cellular losses and hyperkalemia. These complications can be avoided by careful attention to serum ion composition and fluid balance

Vasopressin is Antidiuretic hormone (ADH) is released from the posterior pituitary gland)

- It act on V1 and V2 receptors in the collecting tubule, controls the permeability of the colleting tubule to water by regulating the water channels (aquaporin-2, AQP2) into the apical membrane

Antidiuretic Hormone (ADH)
(AQP2, apical aquaporin water channels; AQP3, 4, basolateral aquaporin water channels; V2 , vasopressin
V2 receptor.



ADH Agonist

Vasopressin & Desmopressin

- Parenterally administration
- ↓urine volume & ↑ their concentration

Clinical Uses

Central diabetes insipidus

- **ADH agonist** controls the permeability of the colleting tubule to water(Water restriction, salt restriction)

Antidiuretic Hormone Antagonists

- Inhibit the effects of ADH in the collecting tubule.
- Conivaptan and tolvaptan are direct ADH receptor antagonists
- lithium and demeclocycline reduce ADH-induced cAMP (indirect antagonist)

Antidiuretic Hormone Antagonists

Tolvaptan

- Selectively active against the V2 receptor
- Only for use in hyponatremia

Conivaptan

- Drug with both V 1a and V 2 antagonist activity, has also for treatment of hyponatremia

Clinical Indications & Dosage

1. **Syndrome of Inappropriate ADH Secretion (**SIADH**)**
   - Demeclocycline, tolvaptan, Lixivaptan and satavaptan for oral use.
   - Conivaptan (intravenously) is not suitable for chronic use in outpatients.

2. Other Causes of Elevated Antidiuretic Hormone

- Heart failure elevates Antidiuretic Hormone in response to decrease blood volume and treatment by volume replacement is not desirable, hyponatremia may result.

1. Nephrogenic Diabetes Insipidus

- ADH antagonists can cause severe hypernatremia and nephrogenic diabetes insipidus
- lithium is being used for a psychiatric disorder, nephrogenic diabetes insipidus associated with lithium side effect can be treated with a thiazide diuretic or amiloride

2. Renal Failure

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

Sodium Glucose Cotransporter 2 (Sglt2) Inhibitors

Dapagliflozin

Canagliflozin

- Rapidly absorbed by the GIT.
- Reduce the hemoglobin A1c.

Adverse Effects

- Urinary tract infections& genital fungal infection in female
- Associated with a low incidence of hypoglycemia

Adenosine Receptor Antagonists

- Interfere with the activation of NHE3 apical membrane (Na+/H +) Exchanger in the PCT and the adenosine-mediated enhancement of collecting tubule K+ secretion.

Caffeine & Theophylline

- Nonspecific inhibition of adenosine receptors (weak diuretics)

Rolofylline

- Selective A1 antagonist
- Was recently withdrawn from study because of CNS toxicity and unexpected negative effects on GFR.