PHYSIO

MODIFIED NO. 6

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Color code

(black)	Slides
(dark blue)	Doctor
(light blue)	Additional info
(red)	Important

Changes in concentration in proximal tubule

Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

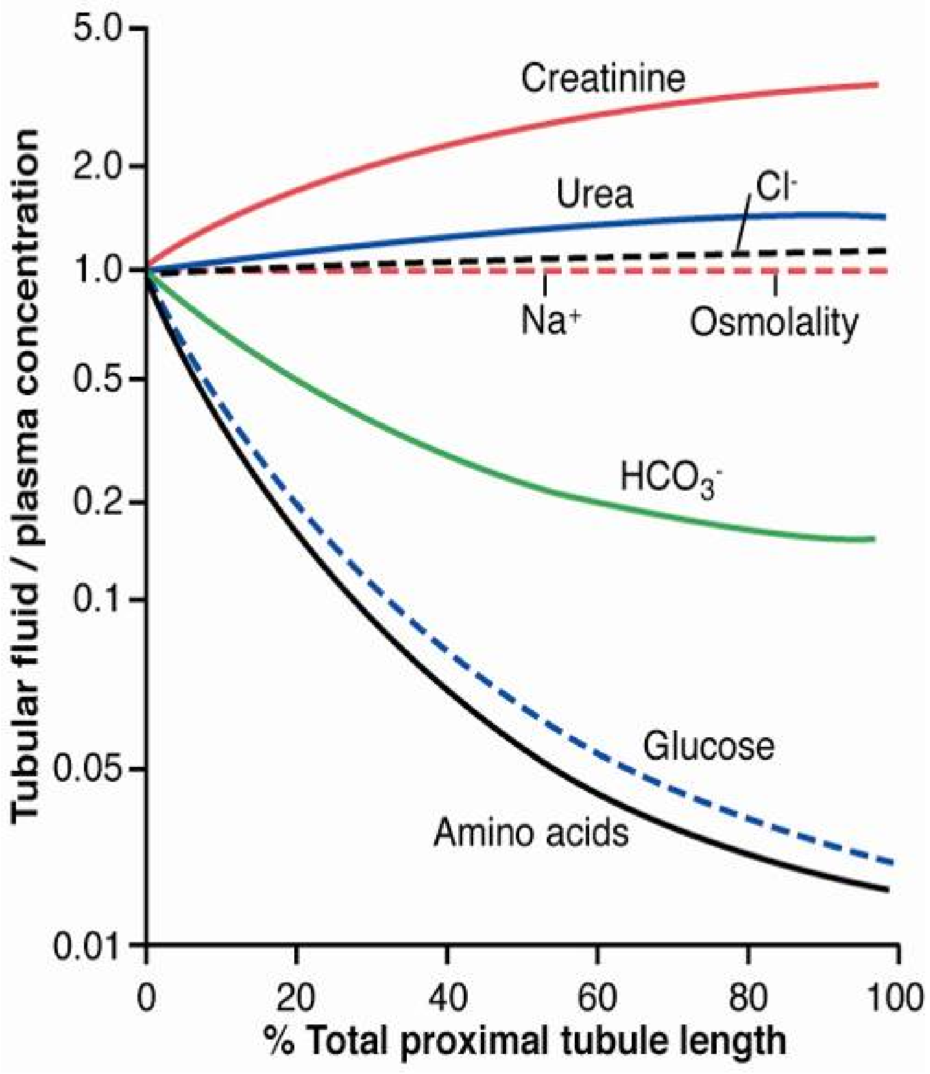


Figure 27-7

- The Y-axis in this curve represents the ratio between the tubular fluid and plasma concentration of a specific substance. Through this curve, we can observe how this ratio changes along the length of the tubule.

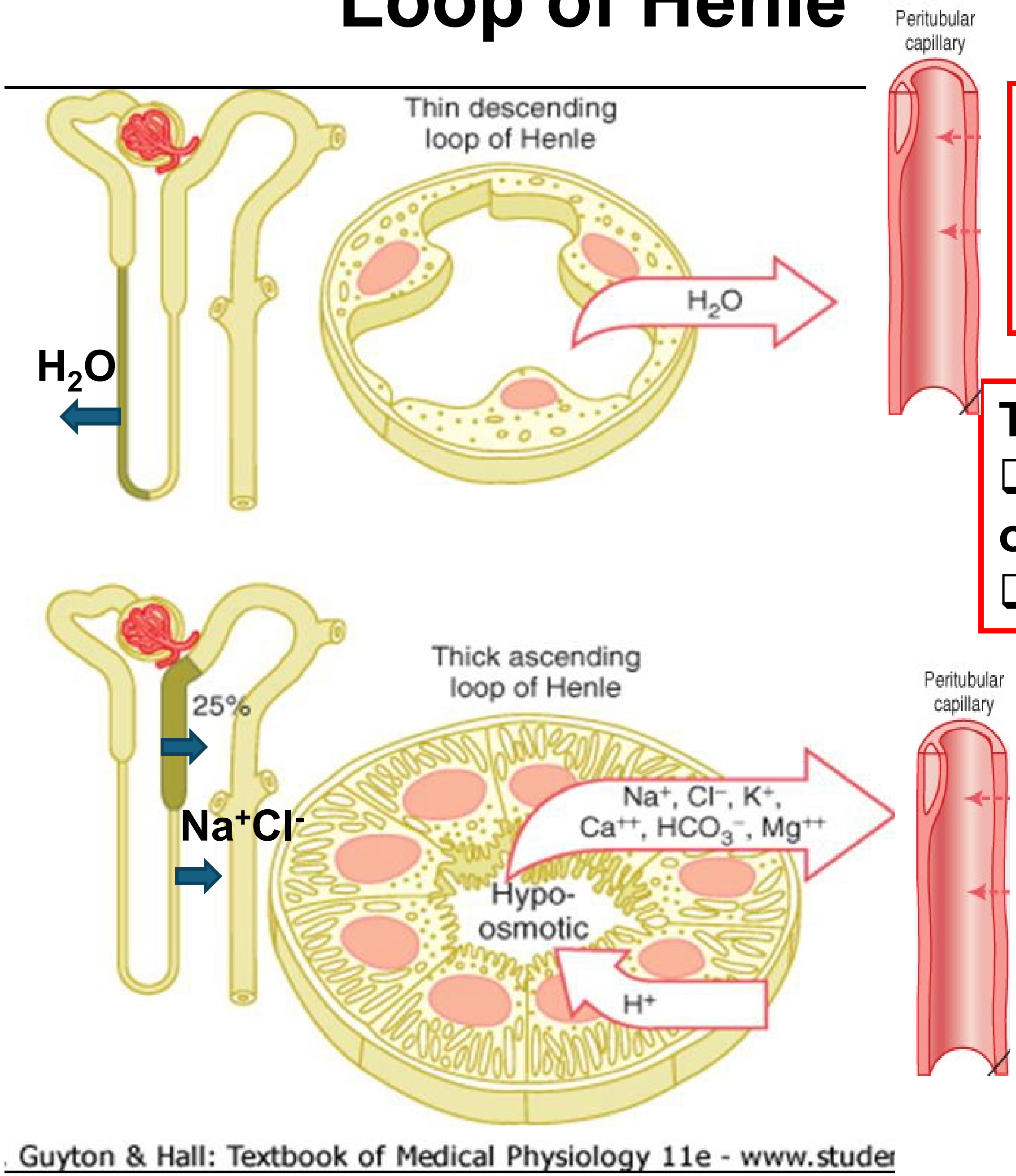
- In the previous curve, substances with a ratio equal to one are reabsorbed at the same rate as water. Examples include sodium (Na^+) and chloride (Cl^-). Remember that Substances are freely filtered across the glomerulus, except for proteins.

- Substances with a ratio greater than one follow one or both of the following mechanisms: (1) water reabsorption exceeds the reabsorption of the substance, which is the primary reason; (2) the substances may either not be reabsorbed at all (as with creatinine), be poorly reabsorbed (as with urea), or undergo secretion. As tubular length increases (X-axis), the concentration of these substances rises because the amount of water reabsorbed is greater than the amount of substance reabsorbed. Urea undergoes some reabsorption but significantly less than water, whereas creatinine undergoes no reabsorption.

- Substances with a ratio less than one are reabsorbed more rapidly than water, such as bicarbonate, glucose, and amino acids. Glucose and amino acids are reabsorbed almost completely.

- Thus, the concentration of various substances along the proximal tubule depends on the relative reabsorption rates of the solutes compared to that of water.

Loop of Henle



Thin Descending
- **15% of H_2O reabsorbed.**

Thin Ascending
- **Passive reabsorption of Na+, K+, Cl-.**
- **Impermeable to H_2O.**

Thick Ascending
25% of Na+, K+, Cl- HCO_3^-, Ca^{++}, Mg^{++} **reabsorbed.**
- **Impermeable to H_2O.**
- **Called = Diluting segment.**
- **Secretion of H^+**

- After the fluid reaches the loop of Henle, which is composed of three physiological segments—the thin descending limb, the thin ascending limb, and the thick ascending limb—each segment exhibits distinct characteristics based on the properties of its epithelial cells.

- The thin descending limb is characterized by a thin wall formed by small epithelial cells with few organelles, including limited mitochondria and transporters. Consequently, this segment is permeable primarily to water through aquaporin channels and exhibits minimal permeability to solutes.

- As the fluid descends deeper into the medulla, the surrounding interstitial fluid becomes increasingly concentrated with osmolytes. The primary function of the thin descending limb is to allow passive movement of water across its walls, driven by the osmotic gradient created by the increasing interstitial osmolarity. Therefore, water reabsorption increases progressively along the descending limb. At the tip of the loop of Henle, equilibrium is achieved (isotonic solution), and the tubular fluid reaches its highest concentration.

- In contrast, the ascending limb—both thin and thick portions—is virtually impermeable to water, a property essential for urine concentration. As the fluid ascends, the interstitial fluid concentration becomes lower than that of the tubular fluid. Since this segment is impermeable to water, passive NaCl reabsorption occurs, driven by the concentration gradient established in the descending limb.

- Upon reaching the thick ascending limb, which consists of larger epithelial cells rich in mitochondria and equipped with Na^+/K^+-ATPase pumps and multiple transporters, active NaCl reabsorption occurs. Due to the impermeability to water, this active ion transport results in a higher concentration of ions in the interstitial fluid compared to the tubular fluid, leading to dilution of the tubular contents. Hence, the thick ascending limb is referred to as the "diluting segment."

- Approximately 25% of the filtered loads of Na^+ , Cl^-, and K^+ are reabsorbed in the loop of Henle, with the majority occurring in the thick ascending limb. Considerable amounts of other ions, such as Ca^+ , HCO_3, and Mg^+ , are also reabsorbed in the thick ascending loop of Henle.

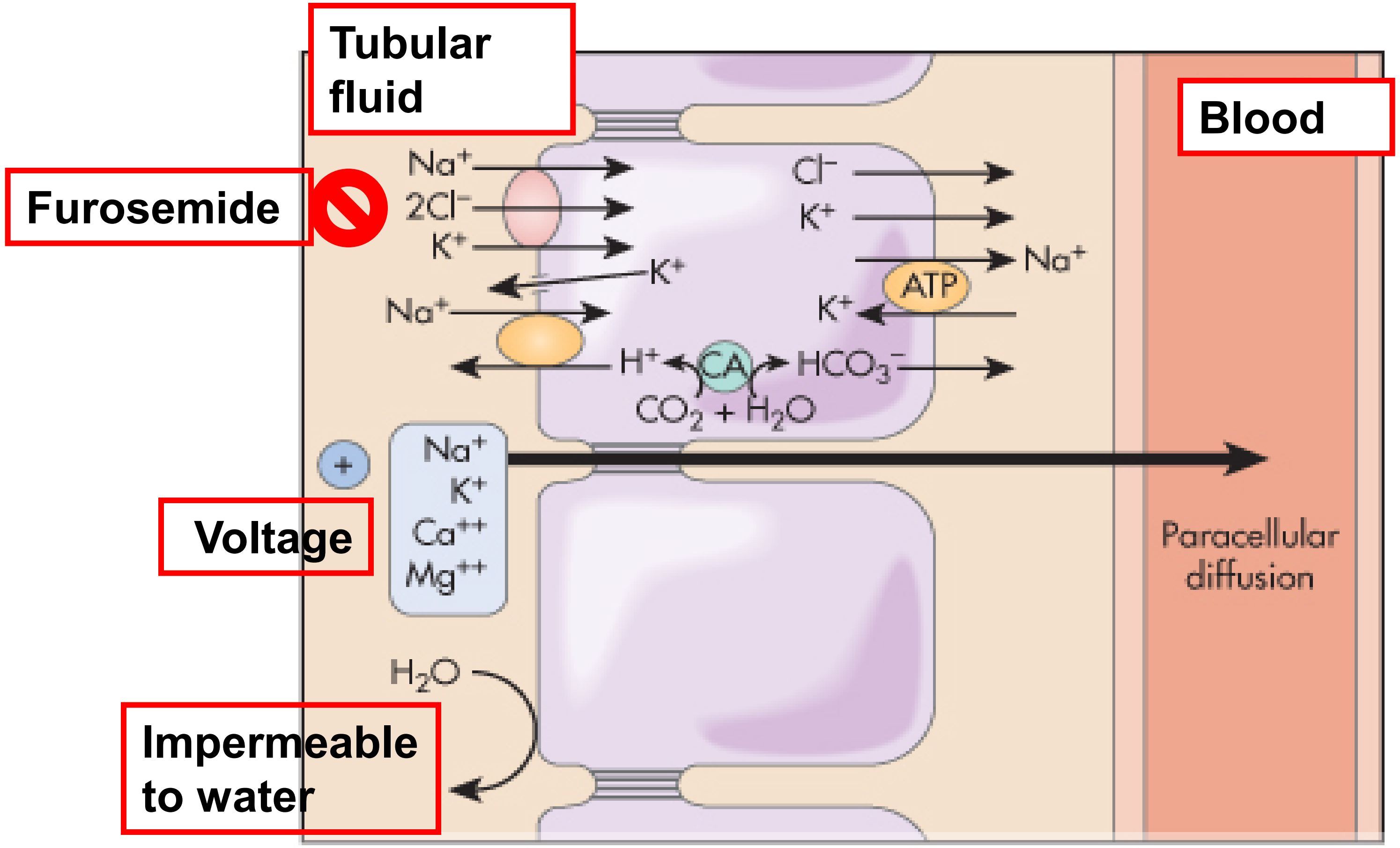
- **SUMMARY OF THE PREVIOUS 2 SLIDES:**
- **Thin descending limb:**
- Permeable only to water (via aquaporins), not solutes.
- Water reabsorption increases as we move deeper into the medulla due to the rising osmotic gradient.
- At the tip, tubular fluid reaches its highest concentration.

- **Thin and thick ascending limbs:**
- Impermeable to water.
- In the thin part, passive NaCl reabsorption occurs.
- In the thick part, active NaCl reabsorption occurs via pumps and transporters.
- Tubular fluid becomes diluted (thick ascending limb = “diluting segment”).

Loop of Henle

- Water reabsorption occurs exclusively in the **thin descending** limb of Henle via AQP1 water channels.(**Aquaporins**)
- Reabsorption of **NaCl** occurs in both thin and thick **ascending** limb of Henle.
- In thin ascending limb NaCl is reabsorbed passively. However, in thick ascending limb NaCl is reabsorbed through Na^+-K^+ ATPase in basolateral membrane ans it mean active transport .
- Ascending limb is impermeable to water.
- Reabsorption of Ca^{++} and $HCO3^-$ occurs also in Loop of Henle.

Thick ascending limb of Henle



of NaCl Reabsorption:
- ❑50% is Transcellular
- ❑50% is Paracellular

- On the apical (luminal) surface of the thick ascending limb, there is a sodium-potassium-chloride ($Na^+/K^+/Cl^-$) channels. On the basolateral surface, there is a Na^+/K^+ ATPase pump that creates a gradient to drive sodium reabsorption. This pump works by moving 3 sodium ions out of the cell and 2 potassium ions into the cell, which promotes the reabsorption of sodium, chloride, and potassium. This $Na^+/K^+/Cl^-$ channel can be blocked by an antihypertensive drug called furosemide (Lasix). Blocking this channel prevents the reabsorption of sodium, chloride, and potassium, leading to decreased water reabsorption. Remember, water follows solutes, so this increases diuresis and lowers blood pressure. However, since potassium reabsorption is also inhibited, it can lead to hypokalemia, which may affect heart rhythm. Therefore, furosemide is not preferred for long-term use unless combined with medications that replace potassium loss.

- Also, on the Apical surface, there is a Na^+/H^+ exchanger that secretes protons (H^+) and reabsorbs sodium (Na^+). The H^+ comes from the reaction between water and carbon dioxide inside the cell, not directly from the plasma. This reaction is catalyzed by the enzyme carbonic anhydrase, producing carbonic acid, which quickly dissociates into bicarbonate (HCO_3^-) and a proton (H^+). The H^+ is secreted, while the bicarbonate is reabsorbed to act as a buffer and help neutralize blood acidity.

- Voltage drag, a phenomenon observed in the thick ascending limb of the nephron, is responsible for significant paracellular reabsorption of cations, including Mg^{2+}, Ca^{2+}, Na^{+}, and K^{+}. This reabsorption is driven by the presence of a slight positive charge within the tubular lumen compared to the surrounding interstitial fluid. The mechanism behind the generation of this positive charge involves the NKCC2 co-transporter, which facilitates the movement of equal amounts of cations and anions into the cell. However, a slight backleak of potassium ions into the lumen occurs as a result. This backleak leads to the development of a positive charge of approximately +8 millivolts within the tubular lumen. The positive charge within the lumen creates an electrostatic force that drives the paracellular reabsorption of cations, such as Mg^{2+} and Ca^{2+}, from the lumen into the interstitial fluid. This process is of significant importance as it accounts for approximately 50% of solute transport in this particular segment. As a consequence of this paracellular reabsorption, the tubular fluid in the ascending limb becomes progressively more dilute as it flows towards the distal tubule. This characteristic plays a crucial role in the kidney's ability to dilute or concentrate urine depending on the body's needs

Sodium chloride and potassium transport in thick ascending loop of Henle

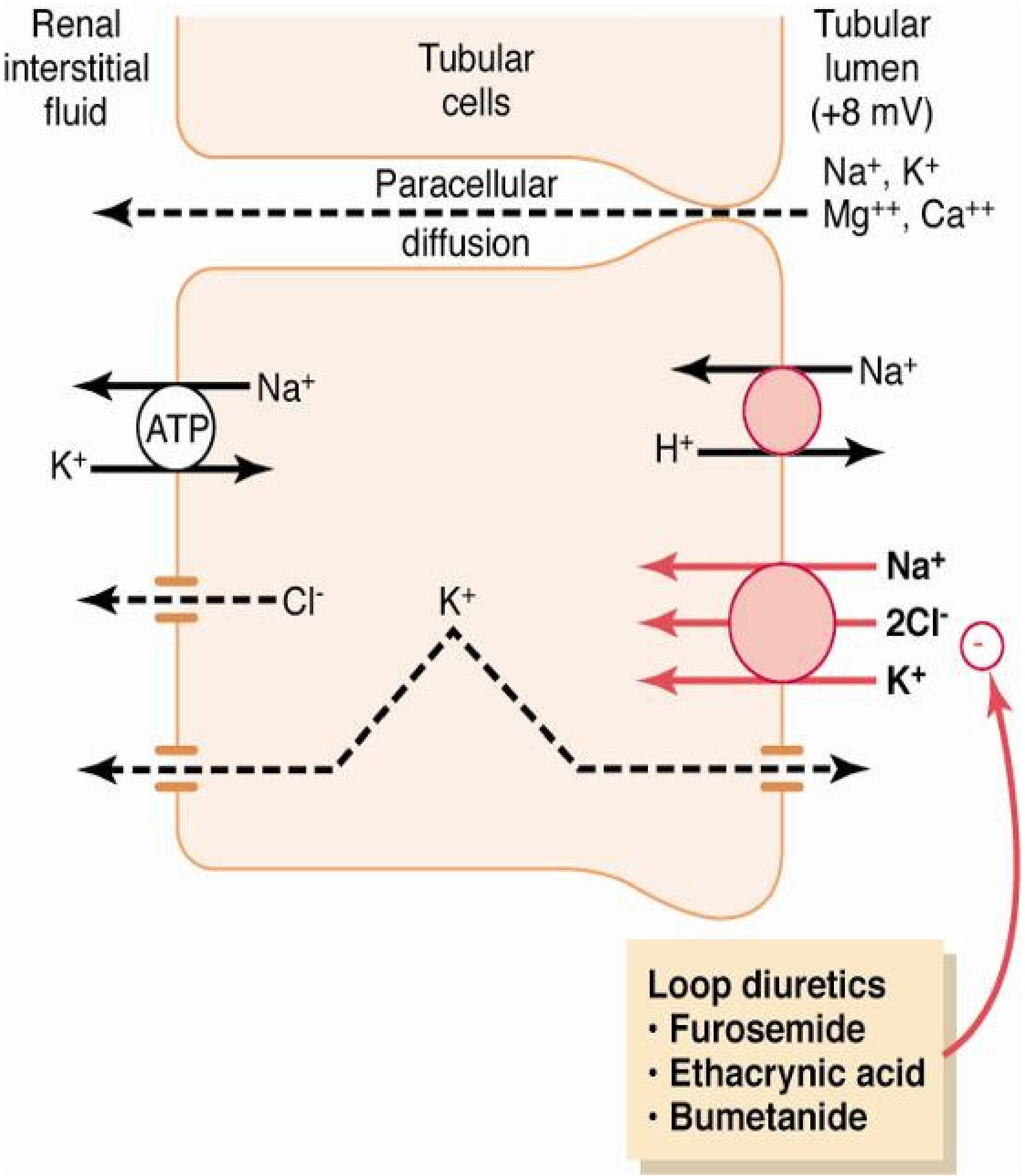


Figure 27-9

Early Distal Tubule

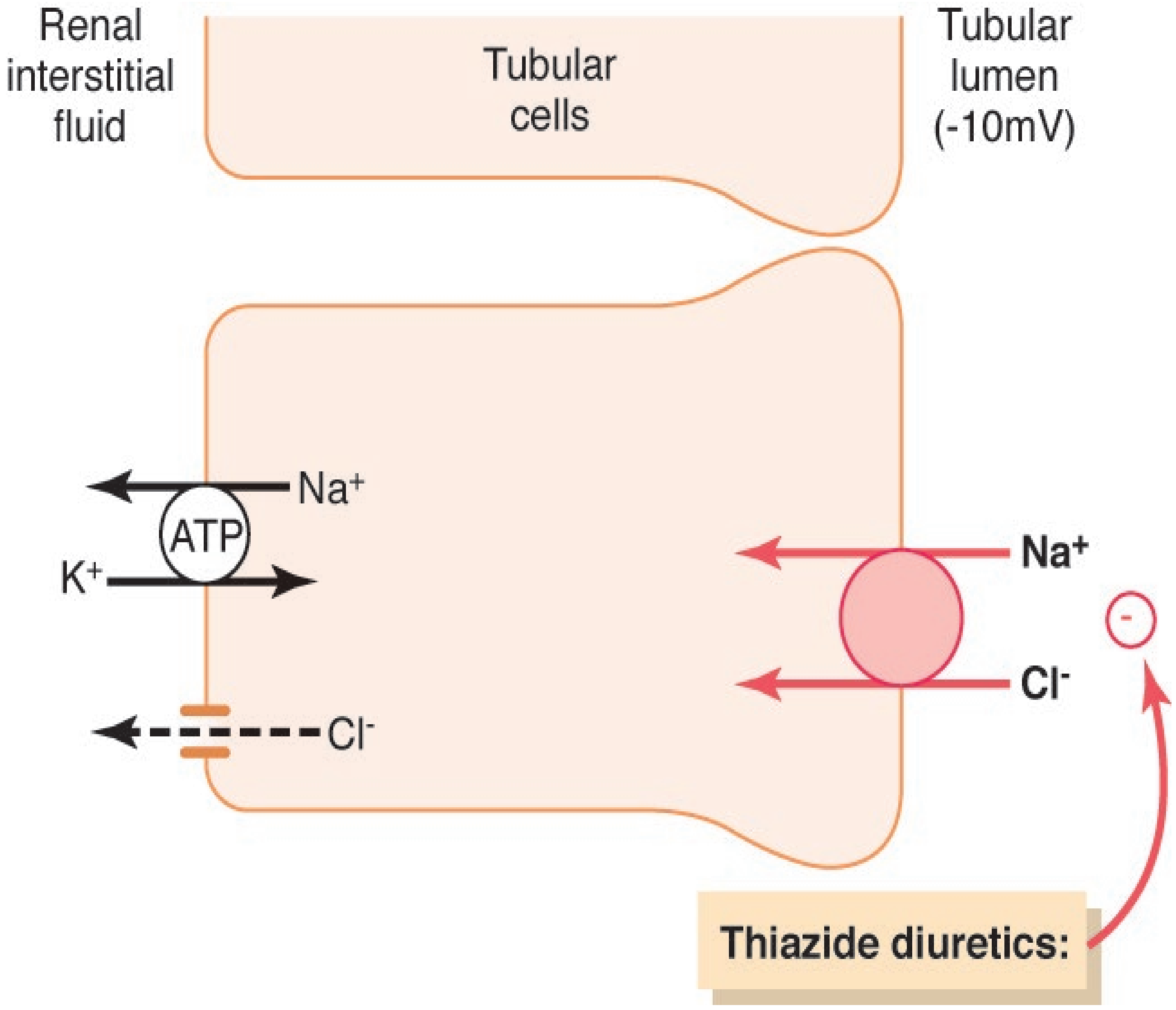


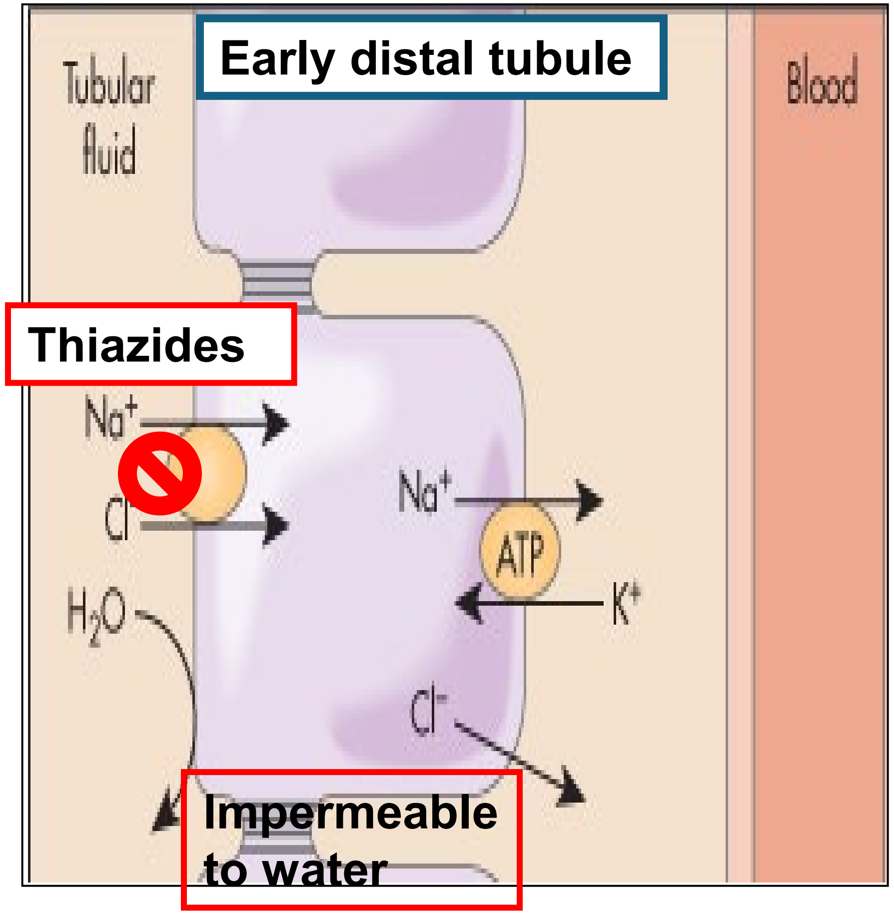
Figure 27-10

- Fluid flows from the thick ascending limb into the early distal tubule. The osmolarity of the early distal tubule becomes diluted due to significant reabsorption of electrolytes and minimal water reabsorption in the ascending limb. This dilution continues in the early distal tubule because of extensive solute reabsorption and its low permeability to water, similar to the ascending limb. However, in the early distal tubule, reabsorption occurs via the Na^+/Cl^- cotransporter.
- From a pharmacological perspective, this Na^+/Cl^- channel is inhibited by thiazide diuretics, leading to diuresis. This occurs because more sodium remains in the tubular fluid, resulting in increased fluid excretion and a subsequent reduction in blood pressure.

Early Distal Tubule

- Functionally similar to thick ascending loop
- Not permeable to water (called diluting segment)
- Active reabsorption of Na^+, Cl^-, K^+, Mg^{++}
- Contains macula densa which is responsible for renal auto regulation (tubuloglomerular feedback).

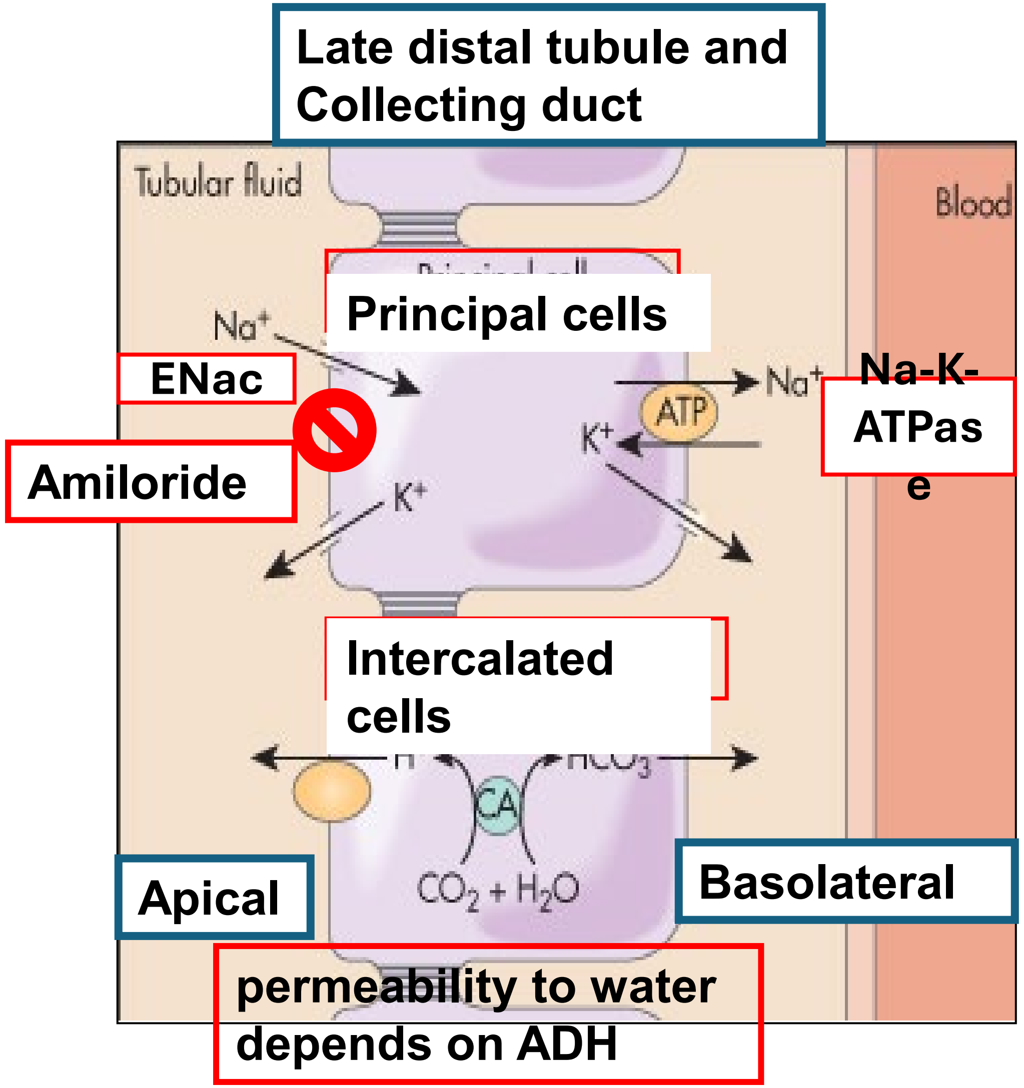
Distal tubule and collecting duct



Again, the distal tubule is divided to early distal and late distal.
The early distal simular to thick assending limb of henle

- impermeable to water
- Na+/Cl channeles
- Na+/K+ATPase

Distal tubule and collecting duct



In the late distal tubule, the collecting tubule, and the collecting duct are grouped together because they share similar characteristics.

The distal tubule primarily consists of two types of cells: **principal cells and intercalated cells.**

Principal cells have the following features:

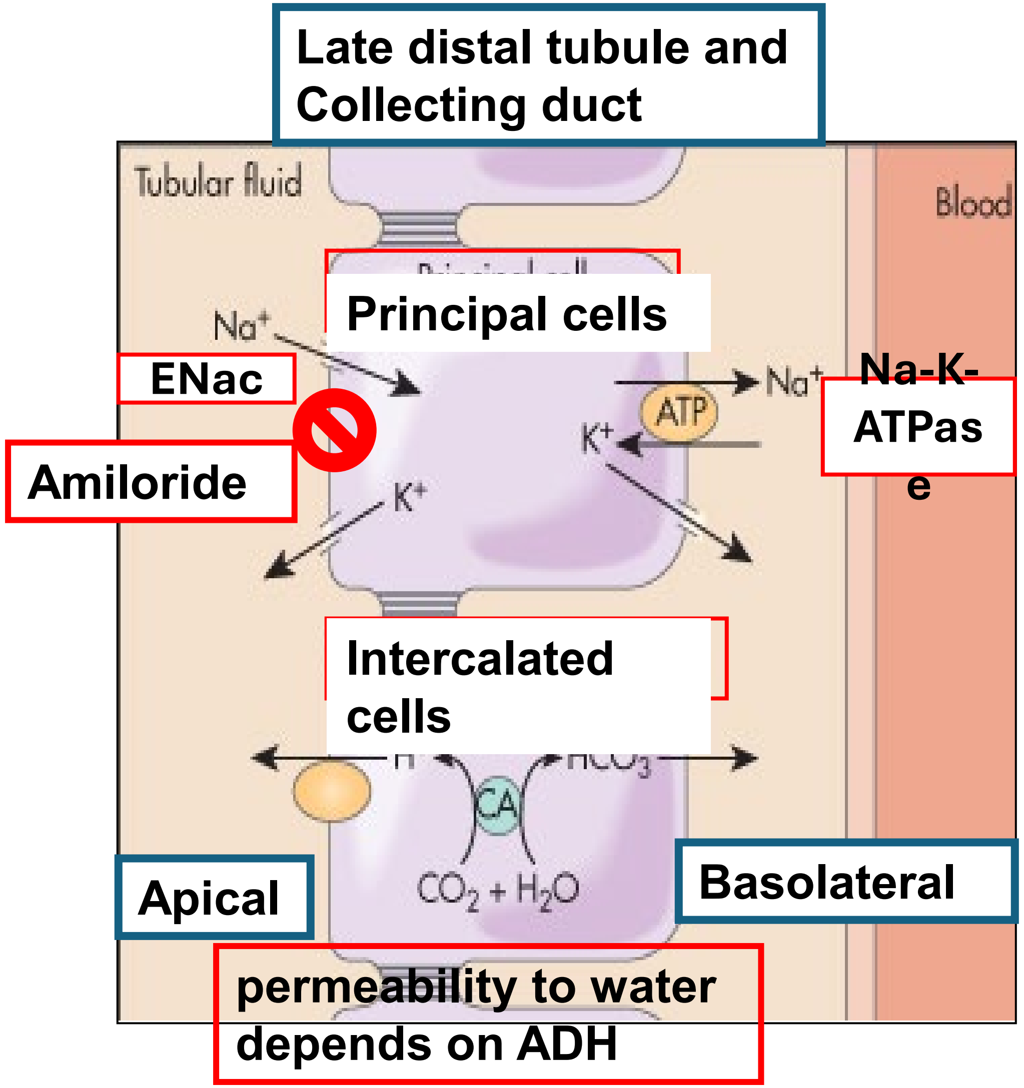
- They are more numerous than intercalated cells.
- They possess Na^+/K^+-ATPase pumps on the basolateral membrane.
- They have ENaC (epithelial sodium channels) on the luminal membrane (facing the tubular fluid).

When Na^+/K^+-ATPase activity increases (transporting more Na^+ into the blood and K^+ into the principal cell), ENaC channels reabsorb Na^+ from the lumen, and K^+ is secreted into the tubular fluid.

The net effect is Na^+ reabsorption and K^+ secretion.

Aldosterone acts on principal cells by binding to its intracellular receptor, leading to increased Na^+/K^+-ATPase activity and enhanced expression of ENaC channels. As a result, Na^+ reabsorption and K^+ secretion are both increased. Through this mechanism, aldosterone helps regulate potassium levels and prevents hyperkalemia while simultaneously contributing to blood pressure elevation.

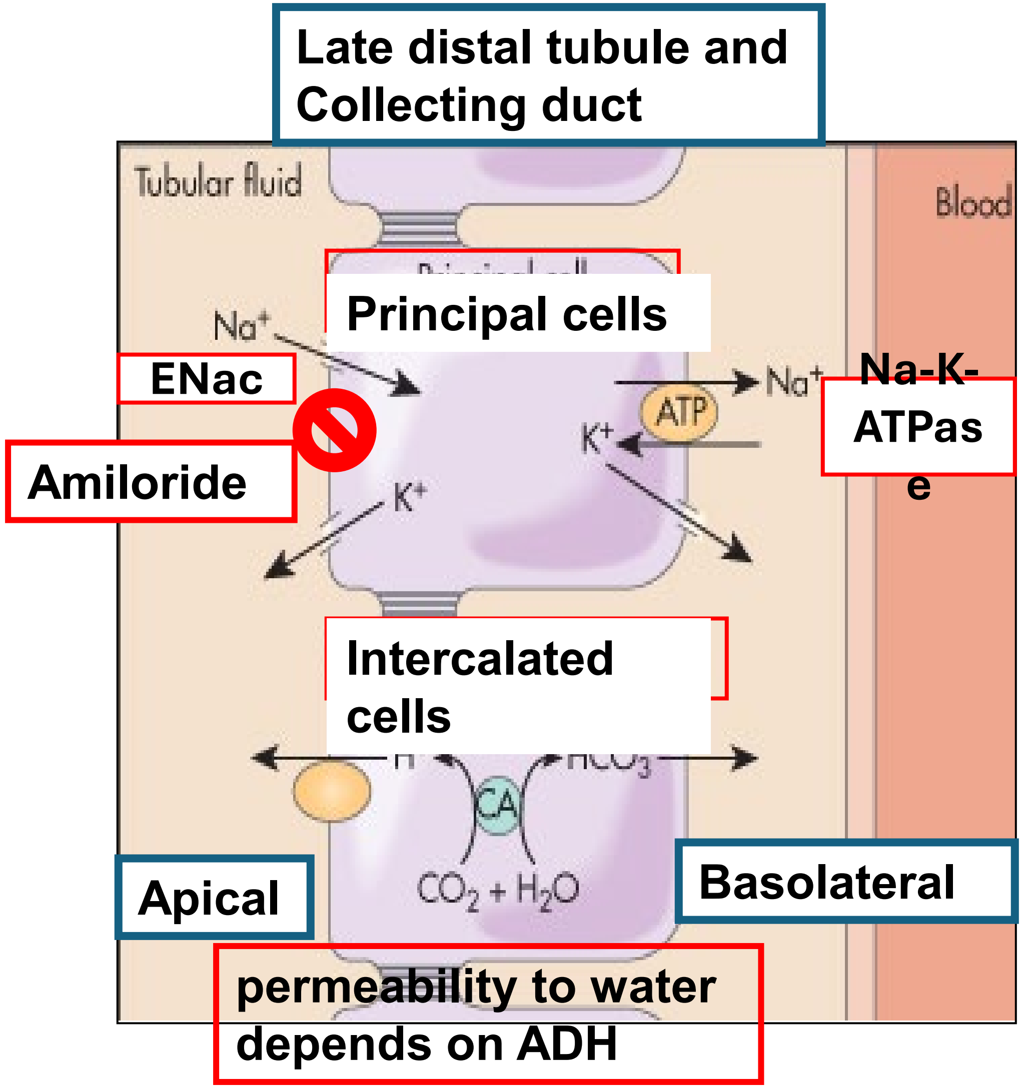
Distal tubule and collecting duct



- If an aldosterone antagonist (such as spironolactone) is administered, it decreases Na^+/K^+-ATPase activity, leading to reduced Na^+ reabsorption. This results in diuresis. However, potassium is not lost, as K^+ secretion is also decreased. Therefore, these drugs are classified as potassium-sparing diuretics.

- Similarly, diuretic drugs that block ENaC channels prevent Na^+ reabsorption, which also inhibits K^+ secretion (because Na^+ reabsorption is necessary for K^+ secretion). Thus, blocking ENaC channels produces an effect comparable to using aldosterone antagonists, and these drugs are also considered potassium-sparing diuretics.

Distal tubule and collecting duct



Intercalated cells:

These cells are less prominent than principal cells, comprising about 30–40% of the cells in the late distal tubule and collecting duct.

Their primary function is maintaining acid-base balance.

There are two types: Type A and Type B, with Type A being the most commonly used by the body.

Type A intercalated cells:

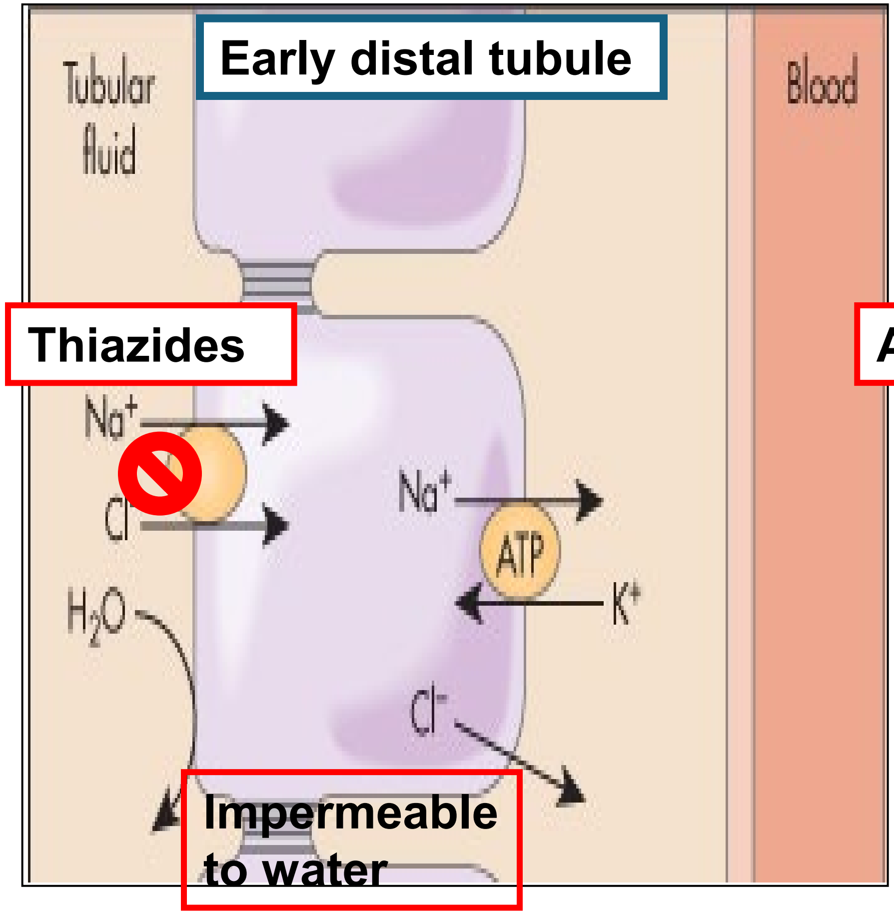
- Possess an H^+-ATPase pump on the luminal membrane.
- Produce both HCO_3^- and H^+ (the production mechanism is detailed in slide 11).
- Have channels for HCO_3^- located on the basolateral membrane.
- Thus, they secrete H^+ into the tubular lumen and reabsorb HCO_3^- into the blood.

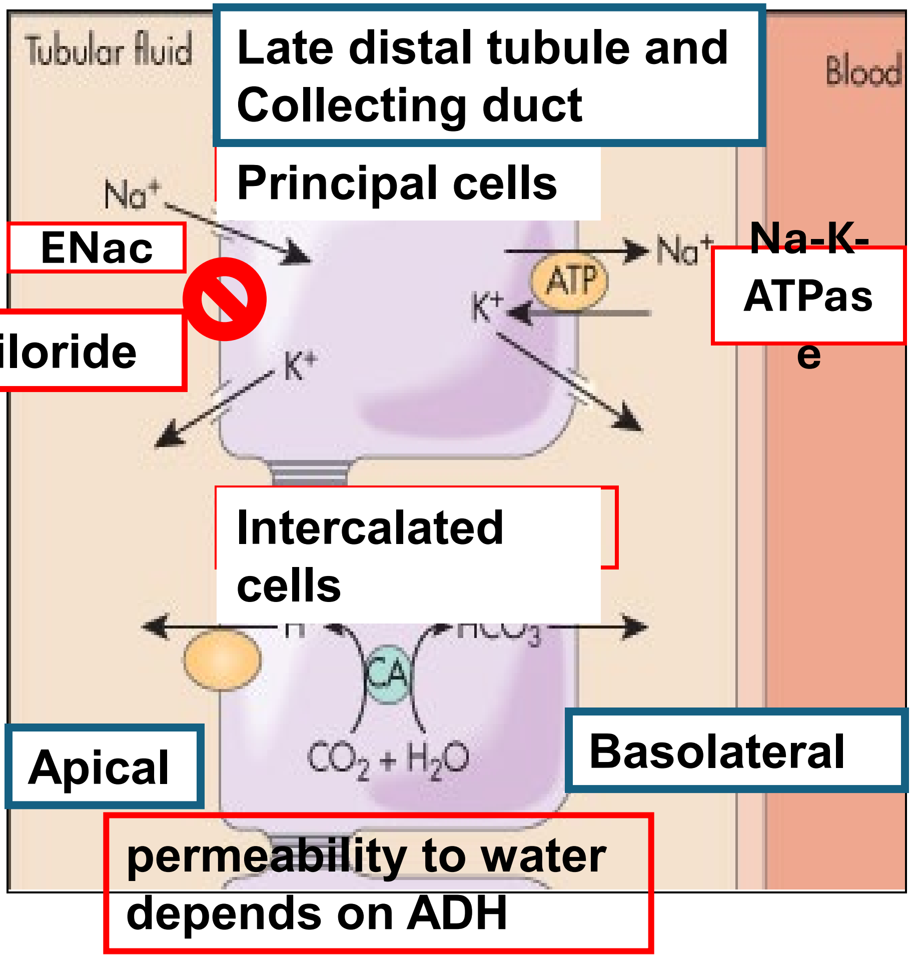
The H^+-ATPase pump is significantly stronger than the secondary active Na^+/H^+ exchanger found in the thick ascending limb of Henle. The H^+-ATPase can secrete H^+ against a concentration gradient up to 1000 times, compared to the Na^+/H^+ exchanger, which can secrete H^+ against a concentration gradient only about 10 times.

Distal tubule and collecting duct

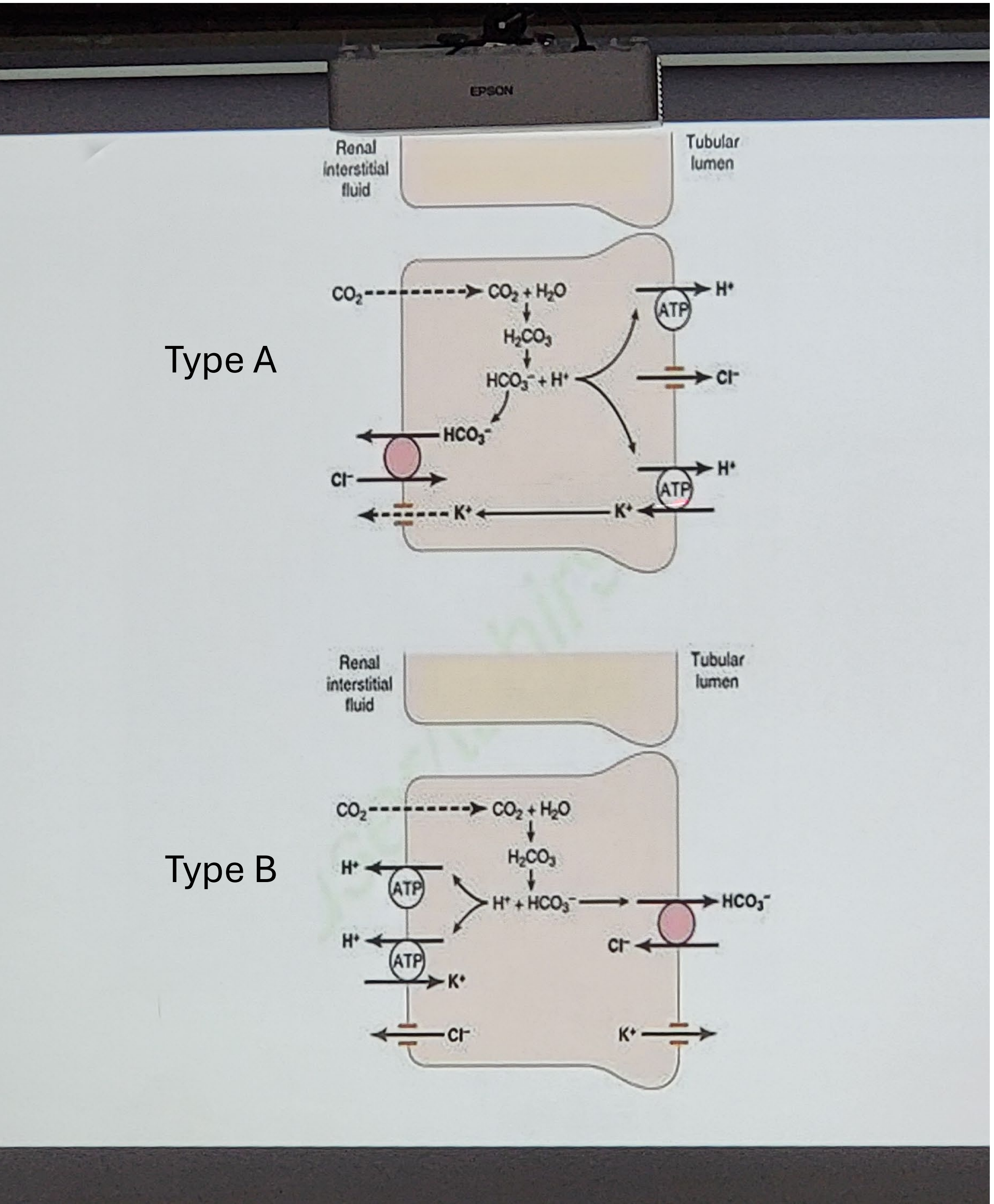
❑ Reabsorbs 7% NaCl, secrets K+ and H+ and reabsorbs 8-17% H_2O

- Now the permeability to water in distal tubule and collecting duct is variable, depending on the presence of ADH, if ADH present they become permeable, if not they become impermeable.





- Antidiuretic hormone (ADH), through specific receptors and intracellular signaling pathways, induces the insertion of aquaporins into both the luminal and basolateral membranes. In the absence of ADH, aquaporins remain stored within the cells and are not inserted into the membranes.



These are type A and type B intercalated cells

Type A intercalated cells:

- CO_2 and H_2O are converted into HCO_3^- and H^+.
- H^+ is secreted into the tubular lumen via an H^+-ATPase pump.
- An additional H^+/K^+-ATPase counter-transporter also secretes H^+ into the lumen in exchange for K^+, with its activity depending on K^+ levels (to be explained later).
- HCO_3^- is reabsorbed into the blood through an HCO_3^-/Cl^- exchanger located on the basolateral membrane.

Type B intercalated cells:

Type B cells perform the opposite function of type A cells: they reabsorb H^+ and secrete HCO_3^-.
These cells are important during states of alkalosis, when the body needs to secrete excess HCO_3^- and reabsorb H^+ to restore acid-base balance.

Early and Late Distal Tubules and Collecting Tubules.

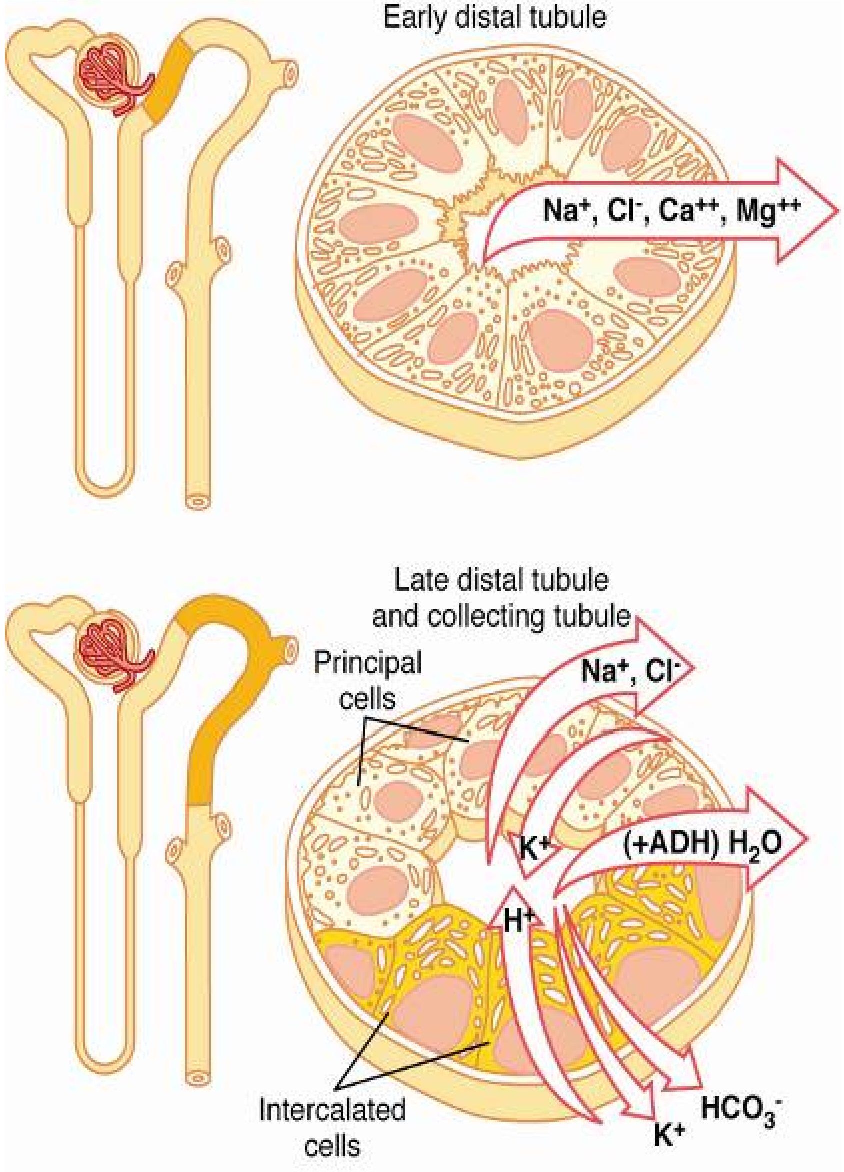


Figure 27-11

~ 5% of filtered load NaCl reabsorbed

- not permeable to H_2O
- not very permeable to urea

Cortical tubule

- permeablility to H_2O depends on ADH
- not very permeable to urea

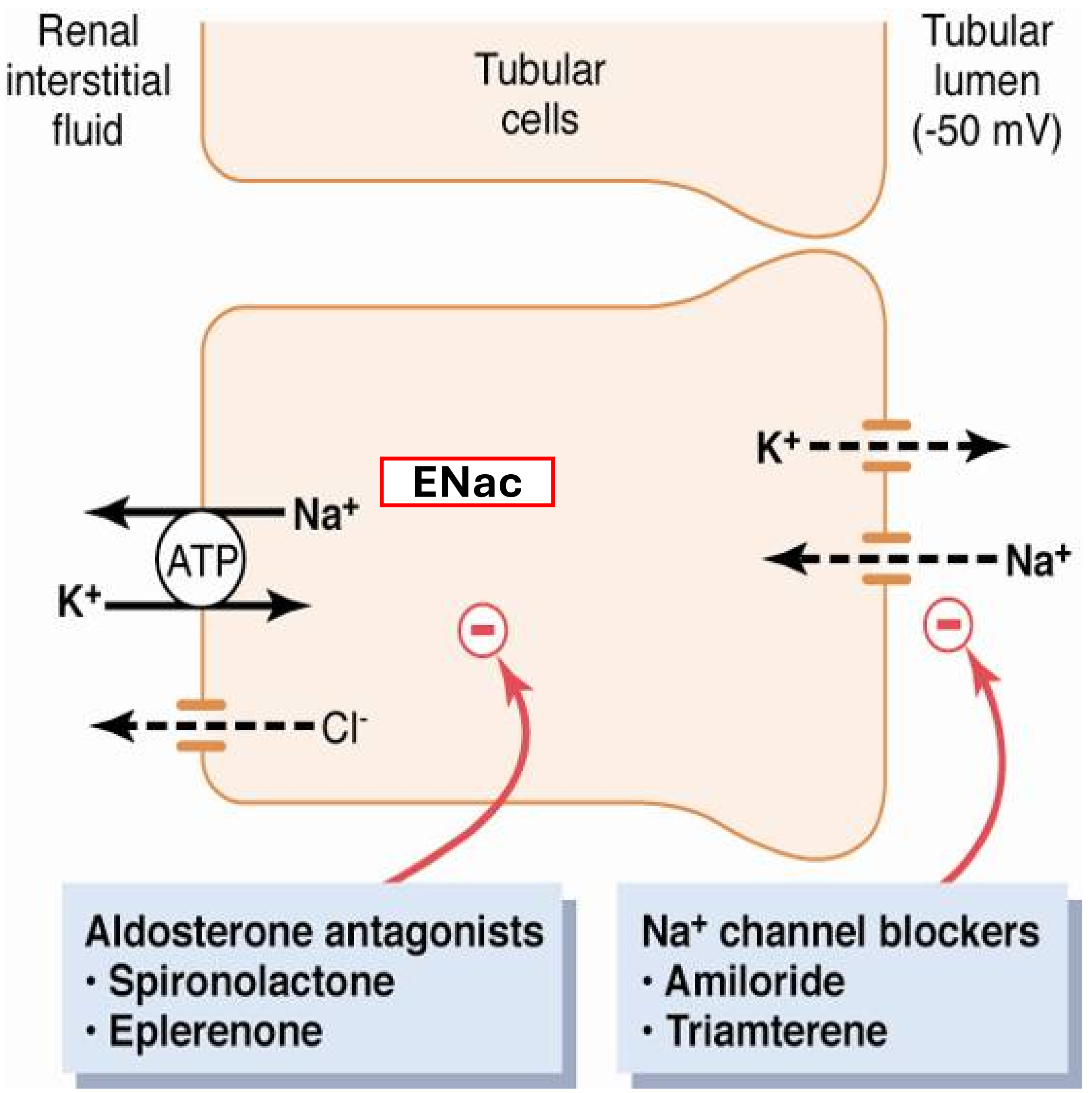
The medullary collecting duct is permeable to urea, and the permeablity increase with the existence of ADH, more insertion of urea transporter.

Late Distal and Cortical Collecting Tubules **Principal Cells** – Secrete K^+

Again this is the action of antagonizing aldosterone or the inhibition of ENac channles

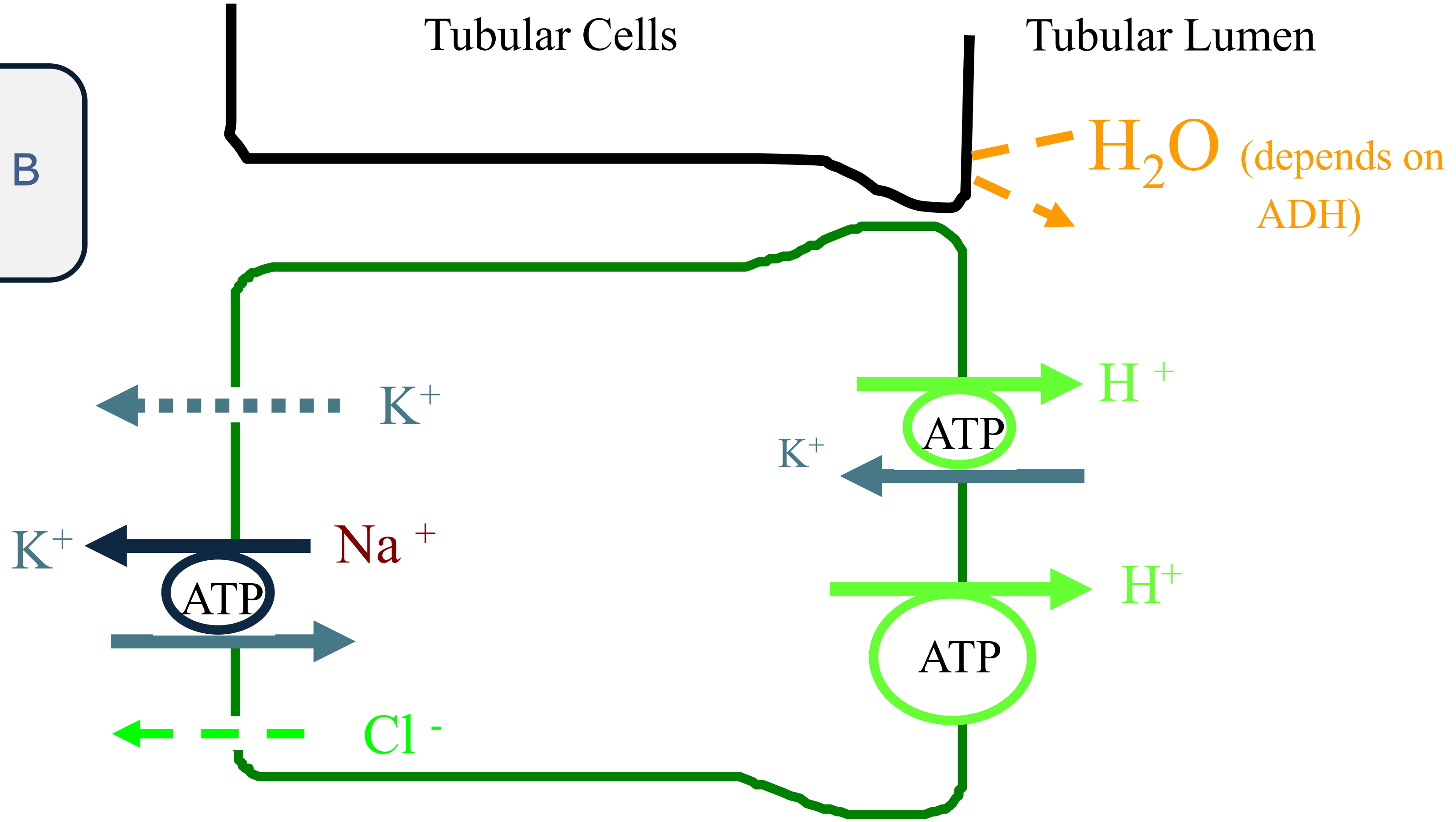
When we inhibit ENac (Amiloride) we prevent Na+ reabsorption (increase Na+ loss) and at the same time we spared K+

Aldosterone antagonist (spironolacton) reduces the expression and activity of Na+/K+ATPase and then reduces the action of other channels (we prevent Na+ reabsorption (increase Na+ loss) and at the same time we spare K+).



Late Distal and Cortical Collecting Tubules **Intercalated Cells** –Secrete H^+

This is type A
Remember, type B
is the opposite



Transport characteristics of medullary collecting ducts

The medullary collecting duct is permeable to urea, and its permeability increases in the presence of antidiuretic hormone (ADH) due to the enhanced insertion of urea transporters. This urea reabsorption contributes to the high osmolarity of the renal medulla, a characteristic necessary for the concentration of urine (to be explained in more detail later).

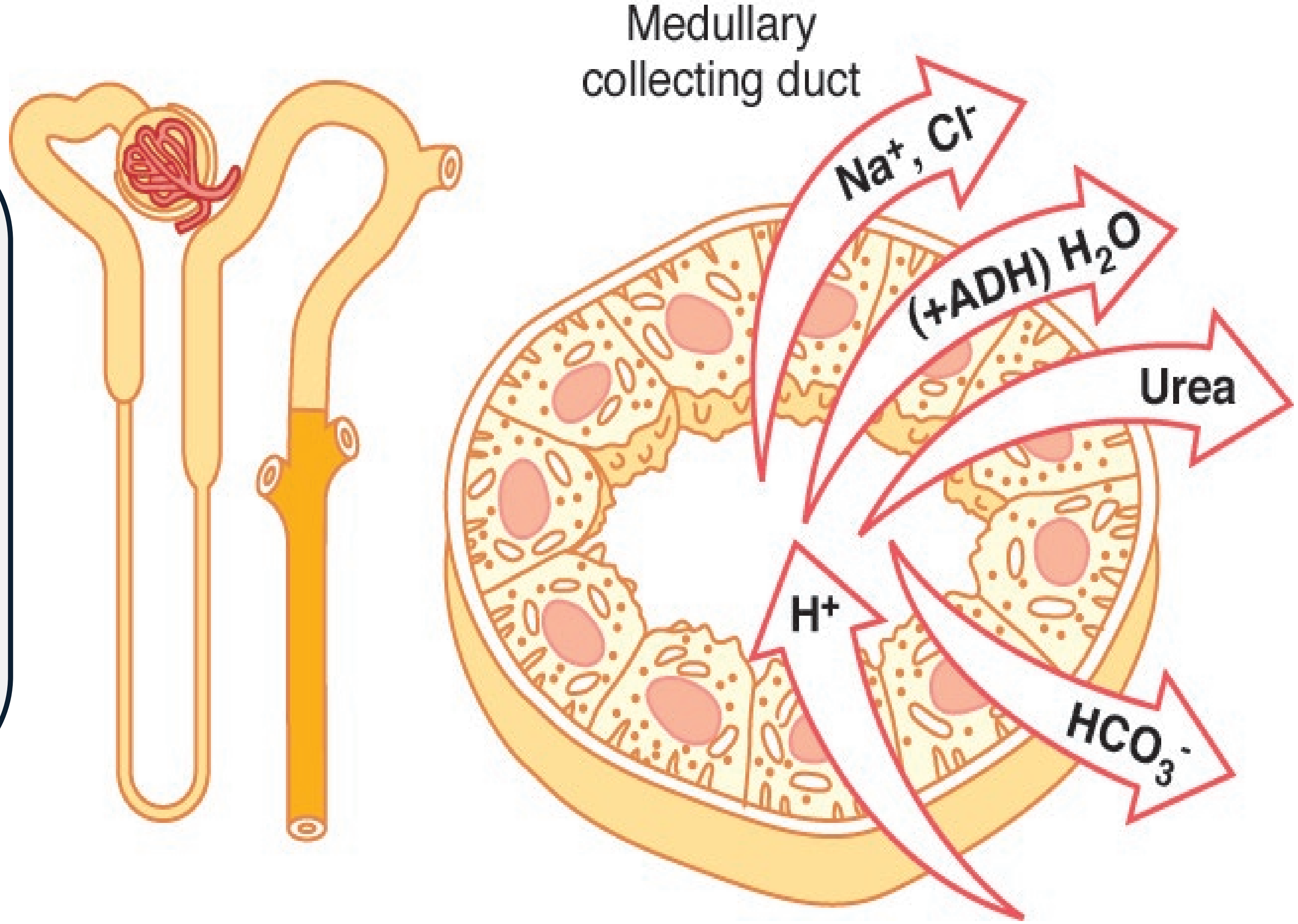
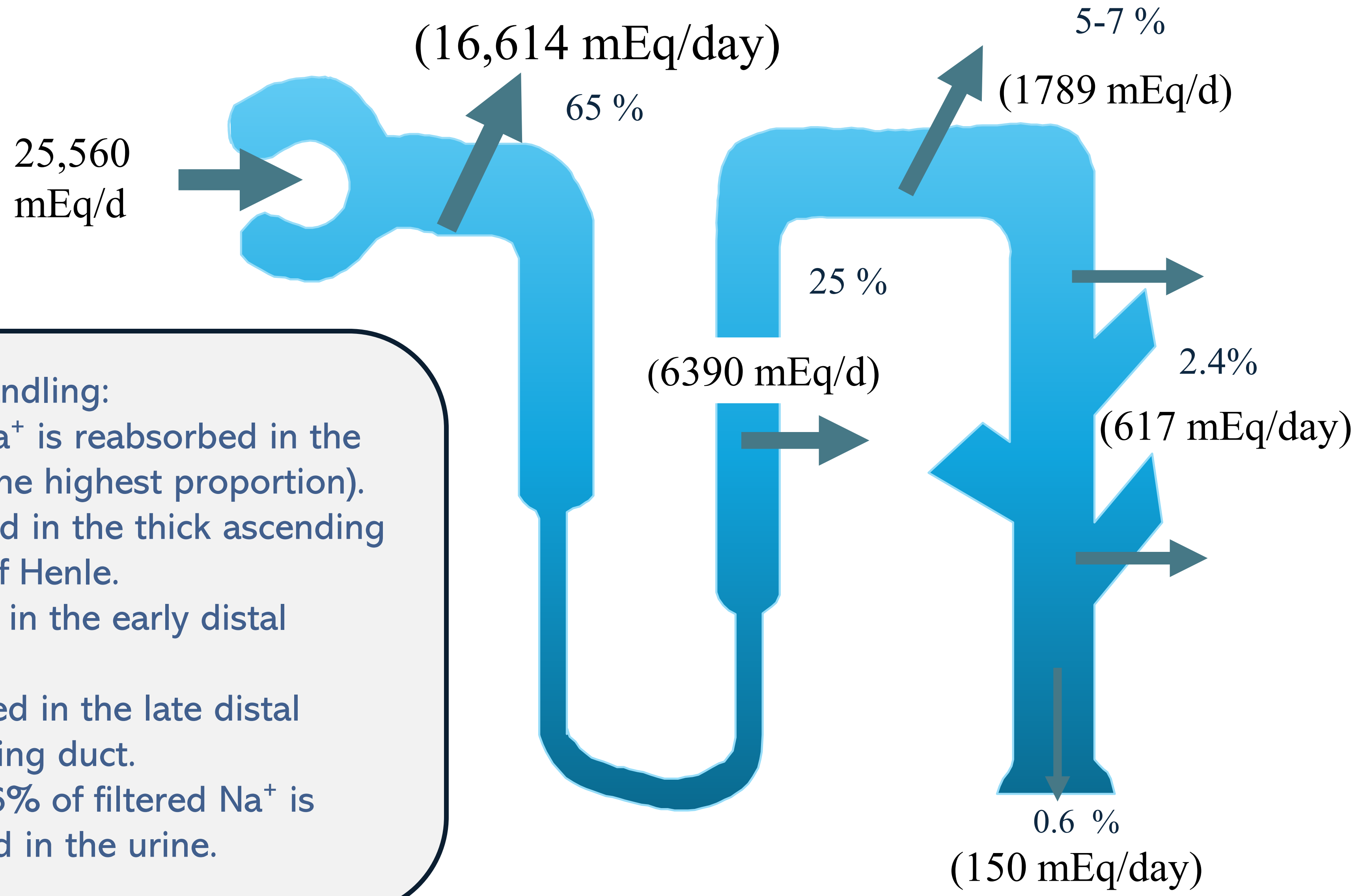


Figure 27-13

Normal Renal Tubular Na^+ Reabsorption



Overall sodium handling:
65% of filtered Na^+ is reabsorbed in the proximal tubule (the highest proportion).
25% is reabsorbed in the thick ascending limb of the loop of Henle.
5% is reabsorbed in the early distal tubule.
2.4% is reabsorbed in the late distal tubule and collecting duct.
Approximately 0.6% of filtered Na^+ is ultimately excreted in the urine.

Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

- If water is reabsorbed to a greater extent than the solute, the solute will become more concentrated in the tubule (the ratio is high)….e.g. creatinine, inulin

The inulin is filtrate, but does not reabsorbed or secreted, so the filtration=excretion
There is no reabsorption of the inulin, so when water is reabsorbed the concentration of it will increase, same as creatinine but here there is little secretion.
We can use creatinine to estimate GFR because it is a substance from the body.

- If water is reabsorbed to a lesser extent than the solute, the solute will become less concentrated inthe tubule (the ratio is low)
(e.g. glucose, amino acids,bicarbonate)

This rule is applied to all parts of the nephron

Changes in concentrations of substances in the renal tubules

Concentrations of solutes in different parts of the tubule depend on relative reabsorption of the solutes compared to water

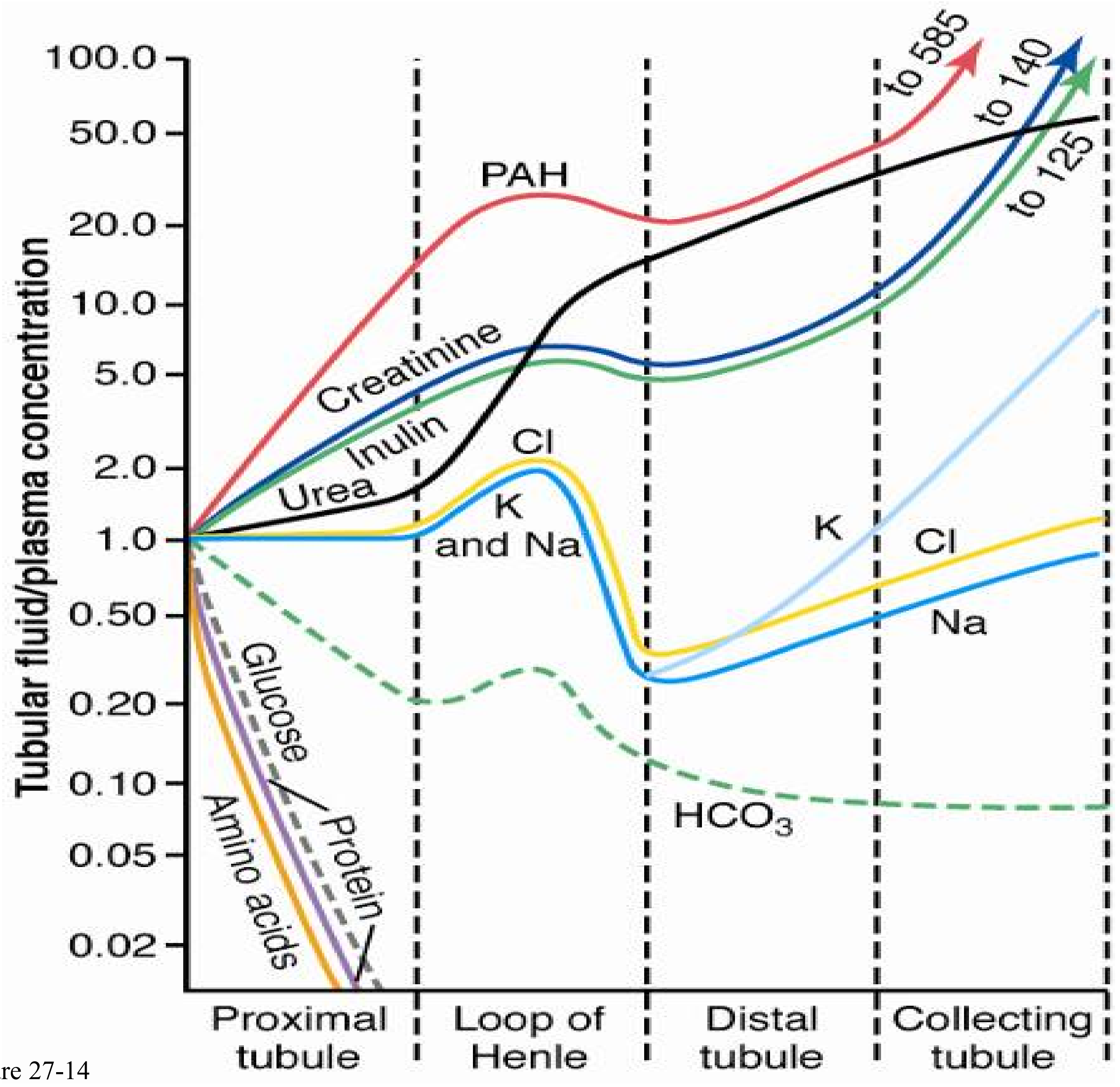
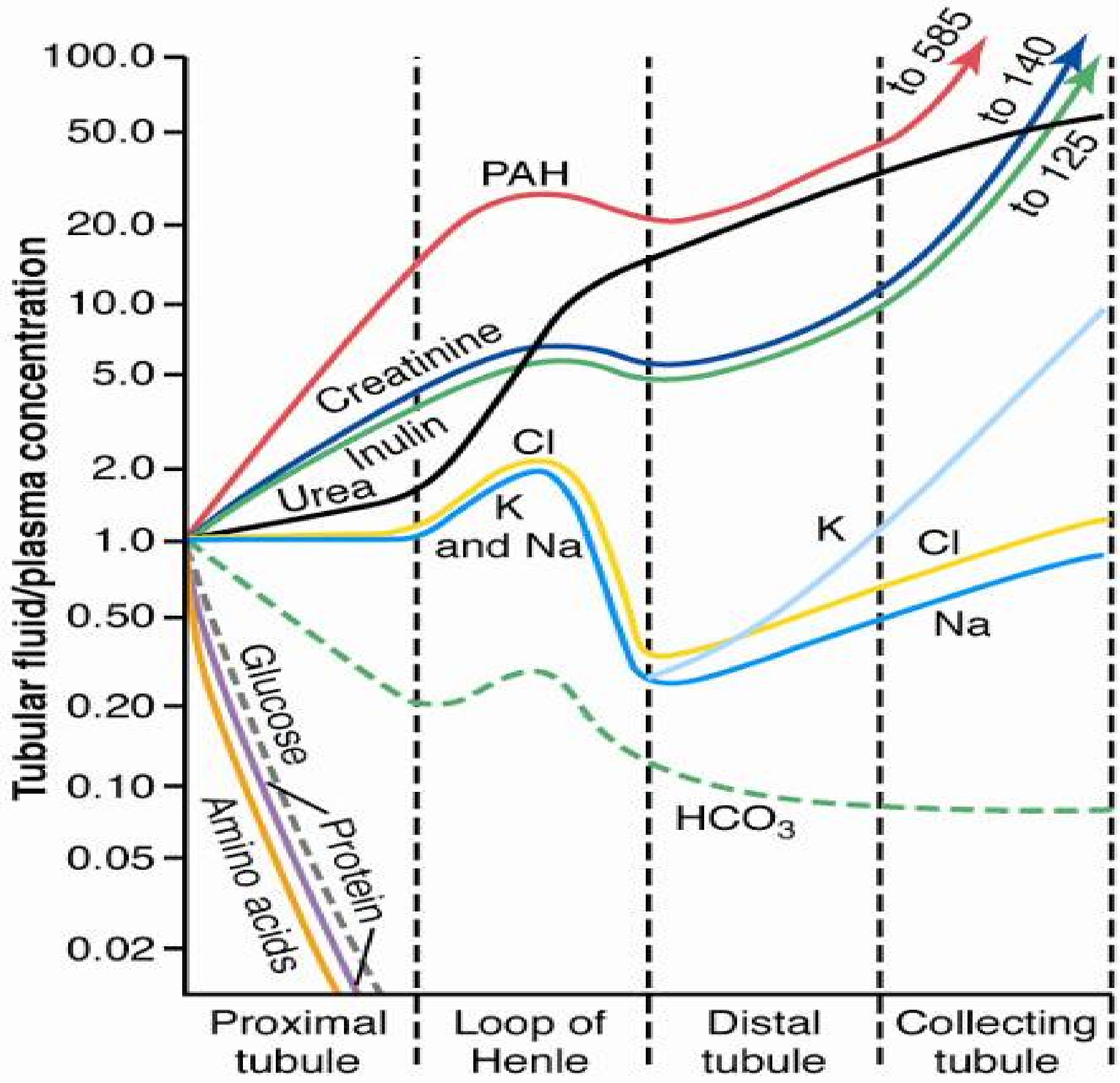


Figure 27-14

Look at this curve:
The X axis represents different parts of nephron, and the Y axis represents the ratio between concentrations of substances in tubular fluid in relation to their concentrations in the plasma.
The ratio is about 1 in the proximal tubule for Na+ / K+/ Cl-.
In the loop of henle the ratio increases then decreases, depending on what happens in each segment.

We are concerned with 2 things:
Is the substance undergoes reabsorption/ secretion or Not?
Is the water undergoes reabsorption or Not?
These two factors determine the concentration of the substance in a given segment.



The reabsorption of HCO_3^- exceeds that of water in all segments of the nephron. In contrast, the reabsorption of creatinine, inulin, urea, and para-aminohippuric acid (PAH) is lower than that of water, resulting in an increase in their concentrations as fluid moves along the nephron.

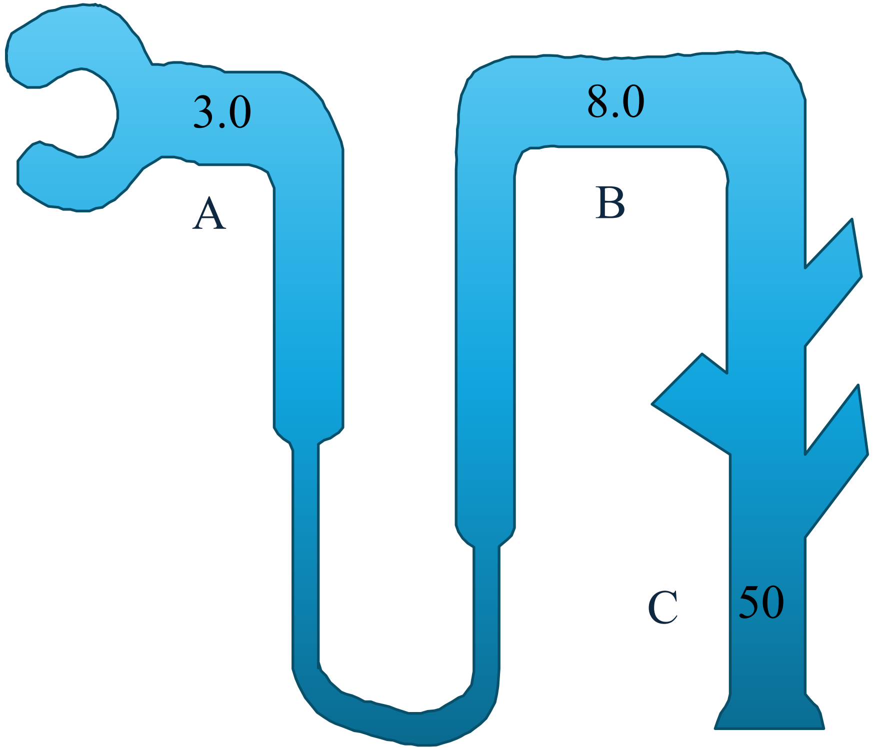
Note that the ratio of PAH is higher than that of creatinine, inulin and urea, this is due to the fact that PAH is exogenous substance, so it undergoes filtration and extensive secretion with NO reabsorption, so it is nearly completely cleared from the plasma, and it’s excretion rate is close to renal plasma flow. So PAH is used to measure the renal plasma flow.

The figure below shows the concentrations of inulin at different points along the tubule, expressed as the tubular fluid/plasma (TF/P_{inulin}) concentration of inulin. If inulin is not reabsorbed by the tubule, what is the percentage of the filtered water that has been reabsorbed or remains at each point ? What percentage of the filtered water has been reabsorbed up to that point?

A = 1/3 (33.33 %) remains
66.67 % reabsorbed

B = 1/8 (12.5 %) remains
87.5 % reabsorbed

C = 1/50 (2.0 %) remains
98.0 % reabsorbed



Now, how can apply the fact that the inulin is not secreted or reabsorbed in order to estimate water reabsorption ?

If we get the concentration of tubular inulin divided on plasma concentration, if we get this ratio and compare it with the ratio at the beginning of filtration (which is 1:1 equal between plasma and tubule)
At proximal convoluted tubule, water will start to reabsorbed and not the inulin.

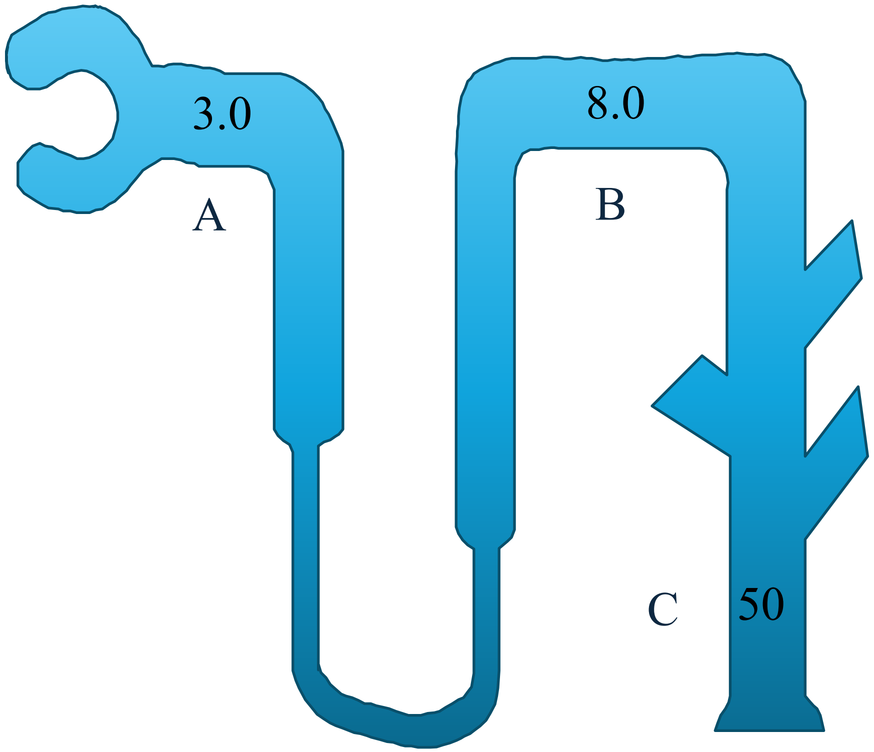
Remember there is no reabsorption of inulin, what make the concentration change is the reabsorption of water.

Now if we measure the ratio at the end of proximal tubule and get the ratio=3 (inulin in tubule more 3 times than in plasma) this means that water at this point is 1/3 the start point...1/3=33.3% , the remaining 66.67% reabsorbed , so we can estimate water reabsorption.

Remember that this the accumulative reabsorption

Here the ratio is 8,
1/8 of water remaining=12.5%
87.5% reabsorbed

If we want to know what happened in the specific segment, we should remove the other



Here the ratio is 50,
1/50 of water remaining=2.0%
98% reabsorbed

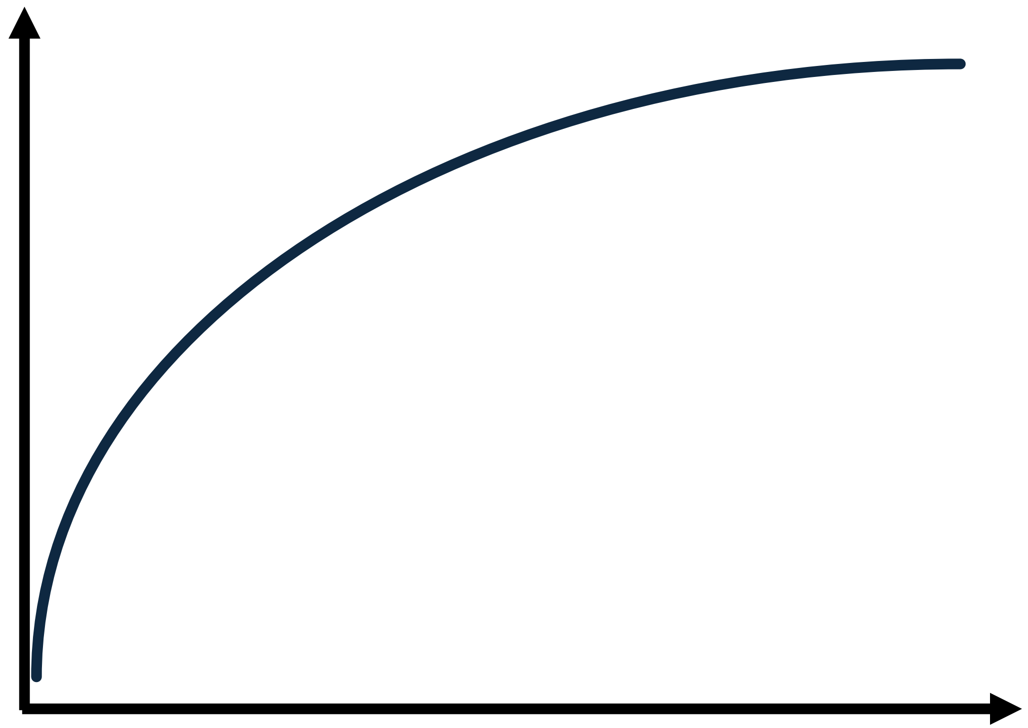
Regulation of Tubular Reabsorption

- Glomerulotubular Balance
- Peritubular Physical Forces
- Hormones
  - aldosterone
  - angiotensin II
  - antidiuretic hormone (ADH)
  - natriuretic hormones (ANF)
  - parathyroid hormone
- Sympathetic Nervous System
- Arterial Pressure (pressure natriuresis)
- Osmotic factors

The regulation of reabsorption adjust the changes that occur in the filtration, this adjustment is not necessarily related to hormone or nervous control, it depends on hemodynamic forces within same tubule (between the tubule and interstitium and peritubular capillary)
When filtration increases reabsorption would increase to match the increase in filtration,,,they call this Glomerulotubular Balance (different from tubuluglomerular feedback), here changes in GFR will be reflected on tubular reabsorption (tubule adjust the changes).
Although this depend on hemodynamic (physical) activities, the body has the ability to change the rate of reabsorption selectively for some element especially Na+(Cl-,H2O) via regulate their channels or transporters by hormone , nervous controls and some other factors in addition to physical factors like arterial pressure and osmotic pressure.

Glomerulotubular Balance

Tubular Reabsorption



Tubular Load: depends on filtration, that is mean filtered substances generate a load on tubule to be reabsorbed.

Higher Filtration —> Higher tubular load —> higher tubular reabsorption is recognised to match this increase in tubular load due to physical forces.

If the glomerular filtration rate (GFR) increases without effective glomerulotubular balance (as shown in the second row), the percentage of reabsorption decreases. This occurs because the volume of filtrate increases while the absolute amount of reabsorption remains unchanged, leading to an increase in urine volume.
However, when glomerulotubular balance is intact (as shown in the third row), an increase in GFR is accompanied by a proportional increase in reabsorption. Thus, the percentage of reabsorption remains constant, and urine volume does not increase significantly.

Importance of Glomerulotubular Balance in Minimizing Changes in Urine Volume

GFR	Reabsorption	% Reabsorption	Urine Volume
	no glomerulotubular balance		
125	124	99.2	1.0
150	124	82.7	26.0
	"perfect" glomerulotubular balance		
150	148.8	99.2	1.2

اللَّهُمَّ صَلِّ وَسَلِّمْ على نَبِيِّنَا مُحمَّد

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	11	Basolateral	Apical
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!