MED439
KING SAUD UNIVERSITY

Physiology Team 439

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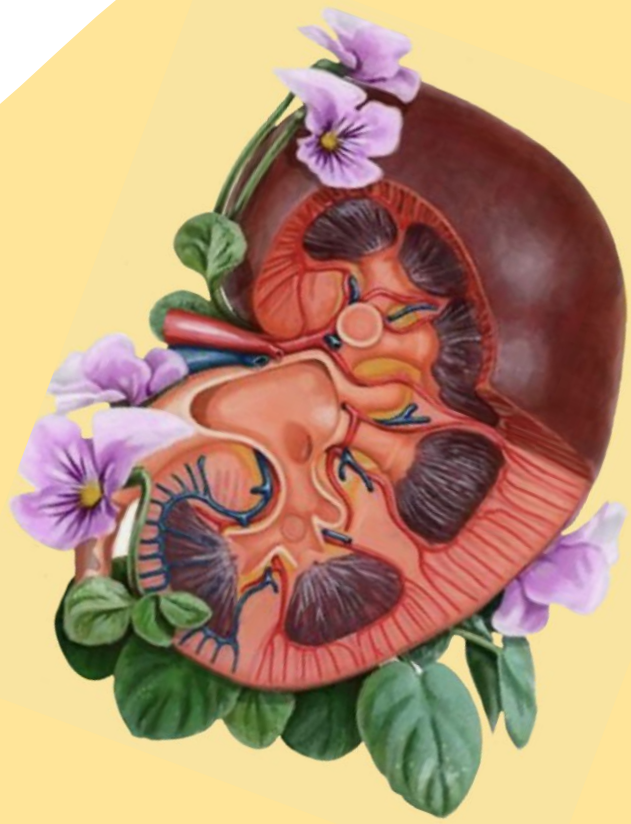
# PHYSIOLOGY

## TUBULAR PROCESSING OF FILTRATE



Black: in male AND female slides
Red : important
Pink: in female slides only
Blue: in male slides only
Green: Notes
Gray: extra information

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# Objectives

- Define tubular reabsorption and secretion.
- Identify the role of each tubular segment in glomerular filtrate modification and the types of substances being transported through each.
- Describe the hormonal/physiological factors regulating tubular function at each segment.
- Describe tubular reabsorption of sodium and water.
- Identify and describe mechanism involved in glucose reabsorption.
- Identify the tubular site and describe how amino acids and urea are reabsorbed.
- Identify and describe the characteristics of the loop of Henle, distal convoluted tubule and collecting ducts for reabsorption and secretion.
- Describe the role of ADH in the reabsorption of water.
- Identify the site and describe the influence of aldosterone on reabsorption of Na+.
- List and explain the factors that control aldosterone and ADH release.
- Identify and describe the juxtamedullary apparatus and its role in checking the filtrate.

# Contents

# Introduction

## What did we discuss so far?

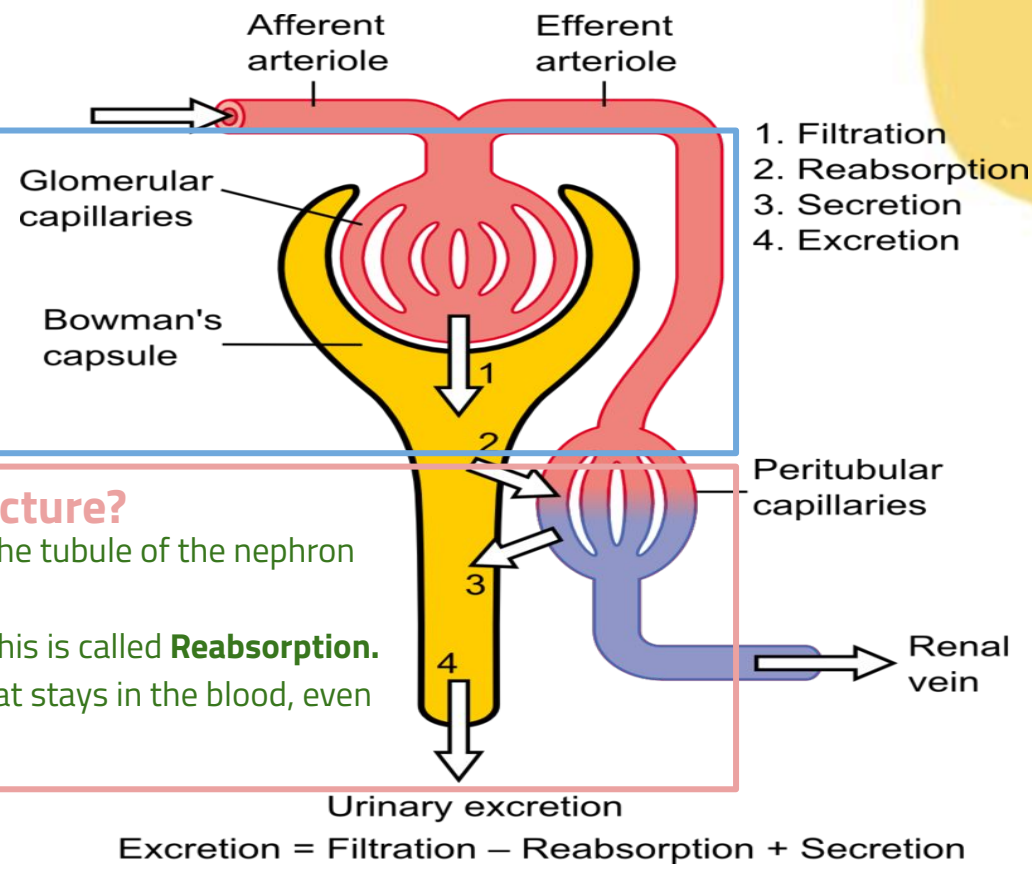
First step of urine formation; the filtrate is reached bowman's capsule and now it will travel along the nephron as traveling along the nephron it will not be excreted in the urine the way it was filtered this is IMPOSSIBLE! therefore...

## What are we going to discuss in this lecture?

it will undergo processing called **Tubular Processing ;** the tubule of the nephron will change the filtrate How?

-it will return the important substance into the blood. this is called **Reabsorption.**

-it will secrete the non important or waste products that stays in the blood, even further the filtrate. this is called **secretion**




**From the previous lecture,**

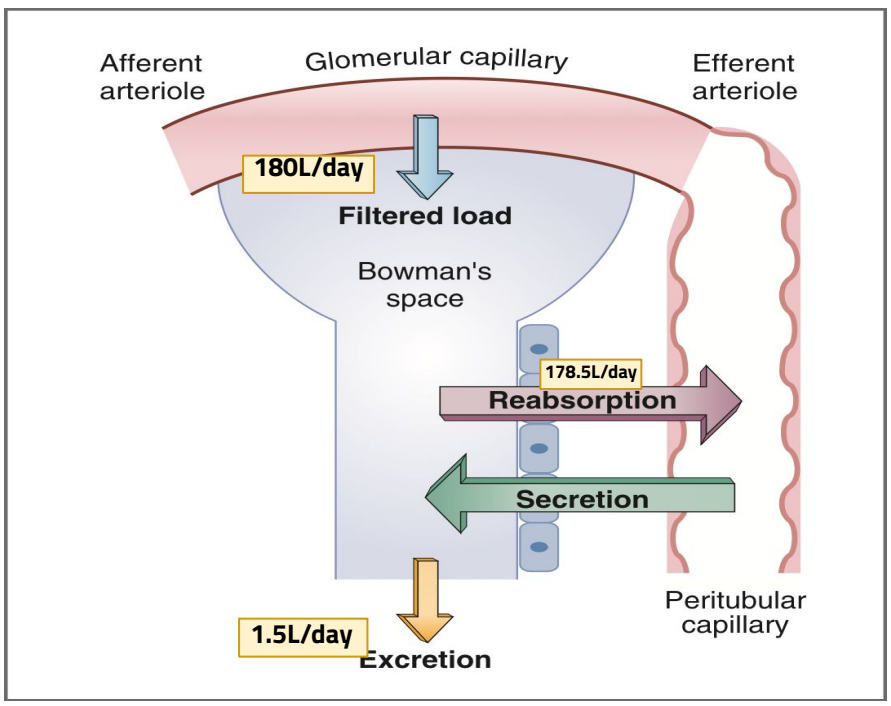
- The kidney filters around **180L/day** of protein & cell-free filtrate by the glomerulus.
- However, a normal human excretes around **0.5-1.5L of urine**..

***What happened to the remaining 178.5L of filtered fluid?*** Go back into the circulation **(Reabsorbed).**

# Tubular Reabsorption

If you remember when we studied the Glomerular filtration we found that it is **non selective** process it just cares about the size (should be small) and the charge (should be Negative) of the substance to get filtered.
The opposite thing we will study here in the Tubular reabsorption it is **MORE selective.** so we can say that:

- Glomerular filtration and tubular reabsorption are quantitatively very large relative to the amount excreted!
- Glomerular filtration is non-selective whereas tubular reabsorption is highly selective.



# Tubular Processing of Ultrafiltrate

- After glomerular filtration the ultrafiltrate gets modified as it passes through the nephron tubule before it is finally excreted.

## Tubular Processing include:

**Tubular secretion**
secretion of substances from peritubular capillary blood into tubular fluid (lumen).

**Tubular reabsorption**
reabsorption of substances from the glomerular filtrate through renal cells into peritubular capillary blood.

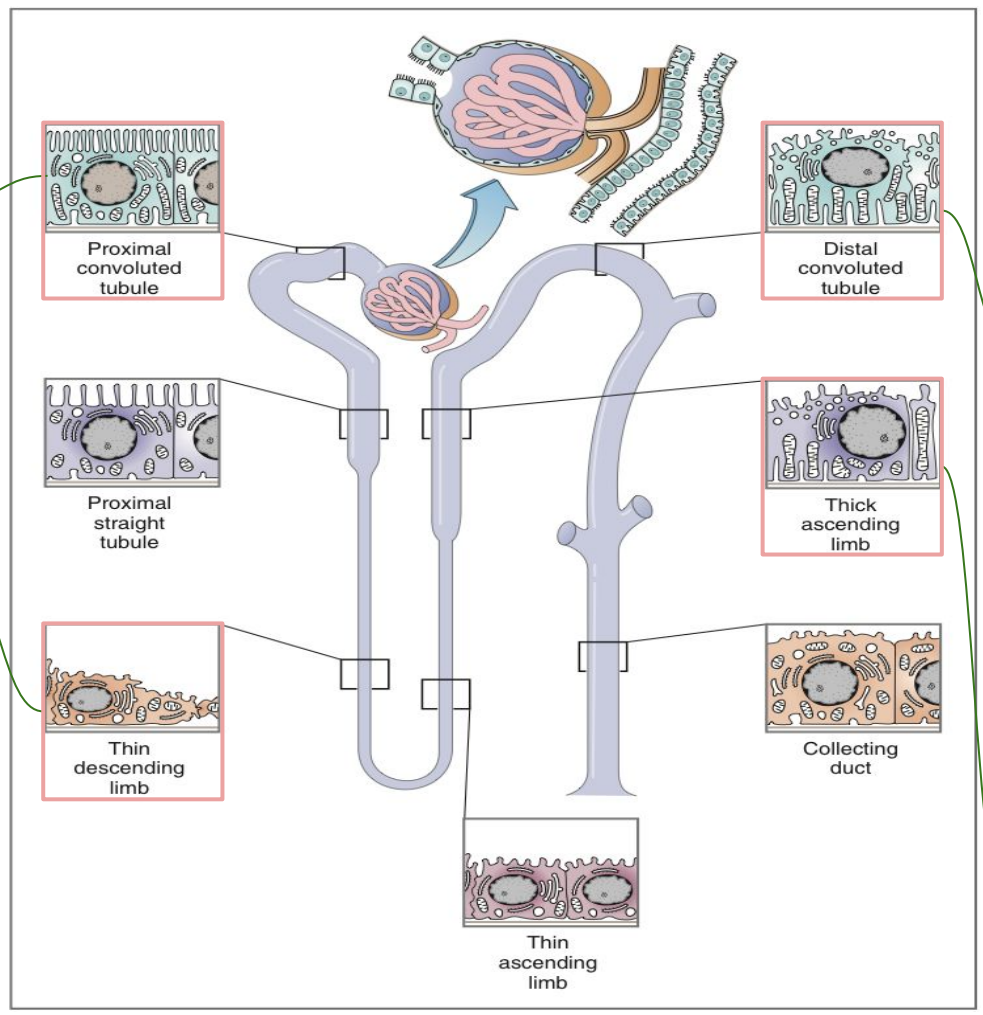
Before we discuss the mechanisms by which the nephron modifies the glomerular filtrate, let us understand the **histologic structure** of the different parts of the nephron.

# Differences in Renal Tubular Cells Reflect Their Function in Tubular Processing

**The nephron is one long tube lying by epithelial cells are NOT homogenous all through the nephron, it changes its characteristics according to the function that perform by that segment of tubule.**

- Rich in mitochondria‹so this cell performs a lot of **active mechanism** that requires energy.
- have a brush border to increase surface area.

- No excessive number of mitochondria So, No active transport mechanism.
- It's very thin to allow of **Passive movement** of substances to go through it.
- It doesn't have brush border because it doesn't perform a lot of active transport mechanism.




It divided into Two parts:
- **First part** resembles the thick ascending limb.
- **Last part** and the cortical collecting duct are **Different** in characteristics, there will show two types of cells in the nephron:
**1. Principal cells.**
**2. Intercalated cells.**
-They have mitochondria but not extensive as others that we have mentioned but it's a good amount of mitochondria to do **Active Mechanism.**

It has a lot of mitochondria and this means it will perform **Active transport mechanism**.

# Tubular Reabsorption & Secretion

## How Does the Nephron Reabsorb Substances

**1- Transport of substances from tubular lumen to Interstitial fluid**

Transport involves:

**1. Active** either primary **or** secondary transport mechanism.

**2. passive** transport ion channel routes.

Occur through:

**1. paracellular** (Between the Cells)

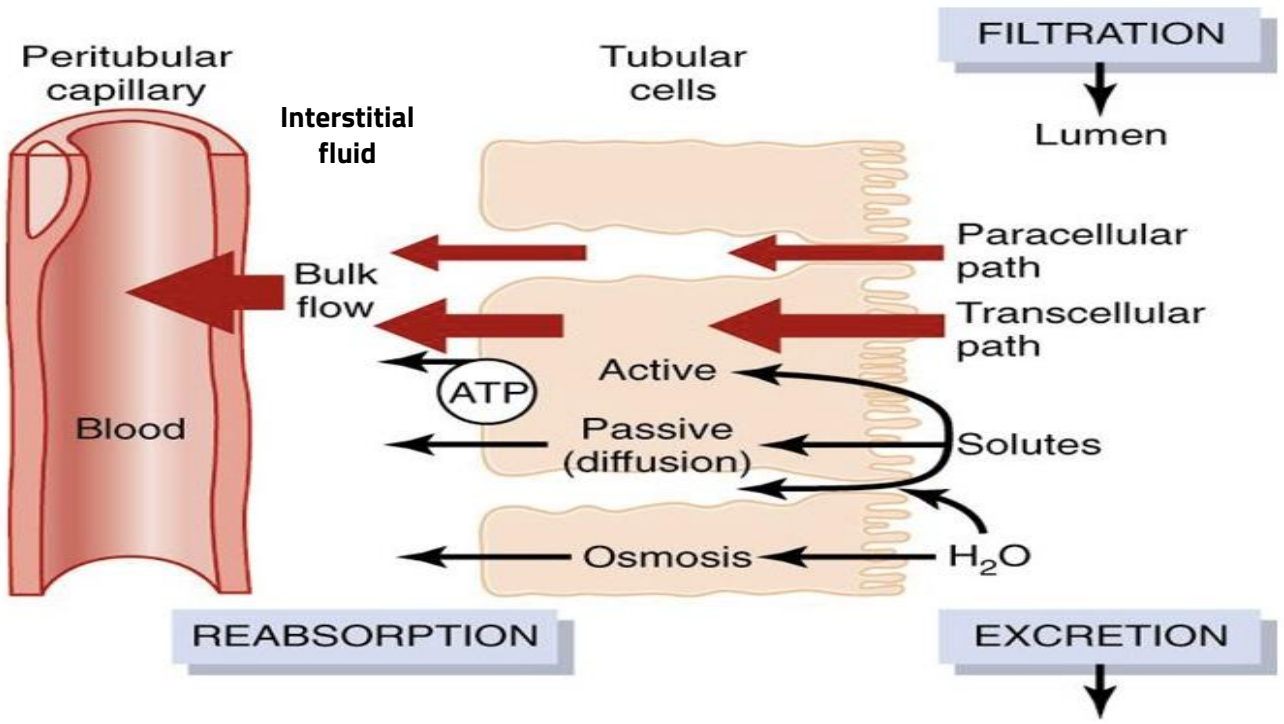
**2.Transcellular** (through the cell itself)

**Reabsorption is a TWO step process:**

**2- Transport from Interstitial fluid to blood**

By ultrafiltration (bulk flow).

(Bulk flow is governing by starling forces; movement by the balance between the hydrostatic and osmotic forces)




Movement of substance from IF to capillary is governed by **Bulk flow.**

Movement of substance from tubular lumen to IF is governed by **cell transport mechanisms.**

Extra:

1- paracellular means between the junctions of two cells بين خليتين متجاورة

2- transcellular: The transport occurs inside the cells داخل الخلايا

# Transport Mechanisms Across the Tubule

## Active Transport

- **Requires** energy
- Moves substances **against** their electrochemical gradient.

### Primary active

**Directly** coupled to energy source.
**e.g**. **Na+-K+ ATPase.**

**At the luminal border:**
Na+ diffuses from the tubular lumen into the cells according to electrochemical gradient.

**At basolateral border:**
Na+-K+ ATPase creates negative potential of about -70 mV and low intracellular Na+ level.

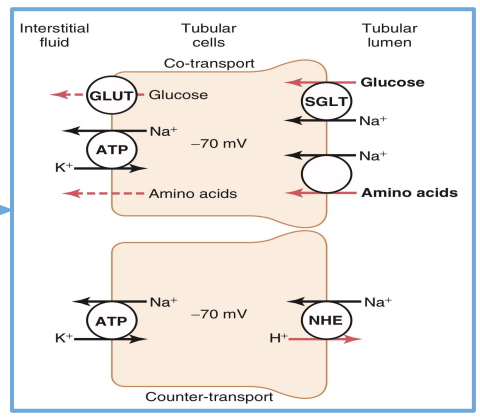
### Secondary active

**Indirectly** coupled to energy source.
**Carrier protein. e.g. Glucose & a.a.**

- Co- transport
- Counter transport

**Counter-transport:**
Secondary active secretion of H+ together with Na+ reabsorption by a Na+- H+ counter transport protein in the brush border of the luminal membrane of the proximal convoluted tubule.

**Cotransport:**
- The reabsorption of a substance is linked to the passive reabsorption of another.
-The 2 substances bind to a specific carrier.
-One substance is transported down its gradient and the other against its chemical gradient. Example: Na+-glucose co-transport:
-At luminal border:Glucose and Na+ bind to common carrier SGLT-2.
-At basolateral border: Glucose is carried by GLUT-2.




In secondary active transport, two or more substances interact with a specific membrane protein (a carrier molecule) and are transported together across the membrane. As one of the substances (for instance, sodium) diffuses down its electrochemical gradient, **the energy released is used to drive another substance** (for instance, glucose) against its electrochemical gradient.

## Passive Transport

- **Does not** need energy.
- Moves substances **down** their electrochemical gradient.

**Passive diffusion Osmosis:**
Water Solutes like Cl- Urea.

**Chloride:**
occurs through paracellular pathway following Na+ reabsorption which creates negativity inside the tubular lumen.

**Urea:**
H2O reabsorption leads to urea concentration in the tubular fluid creating a gradient for its absorption, 50% of urea is reabsorbed.

**Water (osmosis):**
Occurs paracellularly following solute.

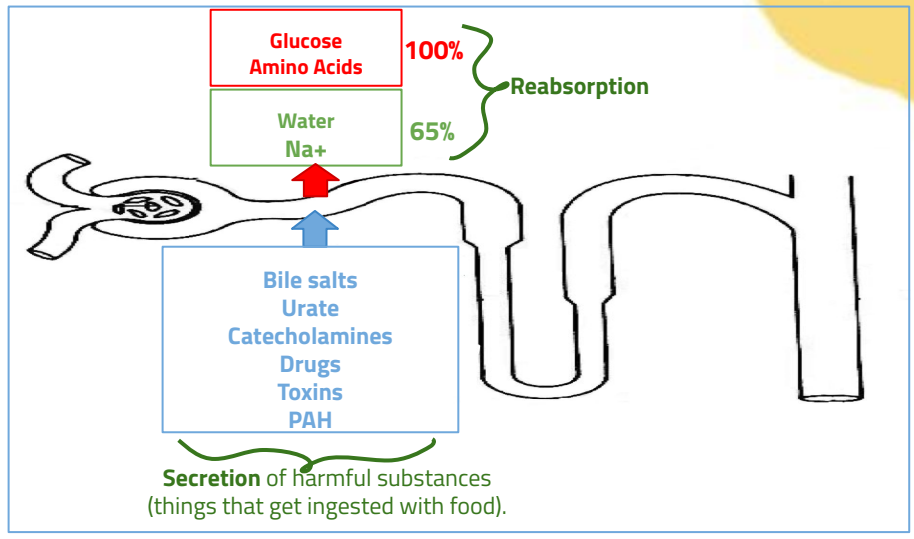
## Pinocytosis

# Tubular Reabsorption Each Part Of The Nephron

# 1- Proximal Tubule

Most of the reabsorption occurs in the PCT (has the biggest job of reabsorption ).. *Why?*

- Highly metabolic cells.
- Extensive brush border.
- Lots of mitochondria.




## How Does the Proximal Tubule Reabsorb Sodium (Na+)?

**Explanation**

Large amounts (65% of filtered load) of Na+ through the glomeruli.

- Na+ is reabsorbed out of all portions of the tubule **except** the thin descending limb of loop of Henle.
- 96 - 99% of filtered Na+ is reabsorbed.
- 90% of the Kidney energy consumption is due to **active Na+ transport** which depends on (Na+/K+ pump).

Na+ can be transported in two pathways:

1. Paracellular (Passive movement).
2. Transcellular Path:

by **Na-K pump (primary active transport)** —> **3Na go out** and **2Ka go in** So,
conc. of K+ inside the cell will be **High**.
conc. of Na+ inside the cell will be **Low.**
But conc. of Na+ in the filtrate will be **higher than in the tubular cell** Why? because as we learned the amount of filtration of substances in filtrate is almost Equal its conc. in the plasma which is Na=140. Therefore,
Gradient of Na will favor what? **Reabsorption (from high to low).**
and because of the charge of Na+ it can't pass plasma membrane so it needs a channel or carrier called **Glucose cotransporter** (will talk about it in the next slide) to be reabsorbed from lumen into the cell **Down its conc. gradient.**
Once **Na+ come inside the cell** its **pumped out by (Na+/K+ ATPase)** into the interstitial fluid or by another transporter.
Once **it reaches interstitial fluid** it will go to the blood by **Bulk flow.**

**There are many types of transporter proteins:**

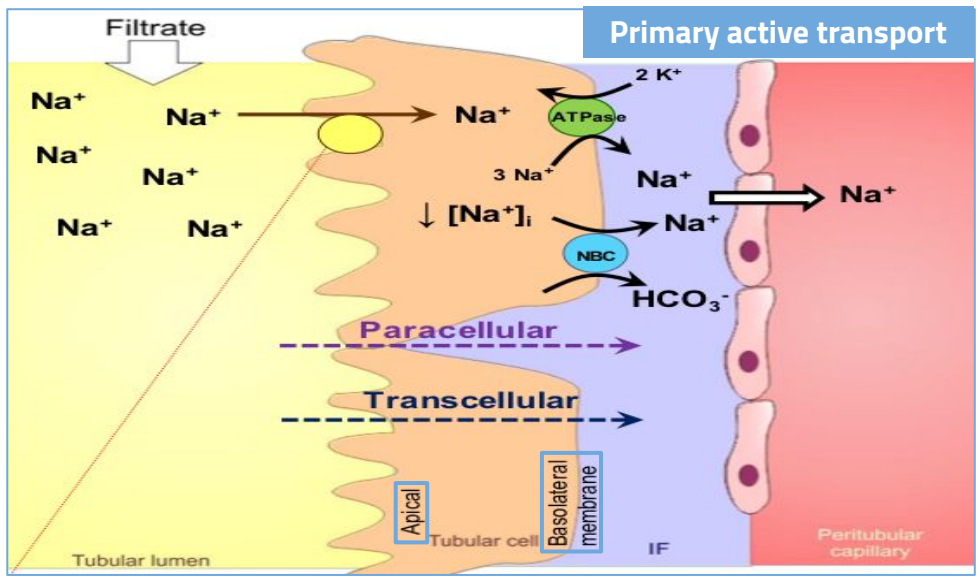
-Co-transporters. (Both substances are moving in the same direction)
-Exchangers (counter transporters). (Both substances are moving in opposite direction)

Although it is an active transport, it has no tubular maximum.
Because the rate of its pumping outside at the basolateral border is greater than the rate of diffusion at luminal border

Basolateral Na+-K+ ATPase pumps 3 Na+ out and 2K+ into the cell

Results in low [Na+]inside the cell

This gradient favours passive entry of Na+ into the tubular cell across the apical membrane **via transport proteins** because Na+ is a charged molecule.




All steps will come after this it depends on your understanding here because the carrier protein that carry Na+ it doesn't only carry Na+, it will carry something else . either it will carry it:

- In the same direction of Na+ (both are moving from lumen into the cell) —> called **Cotransporter.**
- In opposite direction (one move from lumen to the cell and other in opposite direction) —> called **Exchanger or counter transporter.**

# How Does the Proximal Tubule Reabsorb Glucose?

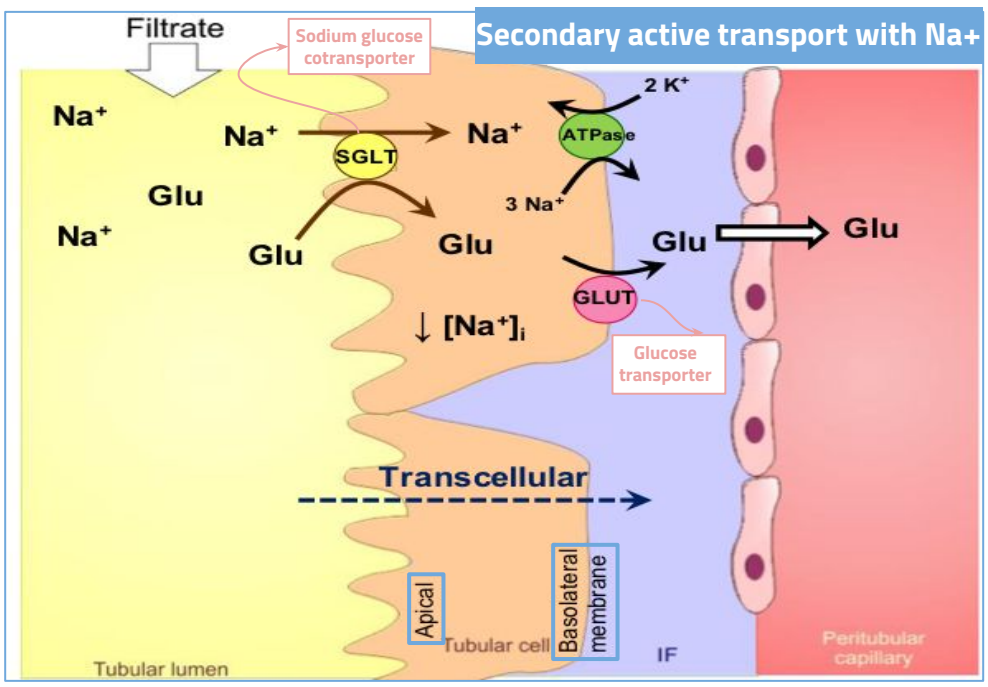
**Explanation**

Reabsorption of Glucose is **Against its gradient** so it **requires energy** to move, from where it will get the energy? from the gradient of Na+ that was created by **(Na+/K+ ATPase).**
The movement of Na+ down its gradient into the cell it will carry Glucose with it by using special carrier protein called **(Sodium Glucose Transporter SGLT)** this carrier will move Na+ down its conc. gradient and glucose against its concentration gradient at the same time **by using ATP from (Na+/K+ ATPase pump)** once Glucose reaches into the cell —> it will pass by facilitating diffusion into the interstitial fluid then from IF into the blood.
**Amino acids and other substances** are absorbed in a **similar way** using transporters specific for the substrate being transported.
-Normally all filtered glucose is reabsorbed at the early portion of PCT.
-At luminal border: Common carrier with Na+, SGLT2 Can be blocked by
1.**Oubain** which blocks Na+ -K+ ATPase.
2.**Phlorhizin** which competes for the carrier.
-At basolateral border: Glucose is carried by **facilitated diffusion** down chemical gradient by carrier GLUT2.

Basolateral Na+-K+ ATPase pumps 3Na+ out and 2K+ into the cell

Results in low [Na+] inside the cell

This gradient Transcellular favours passive entry of Na+ into the tubular cell across the apical membrane **via SGLT carrying glucose with it.**




**An important point** is that a substance is said to undergo **"active" transport** when at least one of the steps in the reabsorption involves primary or secondary active transport, even though other steps in the reabsorption process may be passive. For glucose reabsorption, secondary active transport occurs at the luminal membrane, but passive facilitated diffusion occurs at the basolateral membrane, and passive uptake by bulk flow occurs at the peritubular capillaries.

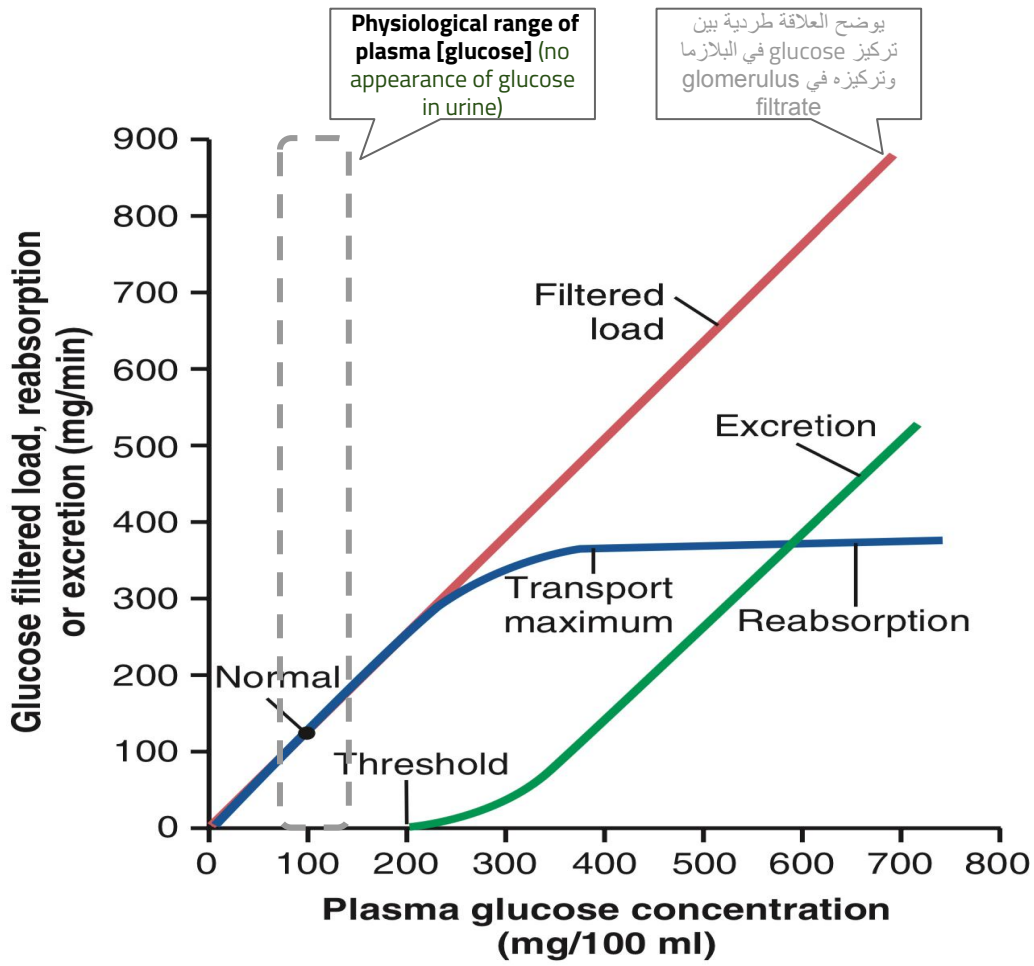
**summary:**

**1.What type of transport mechanism is used in process of Na+ Reabsorption? Active transport mechanism** it requires energy (ATP) because it use (Na-K ATPase pump) and without energy Na-K pump will never happen.
**2.What type of Active transport is used in Na+ Reabsorption, Primary or secondary? Primary active transport mechanism** because it's Na itself who uses the ATPase pump.
**3.Why Sodium charge prevents it from passing into the cell? Cell membrane is a lipid bilayer and Na+ charge is repelled by the membrane** which means: Polar ion will not dissolve easily to the membrane While non-Polar ion will dissolve easily to the membrane.
**4.What type of transport mechanism is used in process of Reabsorption of Glucose, Amino Acids and lactate? Secondary Active transport mechanism.**
**5.why is the reabsorption process more selective than filtration?** Because of these specific carriers for each substrate.

# The Relationship Between Plasma [Glucose] and its Urine Excretion

What happen to the Active transport mechanism? they get saturated easily because it depends on three things: Transport movement, Energy provided, and the Capacity of the transport itself.

- What are the features of this glucose titration curve?
- What is the plasma/renal threshold of glucose? Plasma level at which glucose starts to appear in urine. Value:
  - 200mg/dL in arterial blood
  - 180mg/dL in venous blood.
- What is meant by transport maximum (Tm)? Why does it occur? (TmG) Definition: Maximum amount of glucose in (mg) that can be reabsorbed by renal tubules/min.
- What happens if blood glucose level increased to 400mg/dl? **Full** saturation of transporters (the kidney stops reabsorbing glucose).




**Glycosuria:**
Excretion of glucose in urine in considerable amounts.

**Causes:**

- Diabetes mellitus: Blood glucose exceeds renal threshold.
- Renal glycosuria: Normal blood glucose but decreased renal threshold below 180 mg%. Tm is markedly decreased in renal glycosuria. Due to congenital defects.

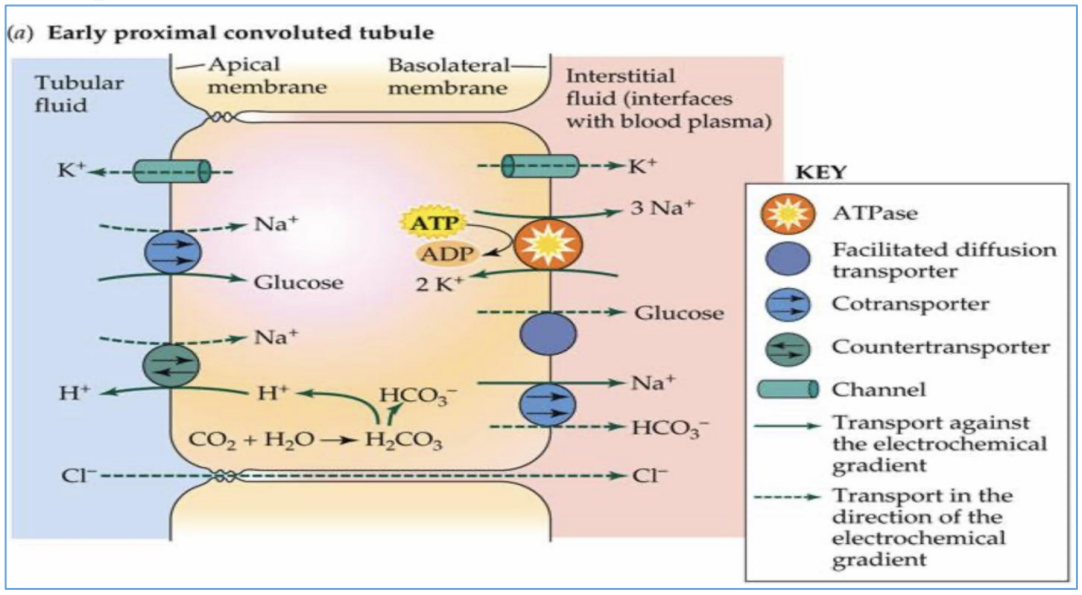
**Important**: when the plasma concentration of glucose rises above 200 mg/100 ml, a small amount of glucose begins to appear in the urine. This point is termed the *threshold* for glucose. *Note that this appearance of glucose in the urine (at the threshold) occurs before the transport maximum is reached Why?* 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.

Extra: if the plasma glucose conc. is more than 200 it means the patient is diabetic.

# Summary of PT Transport Mechanisms

In females slides only

- Basolateral ($Na^+$-$K^+$ ATPase) pumps $3Na^+$ out and $2K^+$ into the cell
- Results in low $[Na^+]i$
- This gradient Transcellular favours passive entry of $Na^+$ into the l tubular cell across the apical membrane via **transporter proteins**



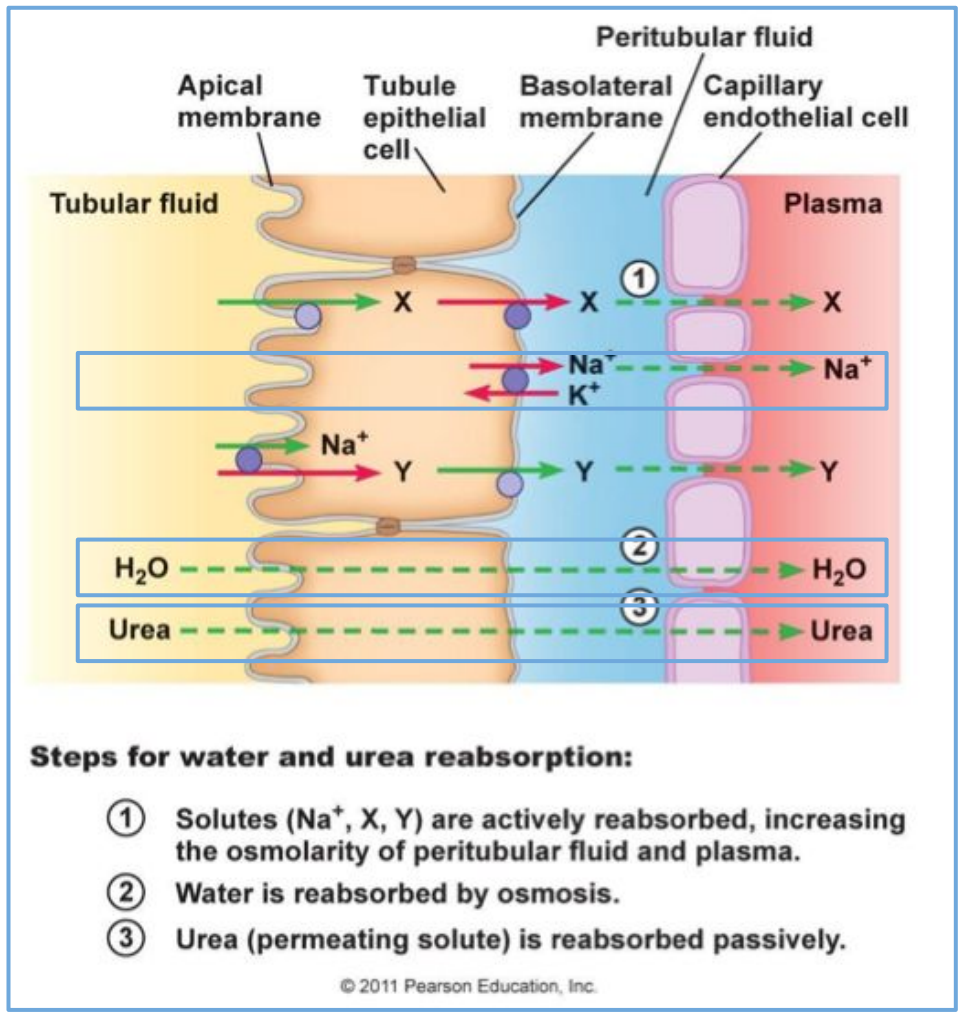
# How Does the Proximal Tubule Reabsorb Water?

## Water is reabsorbed through both:

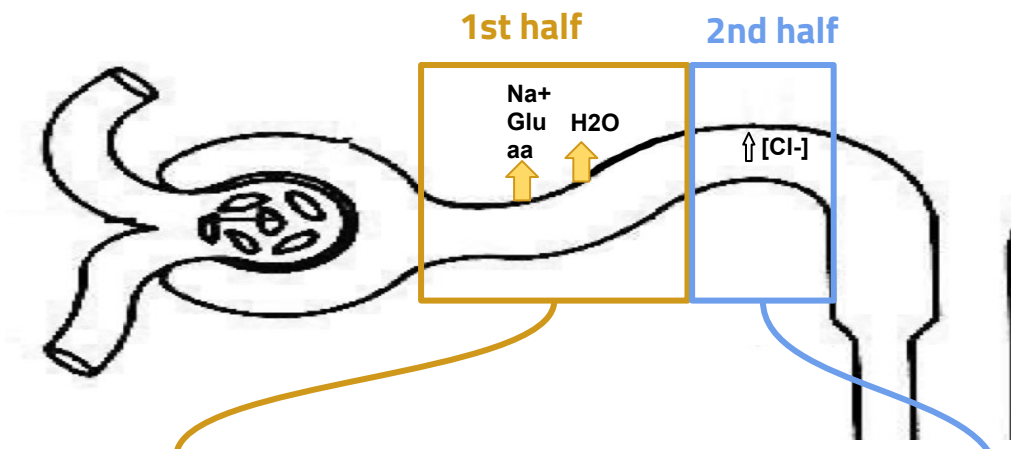
- Paracellular path (Between the Cells)
- Transcellular path (Through the Cells)
  - Transcellular movement is facilitated by the presence of water channels (AQP1) aquaporin

Simply, Sodium will move, then water will follow sodium, then urea will follow water. How?
Na+ will get reabsorbed with other chemicals (glucose, A.A, etc.) and the Na+ K+ pump will create high Na+ concentration in the IF, now you have low Na+ conc. in the tubules, and high conc. in the IF. So Water will move **down its conc. gradient** from the tubule to the IF by **osmosis as a passive process**. Now the amount of water in the tubule is less, thus the concentration of urea in the tubule is high, so urea will move passively to the IF down its concentration gradient.

Na+ movement changes the osmolarity and facilitate water movement




# Differences in Sodium Reabsorption Along PT




**Na+ reabsorption is coupled to that of;**

- Glucose
- Amino acids
- Lactate
- Phosphate

→ Symporters

- H+ → Antiporter

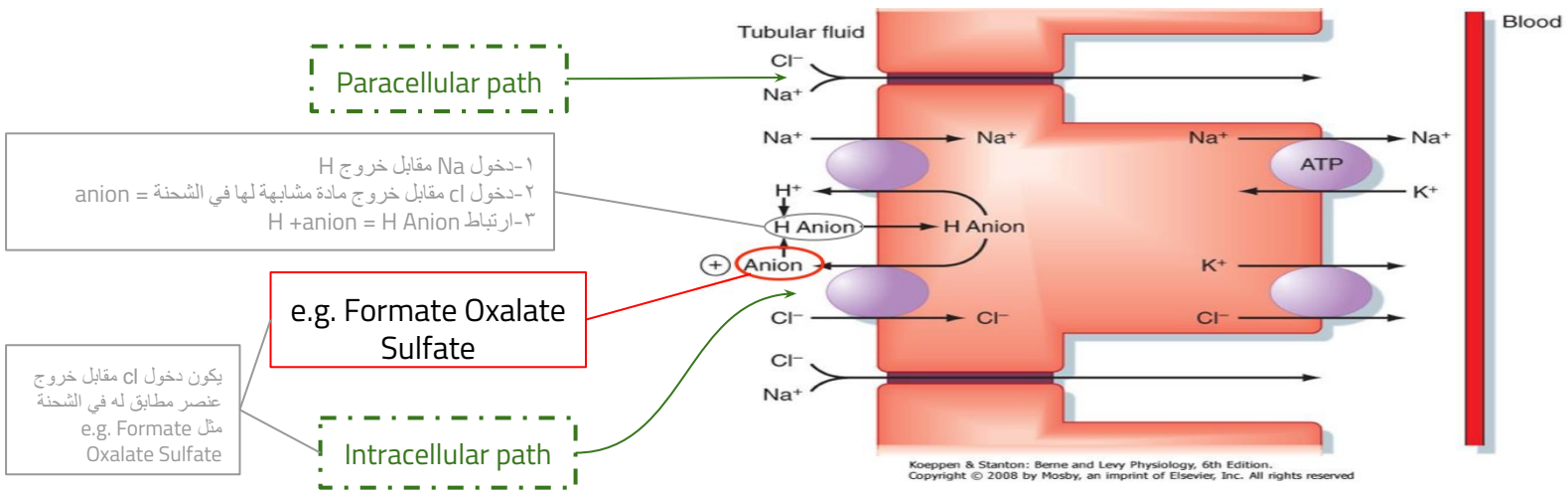
**Na+ reabsorption is mainly coupled to that of;**

- Cl- via either paracellular or transcellular

Why??

1- Increased concentration of $Cl^-$ because of the reabsorbed chemicals (Glu,Na,aa,...) in 1st half.
2- The lack of a specific transport mechanism for it in the 1st half.

# Sodium Chloride Reabsorption in the 2nd Half of PT




**For better understanding**

The fluid entering the late proximal tubule has no glucose or amino acids and little HCO3–. Furthermore, this fluid has a **high Cl– concentration**, so the high tubular fluid Cl– concentration is the driving force for this reabsorption.

**Cl– Reabsorption can be:**

**1) Intracellularly: Cl–-formate– anion exchanger**, **which is driven by the high tubular fluid Cl– concentration**. The combined function of the two exchangers is to transport NaCl from the lumen into the cell. Na+ then is extruded into blood by (Na+-K+ ATPase), and Cl– moves into blood by **diffusion**.

**2)Paracellularly:** The paracellular component also **depends on the high tubular fluid Cl– concentration.** The tight junctions between cells of the proximal tubule are, in fact, not tight: They are quite permeable to small solutes, such as NaCl, and to water. Thus, the Cl– concentration gradient drives Cl– diffusion between the cells, from lumen to blood. This Cl– diffusion establishes a Cl– diffusion potential, making the lumen positive with respect to blood. Na+ reabsorption follows, driven by the lumen-positive potential difference. Like the cellular route, the net result of the paracellular route is reabsorption of NaCl.

# How Does the Proximal Tubule Secrete Hydrogen Ions?

**Explanation**

Same steps again in the basolateral membrane we have (Na+/K+ ATPase) which pump Na+ out and creating low concentration of Na+ inside the cell. this low conc. of Na+ Reabsorbed across the apical membrane with help of Carriers.
one of these carriers called **NaH exchanger**; this carrier when it carries Na into the cell at the same time it **secretes Hydrogen out** of the cell into tubular lumen. and this is how hydrogen ion excreted. The hydrogen from where it comes? Do you remember in Respiratory block we said that when we have (Co2 and water) in the presence of enzyme called carbonic anhydrase they react together and form **Carbonic Acid** and this carbonic acid as soon as it will dissociated into (Hydrogen ion H+ and Bicarbonate HCO3).
and this hydrogen which will be secreted by NHE (Na+ H+ exchange).

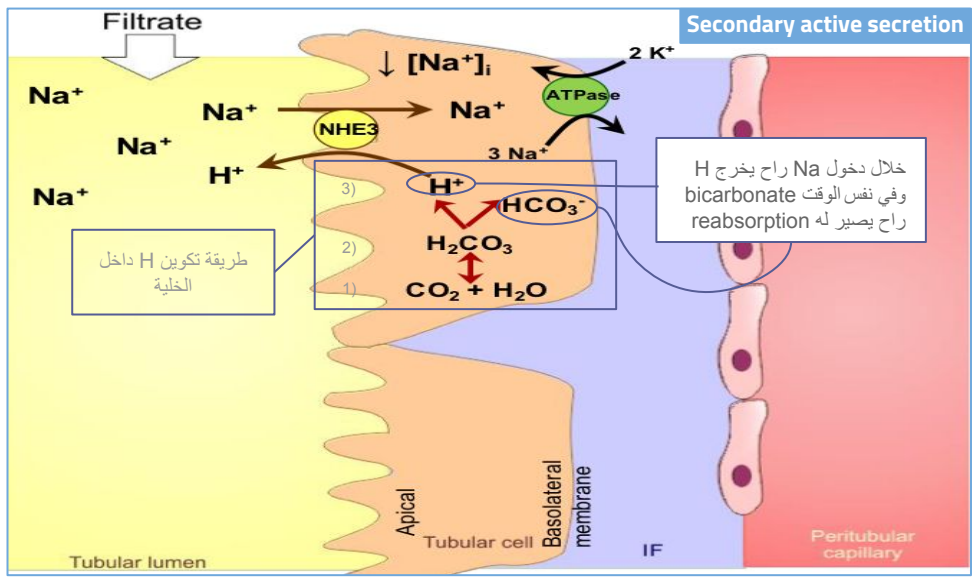
**Bicarbonate reabsorption in the proximal tubule**

-Filtered HCO3 is titrated by secreted protons to CO2 and water.
-Hydration of CO2 in the cell produces protons for secretion and HCO3 is transported into the ISF by Na-HCO3 cotransporter in a ratio of 3HCO3:1Na.
-Thus one HCO3 disappears from tubular fluid and another appears in the ISF.
-The net effect is reabsorption of bicarbonate.

Basolateral (Na+-K+ ATPase) pumps 3Na+ out and 2K+ into the cell

Results in low [Na+]i

This gradient favours passive entry of Na+ into the tubular cell across the apical membrane via NHE in exchange with H+.

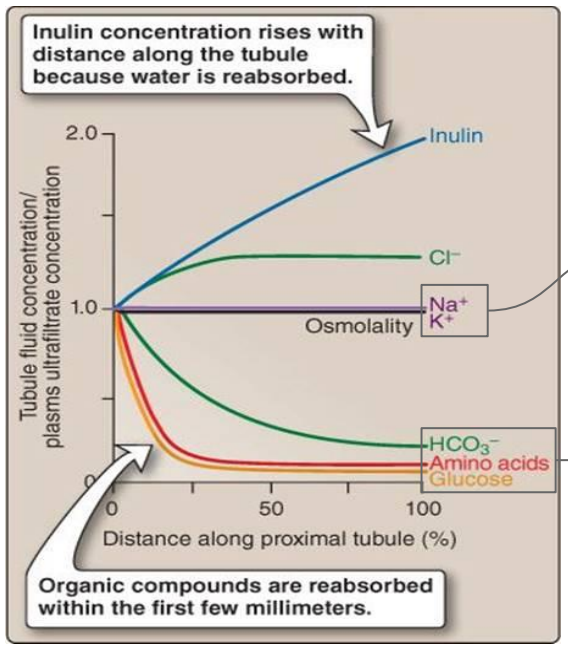



Explanations: sodium entry into the cell is coupled with hydrogen extrusion from the cell by sodium-hydrogen **counter-transport.** This transport is mediated by a specific protein (sodium-hydrogen exchanger) in the brush border of the luminal membrane. As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen.

# Organic Anion/Cation Secretion

| Organic Anions | | Organic cations | |
|---|---|---|---|
| **Endogenous** | | **Endogenous** | |
| ○ Bile salt<br>○ Oxalate | ○ Urate<br>○ Vitamins (ascorbate,folate) | ○ Creatinine<br>○ Dopamine | ○ Epinephrine<br>○ Norepinephrine |
| **Exogenous** | | **Exogenous** | |
| ○ Acetazolamide<br>○ Furosemide | ○ Salicylate<br>○ Penicillin | ○ Atropine<br>○ Morphine | ○ Amiloride<br>○ Procainamide |

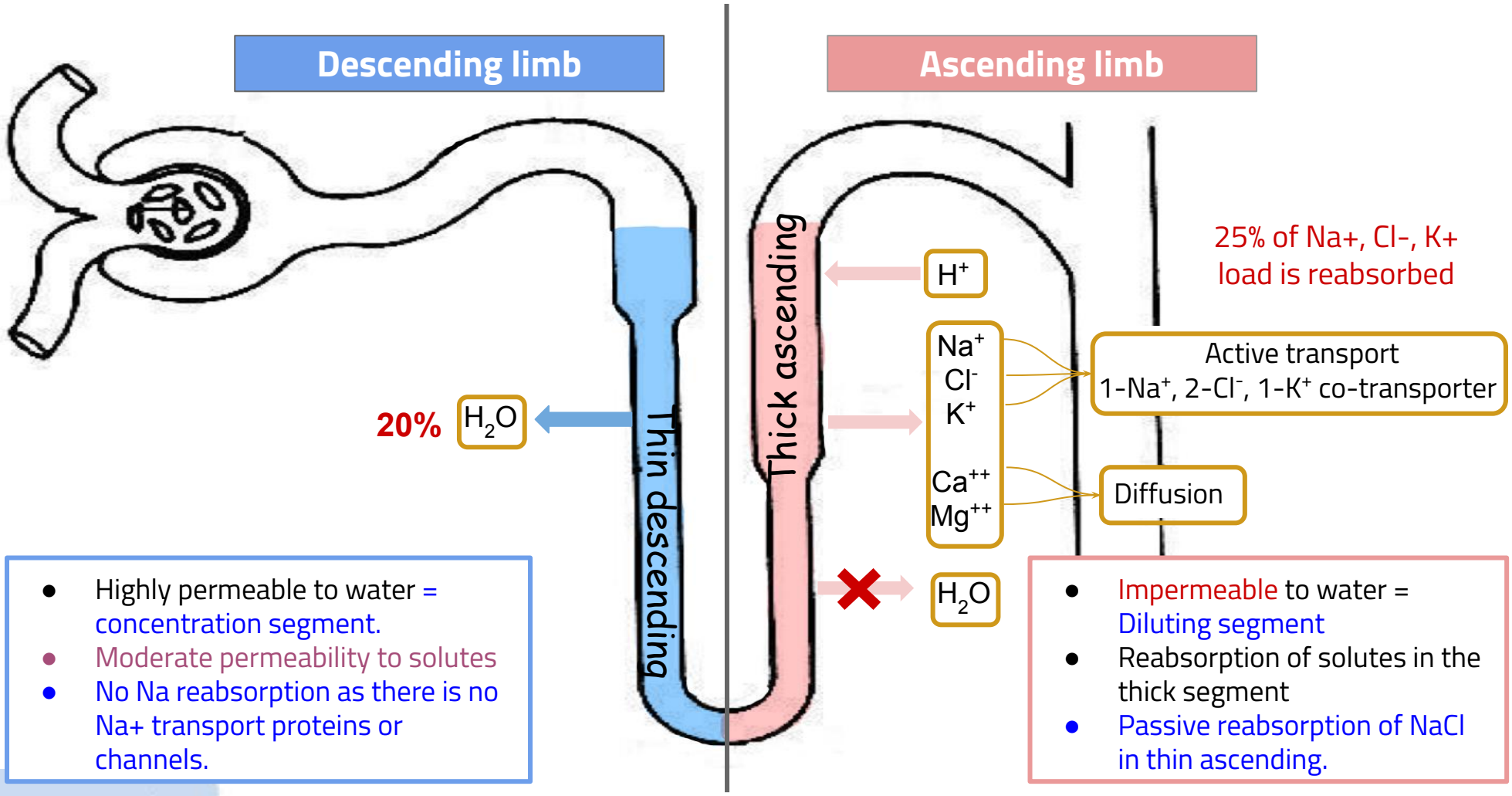
# Summary of PCT Filtrate Modification




تركيز الأملاح ثابت لان خلال خروجها يخرج معها الماء نتيجة للخاصية الاسموزية لذا التركيز ثابت لا يعني أنها لم تتحرك أو لم تمتص من tubular الى الدم

تركيزها يقل في PCT نتيجة reabsorption

# 2- LOOP OF HENLE



# Transport Mechanisms in the TAL and Early Distal

Basolateral ($Na^+$-$K^+$ ATPase) pumps $3Na^+$ out and $2K^+$ into the cell

Results in low [Na+]inside the cell

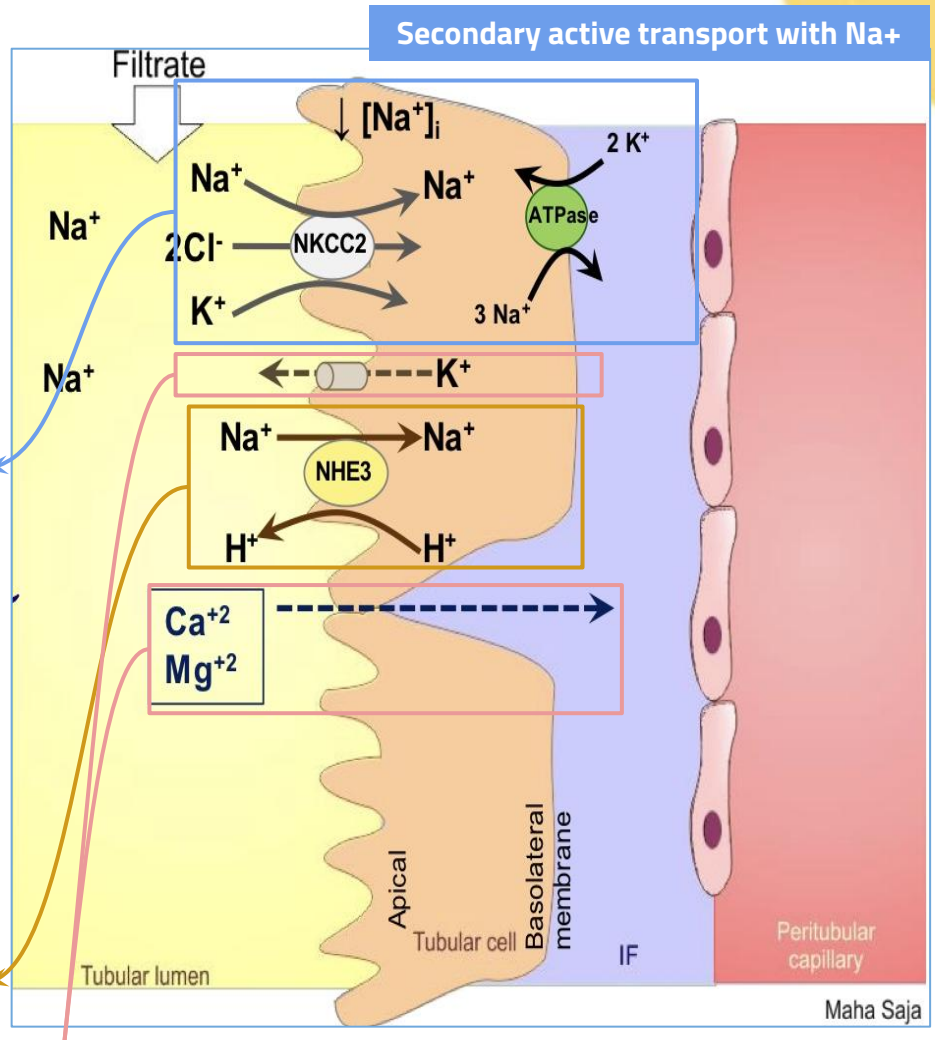
This gradient favours passive entry of Na+ into the tubular cell across the apical membrane via the triple transporter **NKCC2** along with Cl- & K+ (25% of Na+, K+& CL- are reabsorbed by cotransport ( Na+- K+- 2 CL-).

**Loop diuretics block NKCC2**

TAL also has Sodium Hydrogen exchanger NHE3, like the PT.

Although the 1-sodium, 2-chloride, 1-potassium co-transporter moves equal amounts of cations and anions into the cell, **there is a backleak of potassium ions into the lumen (Most of reabsorbed K+ fluxes back to the lumen via K+ channels**),

This serves 2 purposes:
1- Ensure sufficient K+ for the co- transporter.
2- Results in net positive potential of about +8 millivolts in the lumen that helps paracellular reabsorption of several cations, Na+, K+, Ca++& Mg++ (This positive charge forces cations such as Mg++ and Ca++ to diffuse from the tubular lumen through the paracellular space and into the interstitial fluid).




## Barter's syndrome In male's slides only

Defect in the Na+- K+ -2 CL- cotransporter in the luminal membrane of the thick ascending limb → loss of Na+, K+ ,CL- and Ca++ in urine.

**Manifestations**:

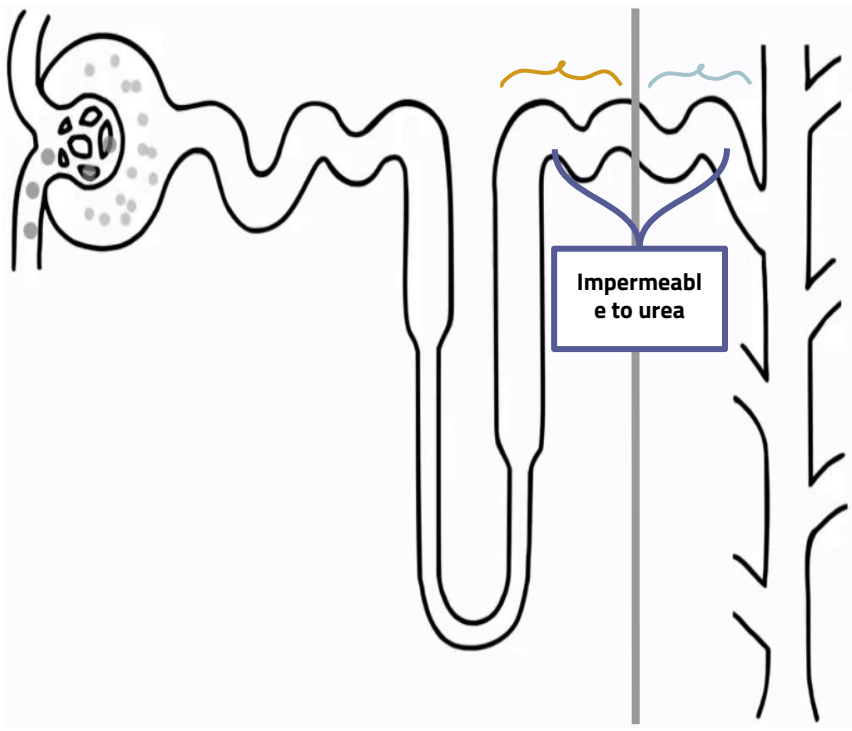
- Renal salt wasting.
- Volume depletion.
- hypercalciuria.
- Hypokalemia.
- Metabolic alkalosis.

# 3- DISTAL TUBULE

## Early part

Resembles the thick ascending loop of Henle
Known as
**the diluting segment**
Reabsorbs 5%of NaCl
Why it's called Diluting? because it's pump **solutes out** so in every time the solutes pumped out the **water** that trapped in the lumen will become **hypotonic**. How the solutes pumped out? by two: Thick ascending tubule then by distal convoluted tubule, therefore the water get trapped in the lumen without solutes.

**-Impermeable to water.**
**-Permeable to Solutes.**




## Late part

Resembles the thick the cortical ascending collecting loop of tubule

| Principal cells | Intercalated cells type A |
|---|---|
| Reabsorb Na+ & H2O<br>Secret K+<br>10% of Na+ are reabsorbed as **counter-transporter** | Reabsorb K+<br>Secret H+ |
| Controlled by **Aldosterone**<br>which is powerful hormone enhances Na+ and water Reabsorption. | Acid-base Regulation<br>will learn it in the next lectures |

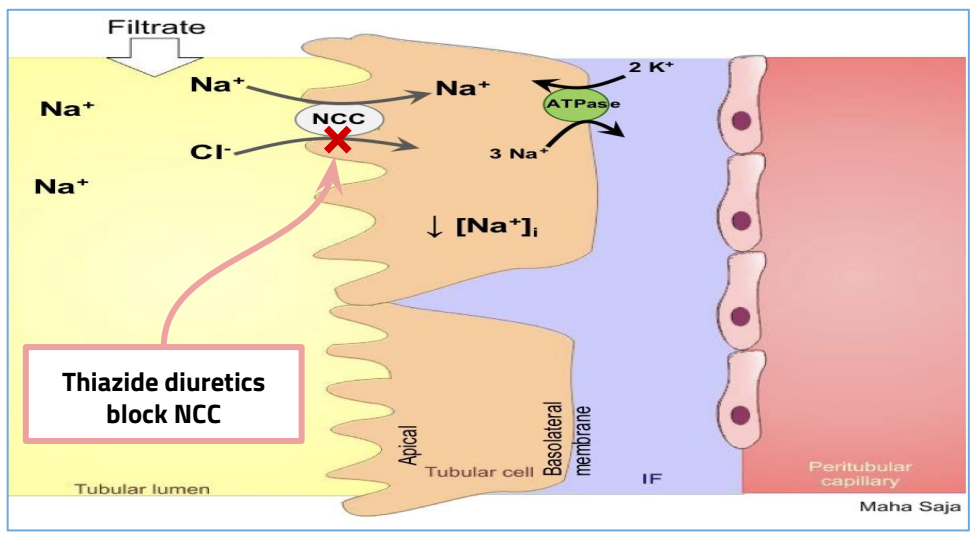
**Permeability to H2O depends on ADH**
if ADH present —> will be permeable to H2O.
if ADH absence —> will be Impermeable to H2O

# Transport Mechanisms in the Early DT

**Explanation**

Same mechanism again; i have (Na+ K ATPase) in basolateral membrane of the tubular cell. it pumps Na+ out and K in —> will lead to low conc. of Na+ inside the cell and this favors Sodium to pass from the lumen into the cell with help of carrier (it's a different carrier) It ONLY carries Sodium and Chloride so it's called NCC (Na+ Cl cotransporter) Not same thick ascending it was triple transporter. What's the important of NCC? again there is a class of diuretic that act on NCC transporter and block it which is called **Thiazide diuretic.** So Na+ and Cl- will NOT be reabsorbed and they will be trapped into the lumen and water will be trapped also with them —> this is how diuretic works.

- Basolateral (Na+-K+ ATPase) pumps 3Na+ out and 2K+ into the cell
- Results in low [Na+]inside the cell
- This gradient favours passive entry of Na+ into the tubular cell across the apical membrane via **NCC** along with cL-

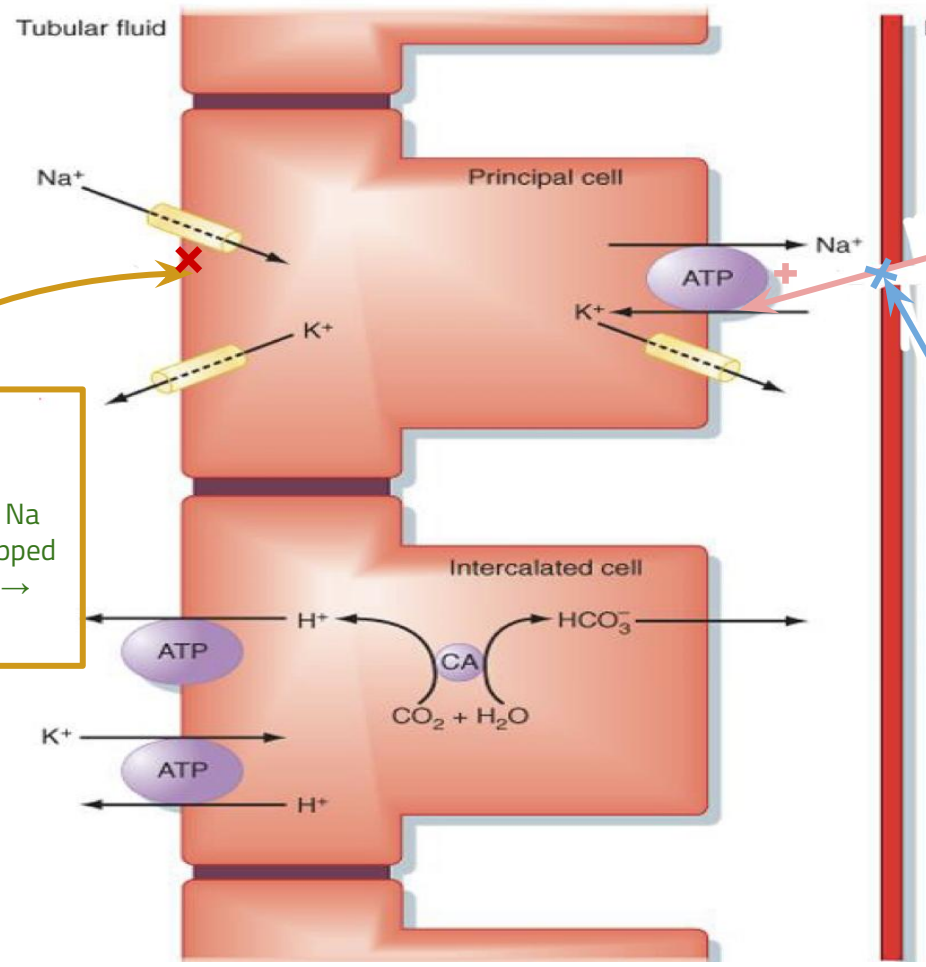



**Which Diuretic Loop or Thiazide has the Powerful diuretic effect (amount of urine)? Loop diuretic Why?** because it blocks the Triple transporter and Triple reabsorbed **20%** of the filtered load Therefore the amount of solutes that get trapped is MORE —> amount of water will get trapped is MORE also.
But Thiazide blocks NCC. early distal tubule is contribute **only 5%** to the Reabsorption of filtered load.

# Transport mechanism in the Late Part of DT

**Explanation**

In the Apical membrane the principle cells are differ from others. (others use carriers in apical membrane) But here these cells they use **channels ( Na channel and k channel).**
-Na will move **from lumen to the cells** through Na channel. because Na in luman higher than in the cells. (**Na is Reabsorbed**).
-K will move **from inside the cells to the lumen** because K inside the cells is higher than in the lumen .(**k is Secreted**).




**2-Na+ channel blockers**
It's a **diuretic** that blocks Na channel → Na will be trapped → Water will be trapped → **diuresis happen.**

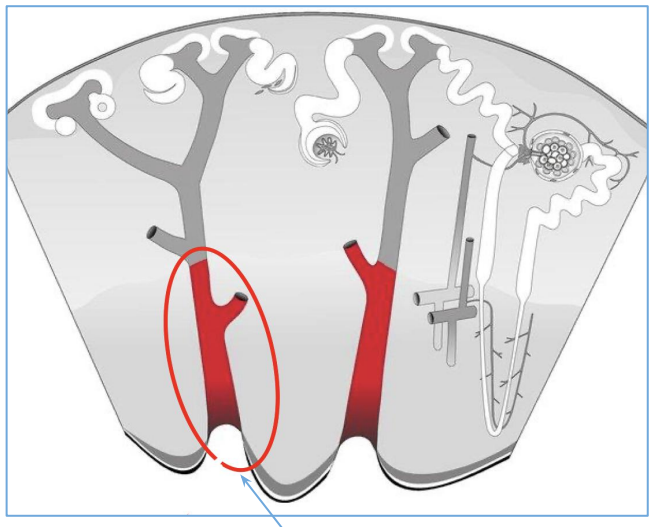
**Aldosterone**
Enhance the work of ATP (stimulate ATPase) so → more Na out and more K in.
-conc. of Na inside the cells will drop further. -conc. of K will increase more. and this will cause:
-Na to be Reabsorbed **more**.
-K to be excreted **more**.

**Aldosterone antagonists e.g. Spironolactone**

we have **two** classes of Diuretic here:

**1-Potassium-sparing diuretics**
**Block aldosterone effect** this diuretic is better than others because other diuretics **in chronic use they cause Hypokalemia** but **Spironolactone it's Potassium sparing diuretic** therefore we give it to patients with Hypokalemia.

# Medullary Collecting Duct



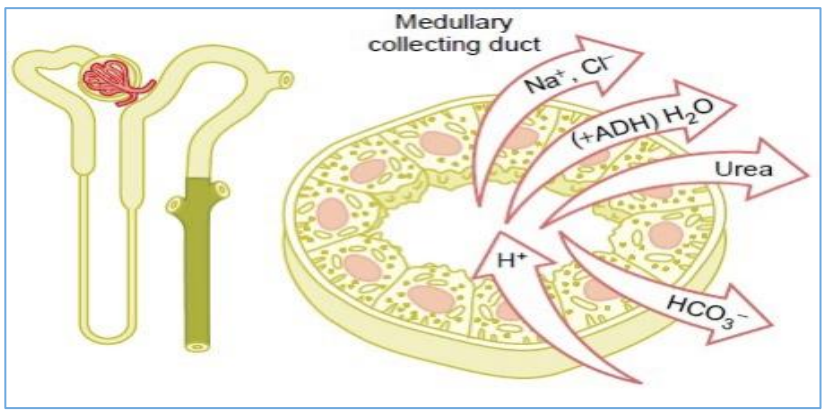
**Reabsorbs ≈ 3% of filtered Na+**

-**Reabsorbs ≈ 3% of filtered Na+.**

-Permeability to water is under ADH control.

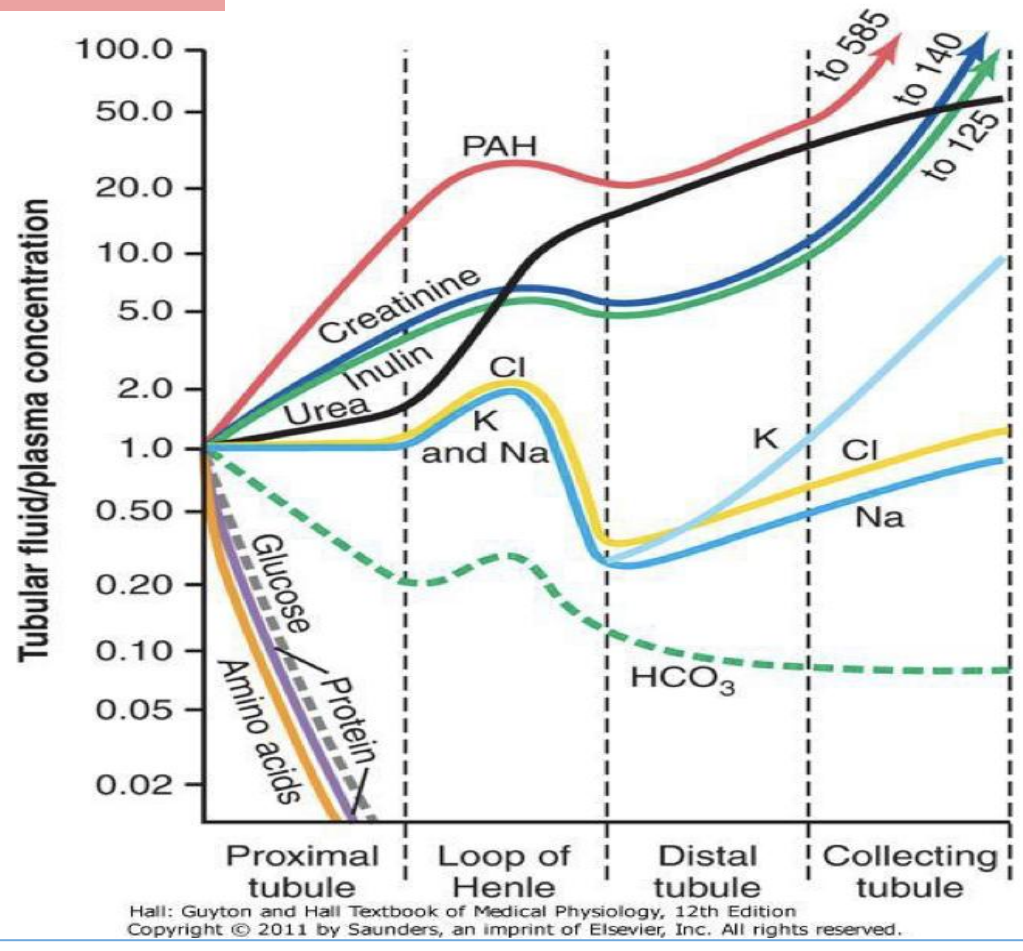
-Permeable to urea.

-Secrete H+.
from late distal tubule → cortical collecting → medullary collecting; water permeability depends on ADH:
if ADH is present → it's permeable to water
if ADH is absent → it's impermeable to water



# Summary of the Concentrations of the different Solutes in the Different Tubular Segments

**Females slides only**






# Regulation of Tubular Reabsorption

**Regulation of tubular reabsorption depends on :**

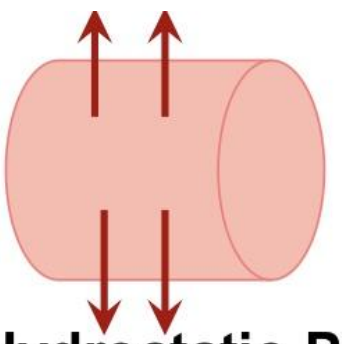
- **Physical forces that govern reabsorption.**
- **Hormonal and neural mechanisms.**

- Tubules can increase their reabsorption in response to increased tubular load → **glomerulo-tubular balance**

# What are the physical forces that govern tubular reabsorption?

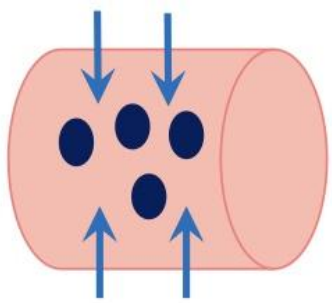
**Females slides only**

**Pushes fluid out**



**Hydrostatic Pr. (P)**

(Pressure exerted by water or fluid in the wall of the container)



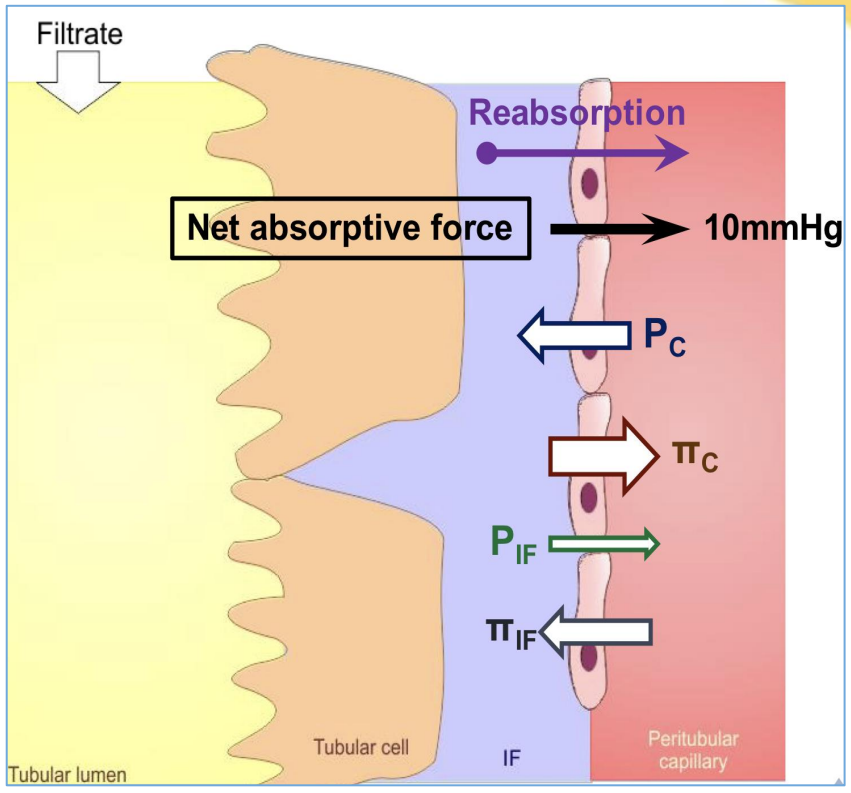
**Pulls fluid in**

**Oncotic Pr. (π**

What cause it? non diffusible proteins that get trapped and concentrated inside the vessel —> create osmotic gradient that cause fluid to move in the vessel.

# Physical Forces that Govern Tubular Reabsorption

- **$P_C$ is influenced by:**
  - ABP if it increases —> Pc will increase.
  - Aff & Eff arteriolar resistance
- **$\pi_C$ is influenced by:**
  - FF.
  - Systemic plasma colloid osmotic pr. (amount of proteins found systemically in plasma).




| Reabsorption | |
|---|---|
| **Favouring** | **Opposing** |
| $\pi_C$=32<br>$P_{IF}$=6 | $P_c$=13mmHg<br>$\pi_{IF}$=15 |
| **38** > | **28** |

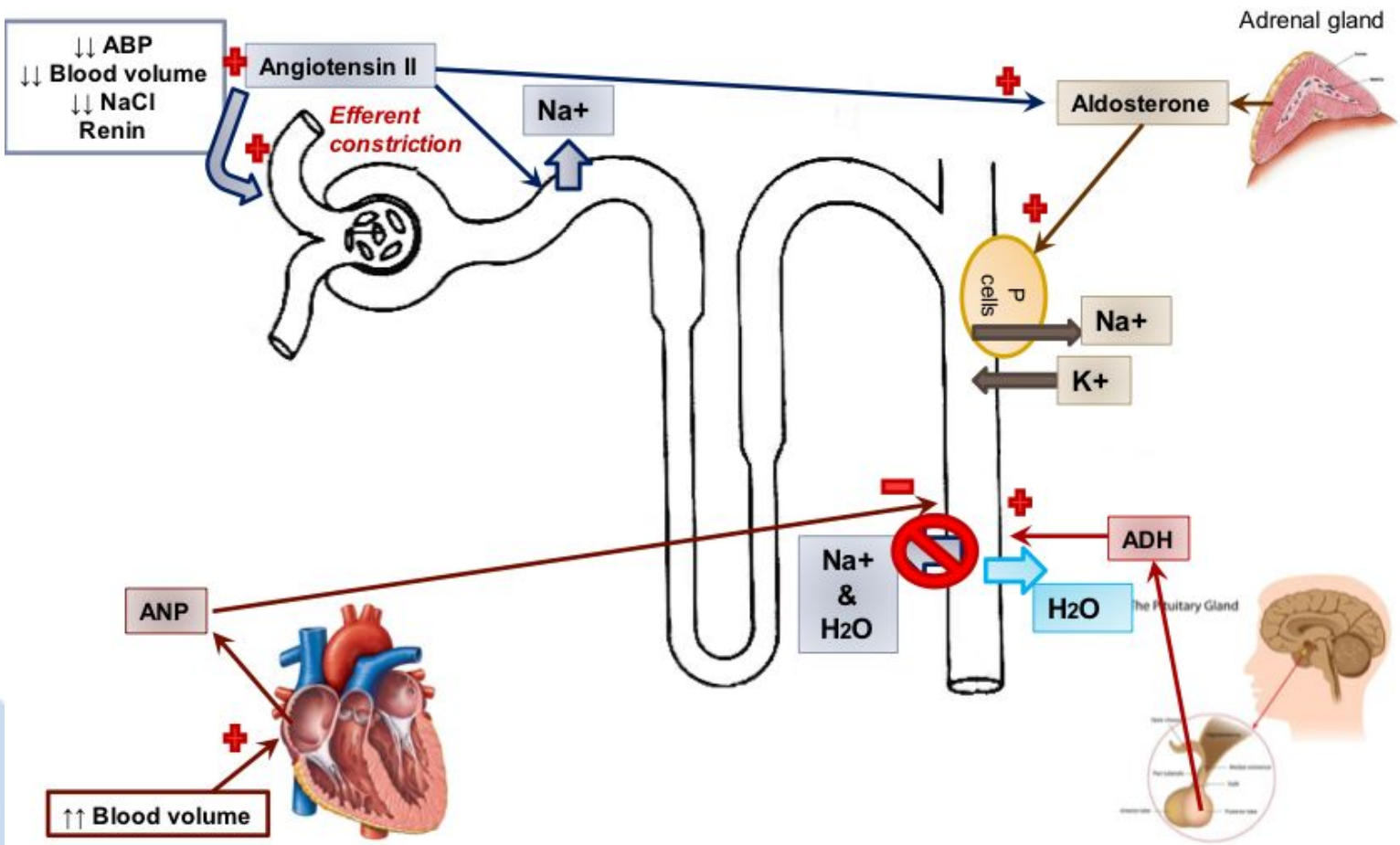
**Explanation:**

**Efferent vasoconstriction:** Efferent arteriole is located before peritubular capillary so when it constricted —> blood that flows into peritubular capillary will decrease —> GFR (amount of filtered) will Increase —> **Pc will Decrease** —> **Reabsorption will increase.**

**Afferent vasodilation:** If there is vasodilation in afferent arterioles —> Pc will increase —> More blood flows to the kidney.

**Filtration Fraction (FF):** If FF increases —> Oncotic pressure in peritubular capillary ( $\pi_C$ ) will increase why? because there is more water get filtered and proteins get concentrated in the vessel. vica versa.

# Hormonal Regulation of Tubular Reabsorption



# Regulation of Potassium

**01**

Potassium is one of the most abundant cations in the body

**02**

98% is in the ICF and 2% is in the ECF.
Regulates:

- cell volume
- acid/base status (pH)
- cell growth & division

**03**

$[K^+]_I > [K^+]_o$ → ICF 150 mEq/L > ECF 3.5-5 (4.8) mEq/L

Regulates:

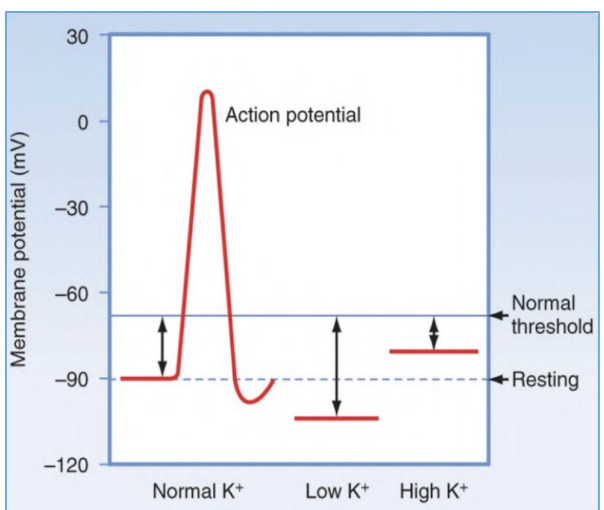
- membrane potentials in excitable cells

**04**

$K^+$ concentrations in equilibrium → Equal diffusion into and out of cell

Decrease EC K+ → increase diffusion of K+ out of cell → cells hyperpolarized

When K+ conc. decreases in the blood (hypokalemia), it becomes easier for the intracellular K+ to leak, increasing the K+ exit current, thus decreasing the threshold.




Increase EC K+ → decrease diffusion of K+ out of cell → cells partially depolarized

When K+ conc. increases in the blood (hyperkalemia), it becomes harder for the intracellular K+ to leak, decreasing the K+ exit current, thus increasing the threshold.

# Importance of Potassium

Female slides only

| Roles of intracellular $K^+$ | |
|---|---|
| **Cell-volume maintenance** | Net loss of $K^+$ → cell shrinkage<br>Net gain of $K^+$ → cell swelling |
| **Intracellular pH regulation** | Net loss of $K^+$ → cell acidosis<br>Net gain of $K^+$ → cell alkalosis |
| **Cell enzyme functions** | $K^+$ dependence of enzymes<br>(e.g. some ATPases, succinic dehydrogenase) |
| **DNA/protein synthesis, growth** | Lack of $K^+$ → reduction of protein synthesis, stunted growth |
| **Roles of transmembrane $K^+$ ratio** | |
| **Resting cell membrane potential** | Reduced $[K^+]_I > [K^+]_o$ → membrane depolarization<br>Increased $[K^+]_I > [K^+]_o$ → membrane hyperpolarization |
| **Neuromuscular activity** | **Low plasma $K^+$:** muscle weakness, muscle paralysis, intestinal distention, respiratory failure.<br>**High plasma $K^+$:** increased muscle excitability, muscle weakness (paralysis). |
| **Cardiac activity** | **Low plasma $K^+$:** slow conduction of pacemaker, arrhythmias<br>**High plasma $K^+$:** conduction disturbances, ventricular arrhythmias , and ventricular fibrillation |

# Potassium Homeostasis

## How does the body protect against the risk of hyperkalemia following each meal?

**Diet 50 and 200 mEq/day**

↓

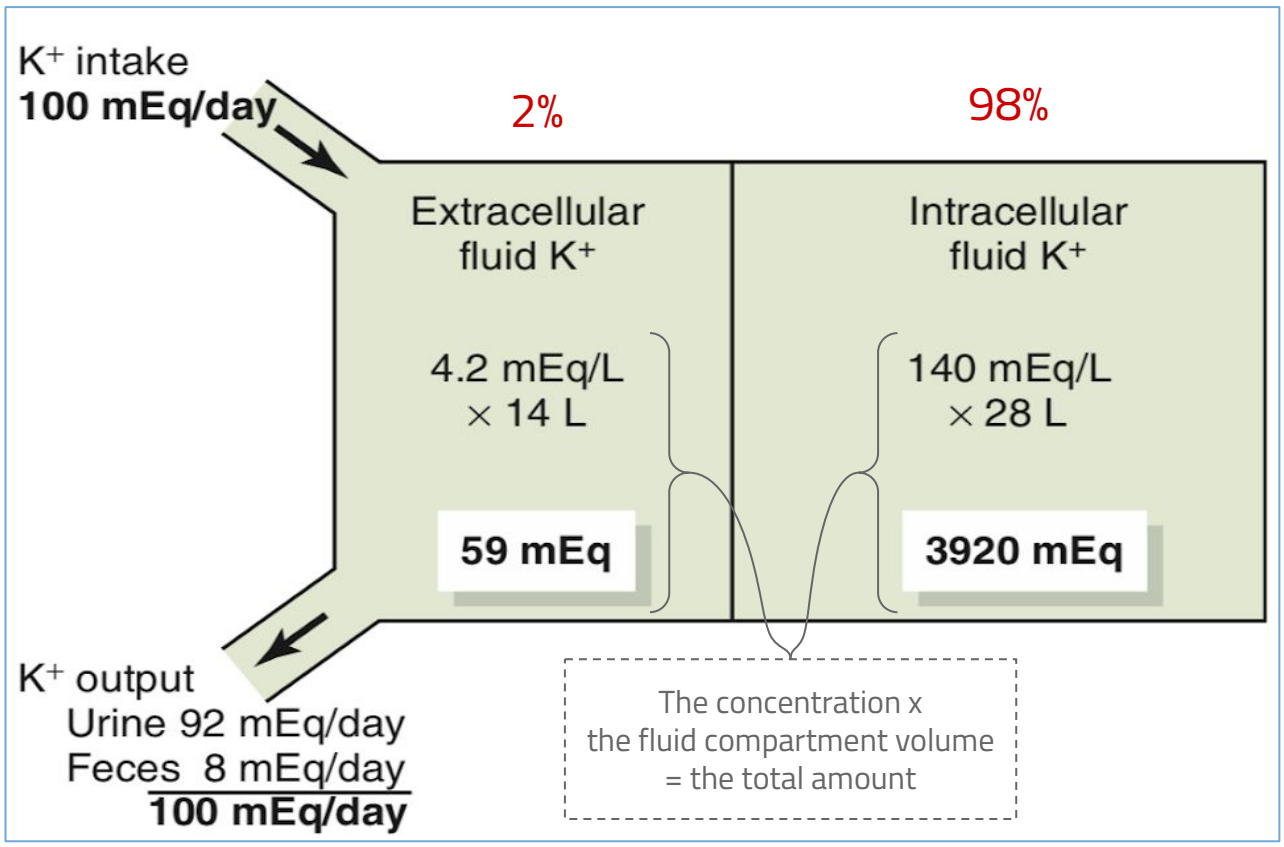
Absorption of 40 mEq of K+

↓

**↑ [K+] in ECF ≈ 2 mEq/L !**

↓

**Potassium output:**
**90-95% Renal excretion**
**5-10% GI loss**




Not only our diet contains way more potassium than what we need (50 - 200 mEq/Day), but our body also absorbs more than what we need (40 mEq/L). And that will increase the plasma potassium (by 2-2.9 mEq/L), and that can cause hyperkalemia, causing arrhythmias. But why we don't feel that? Why doesn't that happen? Yup you guessed it! *Regulation*. 90-95% of the potassium that we consume is excreted by the kidneys, and 5-10% by the GIT. So the kidneys are the major regulators for the potassium levels. But we have a problem. Because of the blood circulation, the absorbed potassium will go to the heart before it even reaches the kidneys. So there got to be a temporary first line defense mechanism. And that is called the *cellular shift.*

1st Line of defense

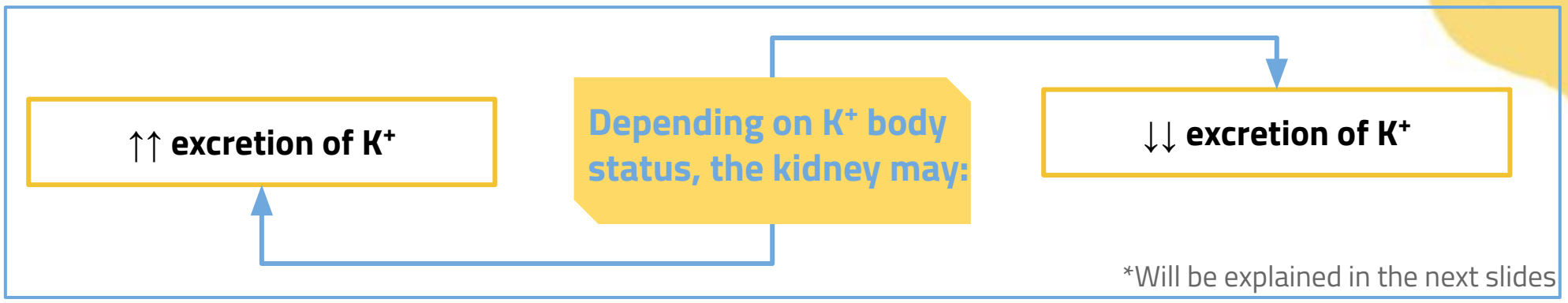
**Cellular shift**

**Body Defense Against K+ Abnormalities**

**Renal excretion**

Click here for Extra information

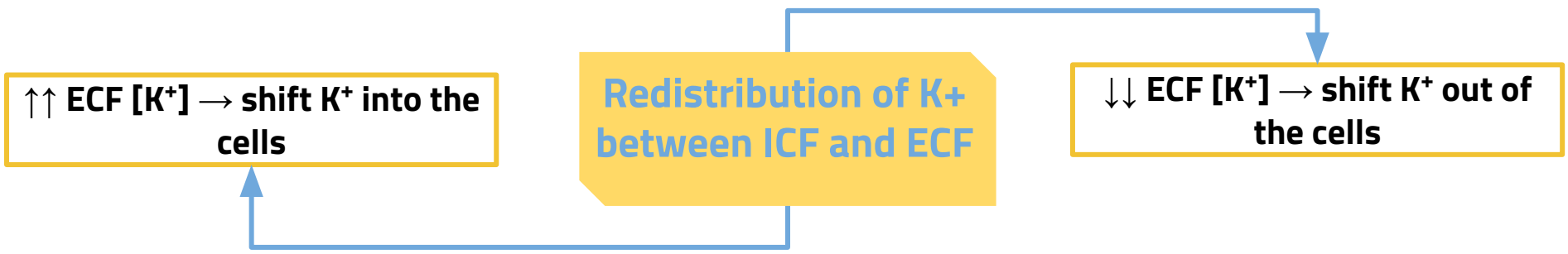
# Renal Excretion




*Will be explained in the next slides

# Cellular Shift

Cellular shift is the **first line of defense** if any disturbance happens in the potassium levels. It stores or secretes potassium until the kidneys can regulate it.




## What are the factors altering K+ distribution between both compartments?

| | Factors that shift K+ into the cells ( ↓extracellular [K+] ) | Factors that shift K+ out of the cells ( ↑extracellular [K+] ) |
|---|---|---|
| Physiological | Insulin | Insulin deficiency (Diabetes mellitus) |
| | Aldosterone | Aldosterone deficiency (Addison's disease) |
| | B- adrenergic stimulation | B-adrenergic blockade |
| Pathological | Alkalosis | Acidosis |
| | | Cell lysis |
| | | Strenuous exercise |
| | | ↑ECF osmolarity |

*Will be explained in the next slides

# Factors affecting $K^+$ distribution between ICF & ECF

In female slides found as points while in Male's slides with explanations.

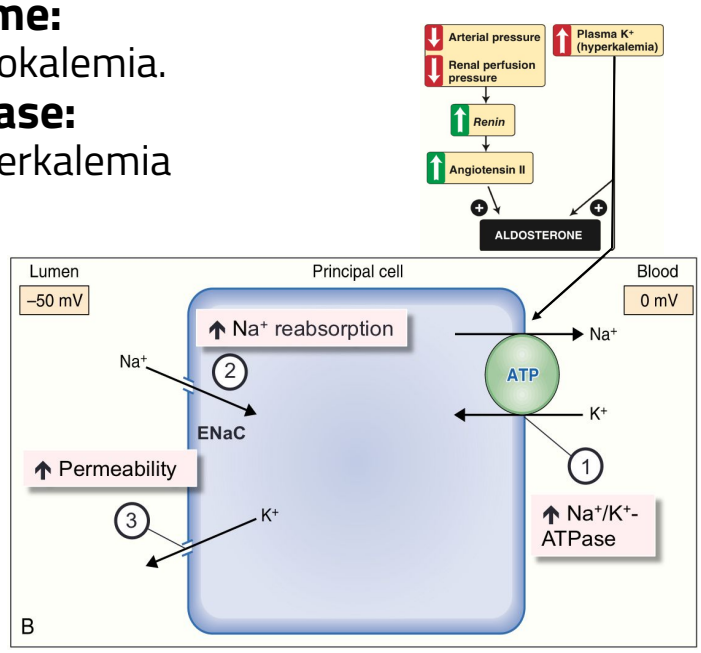
01

## Aldosterone: ↑K+ secretion by:

**1.** ↑Na/K ATPase —> Na+ reabsorption —>↑K+ secretion.
**2.** ↑Na+ reabsorption (↑ENaC) —> -ve lumen potential —>↑K+ secretion.
**3.** ↑Permeability of apical membrane —>↑K+ secretion.

❖ **Conn's syndrome:**
↑aldosterone —> Hypokalemia.

❖ **Addison's disease:**
↓aldosterone —> Hyperkalemia




02

## Insulin:

Insulin is important for increasing cell potassium uptake after a meal.
In people who have insulin deficiency owing to diabetes mellitus, the rise in plasma potassium concentration after eating a meal is much greater than normal. Injections of insulin, however, can help to correct the hyperkalemia.

03

## Epinephrine:

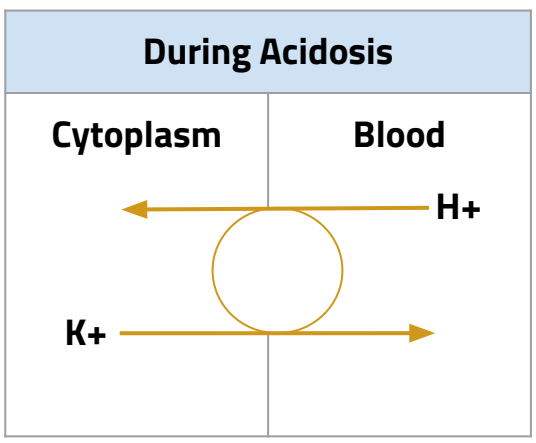
Increased secretion of catecholamines,especially epinephrine, can cause movement of potassium from the extracellular to the intracellular fluid, mainly by activation of β2-adrenergic receptors.
Conversely, treatment of hypertension with β-adrenergic receptor blockers, such as propranolol, causes potassium to move out of the cells and creates a tendency toward hyperkalemia.

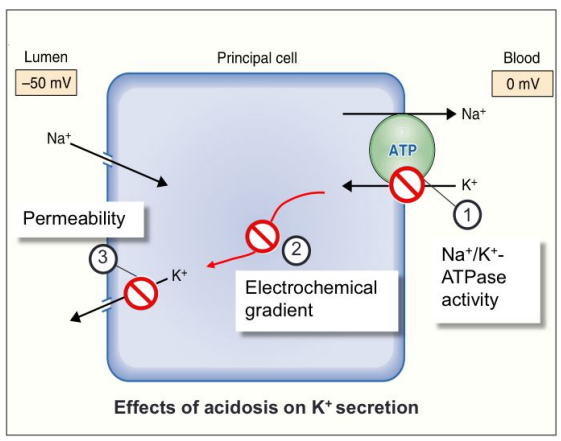
04

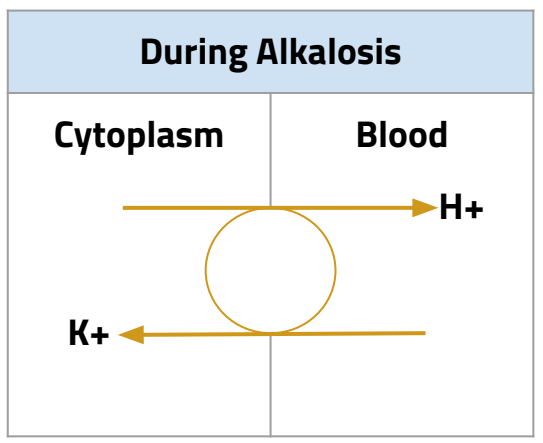
## Acid-Base disturbance:

❖ **Acidosis inhibit K+ secretion. in principal cells by Inhibiting of:**
1. Na/K ATPase —>↓K+ uptake from blood —>↓conc. gradient for K+ efflux into the lumen.
2. K+ Channels (Apical) —> ↓K+ secretion directly —> Hyperkalemia.

❖ **Alkalosis:**
has the opposite effect, promoting K+ secretion and Hypokalemia.




Click here for better understanding of some points

05

**Change in plasma osmolality:**

Increased extracellular fluid osmolarity —> K+ moves out secondary to H2O movement out of cells.

The cellular dehydration increases intracellular potassium concentration, thereby promoting diffusion of potassium out of the cells and increasing extracellular fluid potassium concentration. Decreased extracellular fluid osmolarity has the opposite effect.

06

**Cell lysis:**

As cells are destroyed, the large amounts of potassium contained in the cells are released into the extracellular compartment. This release of potassium can cause significant hyperkalemia if large amounts of tissue are destroyed, as occurs with severe muscle injury or with red blood cell lysis.

07

**Exercise:**

During prolonged exercise, potassium is released from skeletal muscle into the extracellular fluid. Usually the hyperkalemia is mild, but it may be clinically significant after heavy exercise, especially in patients treated with β-adrenergic bloc; with insulin deficiency. In rare instances, hyperkalemia after exercise may be severe enough to cause cardiac toxicity.

08

**Flow rate of tubule fluid:**

↑$K^+$ excretion

09

**Adrenaline:** via β2 receptors

β blockers increase plasma K+ level after a meal or an exercise.

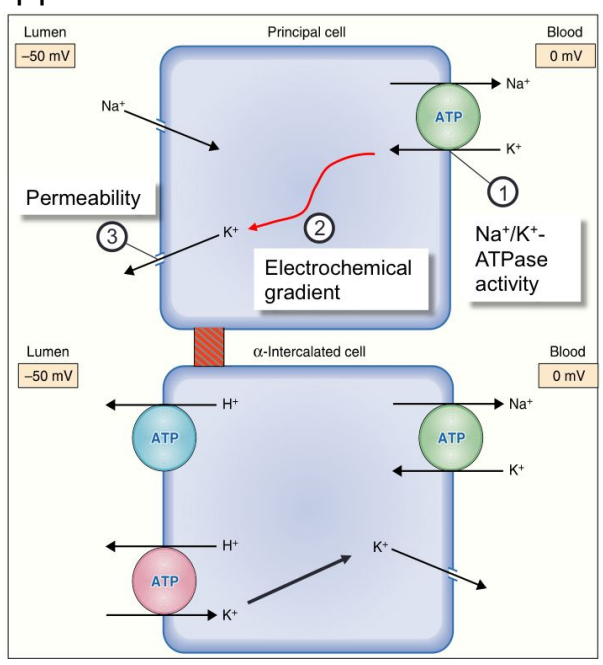
10

**Plasma potassium:**↑$K^+$ excretion

**Hyperkalemia** stimulates potassium secretion within minutes. How?

1. Stimulates Na/K- ATPase → ↑ $K^+$ uptake (basolateral) → ↑ electrochemical gradient.
2. ↑ permeability to $K^+$ (apical).
3. ↑ aldosterone →↑ secretion of $K^+$ .

**Hypokalemia** produces an opposite effect.



# Factors Regulating Potassium Secretion

## ◇ Factors that <u>stimulate</u> potassium secretion:

1. ↑↑ ECF [K+].
2. ↑↑ aldosterone.
3. ↑↑ tubular flow rate.

## ◇ Factors that <u>decrease</u> potassium secretion:

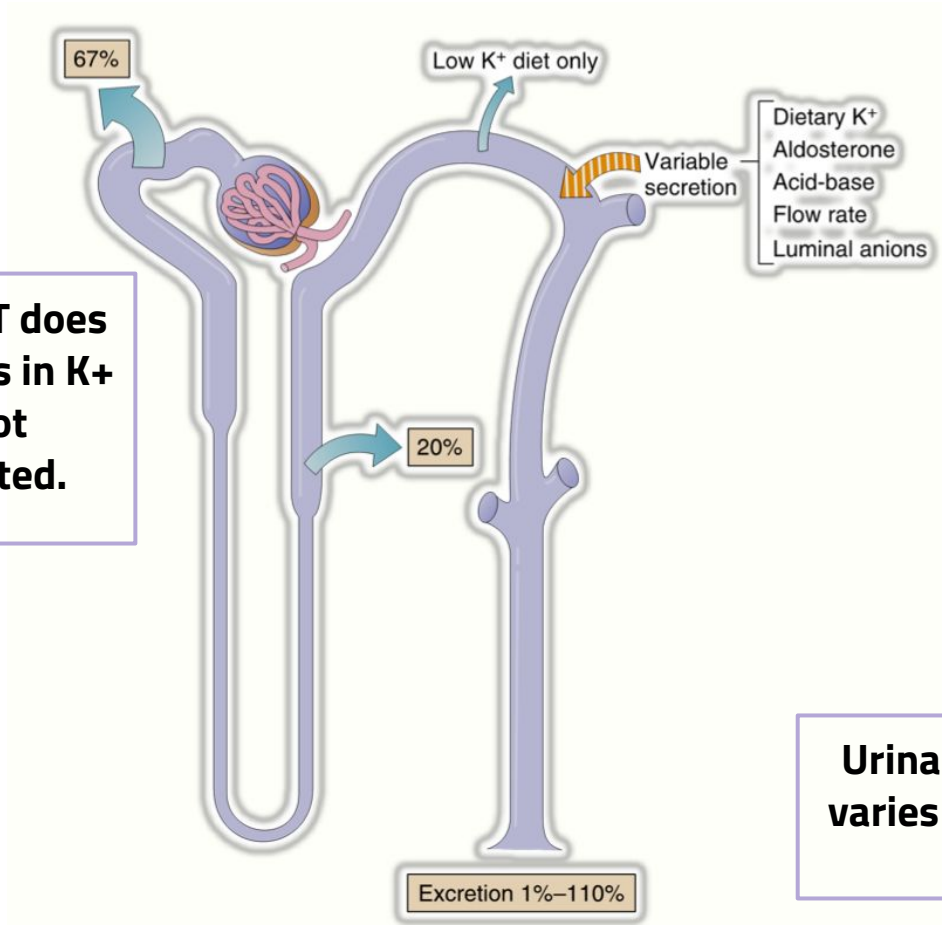
1. **Acidosis** (↑↑ [$H^+$]):
   ICF $K^+$ is exchanged for extracellular $H^+$.
2. **Alkalosis**:
   $H^+$ is exchanged for extracellular $K^+$.

My diet actually is rich in Potassium so when i eat —> K+ will increase in ECF and my body doesn't want this happen —> it needs to a defence mechanism, we have two defense mechanisms:
**1. Kidney** because it has a major role of excretion but kidney needs time to work until it works i have another mechanism called **Cellular shift**: shift the K+ in or out the cell depends on what i want.
**2. GI** (only 5%).

# Renal Potassium Excretion

**Male's slides ONLY**

**K+ reabsorption at PCT does not respond to changes in K+ balance and are not physiological regulated.**




**Urinary K+ excretion varies with dietary K+ intake**

# Major Factors and Hormones influencing K+ Excretion

**Homeostatic:** Keep K+ balance constant

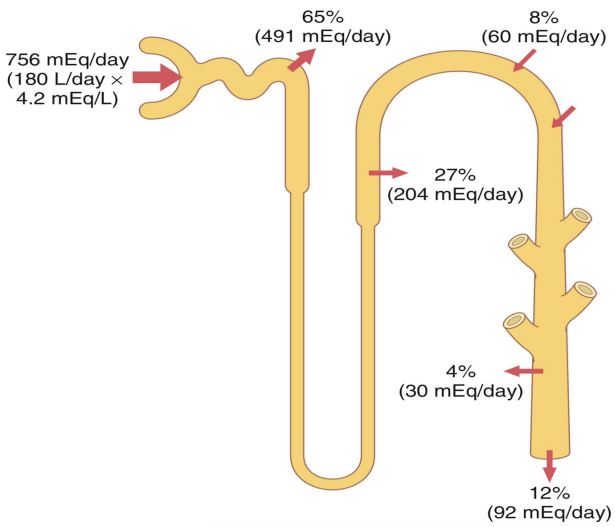
- Plasma [K+] (increase K+ excretion)
- Aldosterone (increase K+ excretion)

**Pathophysiological:** Displace K+ balance

- Flow rate of tubule fluid ( increase K+ excretion)
- Acid-base balance.

**Male's slides ONLY**

# Renal Potassium Handling




01

65 % of the filtered potassium is reabsorbed in the proximal tubule.
As a passive process.

25 to 30 % of the filtered potassium is reabsorbed in the loop of Henle, especially in the thick ascending loop

02

03

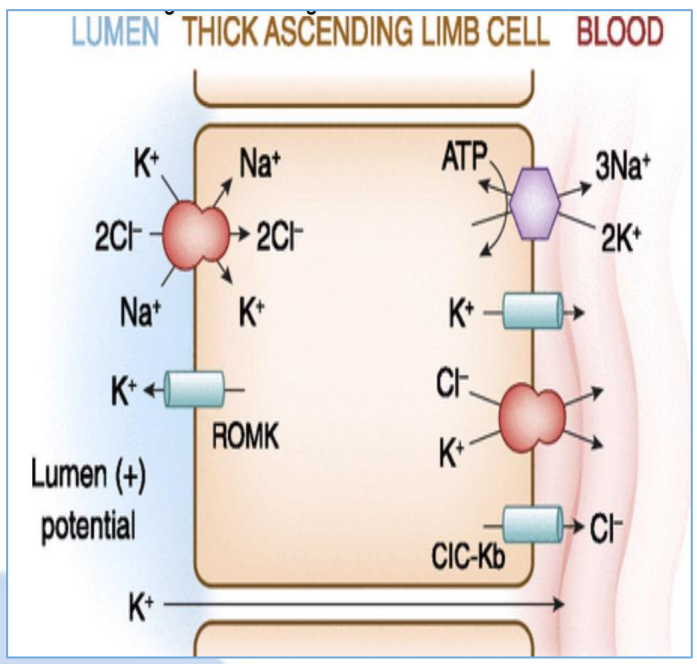
5 to 10 % enters the distal portions of the nephron

**If $K^+$ intake is low** only 1-3 % of filtered $K^+$ will be excreted.

04

05

**If $K^+$ intake is normal/high**, 10- 15 % of filtered $K^+$ will be excreted




60–70% of the filtered potassium ($K^+$) is reabsorbed in the **proximal tubule.** There are **no specific K-transporter**, reabsorption is managed with the absorption of water **(Solvent drag).**

25–35% of the filtered potassium is reabsorbed in the **loop of Henle** with the **Na-K-2Cl-cotransporter mechanism.**

Potassium handling by the **thick ascending loop** is by **secondary active transport using the apical triple transporter (NKCC2)**.

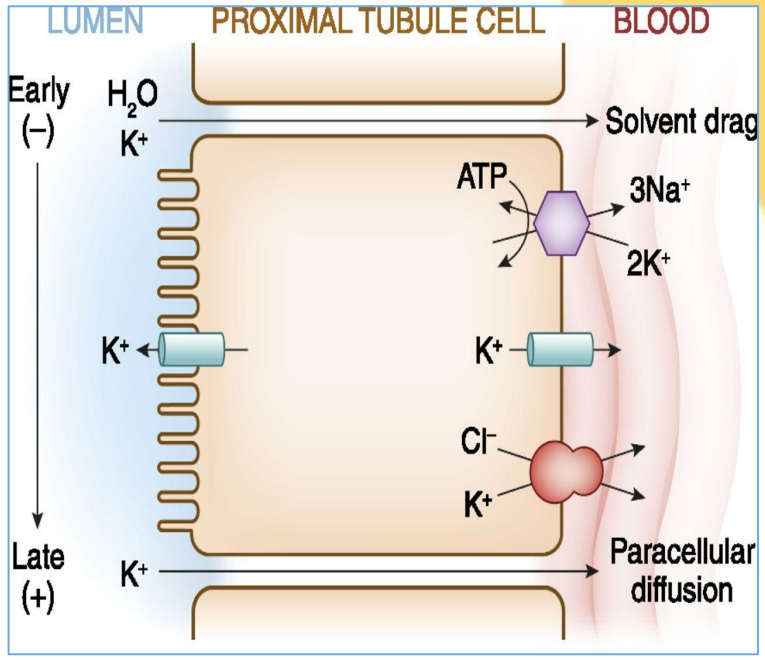
5–15% of the filtered potassium reaches the **distal nephron** Depending on the **metabolism** there are now possibilities of potassium reabsorption or excretion **(controlled by aldosterone).**

## In the PCT → K+ reabsorption is a passive process.. How?

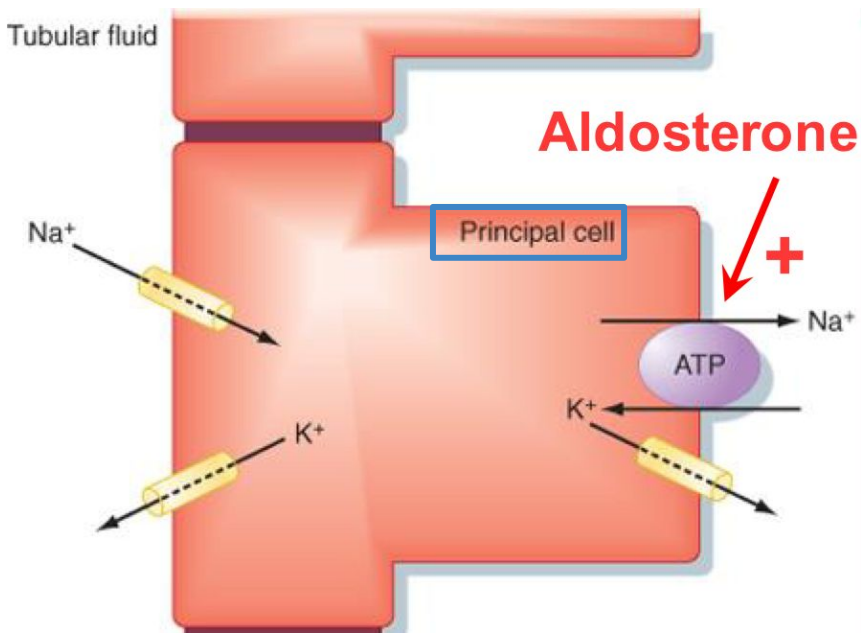
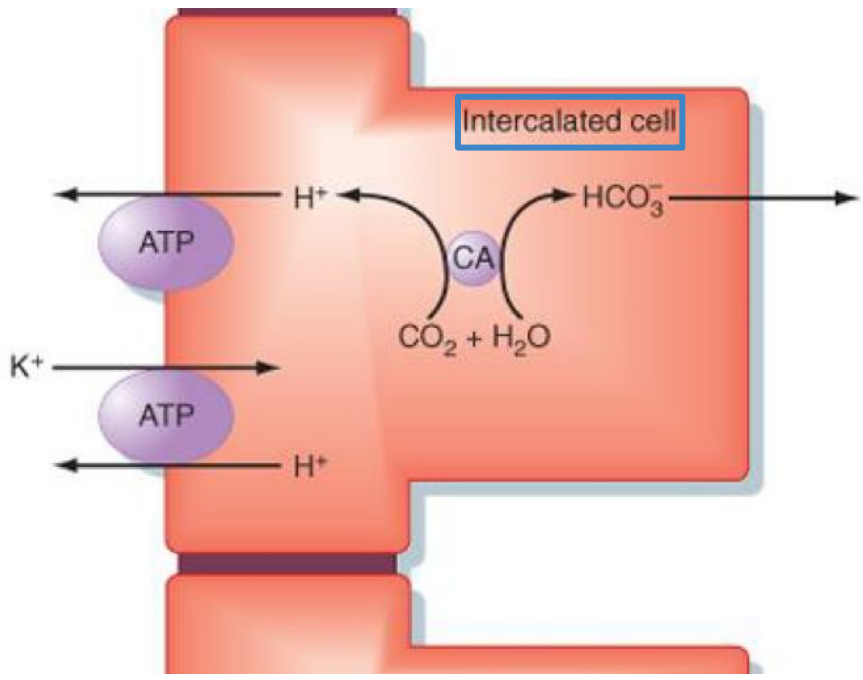
$K^+$ reabsorption is primarily passive within the PCT and roughly 67% is reabsorbed in this section of the nephron. It occurs via a paracellular mechanism and is directly proportional to water and Na+ movement. The $Na^+$-$K^+$-ATPase causes sodium to move out of the proximal tubule cell and drives potassium into the cell.

◇ Water reabsorption through the paracellular route drags K+ with it **(solvent drag).**

**Solvent drag**, also known as bulk transport, refers to solutes in the ultrafiltrate that are transported back from the renal tubule by the flow of water rather than specifically by ion pumps or other membrane transport proteins.




# Potassium Handling by the Distal Portions of the Nephron

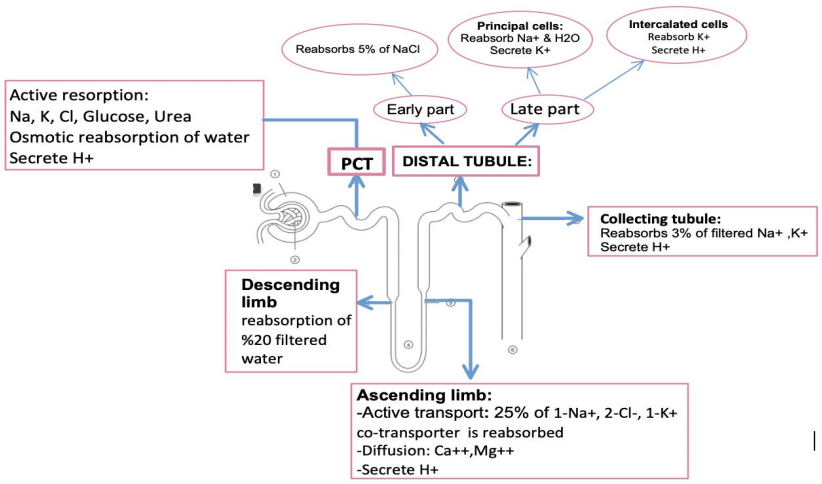
| Principal cells | | α-intercalated cells |
|---|---|---|
| Reabsorb $Na^+$ and water + secrete $K^+$ |   | Secrete $H^+$ and reabsorb $K^+$<br>How? by Primary Active transporter (H+/K+ ATPase) on the apical membrane. it will pump H+ out and K+ in.<br>(Will know the details in Acid base lecture) |
| High $K^+$ intake → ↑secretion/diffusion of $K^+$ → cells hyperpolarized |   | When it works?<br>In $K^+$ depletion → ↑ reabsorption of $K^+$. |
| Low $K^+$ intake → ↓secretion/diffusion of $K^+$ → cells depolarized | | - |

# Summary

## Define tubular reabsorption and secretion.

- ***Tubular secretion* =** secretion of substances from peritubular capillary blood into tubular fluid.
  ***Tubular reabsorption* =** reabsorption of substances from the glomerular filtrate into peritubular capillary blood.

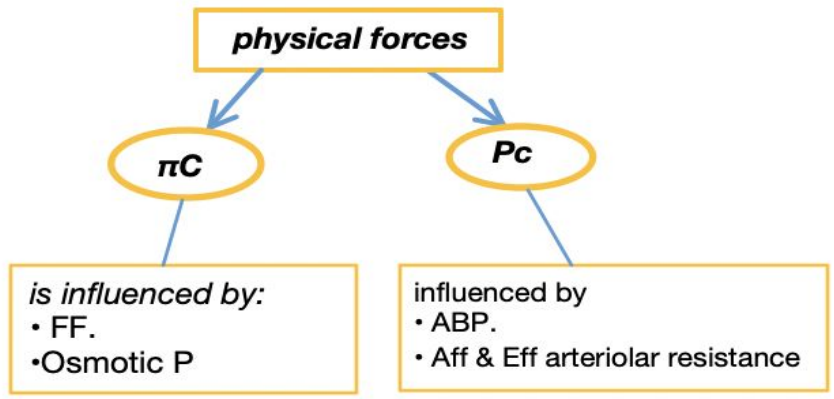
## Identify the role of each tubular segment in glomerular filtrate modification and the types of substances being transported through each.




## Describe the hormonal/physiological factors regulating tubular function at each segment.

**Hormonal and neural mechanisms.**

| | |
|---|---|
| Angiotensin II | PCT, Thick ascending LOH,DCT,CD |
| Aldosterone | CD |
| ADH | DCT,CD |
| ANP | DCT,CD |
| Parathyroid hormone | PCT, Thick ascending LOH, DCT |




## Describe tubular reabsorption of sodium and water.

- **Na+:** primary active transport, (Na+-K+ ATPase) pumps 3 Na+ out and 2K+ into the cell => in low [Na+] gradient favours passive entry of Na+ into the tubular cell across the apical membrane via transporter proteins
  **Glucose:** secondary active transport, Na+-K+ ATPase pumps 3 Na+ out and 2K+ into the cell => low [Na+] gradient favours passive entry of Na+ into the tubular cell across the apical membrane via SGLT carrying glucose with it.

## Identify and describe mechanism involved in glucose reabsorption.

- **Secondary active transport:** after Na+-K+ ATPase pumps 3 Na+ out and 2K+ into the cell => low intracellular Na+ => gradient favours passive entry of Na+ into the tubular cell across the apical membrane via SGLT carrying glucose with it.

## Identify the tubular site and describe how amino acids and urea are reabsorbed.

- **Amino acid:** reabsorbed in Proximal tubules, by secondary active mechanism.
  **Urea:** permeable in medullary collecting duct, reabsorbed by passive diffusion.

## Identify and describe the characteristics of the loop of Henle, distal convoluted tubule and collecting ducts for reabsorption and secretion.

- Answer on the next slide

# Summary

TUBULAR PROCESSING

## Proximal Tubule

- Early Proximal Tubule
  - Reabsorption: Glucose 100%, Amino acids 100%, Water 65%, Na+ 65%
  - Secretion: H+
- Late Proximal Tubule
  - Reabsorption: Cl-

## LOOP OF HENLE

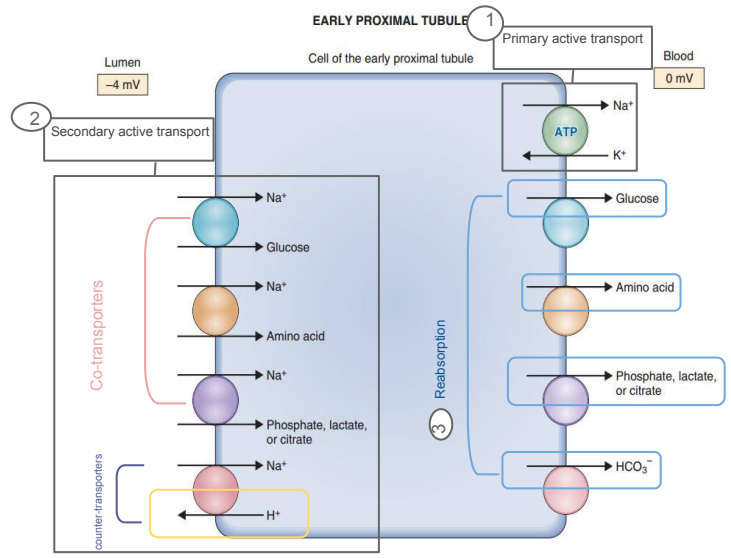
- Thin Descending limb
  - Reabsorption: Water 20%
  - Moderate permeable to: Solut
- Thick Ascending limb
  - Reabsorption: - 25% of Na+ , cl- , k+ ; - ca++ , Mg++
  - Impermeable to: Water

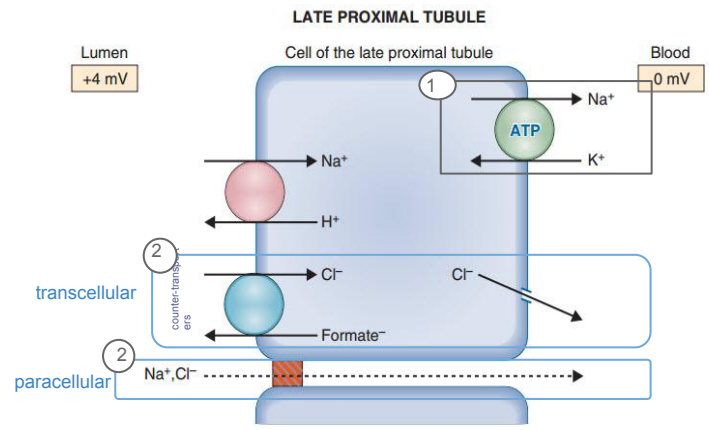
## Distal tubule

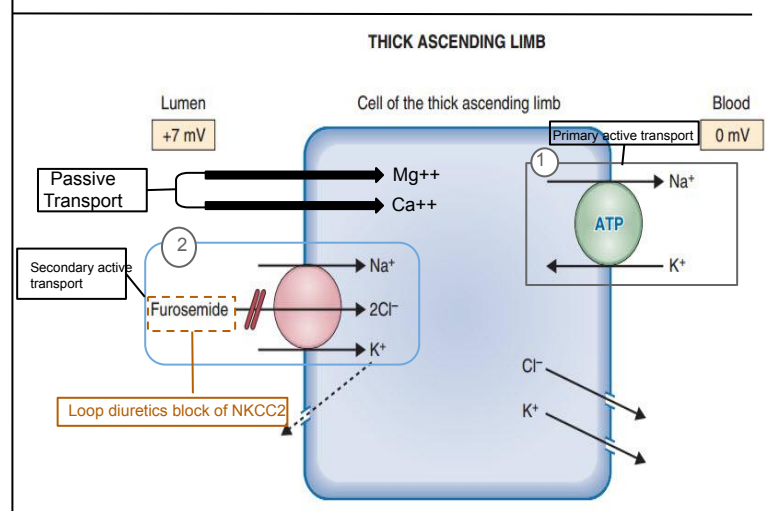
- Early distal tubule
  - Reabsorption: - Nacl 5%
  - Impermeable to: - urea
- Late distal tubule
  - Impermeable to: - urea
  - Consist of:
    - Principal cells
      - Reabsorption: Na+ Water
      - Secretion: K+
    - Intercalated Cells Type A
      - Reabsorption: K+
      - Secretion: H+
- cortical collecting tubule

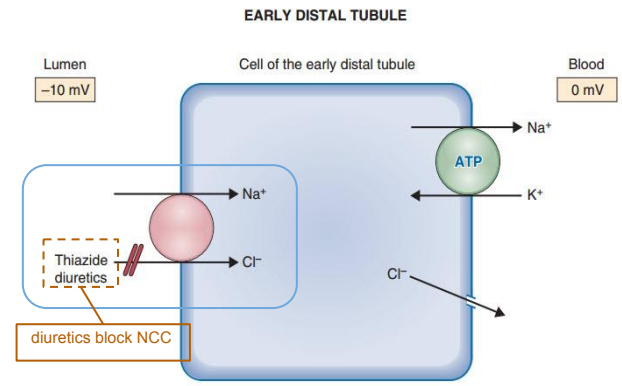
## Distal tubule

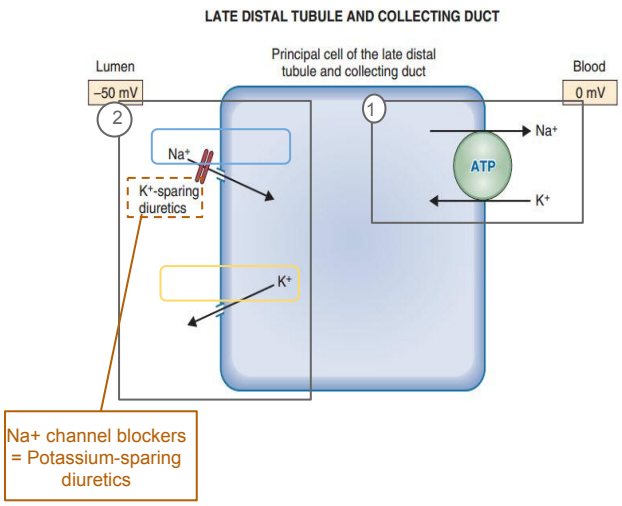
- Medullary Collecting Duct
  - Reabsorption: -Na 3% ; -water under ADH control ; -urea
  - Secretion: H+



# Summary

- **Describe the role of ADH in the reabsorption of water.**
- **Antidiuretic hormone** binds to receptors on cells in the collecting ducts of the kidney and promotes reabsorption of water back into the circulation. ... These channels transport solute-free water through tubular cells and back into blood, leading to a decrease in plasma osmolarity and an increase osmolarity of urine.
- **Identify the site and describe the influence of aldosterone on reabsorption of Na+.**
- **Aldosterone** is a hormone produced in the outer section (cortex) of the adrenal glands, which sit above the kidneys. It plays a central role in the regulation of blood pressure mainly by acting on organs such as the kidney and the colon to increase the amount of salt (sodium) reabsorbed into the bloodstream and to increase the amount of potassium excreted in the urine. Aldosterone also causes water to be reabsorbed along with sodium; this increases blood volume and therefore blood pressure.
- **List and explain the factors that control aldosterone and ADH release.**
- **Low blood volume** stimulate secretion of **ADH**, to reabsorb water into the bloodstream to maintain the blood volume .
- **Low blood pressure** stimulate secretion of **aldosterone**, to reabsorb water and sodium into the bloodstream to maintain the  blood volume therefore the blood pressure.
- **Increased potassium intake** stimulates secretion of **aldosterone**, which increases cell potassium uptake.
- **Identify and describe the juxtamedullary apparatus and its role in checking the filtrate.**
- **The juxtamedullary apparatus** is a specialized structure formed by the distal convoluted tubule and the glomerular afferent arteriole. Its **main function** is to regulate blood pressure and the filtration rate of the glomerulus.

# MCQ & SAQ

**Q1:** Which of the following transportes Na through passive diffusion

**A.** Collecting tubules
**B.** Collecting duct
**C.** Thin ascending limb
**D.** Thick ascending limb

**Q2:** Which of the following tubules never reabsorbs water

**A.** Proximal convoluted tubule
**B.** Descending loop of Henle
**C.** Ascending limb
**D.** Collecting tubules

**Q3:** $H^+$ ion is secreted in the distal tubules by which mechanism?

**A.** $K^+$ / $H^+$ antiport
**B.** $H^+$ ATPase
**C.** Na / $H^+$ cotransport
**D.** None of the above

**Q4:** When 3 Na / 2 K pumped in Basolateral membrane, the net result is:

**A.** High intracellular Na concentration
**B.** Low Extracellular Na concentration
**C.** Increase osmolarity in the basolateral space
**D.** Decrease osmolarity in the basolateral space

**Q5:** The amount of water, solute reabsorption and secretion depends on :

**A.** Body's needs
**B.** Weight
**C.** Age
**D.** Secrete $H^+$

**Q6:** When plasma glucose reaches "glucose renal threshold" , what is the glucose level that will appear in urine ?

**A.** 250 mg/dl
**B.** 375 mg/dl
**C.** 200 mg/dl
**D.** 180 mg/dl

answer key:
1: C
2: C
3 B:
4: C
5: A
6: D

**1- List the factors that stimulate potassium secretion.**

**2- How does the proximal tubule secrete hydrogen ions?**

**3- How does the proximal tubule reabsorb Na?**

**4- What are the Physiological factors affecting $K^+$ distribution between ICF & ECF?**

**A1:** ↑↑ ECF [K+]., ↑↑ aldosterone., ↑↑ tubular flow rate.

**A2:** Basolateral (Na+-K+ ATPase) pumps 3 Na+ out and 2K+ into the cell, resulting in low [Na+]i. This gradient favours passive entry of Na+ into the tubular cell across the apical membrane via NHE in exchange with H+.

**A3:** Basolateral (Na+-K+ ATPase) pumps 3 Na+ out and 2K+ into the cell, Resulting in low [Na+]i.
This gradient Transcellular favours passive entry of Na+ into the l tubular cell across the apical membrane via transporter proteins

**A4:** Aldosterone, Insulin, Epinephrine, Acid-Base disturbance, Change in plasma osmolality, Cell lysis, Exercise.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