Pharmacology - GUS

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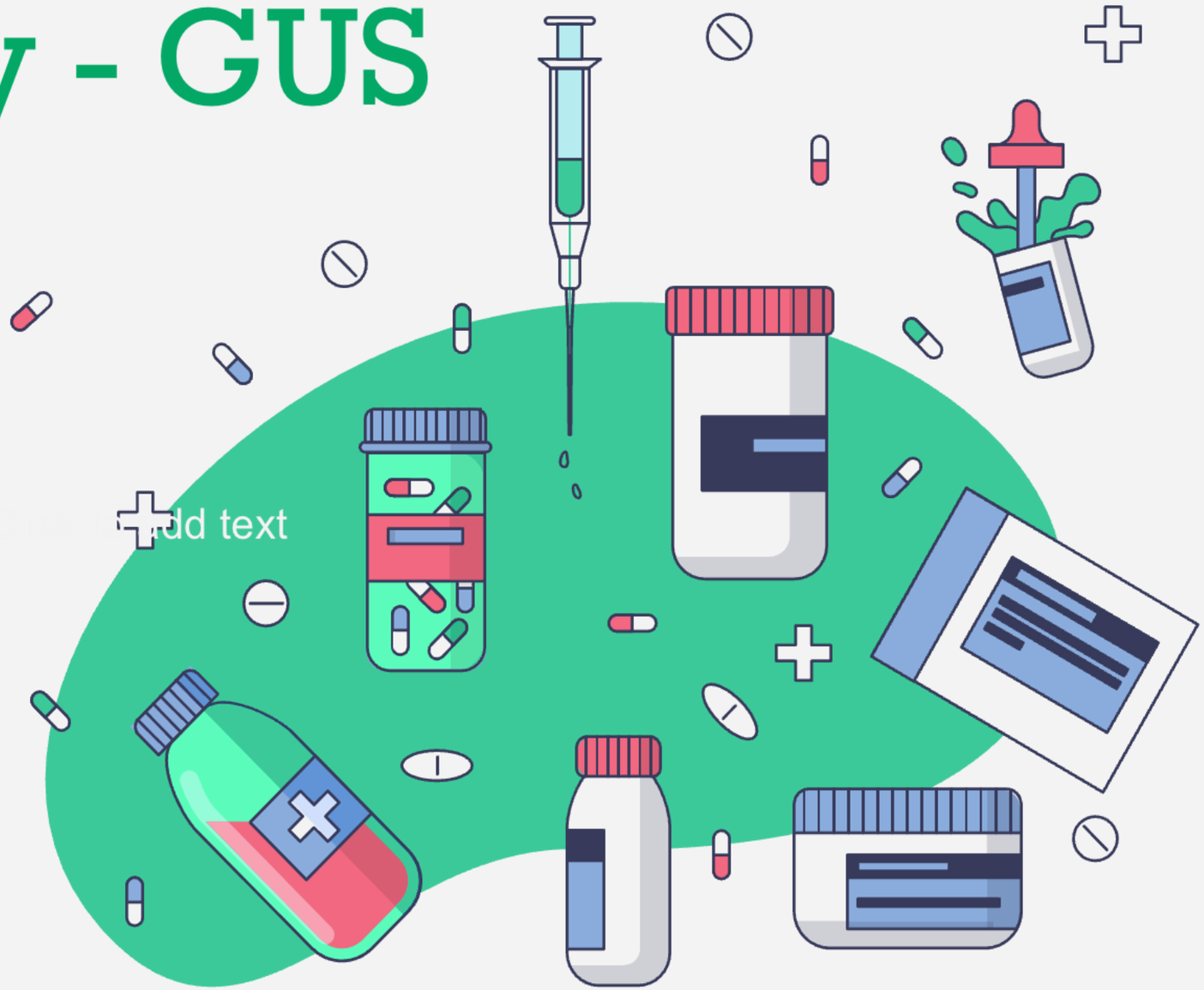

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Diuretic Agents

2020

- A "diuretic" is an agent that increases urine volume.
- They decrease extracellular fluid (ECF) and effective circulating volume. (Because the increase the urine output)
- A Natriuretic causes an increase in renal sodium excretion.
- Because natriuretics also increase water excretion, they are usually called diuretics.
- Osmotic diuretics like mannitol are diuretics that are not directly natriuretic.(when they are filtered they are not reabsorbed so they retain water by osmotic pressure so increase the urine output , and water pulls Na+ with it so they are not direct natriuretics)

- ✓ 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 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. (acetazolamide increases the excretion of hco3- and so the ph & alkalization of the urine increases)

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

- When you drink more water , urine volume increases
- Digitalis is used to treat congestive heart failure, when the cardiac output is improved , the perfusion to the kidney is improved , so more urine volume but we can't call digitalis a diuretic .

General consideration

- Diuretics are widely used in the management of any condition associated with salt and water retention. (When there is edema caused by heart failure for ex , we use diuretics to remove the excess fluid)

- Diuretics act at different sites of the nephron (the basic unit of the kidney).
  - Loop diuretics work on loop of Henle)

- Diuretics are highly effective, relatively safe and cheap.(recent drugs are more expensive)

- 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 → ↓ plasma and stroke volume → ↓ CO → ↓ BP

The initial ↓ in CO leads to ↑ peripheral resistance (as a refelex) , but with chronic use extracellular fluid and plasma volume return to normal and peripheral resistance ↓ to values lower than those observed before diuretic therapy

- Thiazides also have direct vasodilating effect.

Stroke volume is the amount of blood ejected by the heart in one stroke

BP depends on blood volume & CO & peripheral resistance

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 electrolytes like k+) 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) (increases osmosis so pulls water and Na+)
- Still others inhibit enzymes (acetazolamide) (Carbonic anhydrase inhibitor)
- Some others block hormone receptors in renal epithelial cells (spironolactone). (block aldosterone receptors)

Classification of diuretics

Diuretics are usually classified according to their site of action in the kidney (like loop diuretics) ; their mode of action (aldosterone antagonists) and to a lesser extent by their potency (high ceiling diuretics , low ceiling diuretics)

Diuretic resistance (Therapeutic Failure)

This resistance could be seen in these situations:

- Continued ingestion of salt

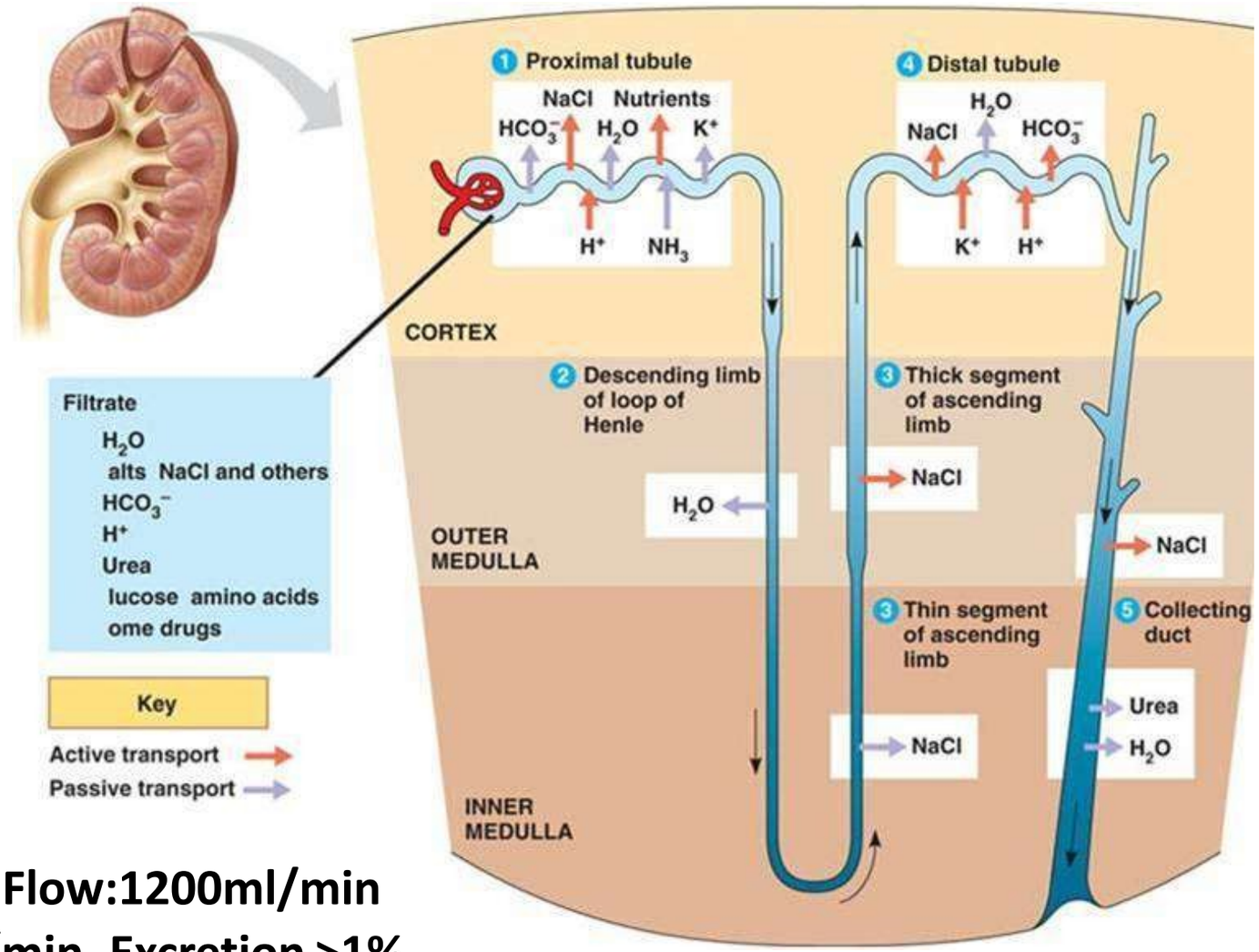
Diuretics increase the excretion of sodium so ingestion of too much salts antagonize the effect of diuretics

- Impairment of organic acid secretion mechanisms in the proximal tubules due to diseases or drugs
- Secondary hyperaldosteronism
- Lowered renal blood flow $\rightarrow\uparrow$ 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 (loop diuretics are usually combined with thiazides diuretics)

Permeability of the segments



Don't spend much time on this since you have taken it in physiology

Renal Blood Flow:1200ml/min

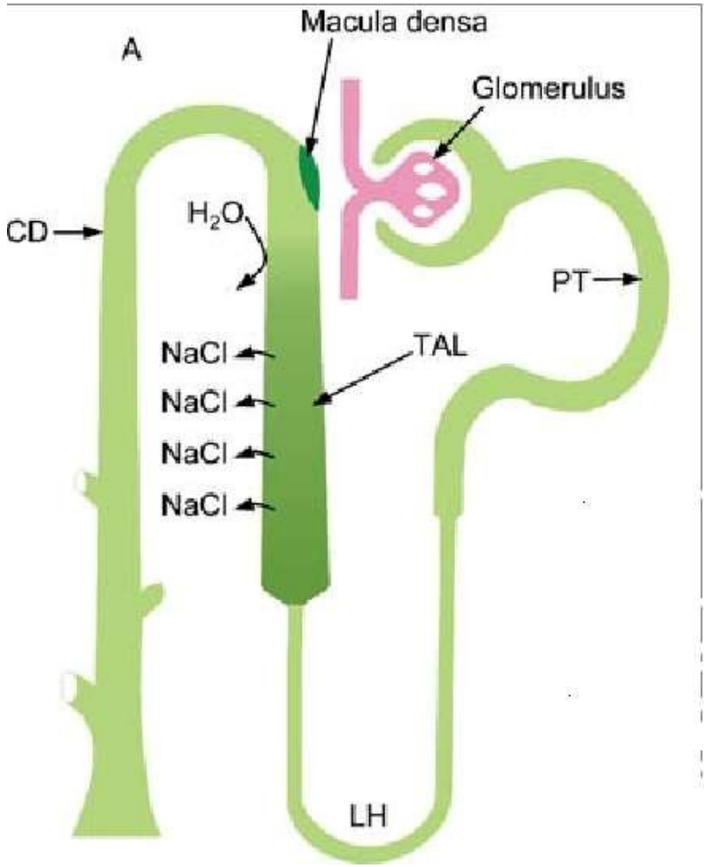
GFR:120 ml/min. Excretion >1%

Reabsorb Na+, Cl-, & HCO3 99% while 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.

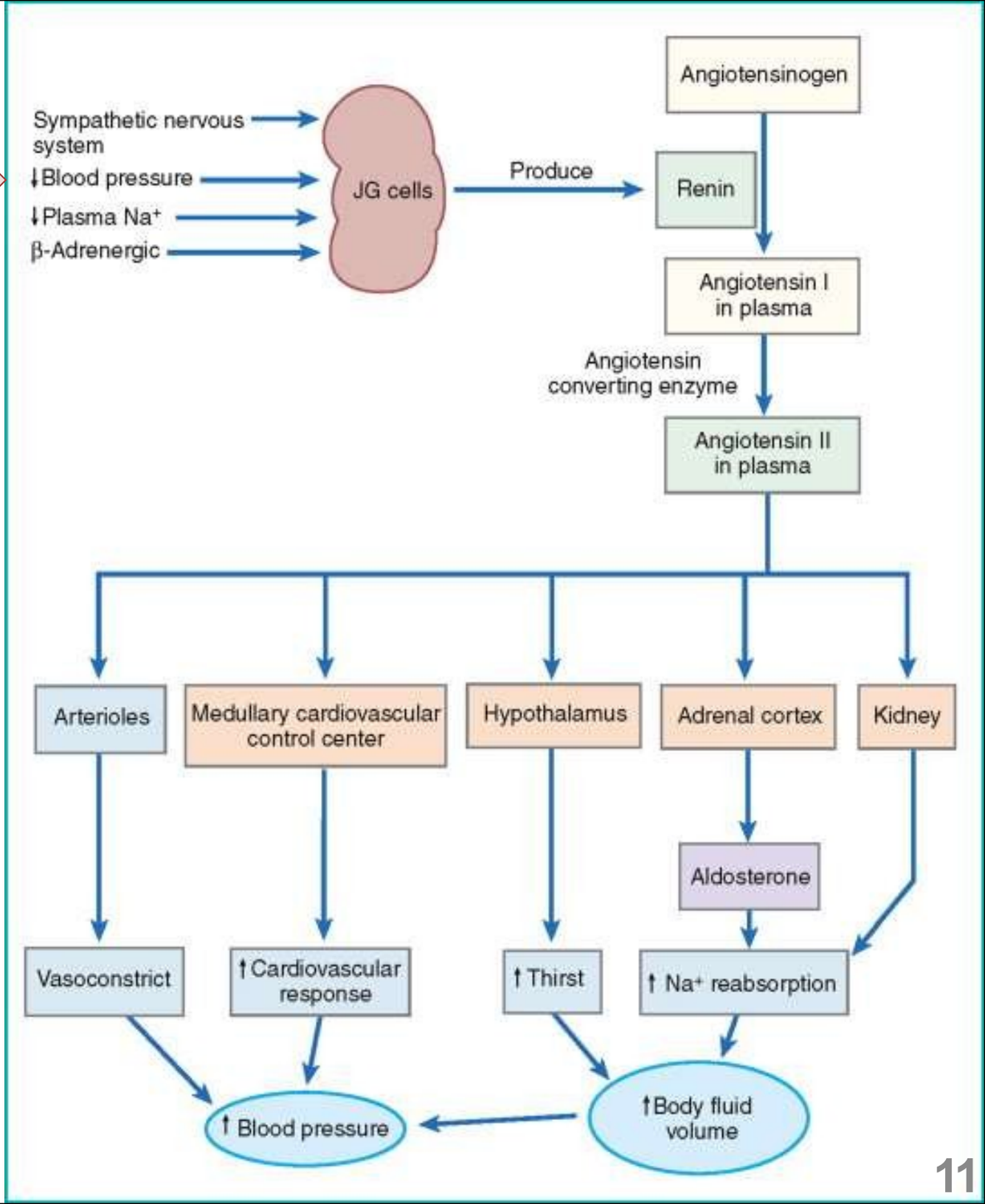
If the conc. of NaCl is too high (we are losing too much sodium) , it sends a chemical signal to the afferent arteriole of the same nephron, causing it to constrict. This, in turn, causes a decrease in Glomerular filtration rate GFR (and this preserves water and sodium)



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+ retention.

You can follow the diagram to see the effect of renin and angiotensin ll

Juxtaglomerular cells are stimulated by :



- **Caffeine** is a weak diuretic because it nonspecifically and weakly blocks adenosine receptors that participate in the control of proximal tubule Na+ reabsorption in the kidney.

So You Go bathroom more frequently after taking caffeine

Also caffeine is CNS stimulant by blocking adenosine which has inhibitory effect so blocking the inhibitory effect causes CNS stimulation and arousal

- **Rolofylline**, an adenosine A1 receptor antagonists (A new class of drugs)**,** have potent vasomotor effects (vasoconstrictor) in the renal microvasculature and blunts both proximal tubule and collecting duct NaCl reabsorption.

Prostaglandins

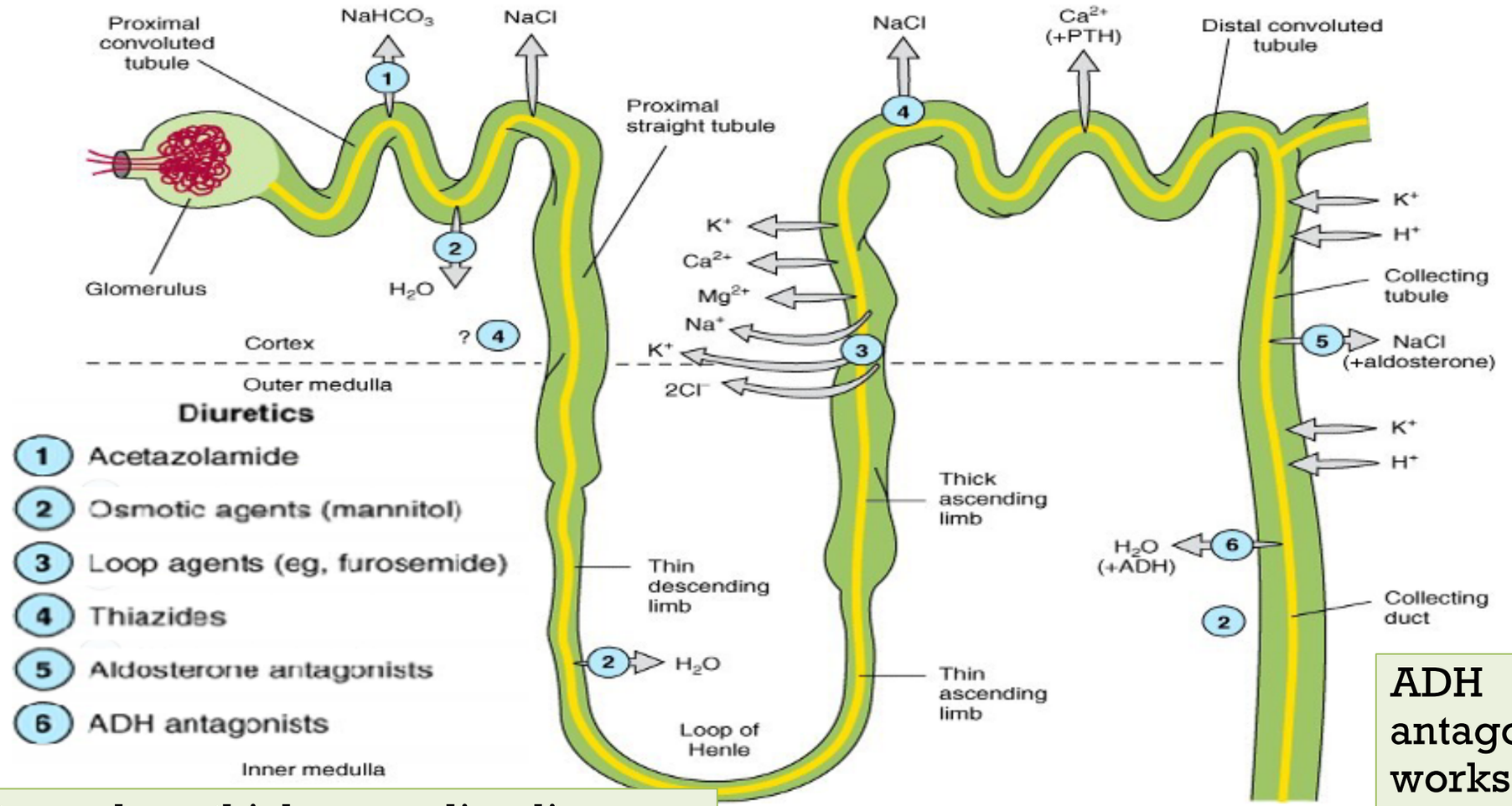
- Five subtypes (PGE, PGI, PGD, PGF, and thromboxanes) are synthesized in the kidney.
- The **PGE** participate in the regulation of salt reabsorption and play a role in the activity of certain diuretics.
- **PGE2** decreases both Na+ reabsorption in the **TAL of Henle's** loop and **ADH-**mediated water 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.

Part of the role of Loop diuretics is to increase the expression of cycloxygenase 2 to produce more prostaglandins so prostaglandins inhibitors decrease the efficacy of diuretics

1) Acetazolamide is Carbonic anhydrase inhibitors, acts in the PCT

4) Because most of the sodium is reabsorped in the thick ascending limp so the efficacy of thiazides which works on DCT is not as high as loop diuretics

Pharmacology of Diuretic Agents



2) Mannitol works on PCT and collecting duct. ,MOA is mentioned before

5)Aldosterone antagonist s Block aldosterone receptors in the collecting tubules so decrease the reabsorption of NaCl

ADH antagonist works here

3) Loop agents work on thick ascending limp , most of sodium is reabsorbed here so they have high ceiling effect and the most potent diuretics