Drugs Acting in the Kidney; Diuretics

PHC 721

Winter 2022

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Common Cardiovascular Health Conditions & Treatment Goals

1. Primary (a.k.a. Essential, Idiopathic) Hypertension

↓ Systemic Vascular Resistance (SVR) & ↓ Extracellular Fluid Volume (EFV)

2. Myocardial Ischemia/Infarction

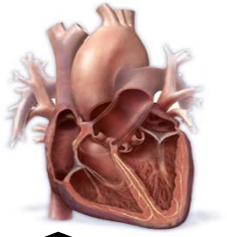
↑ Coronary Blood Flow, ↓ O_2 Demand, Statins, Anti-thrombotics

3. Congestive Heart Failure

↑ Contractility, ↓ SVR, ↓ EFV, ↓ Pathological Ventricular Remodeling

4. Cardiac arrhythmias

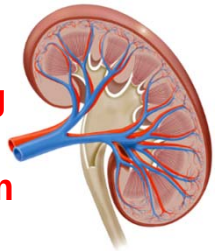
↓ Automatic Rhythms



Venous Return

Blood Volume

Renal Handling of Water & Sodium



Extravascular Volume

Peripheral circulation:

Vasodilation (Blockers: α_1, Ca^{2+} ch, RAA; Direct vasodilators)
↓Blood volume (Diuretics)

Coronary arteries:

Vasodilation (Organic Nitrates; Blockers: Ca^{2+} ch)
↓ Heart Rate /↓Contractility (Blockers: β adrenergic, Ca^{2+} ch)

Cardiomyocytes:

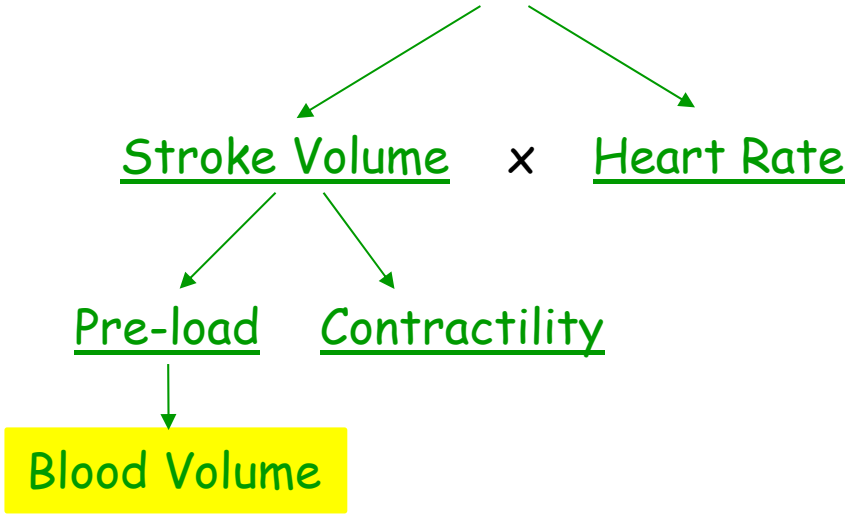
- **↑Contractility (Cardiac Glycosides; β_1 adrenergic Agonists)**
- **↓ Ventricular Remodeling (Blockers: AT_1 receptors)**

Conducting System:

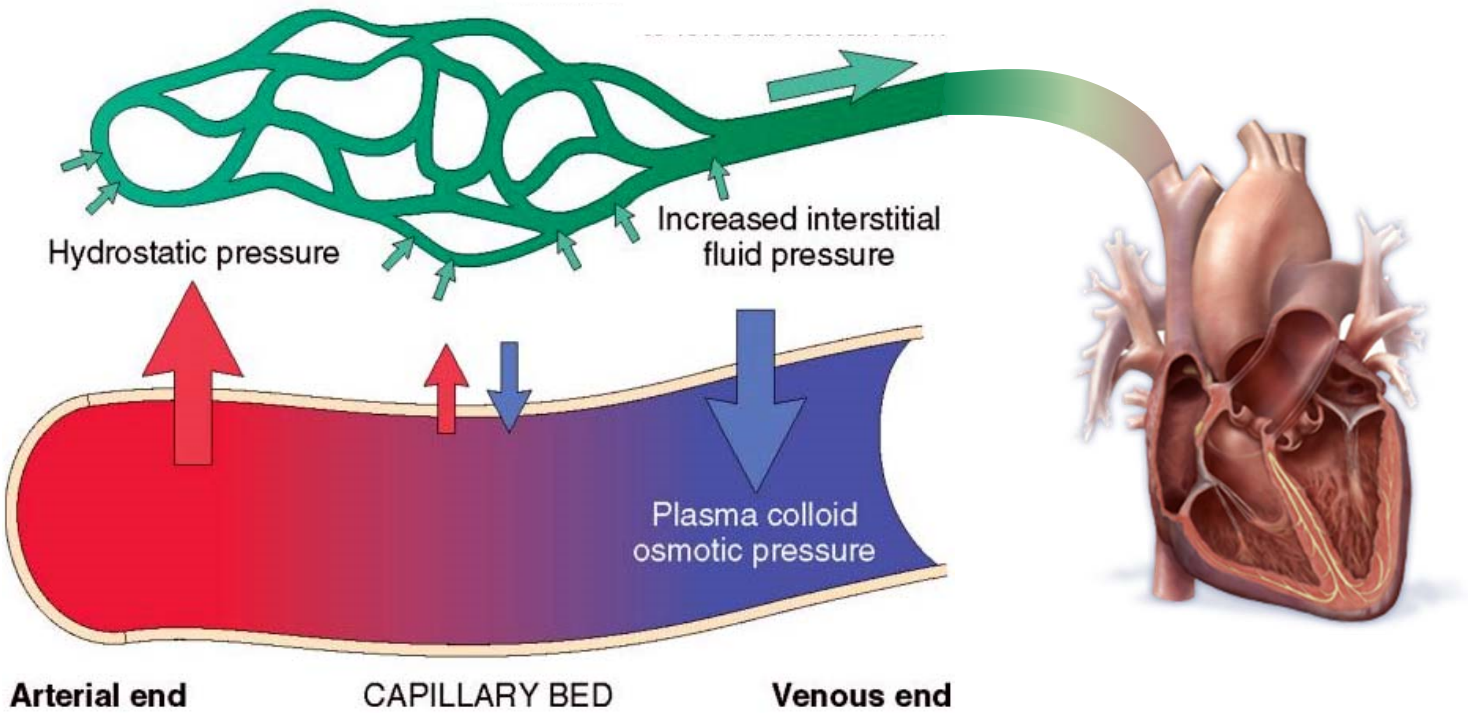
- **Conduction Velocity/Excitability/Refractoriness (Blockers: Na^+ ch (I), β_1 (II), K^+ ch (III), Ca^{2+} ch (IV)**

$$V = I \times R$$

[Mean Arterial Pressure] = [Cardiac Output] x [Systemic Vascular Resistance]



Genesis of Pulmonary and Peripheral Edema



- ↑ Hydrostatic pressure (e.g., Venous Congestion due to Heart Failure)
- ↓ Plasma colloid osmotic (oncotic) pressure (e.g., Hepatic Cirrhosis, Nephrotic Syndrome)

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↑ Water in the Interstitial Space: EDEMA

⇩

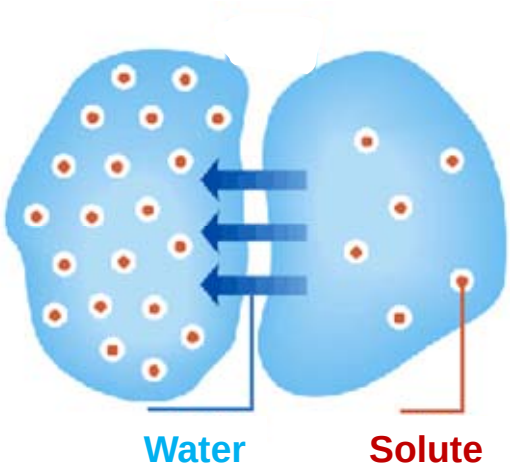
Intervention: ↓ Extracellular Fluid Volume

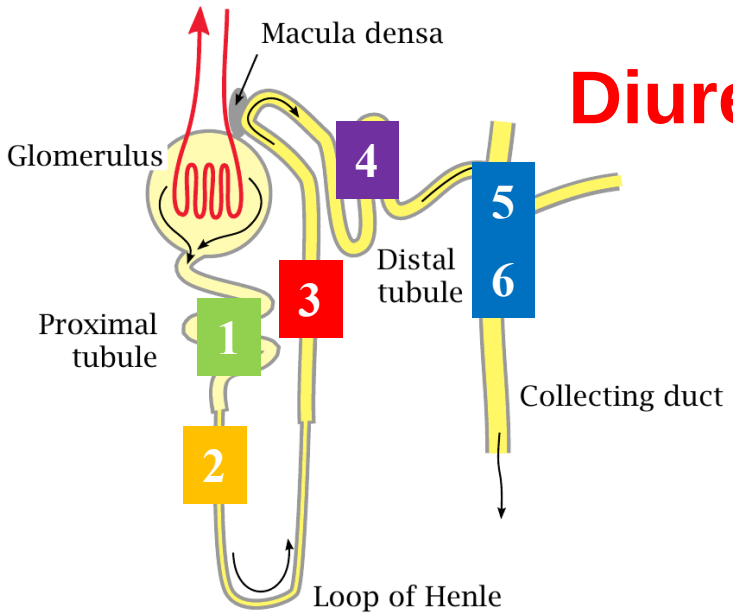
- Left Heart Failure: Pulmonary Edema
- Right (& Left) Heart Failure: Peripheral Edema

Diuretics: An Overview

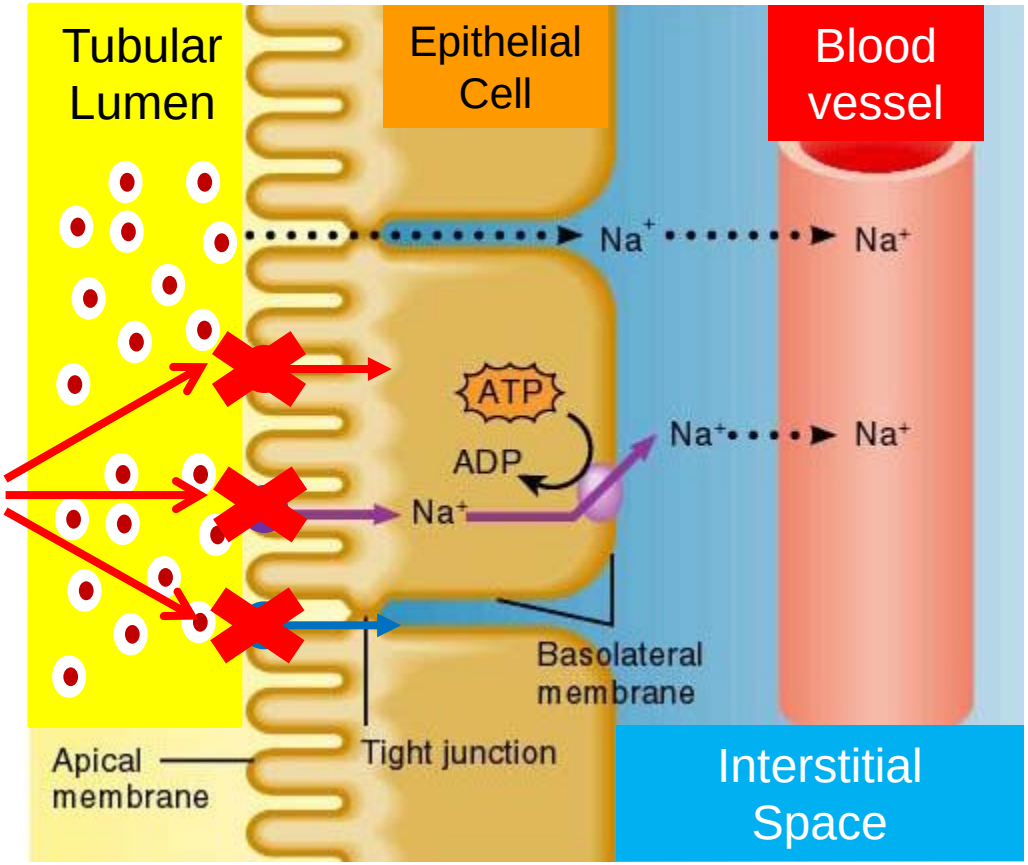
Diuretics increase the rate of urine flow and the rate of Na^+ excretion (natriuresis).
Primary clinical application is to reduce volume of extracellular fluid by:

↓ total-body NaCl ⇒ ↓ water





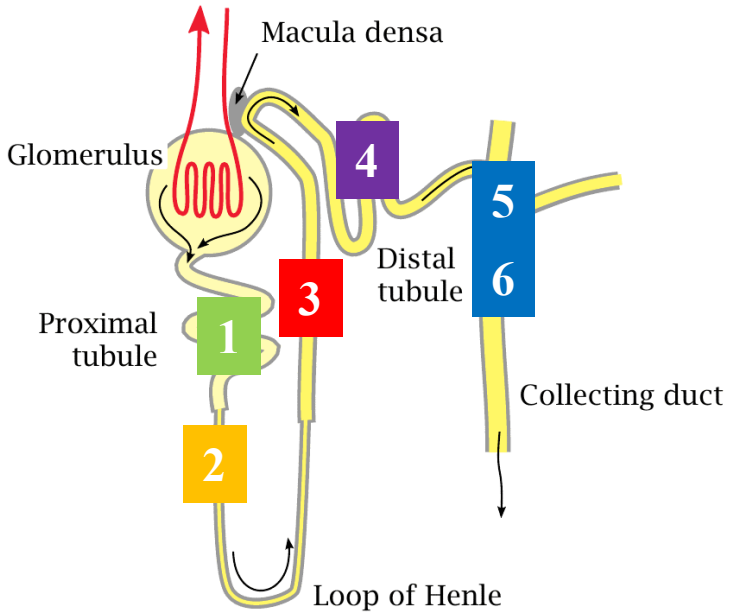
Nephron Segments:



Diuretics

Ion channel / transporter proteins in the apical and basolateral membrane critical for transport of solutes across epithelial cells

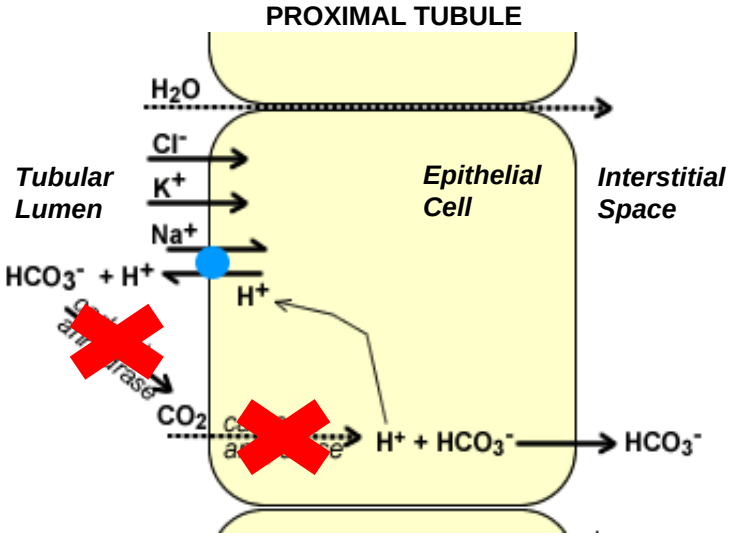
Diuretics: An Overview



1. Inhibitors of Carbonic Anhydrase (*Acetazolamide*)
2. Osmotic Diuretics (*Mannitol*)
3. Loop Diuretics (*Furosemide*)
4. Thiazide Diuretics (*Hydrochlorothiazide*)
5. K^+-Sparing Diuretics (*Amiloride*)
6. Antagonists of Aldosterone (*Spironolactone*)

1. Inhibitors of Carbonic Anhydrase

Limited usefulness as diuretics

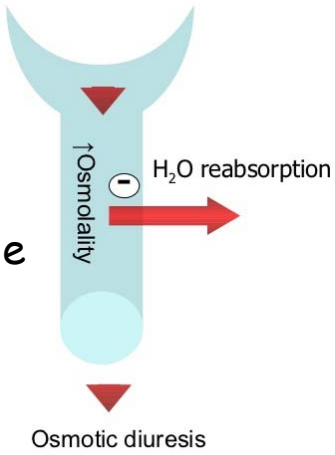


Indications (examples):

- To correct for metabolic alkalosis
- Altitude illness/Acute mountain sickness (prophylaxis; symptomatic relief)

2. Osmotic Diuretics

<u>Mechanism of Action:</u>
↑ osmolarity of plasma ⇒ ↑ osmolarity of tubular fluid
freely filtered in the glomerulus/largely non-reabsorbable



<u>Relatively inert pharmacologically</u> (does not react with tissues)

<u>Indications:</u>
- to restore osmotic equilibrium after hemodialysis
- to decrease intraocular pressure (acute attacks of glaucoma)
- to reduce cerebral edema (neurosurgery)

<u>Side effects/Contraindications:</u>
- Pulmonary edema / heart failure, pulmonary congestion

3. Loop Diuretics

<u>Mechanism of Action:</u>
Inhibition of Na^+-K^+-$2Cl^-$ symport
in Thick Ascending Limb
of the Loop of Henle (TALoLH)
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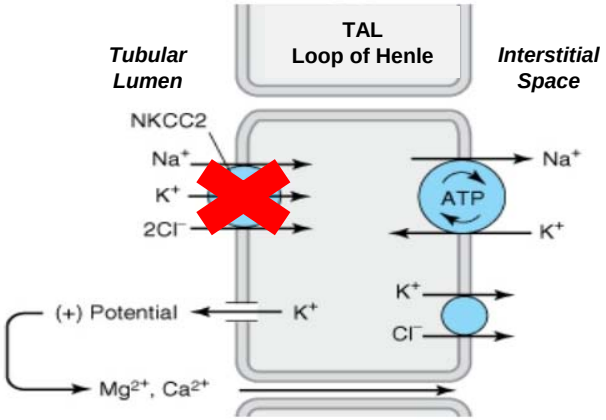
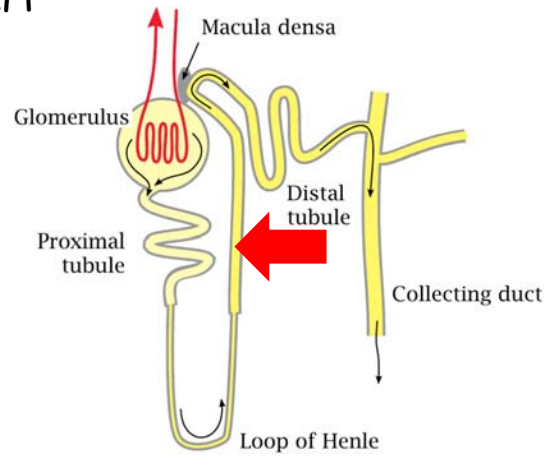
Salt transport in TALoLH at a standstill!



The high efficacy (*high-ceiling diuretics*) is due to:
1) a significant (25%) contribution of TALoLH
to reabsorption of the filtered Na^+ load;
2) nephron segments past TALoLH are not capable
of rescuing the solutes rejected by TALoLH

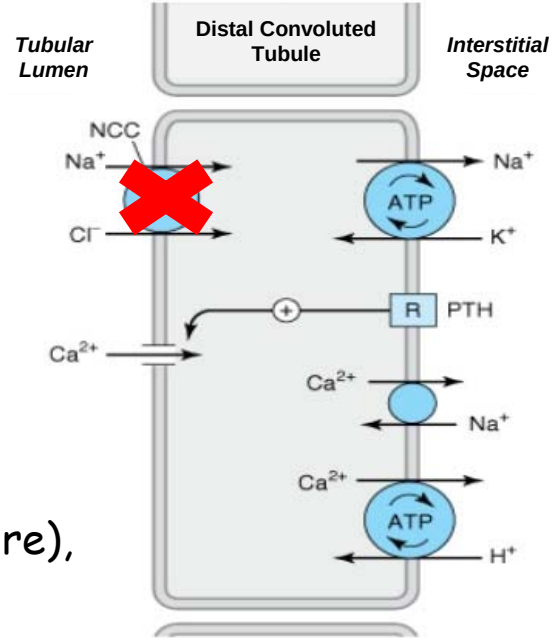
<u>Indications:</u>
- A widely used class of diuretics (e.g. congestive heart failure)
- Particularly beneficial for treatment of pulmonary edema
(↑ venous capacitance ⇒ ↓ left ventricular filling pressure)
- Less useful for hypertension Tx (short elimination half-life),
compared to thiazide-type diuretics



4. Thiazide Diuretics

Mechanism of Action:

Inhibition of Na^+-Cl^- symport in the Distal Convoluted Tubule
$\Rightarrow \uparrow$ NaCl excretion



Indications:

- Hypertension: the best initial therapy in uncomplicated cases; the most frequently used class of antihypertensive agents

- Edema in Congestive Heart Failure (due to ↑ hydrostatic pressure), Hepatic Cirrhosis (due to ↓ oncotic pressure), and Kidney diseases with preserved GFR (>30 mL/min)

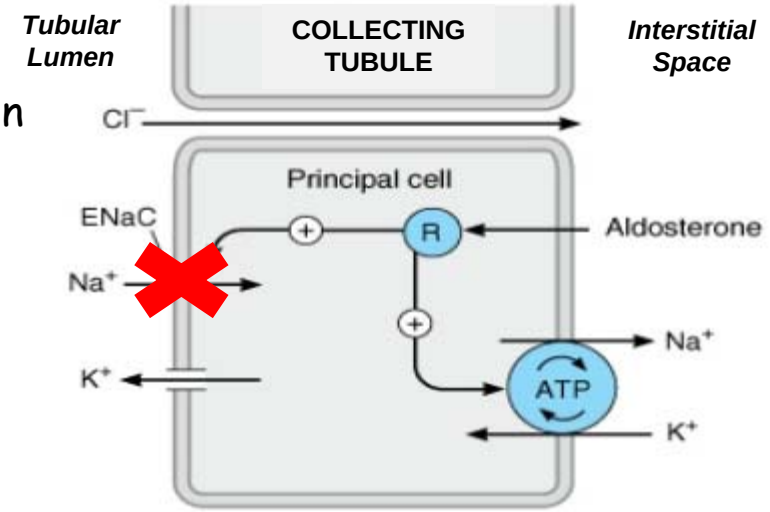
Dental Implications

- NSAIDs blunt the hypotensive effect of thiazide diuretics.
- Triple therapy with an NSAID, plus diuretic and an ACE inhibitor (e.g. Enalapril) or AT_1 receptor blocker (e.g. Losartan) may lead to acute renal failure (nephrotoxicity)

5. K^+-Sparing Diuretics: Na^+ channel inhibitors

Mechanism of Action:

- Inhibition of Na^+ channels in epithelial cells of the Late Distal Tubule & Collecting Duct
  $\Rightarrow \downarrow Na^+$ reabsorption $\Rightarrow$ *small* $\uparrow$ NaCl excretion
  $\Downarrow$
- Inhibition of K+ secretion, otherwise driven by $\uparrow$ Na+ delivery to the late distal tubule/collecting duct (e.g. other diuretic action)



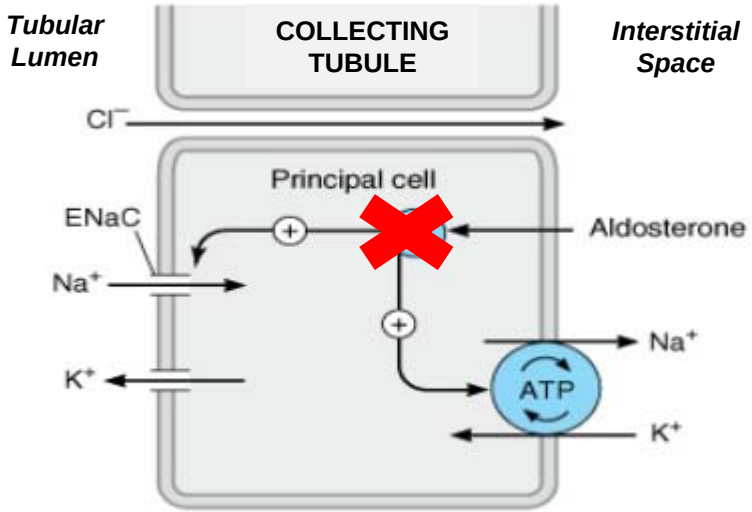
Indications:

- Rarely used alone (modest natriuretic effect)
- Usually applied for their potassium sparing (*anti-kaliuretic*) actions together with other diuretics

6. K^+-Sparing Diuretics: Antagonists of Aldosterone

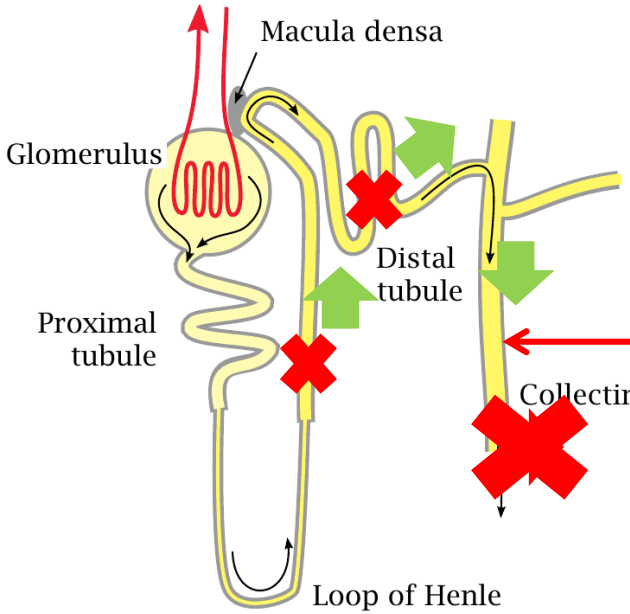
Mechanism of Action:

- Blockade of mineralocorticoid/aldosterone receptors in epithelial cells of Late Distal Tubule & Collecting Duct ⇒ ↓ Na^+ channel expression and activity ⇒ ↓ NaCl transport ⇒ ↑ NaCl excretion
  ⇓
- Inhibition of K+ secretion, otherwise driven by Na^+ influx to epithelial cells and the resulting trans-epithelial voltage (lumen-negative)



Indications:

- Usually co-applied with thiazide or loop diuretics because of the potassium-sparing characteristic (Tx of edema & hypertension)
- Resistant hypertension due to Primary Aldosteronism



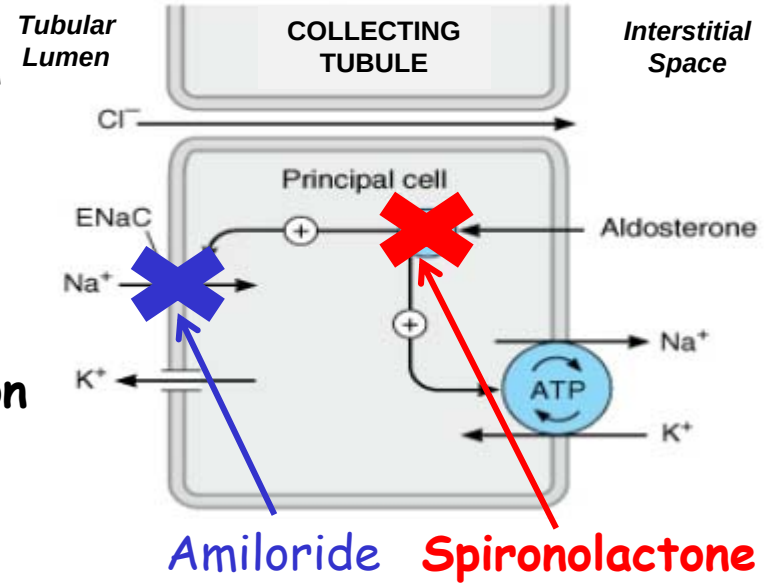
Hyperaldosteronism

⇧⇧⇧ **Aldosterone**

⇧⇧⇧ **Na^+ Channels**

⇧⇧⇧ **Na^+ Reabsorption**

⇧⇧⇧ **K^+ Loss**



Angiotensinogen

↓ [illegible]

Angiotensin I

↓ Angiotensin [illegible] Enzyme (ACE)

Angiotensin II

↓ AT1 [illegible] tors

↓

Aldosterone

↓

Na⁺ Channels

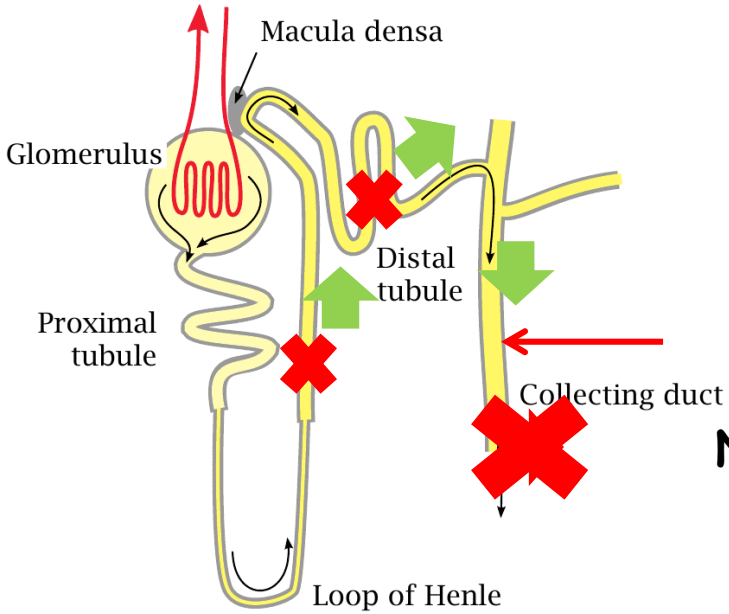
↓

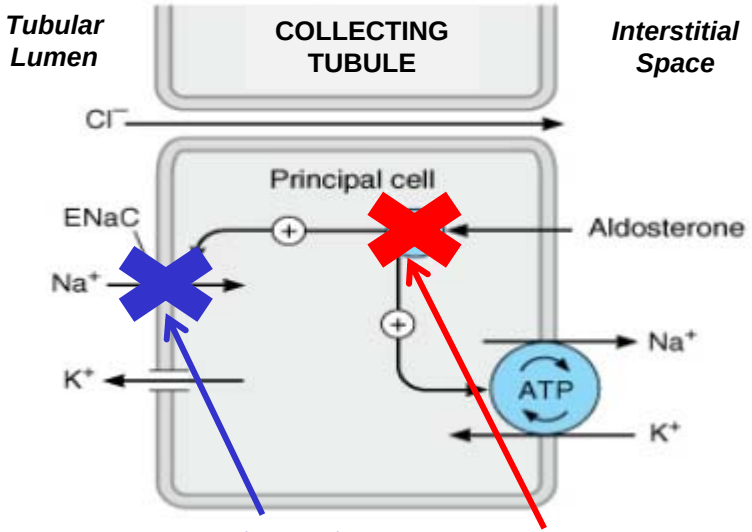
Na⁺ Reabsorption

↓

K⁺ [illegible] ss

Hyperkalemia !!!



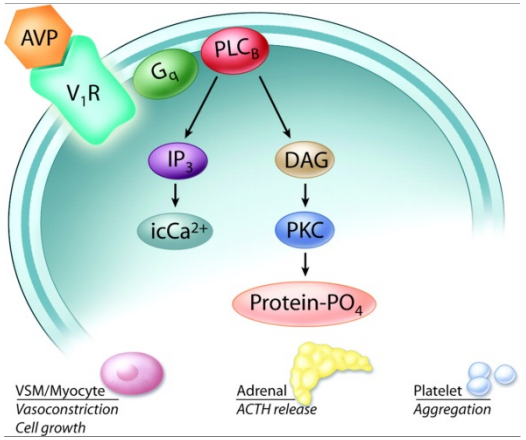


Anti-Diuretics

Vasopressin (Anti-Diuretic Hormone, ADH, AVP): a non-selective activation of V_1 and V_2 receptors, with strong effects on vasoconstriction and GI smooth muscle contraction (**V_1 receptor-mediated**).

Indications: vasodilatory shock, visceral bleeding, ileus.

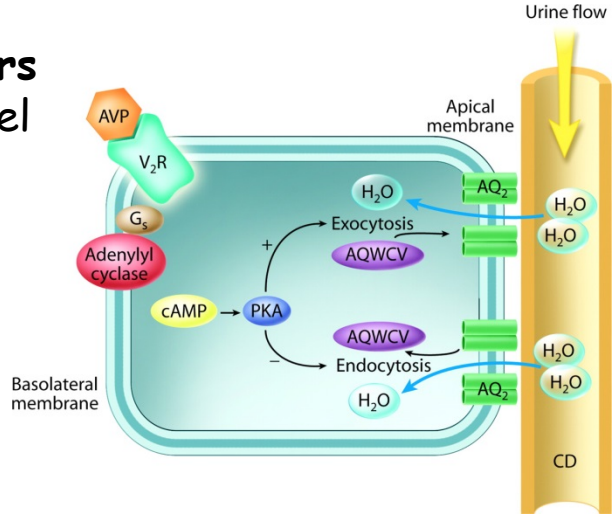
Vasopressin V_1R: Blood vessels



Vasopressin V_2R: Collecting Duct

Desmopressin: preferential activation of **V_2 receptors** in the Collecting Duct ($\Rightarrow \uparrow$ aquaporin 2 (AQ_2) channel insertion to the apical membrane $\Rightarrow$ $\uparrow$ permeability of water from the collecting duct)

Indications: polyuria/polydipsia in *central* Diabetes Insipidus (insufficient ADH supply by the pituitary); primary nocturnal enuresis



Dental Implications:

NSAIDs and Morphine potentiate the anti-diuretic effects $\Rightarrow$ risk of water intoxication (contraindicated in hypertension and heart failure)