Urinary System: Renal Physiology for Medical Students, L4-8

Urine Formation by the Kidneys:
II. Tubular Reabsorption and Secretion

Reference: Guyton & Hall, Jordanian first edition Chapter27

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Objectives

- Describe the mechanisms of renal reabsorption and secretion in the nephron for different substances.
- Identify the functions of the different parts of the nephron tubules and describe the transport mechanisms occurring in each part.
- Describe the changes in concentrations of different substances in the renal tubules and the underlying causes of these changes.
- Understand how inulin can be used to estimate water reabsorption in each segment of the nephron.

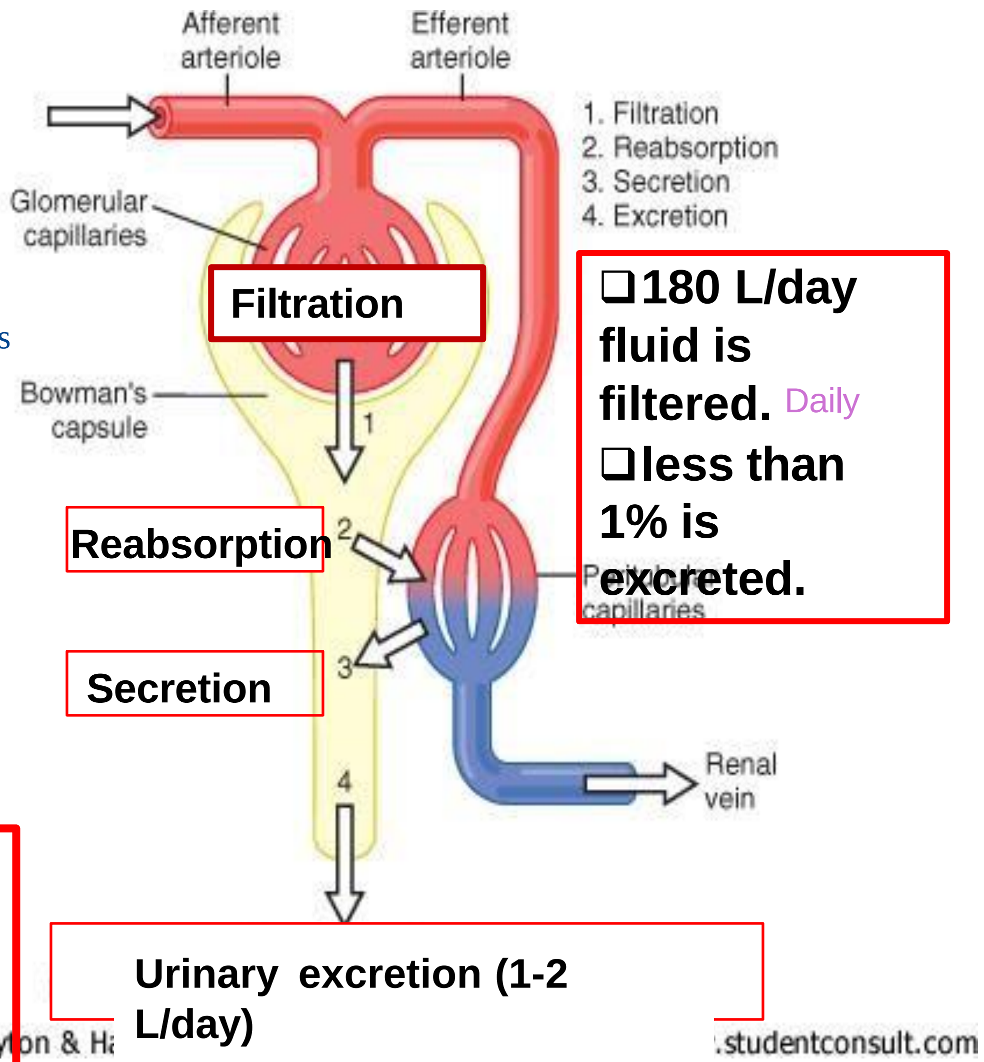
The functional unit of the kidney

Basic Mechanisms of Urine Formation

- Ultrafiltration
- Reabsorption Of different substances in different rates (selective processes), requires energy
- Secretion Eliminate harmful substances faster than filtration
- Excretion

If there is no reabsorption ,we will loss the total volume of plasma in very short time.

Excretion= Filtration-Reabsorption+ Secretion



Audio-Visual Aid

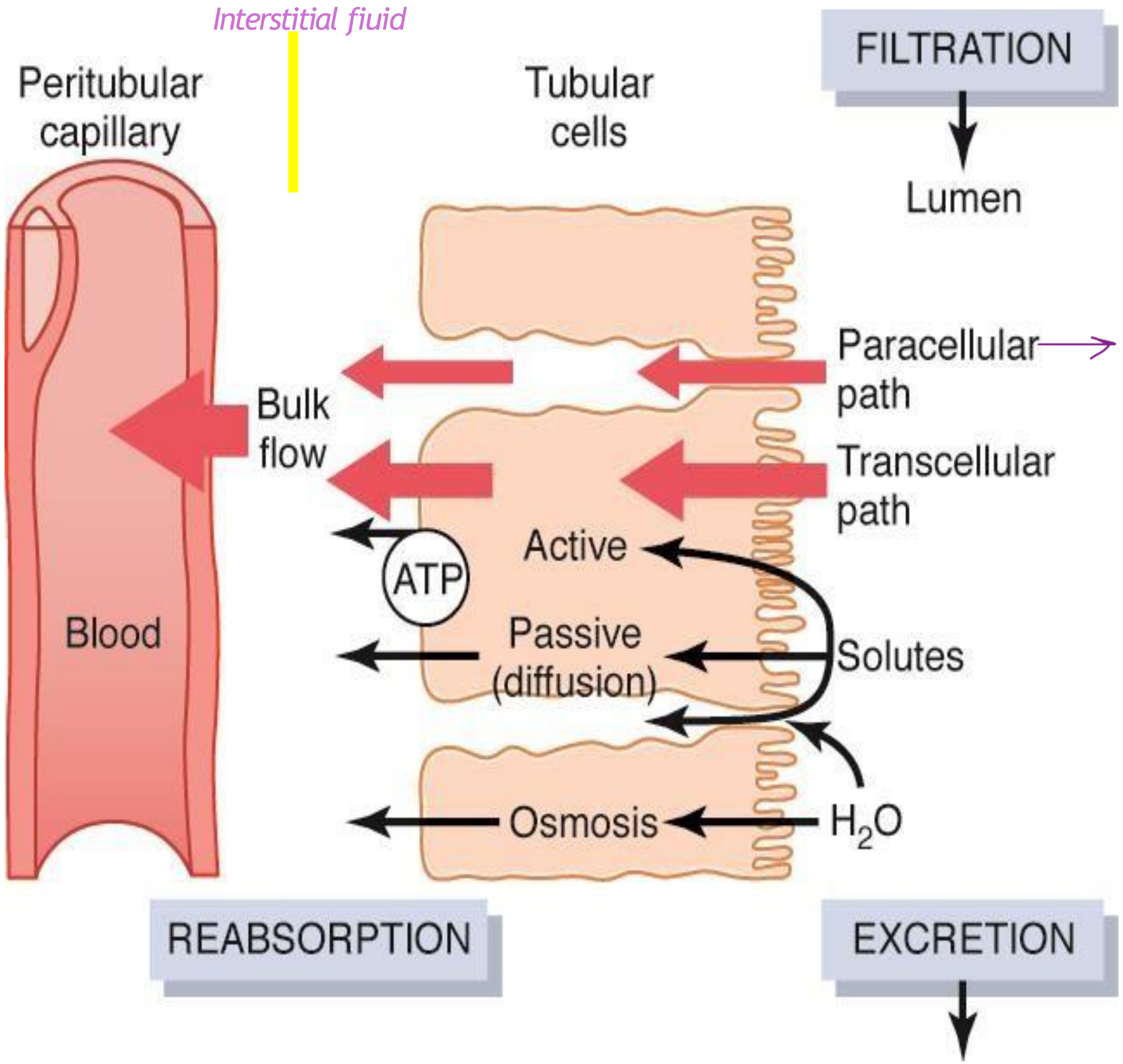
Please watch this animation Demonstarting:

- Reabsorption and Secretion animation - YouTube

Reabsorption of Water and Solutes

-This picture represents a segment in the proximal tubule which composed of epithelial cells that have a brush border in their apical surface to increase the surface area for efficient absorption.

The filtered fluid can be reabsorbed into peritubular capillary through two pathways: the paracellular(between cells) pathway and the transcellular pathway(across the plasma membrane).once they reach the interstitiam ,then they will move according to the bulk flow (hemodynamic forces)we will talk about it more later on .



There are paracellular spaces and tight junctions between the epithelial cells, but they are not much tight ,so they allow passage of water or ions

-Their permeability isn't equal in all nephron's segments, and the permeability for different substances across the membrane differ according to their chemical structures, some substances transport by simple diffusion ,but the charged molecules need channels or transporters in the transcellular pathway

But in the paracellular pathway ,they transport down their gradient if there are a gaps in the tight junctions allow them to pass.

-The Water have paracellular root and transcellular root.

Reabsorption of Water and Solutes

Solutes travel across the tubular epithelial cells (transcellular path) using two main routes:

Passive Diffusion: Some solutes move down a concentration gradient, going from an area of high concentration (lumen) to an area of low concentration (interstitium) without energy expenditure.

Active Transport: Certain solutes require energy to be pumped across the cells, often against their concentration gradient. This active transport creates a concentration difference that drives the movement of other solutes and water.

Alternatively, solutes can pass between the tubular cells (paracellular path) by diffusion, navigating the small spaces between them.

Therefore, solutes have the option to pass either through the tubular cells (transcellular) using energy-dependent mechanisms or between the cells (paracellular) passively, following their concentration gradient.

- Whenever there is solute transport, the tubular fluid will have lower osmolarity compared to the interstitium.
- The difference in osmolarity between the tubular fluid and the interstitium drives osmosis across the two Membranes by aquaporins channels.

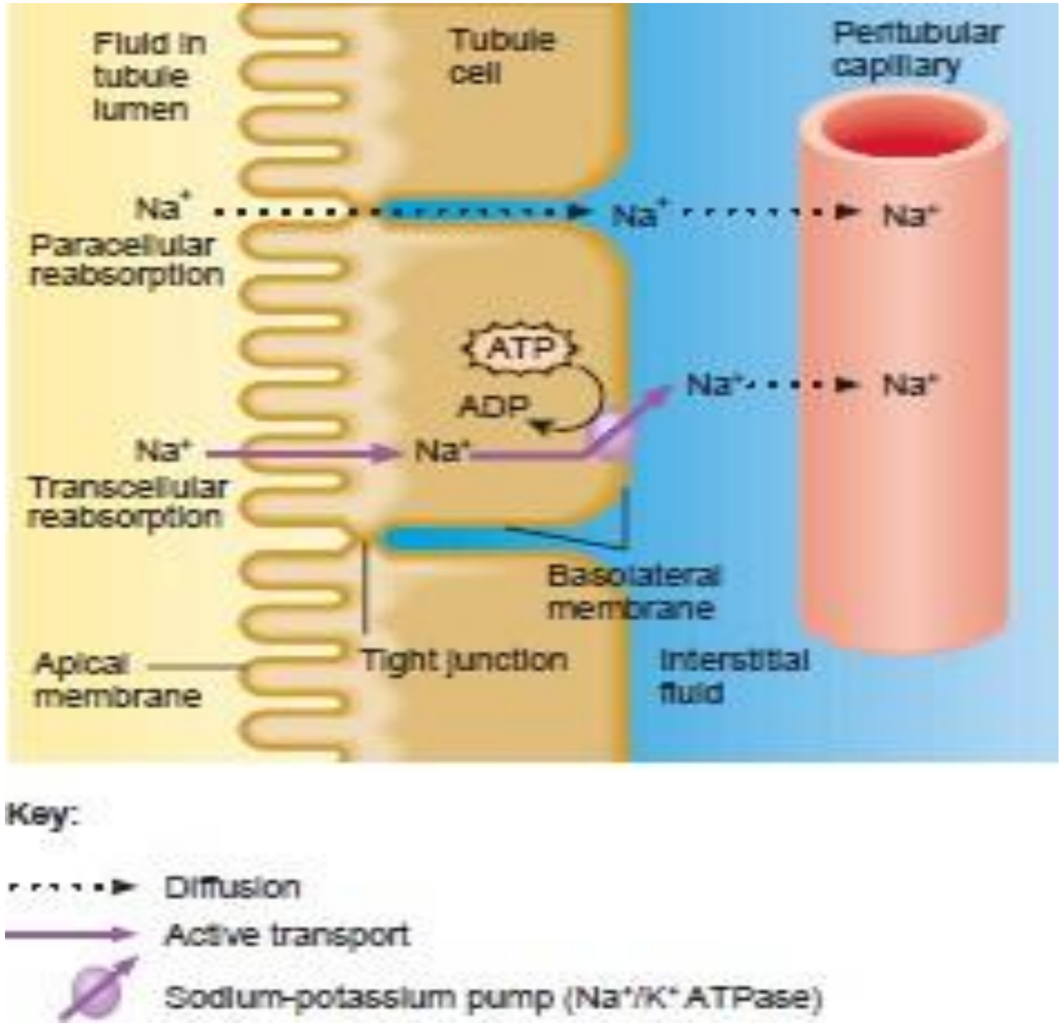
Reabsorption of Water and Solutes

In the proximal convoluted tubules, one of the essential transport processes is the movement of Na^+ across the tubular cells. Sodium is the primary cation found in both the extracellular fluid and the filtered fluid.

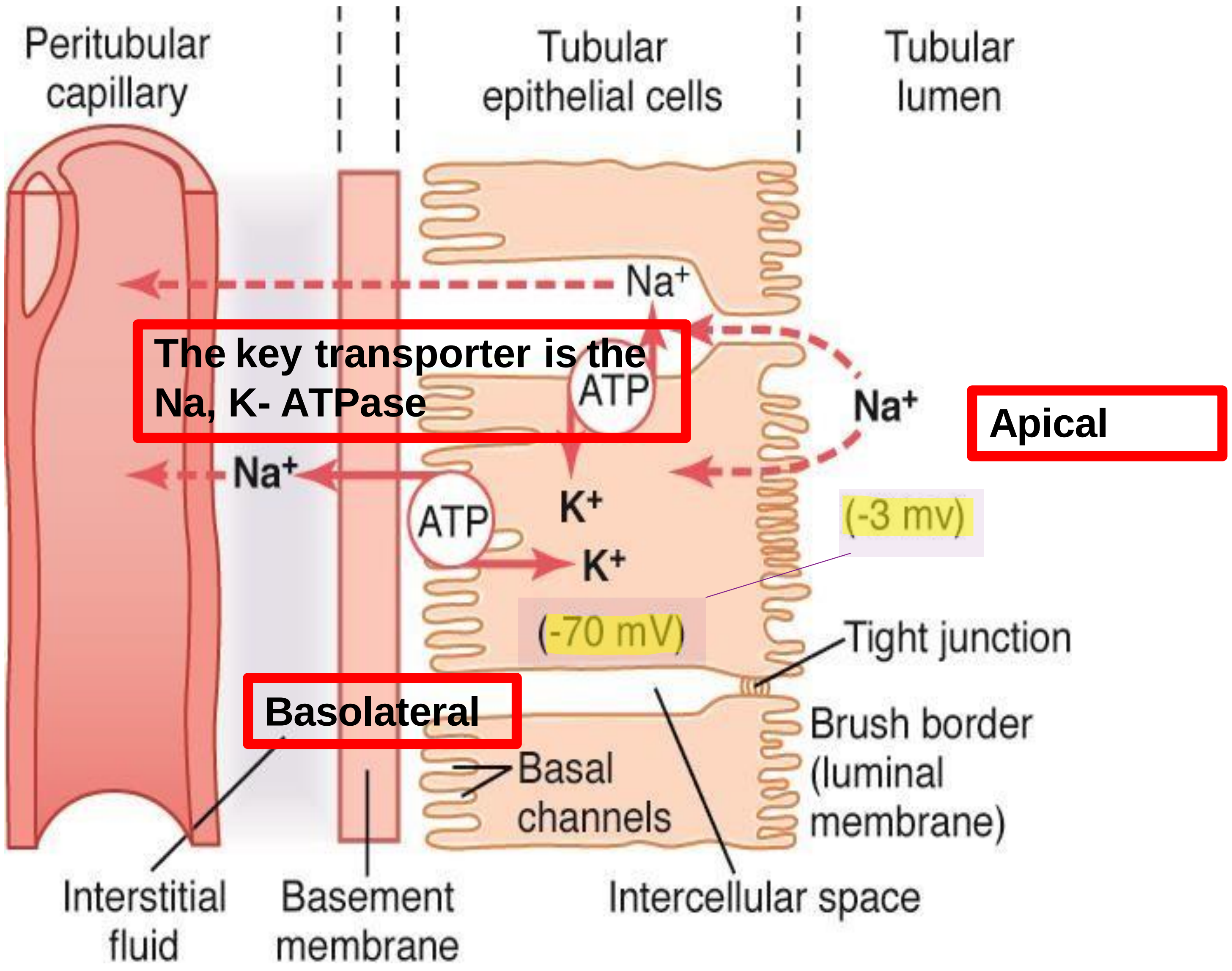
This process is accomplished by the Na^+/ K^+ ATPase pump, which is present on the basolateral side of the tubular cells. It pumps 3 Na^+ out of the cell and 2 K^+ into the cell using energy. Therefore, we can maintain very low Na^+ levels inside the cells. This creates a gradient that favors the reabsorption of Na^+ from the filtered fluid back into the cells.

Also, there is paracellular Na^+ reabsorption, down its gradient.

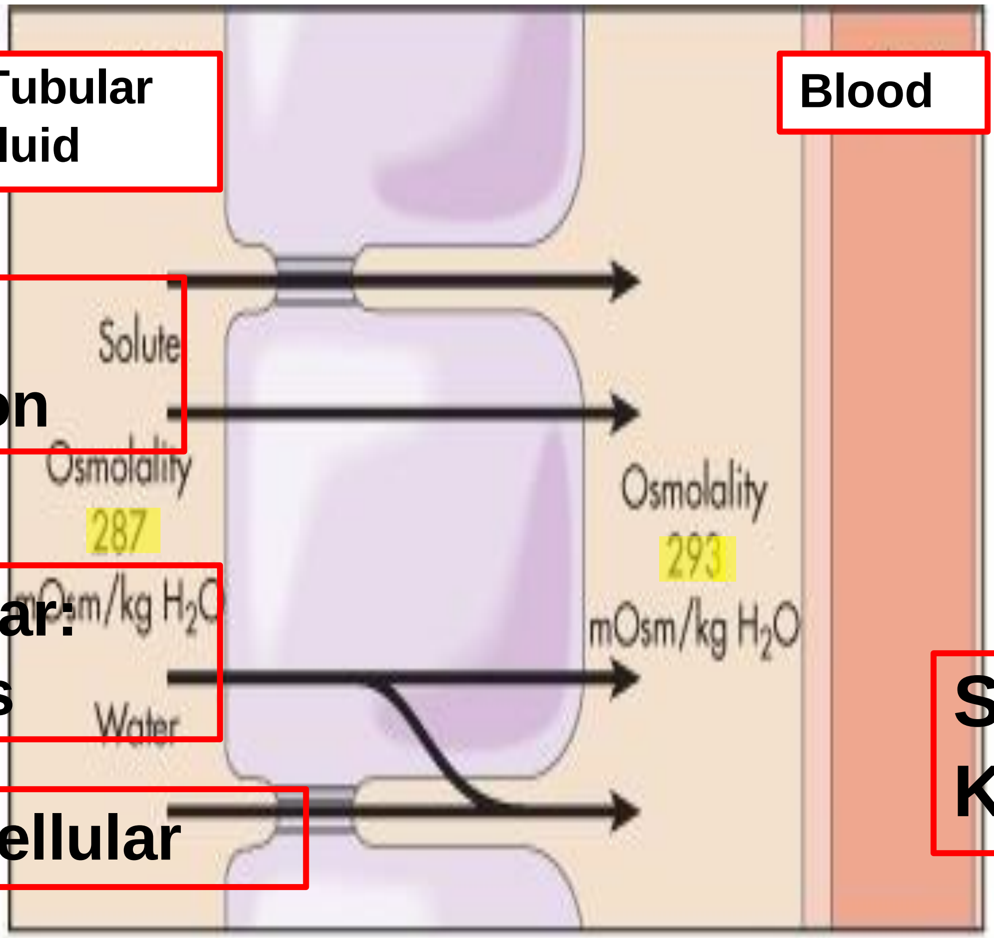
- The Na^+/K^+ ATPase pump creates not only a chemical gradient but also maintains a negative potential electrical gradient so this drive more Na+ to become reabsorbed ,so there is electrochemical gradient favors Na+ reabsorption also(the positive charge move into negative charge).



Active Transport



Proximal tubule reabsorption



Tubular fluid

Blood

High osmolality of intercellular spaces drives water reabsorption

Water reabsorption

Transcellular: Aquaporins

Paracellular

Solvent drag of K^+ and Ca^{++}

me ions that hasn't been filtered or reabsorbed.

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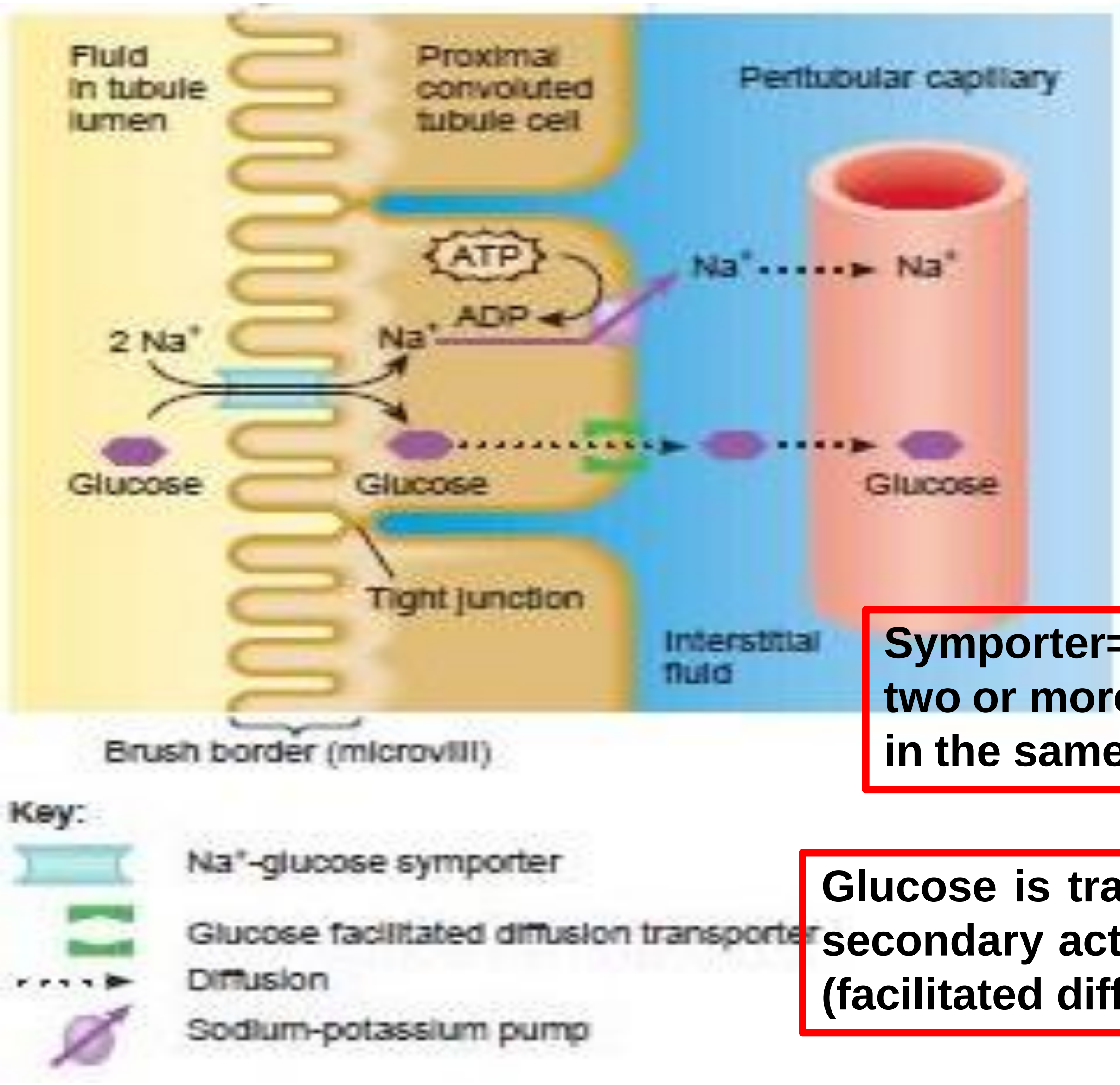
Higher osmolarity, drive water by osmosis.

According to the previous slide :
After the Na+ reabsorption ,the tubular fluid will have lower osmolarity =287 VS 239 in the intersititism (between the capillary and the cell) ,that will drive osmosis transcellular by aquaporins channels that found in high amounts in the proximal tubules + paracellular transport through the tight junctions ,that will result in extensive water reabsorption which follow the Na+ reabsorption in proximal convoluted tubules.

-some of ions that didn’t reabsorb will drag with water in process called “solvents drag” which contribute to many ions like K+,Ca++in the proximal tubules .

Glucose: Proximal Tubules

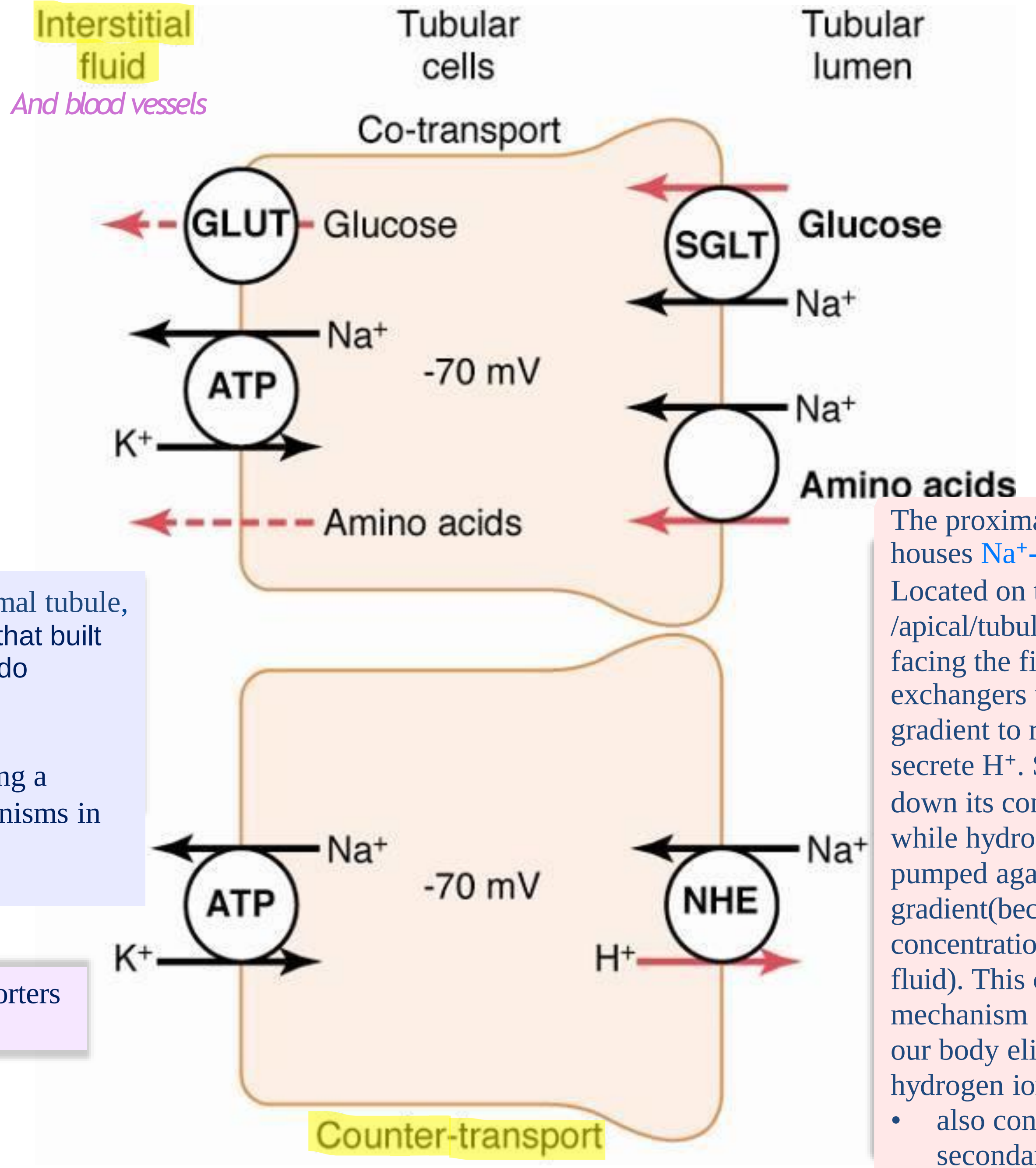
Glucose & amino acids should be completely reabsorbed.
This is mediated by facilitated diffusion or secondary active transport.
We need active transport because we don't need equilibrium , we need transport all glucose and amino acids so surely, they will move against their gradient from the tubular fluid into the capillaries .



Symporter= transports two or more substances in the same direction

Glucose is transported via secondary active transport (facilitated diffusion)

Mechanisms of secondary active transport in Proximal Convoluted Tubules.



SGLT transporters can **co-transport** glucose with sodium in the proximal tubule, SGLT transport 2 Na+ down their gradient and they use the gradient that built by Na+/K+ ATPase pump to transport glucose against its gradient to do complete transportation for glucose then there is another carriers into interstitism and into the peritubular capillary.

. The Na^+/K^+ ATPase pump indirectly facilitates this process by creating a sodium gradient that's used for other secondary active transport mechanisms in the nephron.

- The SGLT transporters work like **symborters**.

The same principle applies to amino acids. They have specific co-transporters that utilize the Na^+ gradient to facilitate their movement into the cells.

Figure 27-3

The proximal tubule also houses Na^+-H^+ exchangers. Located on the luminal /apical/tubular surface (the side facing the filtrate), these exchangers utilize the Na^+ gradient to reabsorb Na^+ and secrete H^+. Sodium moves down its concentration gradient, while hydrogen ions are pumped against their gradient(because H+ have higher concentration in the tubular fluid). This **countertransport** mechanism is one of the ways our body eliminates excess hydrogen ions.

- also considered as secondary active mechanism.

Glucose Transport Maximum

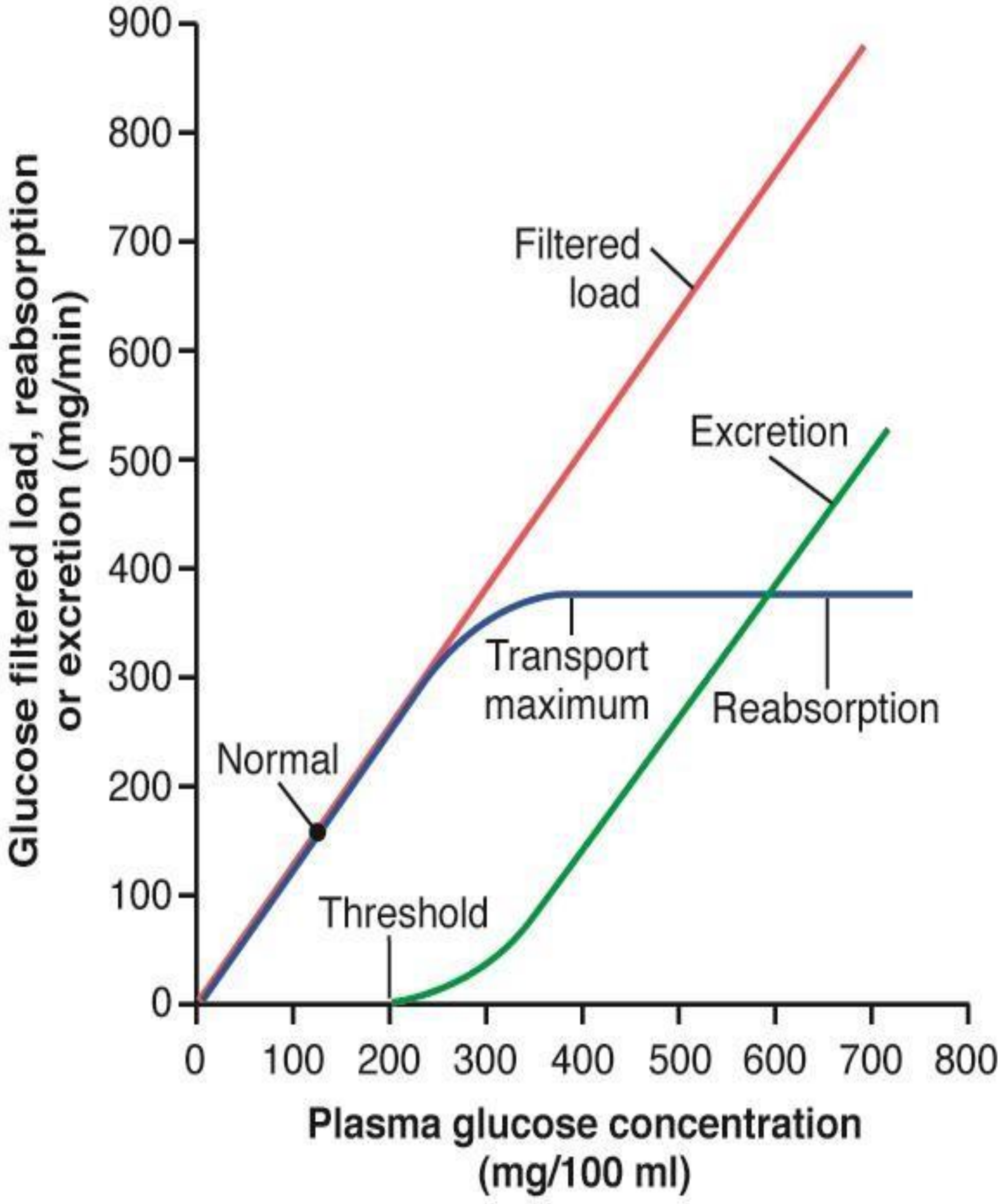


Figure 27-4

Substances follow their concentration gradient directly across the membrane in a process called simple diffusion. However, for substances requiring transporters, like glucose and amino acids, there is a limit to the rate of transport. This is because the transporters have specific number and maximum capacity, and once they are saturated, increasing the blood or plasma concentration won't significantly increase the reabsorption rate. (The Blue line).

- This is due to the filtered glucose load (the amount of glucose that has been filtered).
- The filtered glucose load depends on the GFR(glomerular filtration rate) and the concentration of glucose in the plasma.
- filtered load (mg/min)= GFR*glucose plasma concentration.
- As the filtered load of glucose increases, the reabsorption of glucose also increases. However, there is a limit to this reabsorption, known as the **transport maximum**. At this limit, all the glucose transporters in the nephron become saturated, meaning they are working at their maximum capacity. Consequently, any further increase in the concentration of glucose in the plasma will not result in a further increase in filtration.

- When the transport maximum is reached and the glucose concentration in the plasma continues to rise, the excess glucose that could not be reabsorbed will be excreted in the urine. Prior to a concentration of 200 mg/100 ml, there is no risk of glucose excretion, and the urine will contain no glucose. However, once the concentration exceeds 200 mg/100 ml but remains below the transport maximum, glucose can be detected in the urine. And this point is termed as **Threshold**.
- One reason for the difference between threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons therefore begin to excrete glucose before others have reached their transport maximum. The overall transport maximum for the kidneys, which is normally about 375 mg/min, **is reached when all nephrons have reached their maximal capacity to reabsorb glucose.**

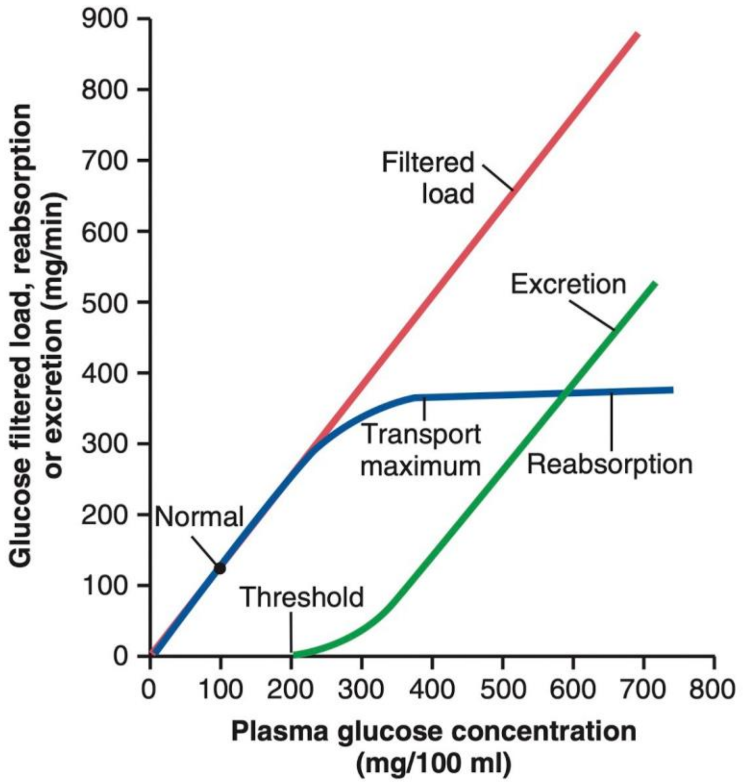


Figure 28-4. Relations among the filtered load of glucose, the rate of glucose reabsorption by the renal tubules, and the rate of glucose excretion in the urine. The *transport maximum* is the maximum rate at which glucose can be reabsorbed from the tubules. The *threshold* for glucose refers to the filtered load of glucose at which glucose first begins to be excreted in the urine.

Substances that are actively transported but don't exhibit a transport maximum

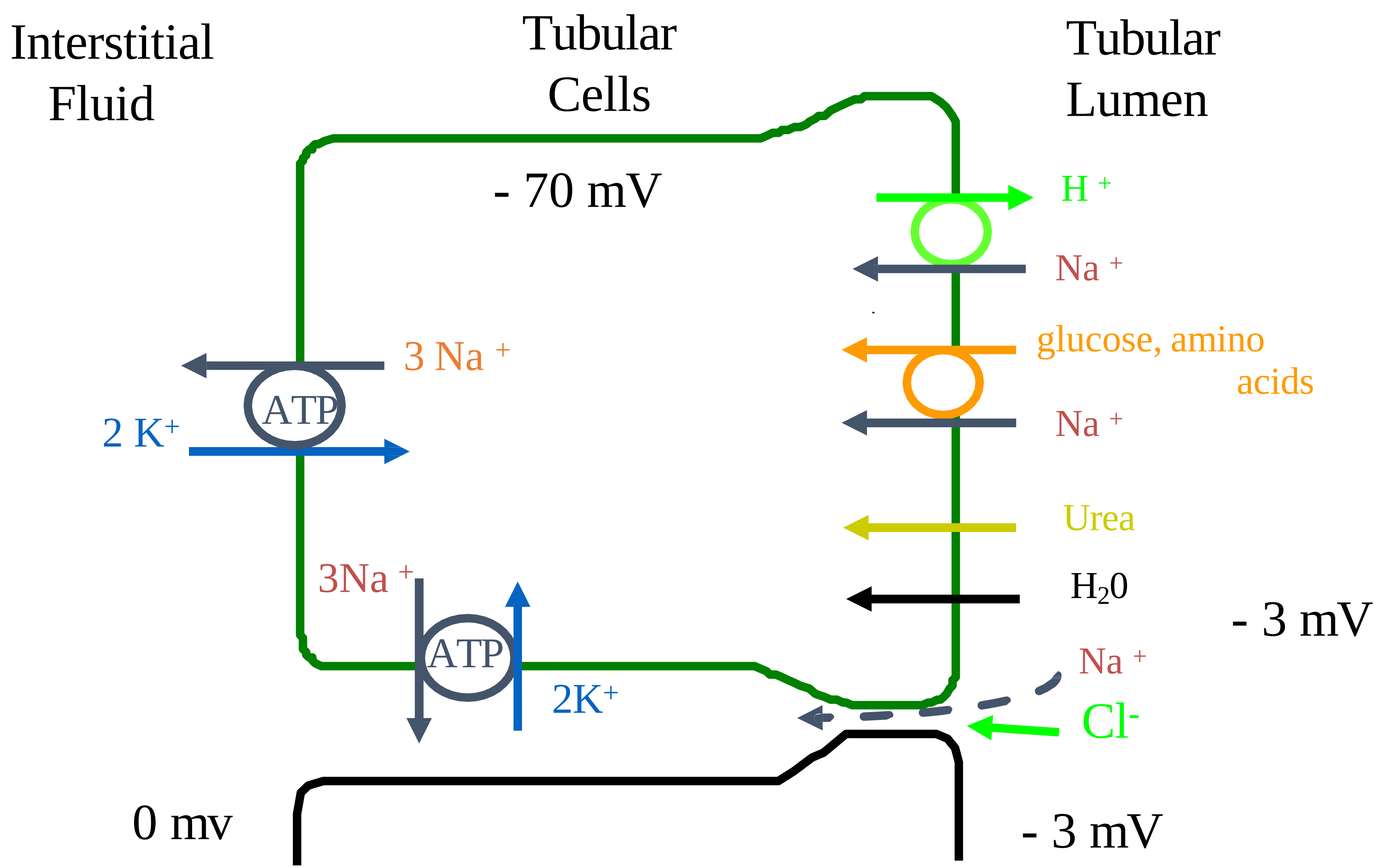
Unlike glucose and other substances that have a transport maximum, sodium follows the **gradient-time transport mechanism**. This means that the filtration rate of sodium (Na^+) depends on two factors:

1. Na^+ electrochemical gradient: The concentration gradient and the electrical charge difference across the membrane influence the movement of sodium. The greater the gradient, the higher the rate of sodium reabsorption or secretion.
2. Time of contact: The duration of time that the fluid containing the sodium remains in contact with the luminal membrane of the tubule also affects the rate of sodium transport. The longer the fluid remains in contact with the membrane, the more time there is for sodium to be reabsorbed or secreted.

This observation means that the greater the concentration of sodium in the proximal tubules, the greater its reabsorption rate. Also, the slower the flow rate of tubular fluid, the greater the percentage of sodium that can be reabsorbed from the proximal tubules.

In the more distal parts of the nephron, the epithelial cells have much tighter junctions and transport much smaller amounts of sodium. In these segments, sodium reabsorption exhibits a transport maximum similar to that for other actively transported substances. Further-more, this transport maximum can be increased by certain hormones, such as aldosterone.

Proximal Convoluted Cells



Summary of Key Points:

1. Sodium Reabsorption:

An electrochemical gradient favors the reabsorption of sodium (Na^+) back into the bloodstream.
This reabsorption can occur through transcellular pathways, osmosis, and paracellular pathways.

2. Na^+ Dependence:

The reabsorption of glucose and amino acids, as well as the secretion of hydrogen ions (H^+), is also dependent on the sodium gradient.

REABSORPTION OF CHLORIDE AND UREA.

Transport of positively charged sodium ions out of the lumen leaves the inside of the lumen negatively charged, compared with the interstitial fluid. This environment causes chloride ions to diffuse passively through the para-cellular pathway. Additional reabsorption of chloride ions occurs because of a chloride concentration gradient that develops when water is reabsorbed from the tubule by osmosis, thereby concentrating the chloride ions in the tubular lumen.

- Thus, the active reabsorption of sodium is closely coupled to the passive reabsorption of chloride by way of an electrical potential and a chloride concentration gradient.

Urea is also passively reabsorbed from the tubule, but to a much lesser extent than chloride ions. As water is reabsorbed from the tubules, urea concentration in the tubular lumen increases. This increase creates a concentration gradient favoring the reabsorption of urea. However, urea does not permeate the tubule as readily as does water. In some parts of the nephron, passive urea reabsorption is facilitated by **specific urea transporters.** However, due to the lack of such transporters, urea reabsorption in the proximal convoluted tubules is much lower compared to other parts of the nephron which are rich in urea transporters.
Yet, only about 1/2 of the urea that is filtered by the glomerular capillaries is reabsorbed from the tubules. The remainder of the urea passes into the urine, allowing the kidneys to excrete large amounts of this *waste product* of metabolism.

Mechanisms of water, chloride, and urea reabsorption coupled with sodium reabsorption

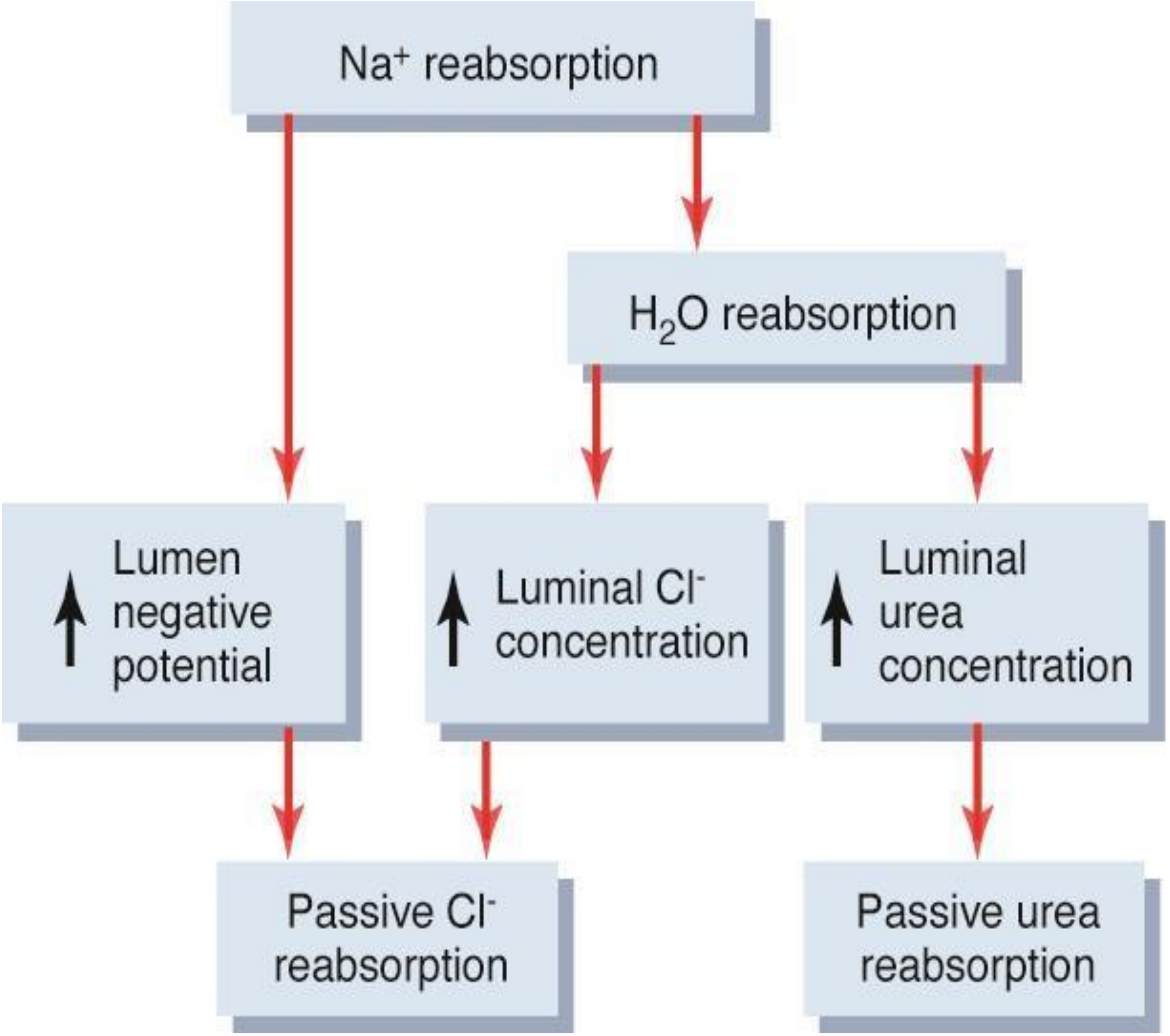
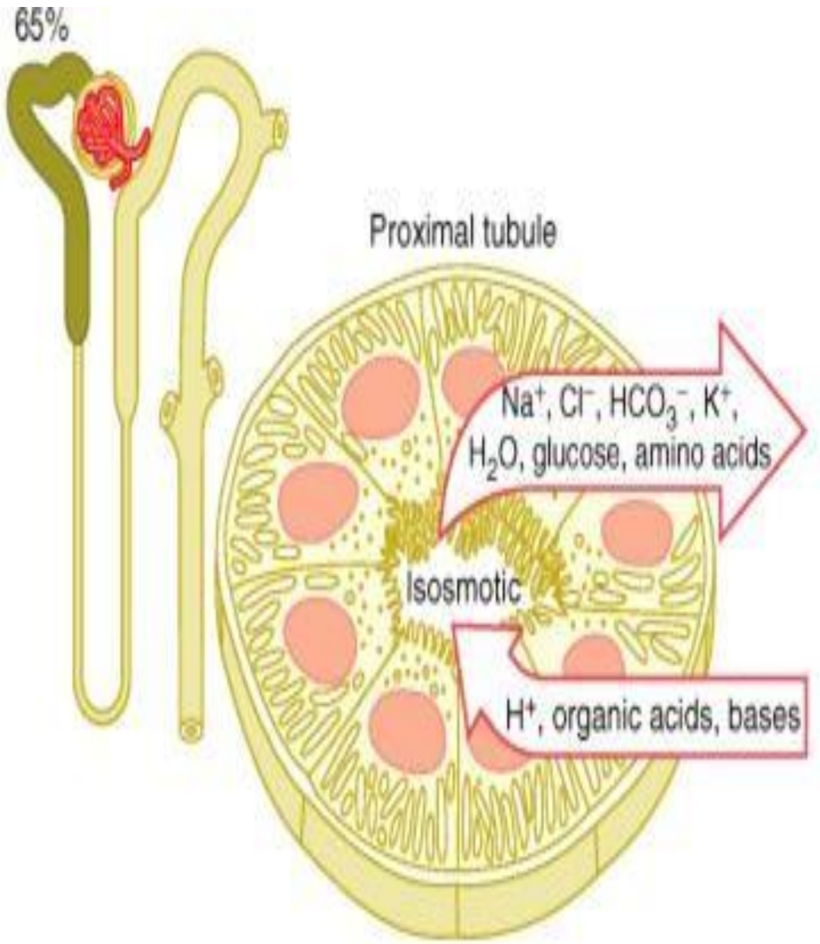


Figure 27-5

Proximal Tubules

- The proximal tubules reabsorbs about 67% of filtered water, Na^+, Cl^-, K^+, HCO_3^-.
- The proximal tubules reabsorbs almost all glucose and amino acids filtered by the glomeruli.
- The key transporter element is the Na, K- ATP ase in the basolateral membrane.



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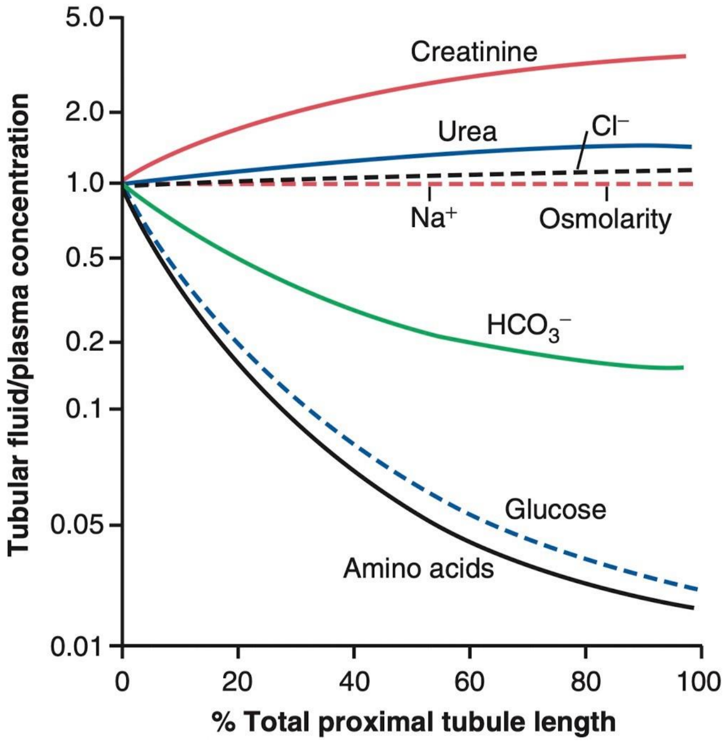
Changes in concentration in proximal tubule

Changes in concentrations of different substances in tubular fluid along the proximal convoluted tubule relative to the concentrations of these substances in the plasma and in the glomerular filtrate.

A value of 1.0: This indicates the substance is reabsorbed at the same rate as it's filtered, meaning its concentration in the urine is the same as in the blood. Such as Na^+, Cl^-.

A value < 1.0: This signifies the substance is reabsorbed more efficiently than water. Its concentration in the urine will be lower than in the blood. Such as HCO_3^-, Glucose and Amino acids.

A value > 1.0: This suggests the substance is reabsorbed less efficiently than water or is actively secreted into the urine. Its concentration in the urine will be higher than in the blood. Such as Creatinine and Urea.



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

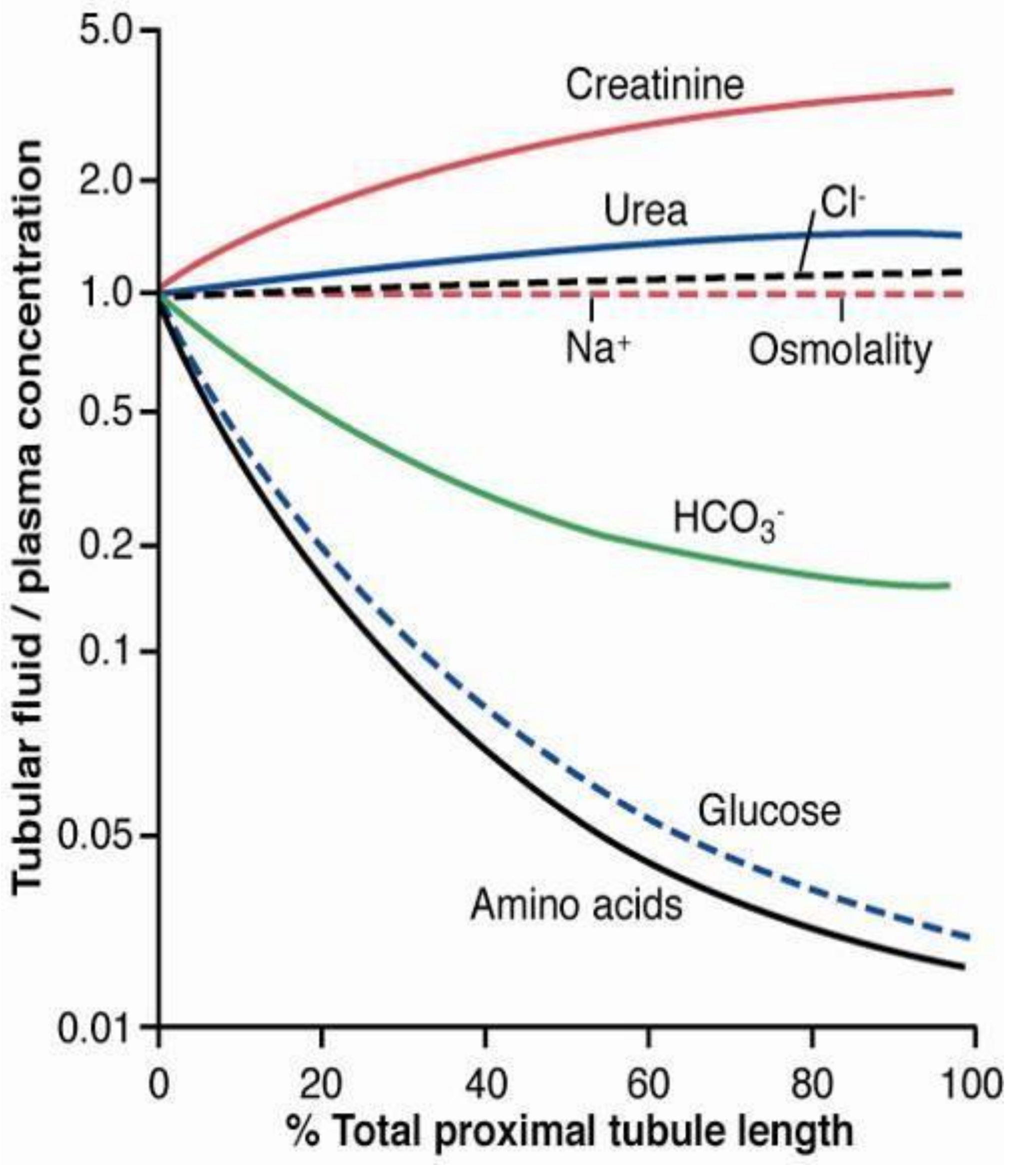
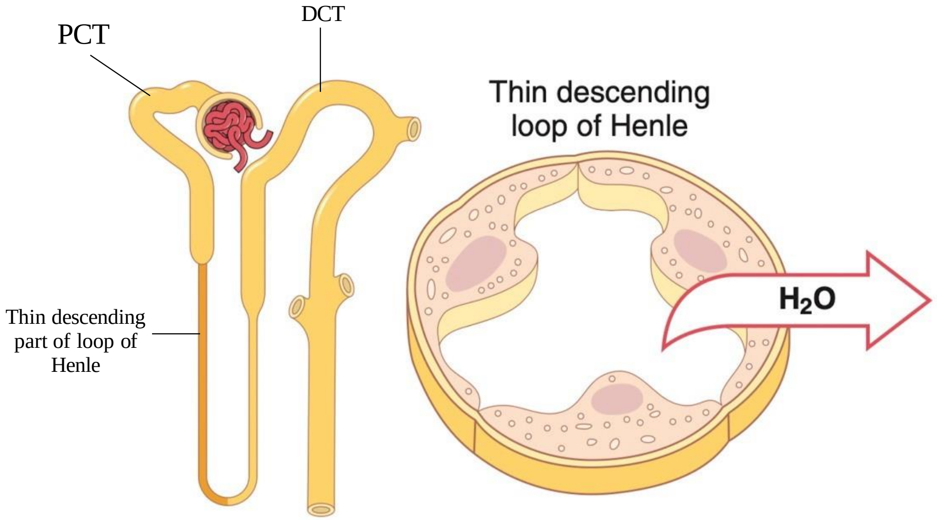


Figure 27-7

Loop of Henle

The loop of Henle consists of three functionally distinct segments: the thin descending segment, the thin ascending segment, and the thick ascending segment.

The descending limb of the thin loop of Henle is highly permosmolyteswater and slightly permeable to most solutes, including urea and sodium. As we descend deeper into the medulla, the surrounding interstitial fluid becomes increasingly concentrated with osmolytes. This nephron segment's primary function is to facilitate the passive diffusion of substances across its walls. As we progress deeper into the medulla, the concentration of osmolytes in the interstitial fluid increases, creating a gradient that drives the passive movement of water out of the descending limb and into the surrounding tissue.Therefore, water reabsorption increases as we descend the descending limb due to the increasing concentration gradient.

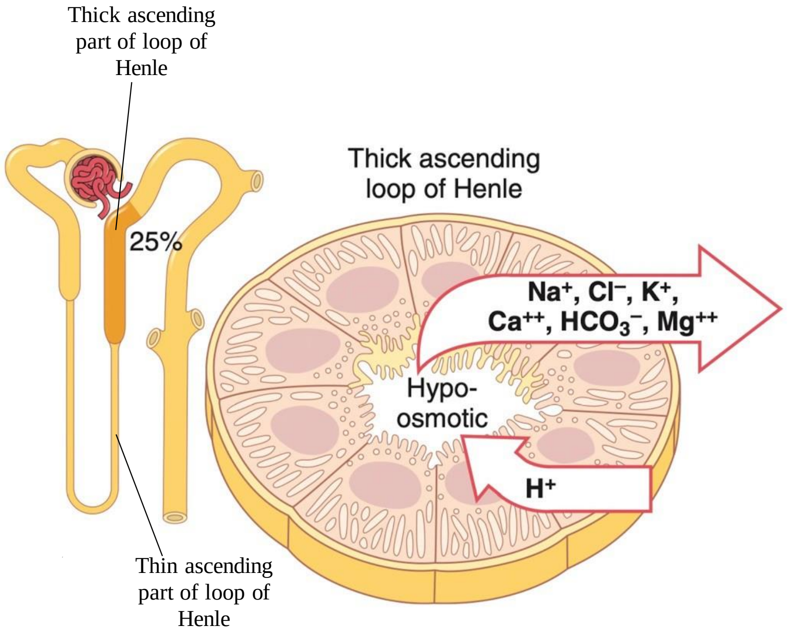


Loop of Henle

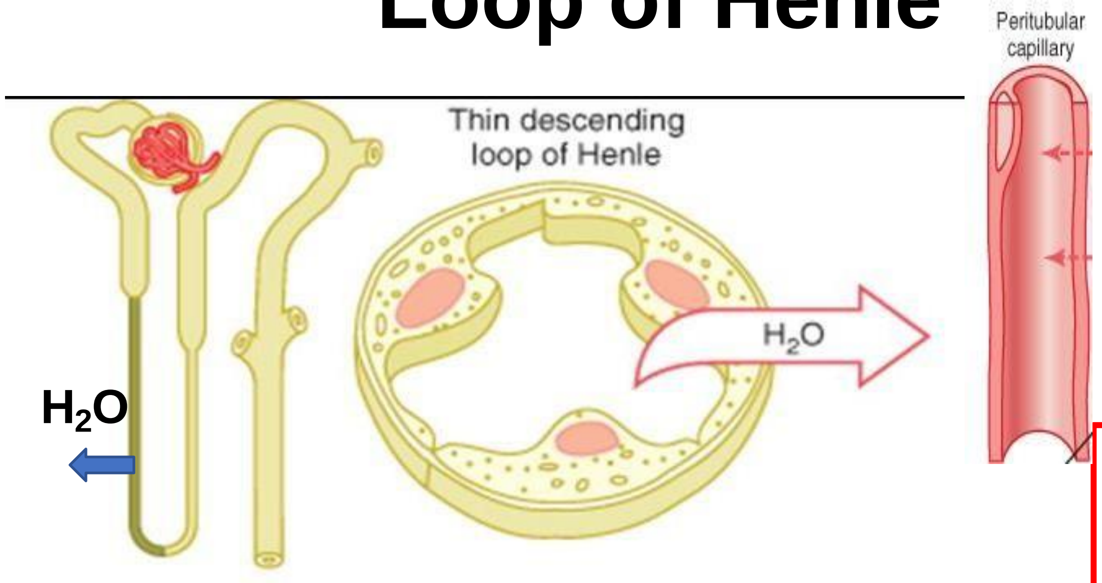
On the other hand, the ascending limb, including both the thin and the thick portions, is virtually **impermeable to water**, a characteristic that is important for concentrating the urine. Since water reabsorption is minimal in the ascending limb, NaCl reabsorption occurs passively and is driven by the concentration gradient established in the descending limb.
As the fluid ascends, the concentration of these ions in the surrounding interstitial fluid becomes higher than within the tubules. This is because the actively reabsorbed ions move out of the tubular fluid and into the interstitium.

As the fluid reaches the thick ascending limb of the loop of Henle, which begins roughly halfway up the ascending limb, it is considered an **isotonic solution**. This segment is characterized by thick epithelial cells with high metabolic activity, capable of **actively reabsorbing** Na^+, Cl^-, Mg^{2+},HCO_3^-, and K^+. 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. And Because the thick ascending limb is impermeable to water, the reabsorption of solutes like Na^+, Cl^-, and K^+ creates a **hypotonic solution** (low osmolarity) within the tubular lumen. This is why the thick ascending limb is also called the **diluting segment**..



Loop of Henle

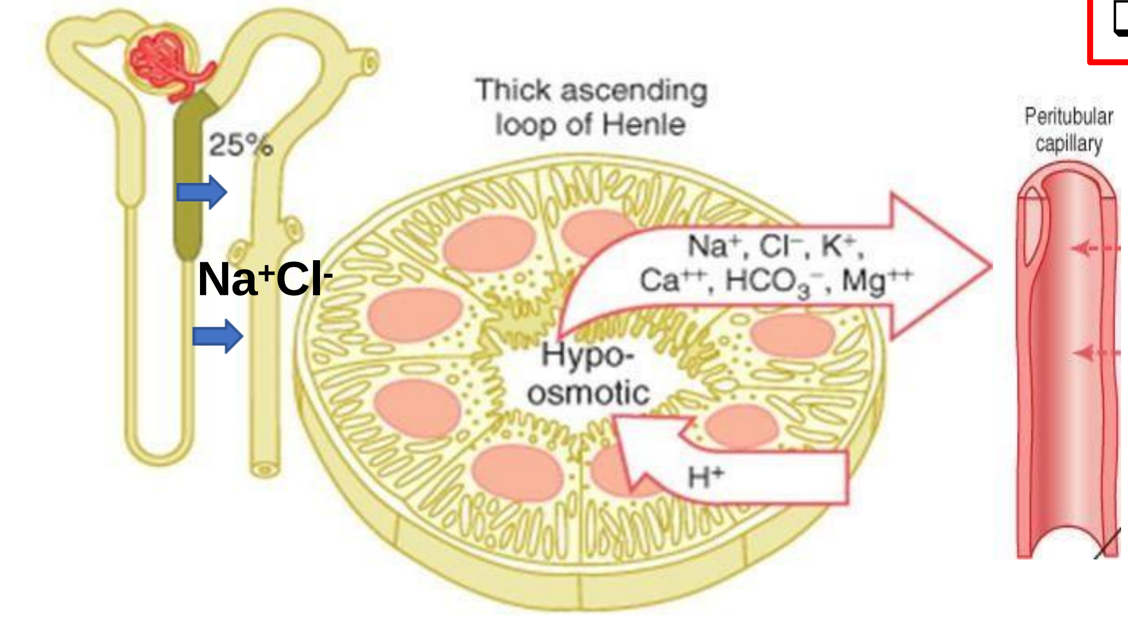


Thin Descending

- **15% of H_2O reabsorbed.**

Thin Ascending

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



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Thick Ascending

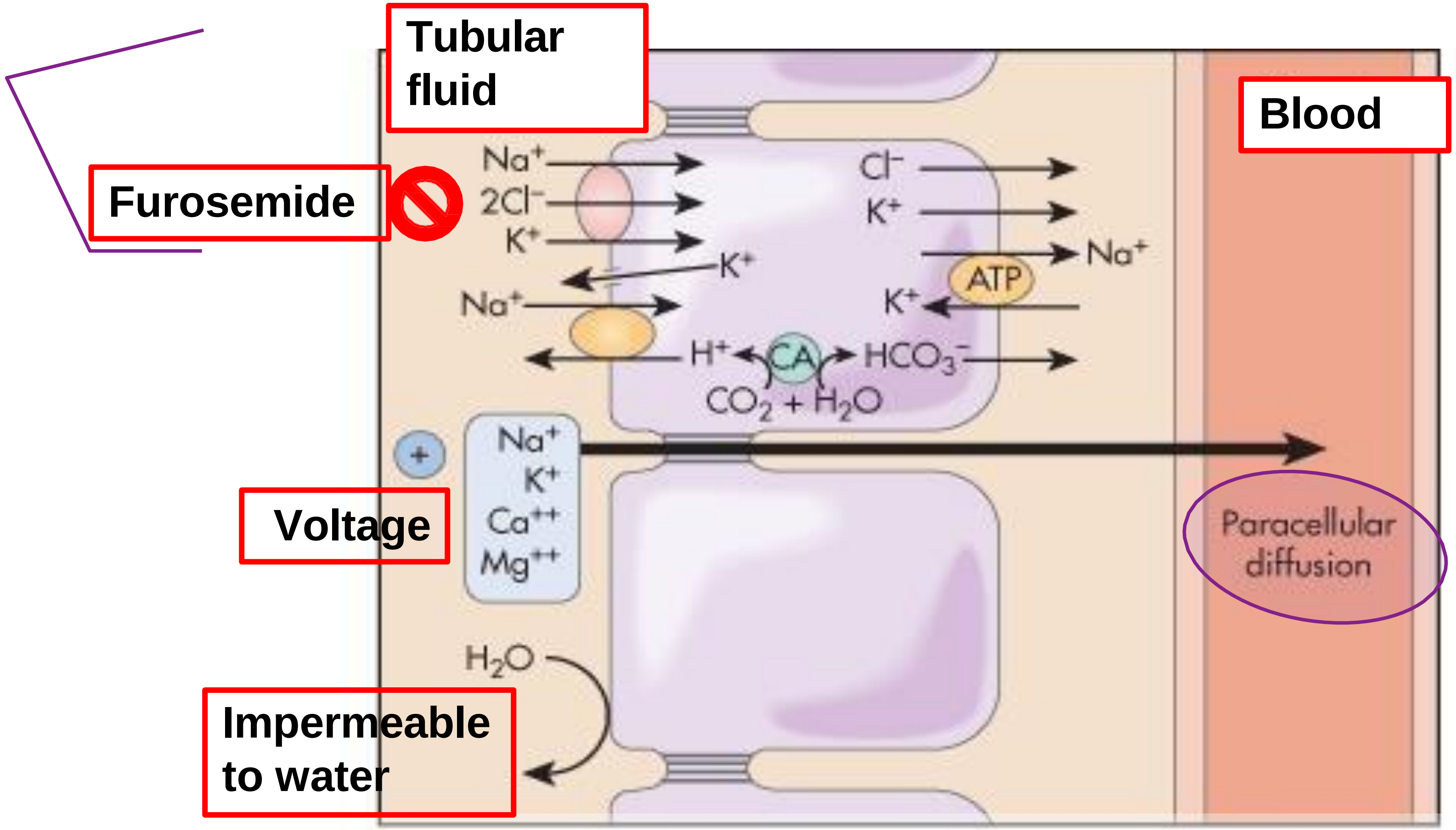
25% of Na+, K+, Cl- HCO_3^-, Ca^{++}, Mg^{++} **reabsorbed.**

- **Impermeable to H_2O.**
- **Called = Diluting segment.**
- **Secretion of H^+**

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 .
- Ascending limb is impermeable to water.
- Reabsorption of Ca^{++} and $HCO3^-$ occurs also in Loop of Henle.

Thick ascending limb of Henle



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of NaCl Reabsorption:

- 50% is Transcellular
- 50% is Paracellular

Thick ascending limb of Henle

In the thick ascending loop of the nephron, the movement of sodium across the luminal membrane is primarily facilitated by a co-transporter called **NKCC2** (1-sodium, 2-chloride, 1-potassium). This co-transporter protein, located on the luminal membrane, utilizes the potential energy released from the downhill diffusion of sATPaseinto the cell. It uses this energy to drive the reabsorption of potassium against its concentration gradient, which is primarily established by the ATPase pump.

The thick ascending limb also has a **sodium-hydrogen** exchanger, counter-transport mechanism, in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.

How does H^+ reach the tubular cells?

The H^+ is initially synthesized inside cells by a reaction involving bicarbonate formation (carbonate buffer system).

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

This reaction, facilitated by the enzyme carbonic anhydrase, involves the conversion of CO_2 and H_2O into H_2CO_3, which then dissociates into H^+, which is excreted in the urine, and HCO_3^-, which is reabsorbed into the blood.

The thick ascending limb of the loop of Henle is the primary site of action for the powerful loop diuretic furosemide. This medication exerts its diuretic effect by inhibiting the action of the NKCC2 co-transporter.

Long-term use of furosemide can lead to hypokalemia. This depletion of potassium can have significant consequences for heart function, potentially leading to arrhythmias and other complications. .

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

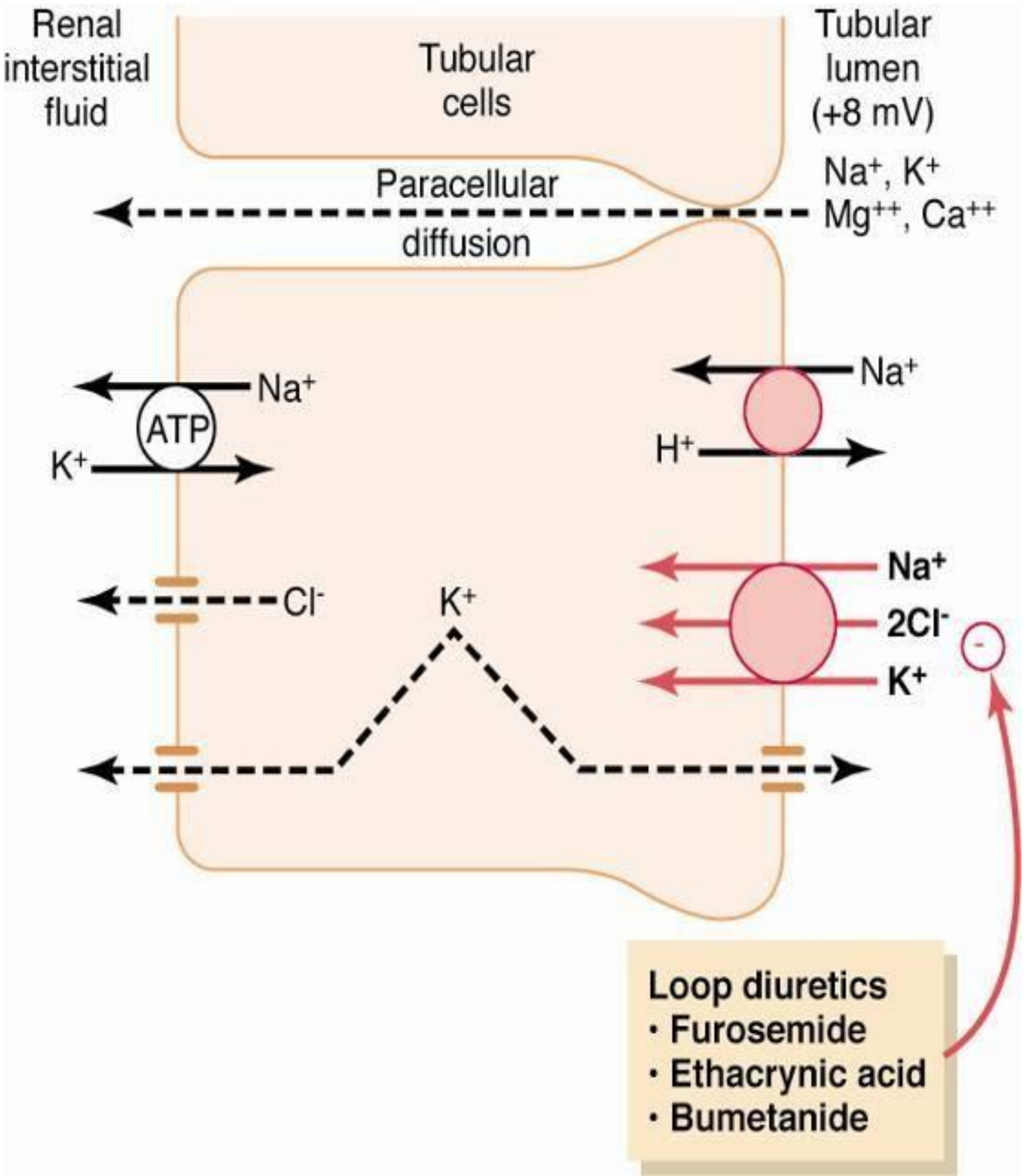

Figure 27-9