

# TUBULAR PROCESSING OF FILTRATE

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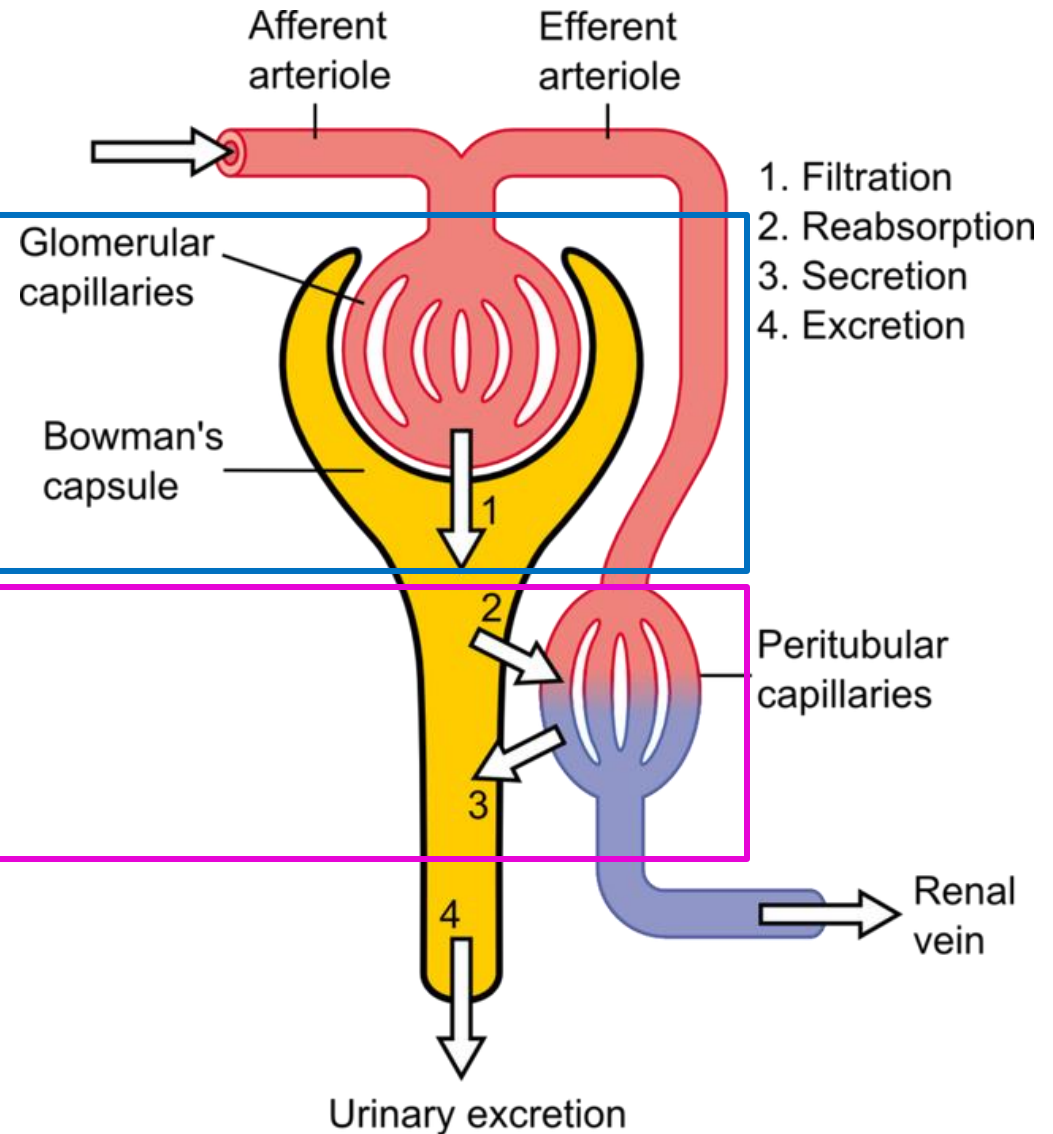
# Objectives

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- 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  $\text{Na}^+$ .
- List and explain the factors that control aldosterone and ADH release
- Identify and describe the juxtamedullary apparatus and its role in checking the filtrate.

*What did we discuss so far?*

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

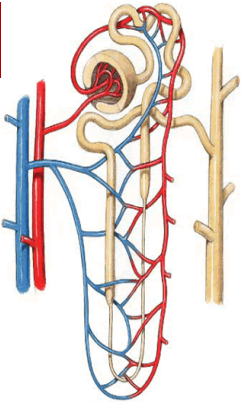


1. Filtration
2. Reabsorption
3. Secretion
4. Excretion

$$\text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion}$$

# Contents

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- The mechanisms of tubular transport through the different parts of the nephron.
- Tubular reabsorption and tubular secretion.
- Regulation of tubular processing.

# Introduction

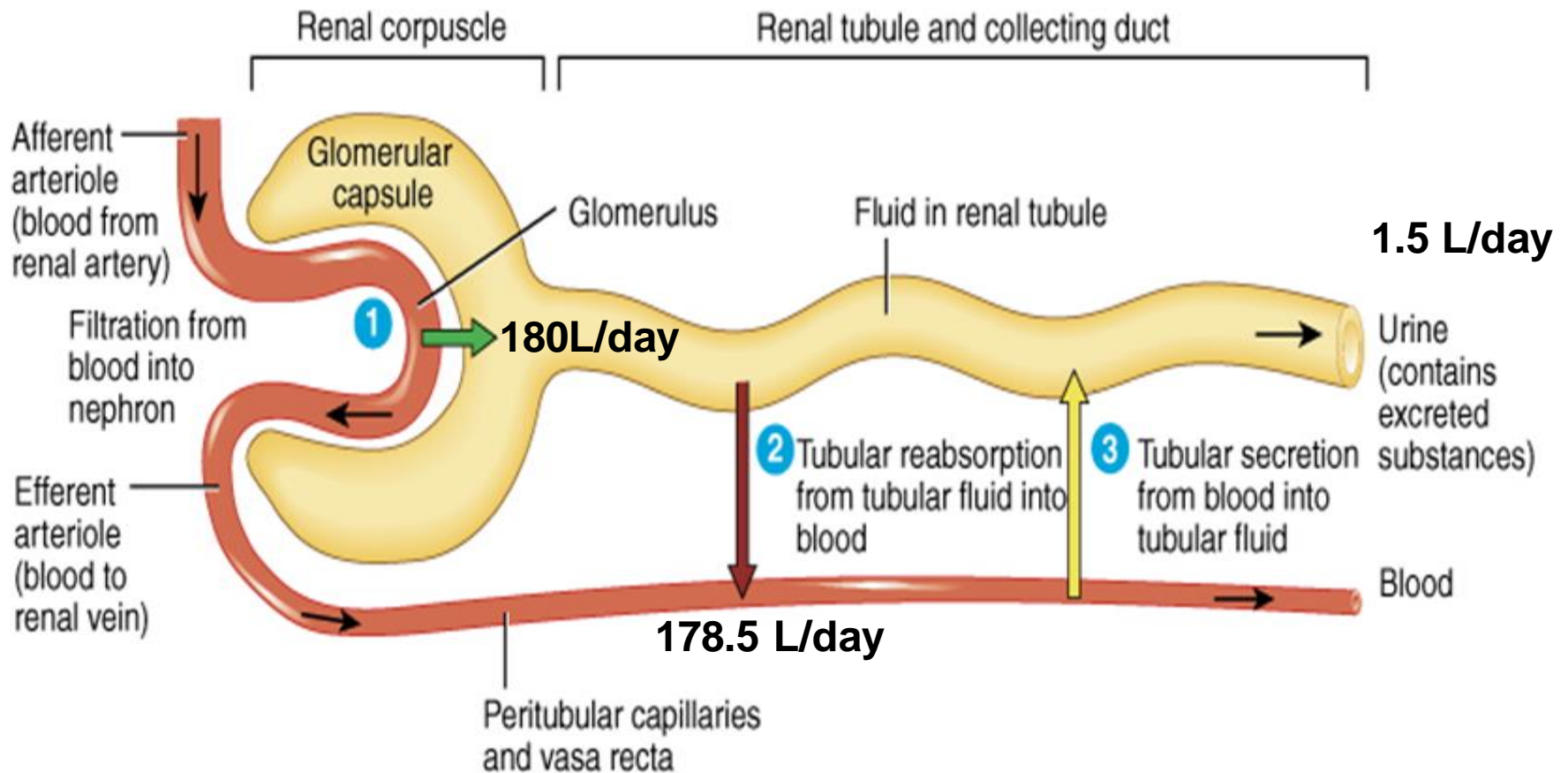
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*From the previous lecture,*

- 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?***

# Tubular Reabsorption

- **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

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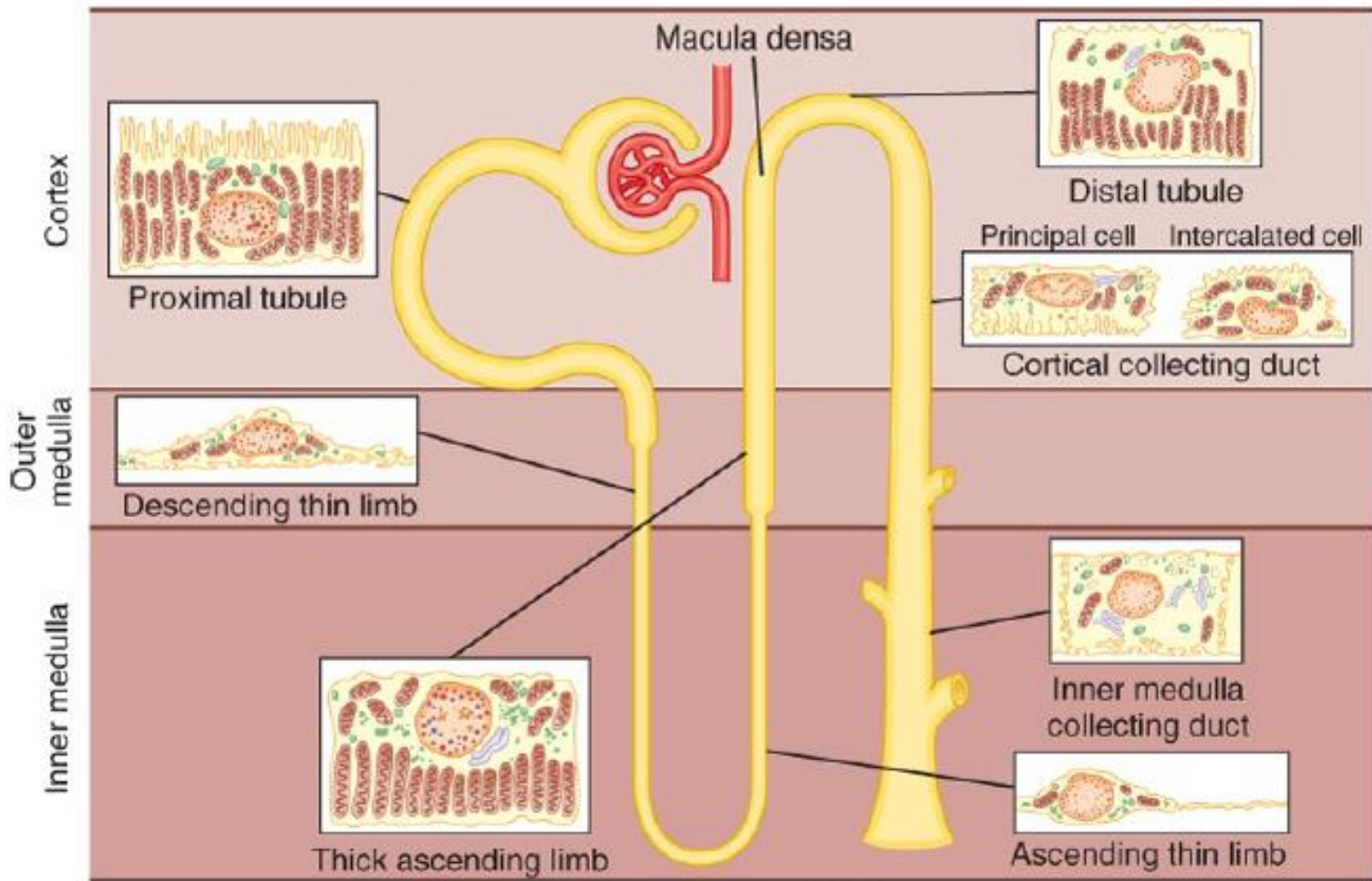
- After glomerular filtration the ultrafiltrate gets modified as it passes through the nephron tubule before it is finally excreted.
- **Tubular processing includes:**
  - ***Tubular reabsorption*** = reabsorption of substances from the glomerular filtrate into peritubular capillary blood.
  - ***Tubular secretion*** = secretion of substances from peritubular capillary blood into tubular fluid

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



Koepfen & Stanton: Berne and Levy Physiology, 6th Edition.

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Figure 32-3 Diagram of a nephron, including the cellular ultra-structure.

# **TUBULAR REABSORPTION & SECRETION**

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# How Does the Nephron Reabsorb Substances

- **Reabsorption is a 2 step process:**

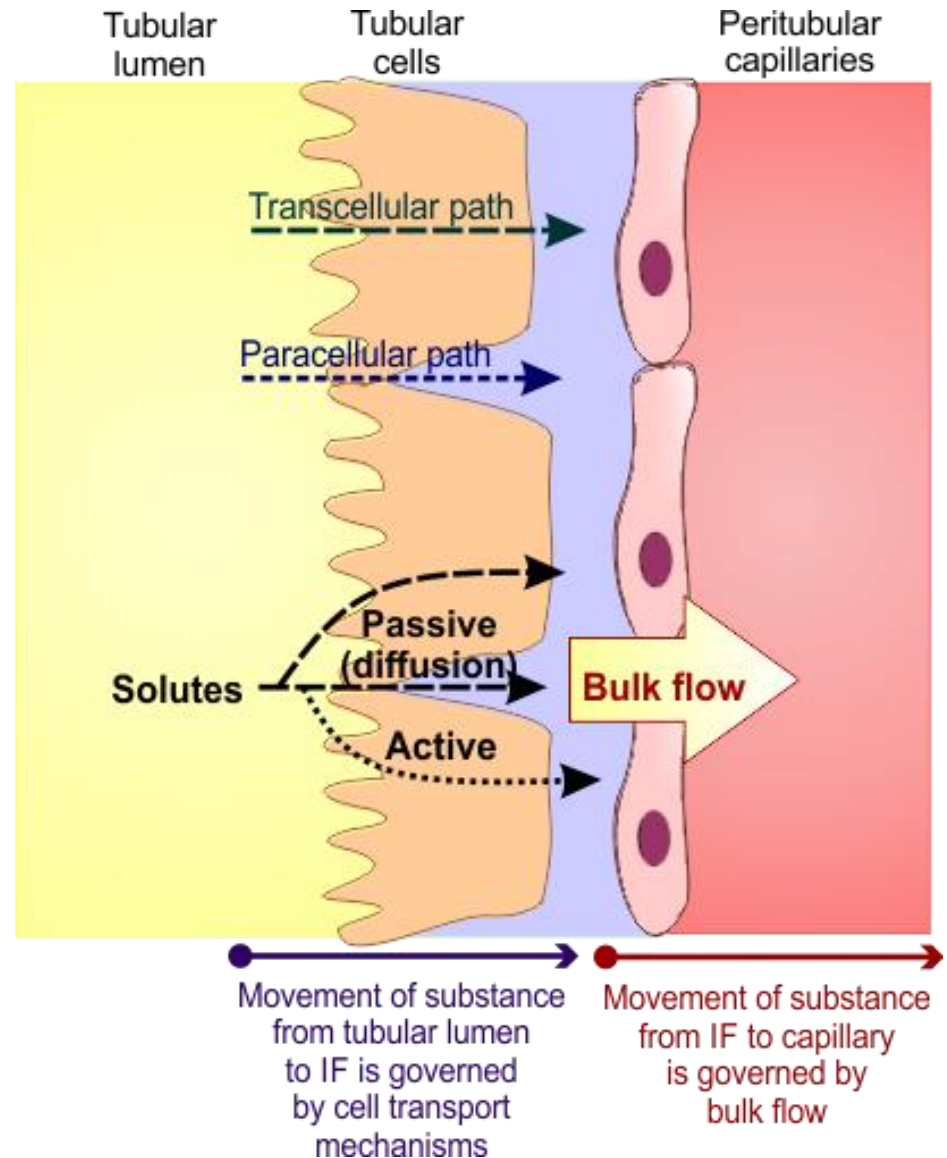
1. Transport of substances from tubular lumen to IF.
2. Transport from IF to blood.

- From tubular lumen to IF;

- Transport involves **active** & **passive** mechanisms.
- Occur through **paracellular** and/or **transcellular** routes.

- From IF to blood:

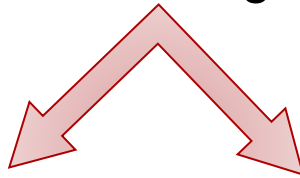
- By ultrafiltration (bulk flow).



# 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<sup>+</sup>-K<sup>+</sup> ATPase.

### Secondary active

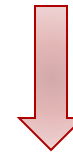
Indirectly coupled to energy source.

Carrier protein.

e.g. Glucose & a.a.

## Passive Transport

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



### Passive diffusion Osmosis

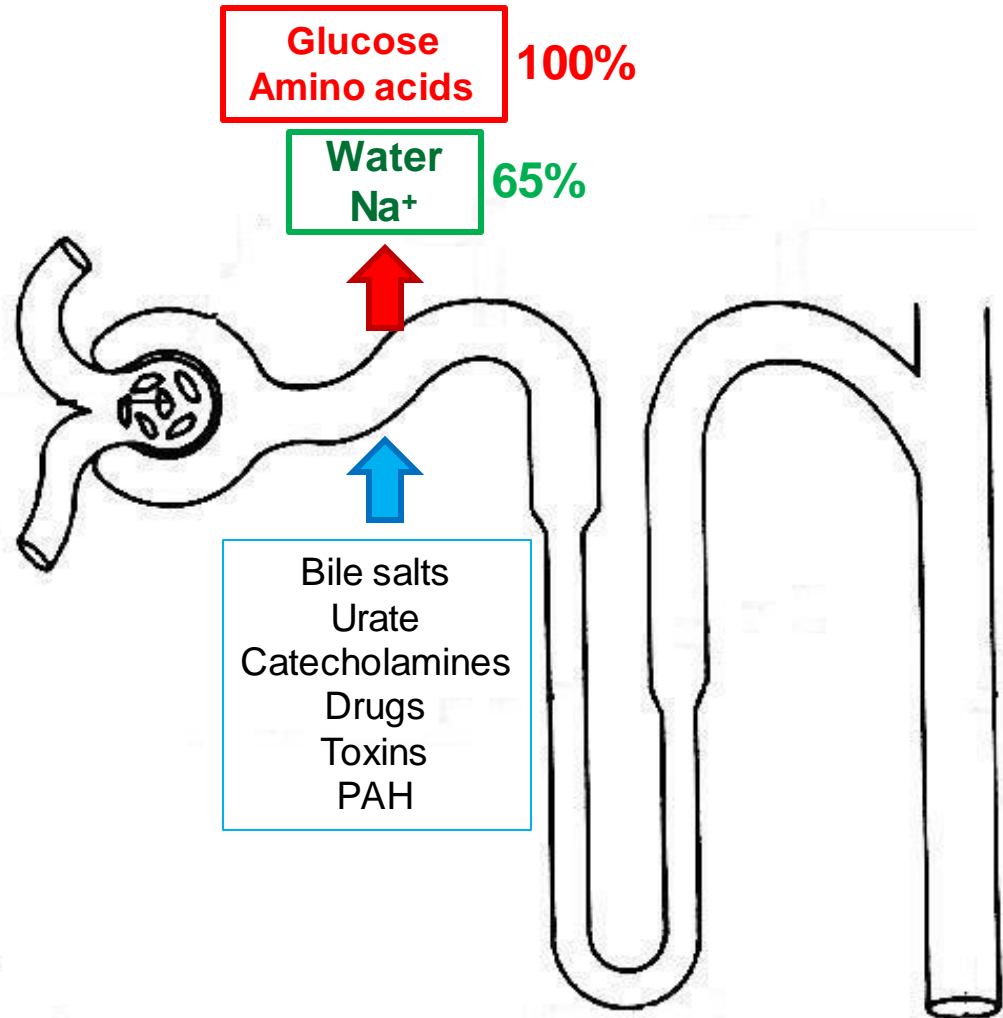
Water  
Solute like Cl<sup>-</sup>  
Urea

# **TUBULAR REABSORPTION IN EACH PART OF THE NEPHRON**

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# Proximal Tubule

- Most of the reabsorption occurs in the PCT.. **Why?**
  - Highly metabolic cells.
  - Extensive brush border.
  - Lots of mitochondria.



nephron

# How Does the Proximal Tubule Reabsorb Sodium ( $\text{Na}^+$ )?

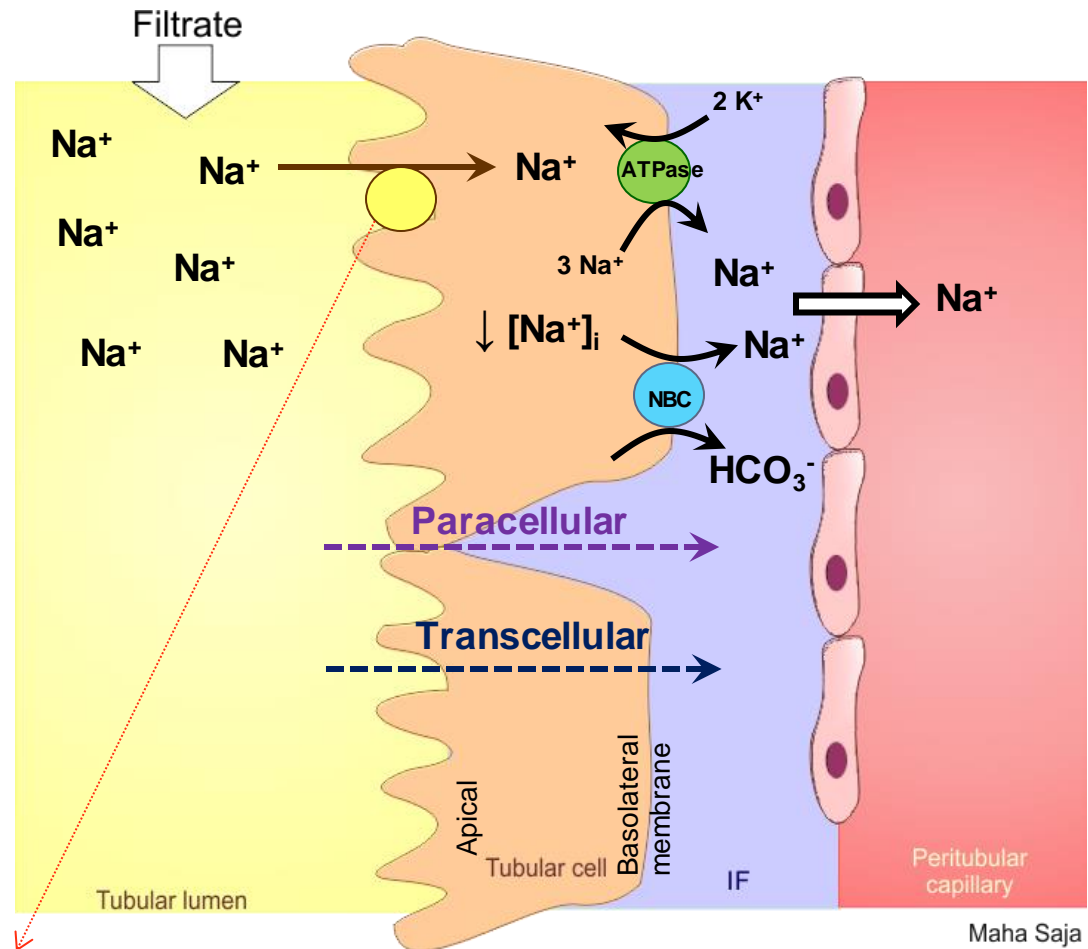
Basolateral  $\text{Na}^+\text{-K}^+$   
ATPase pumps  
 $3\text{Na}^+$  out and  $2\text{K}^+$   
into the cell



Results in low  $[\text{Na}^+]_i$



This gradient  
favours passive  
entry of  $\text{Na}^+$  into the  
tubular cell across  
the apical  
membrane via  
transporter proteins



Maha Saja

**Many types of transporter proteins;**

- Co-transporters.
- Exchangers (counter-transporters).

# How Does the Proximal Tubule Reabsorb Glucose?

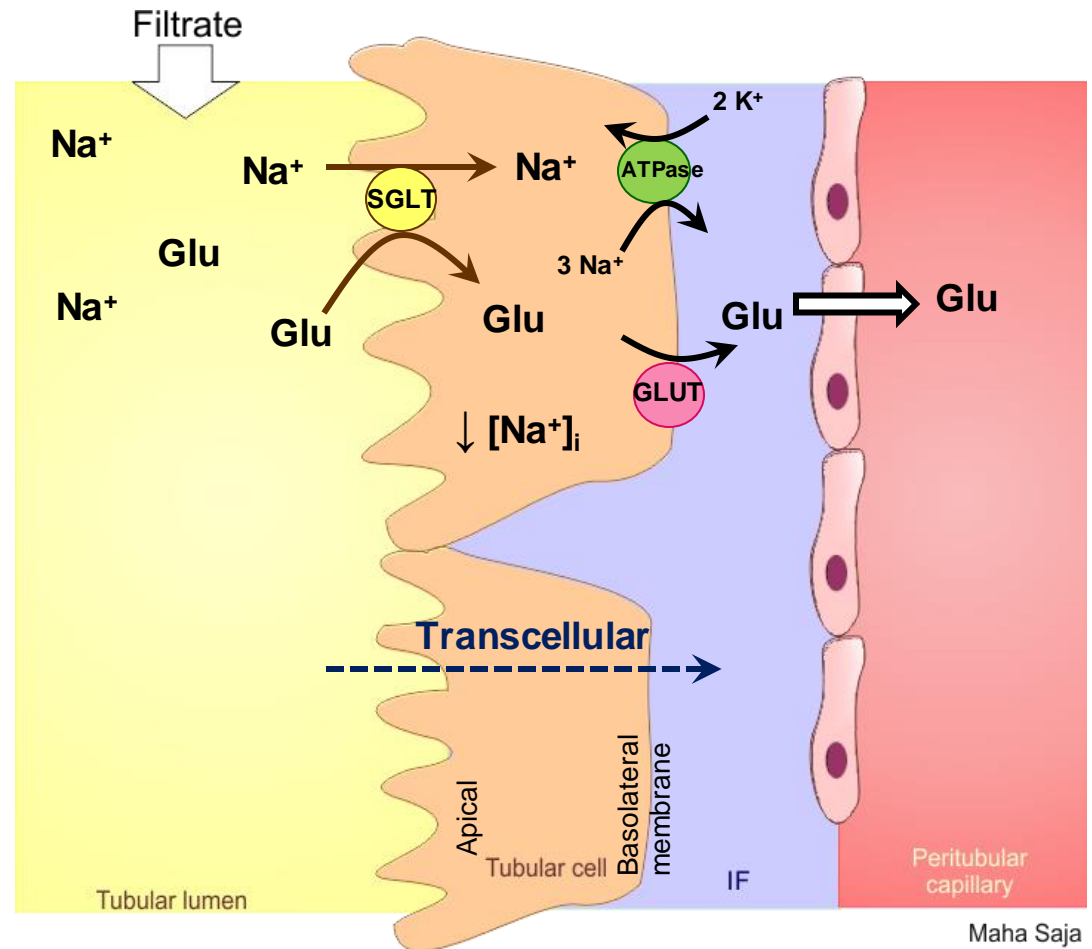
Basolateral  $\text{Na}^+\text{-K}^+$  ATPase pumps  $3\text{Na}^+$  out and  $2\text{K}^+$  into the cell



Results in low  $[\text{Na}^+]_i$



This gradient favours passive entry of  $\text{Na}^+$  into the tubular cell across the apical membrane via SGLT carrying glucose with it.

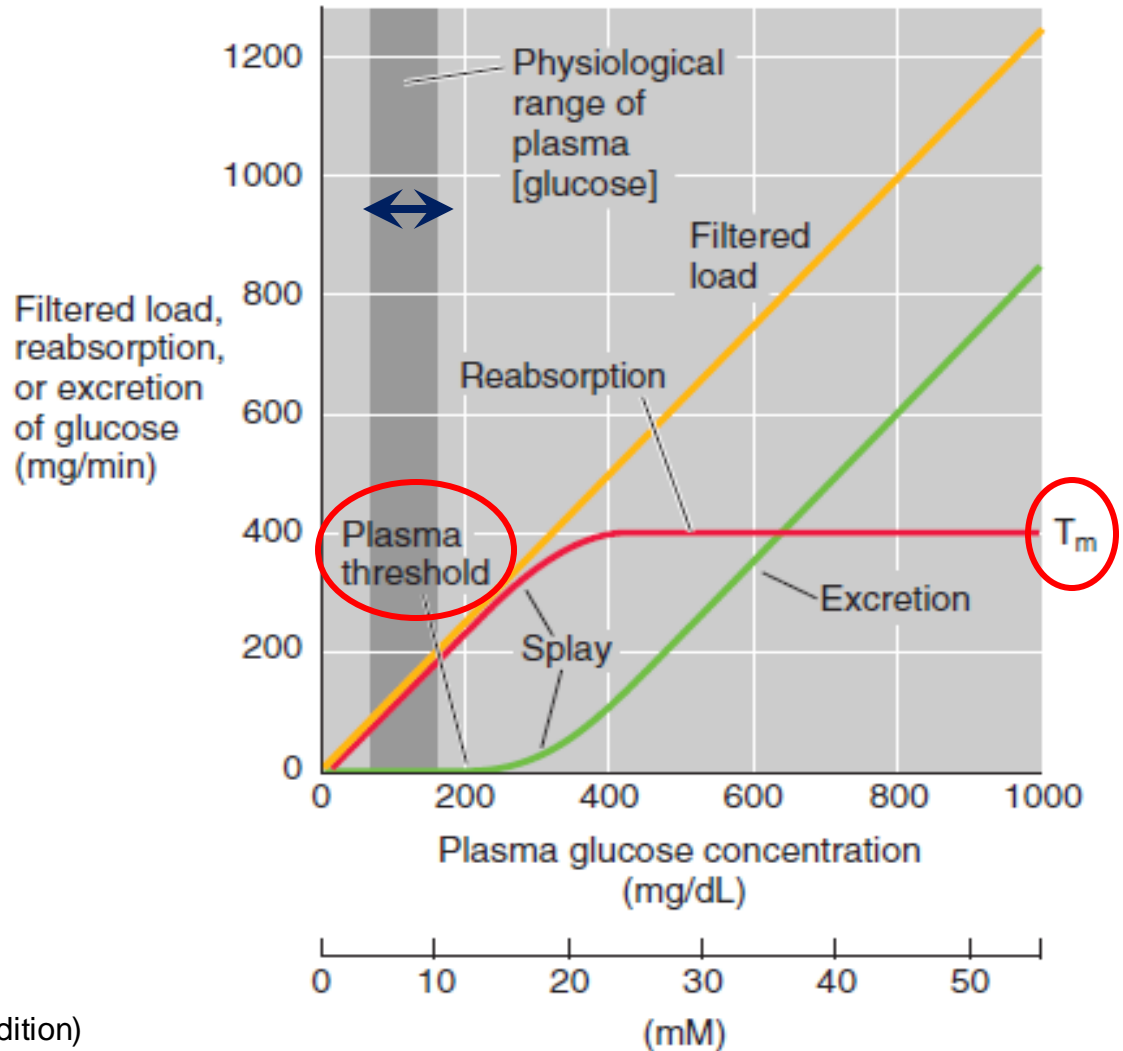


Amino acids and other substances are absorbed in a similar way using transporters specific for the substrate being transported



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

A GLUCOSE TITRATION CURVE



*What are the features of this glucose titration curve?*

*What is the plasma threshold of glucose?*

*What is meant by transport maximum ( $T_m$ )? Why does it occur?*

*What happens if blood glucose level increased to 400mg/dl?*

# Summary of PT Transport Mechanisms

Basolateral  $\text{Na}^+\text{-K}^+$  ATPase pumps  $3\text{Na}^+$  out and  $2\text{K}^+$  into the cell

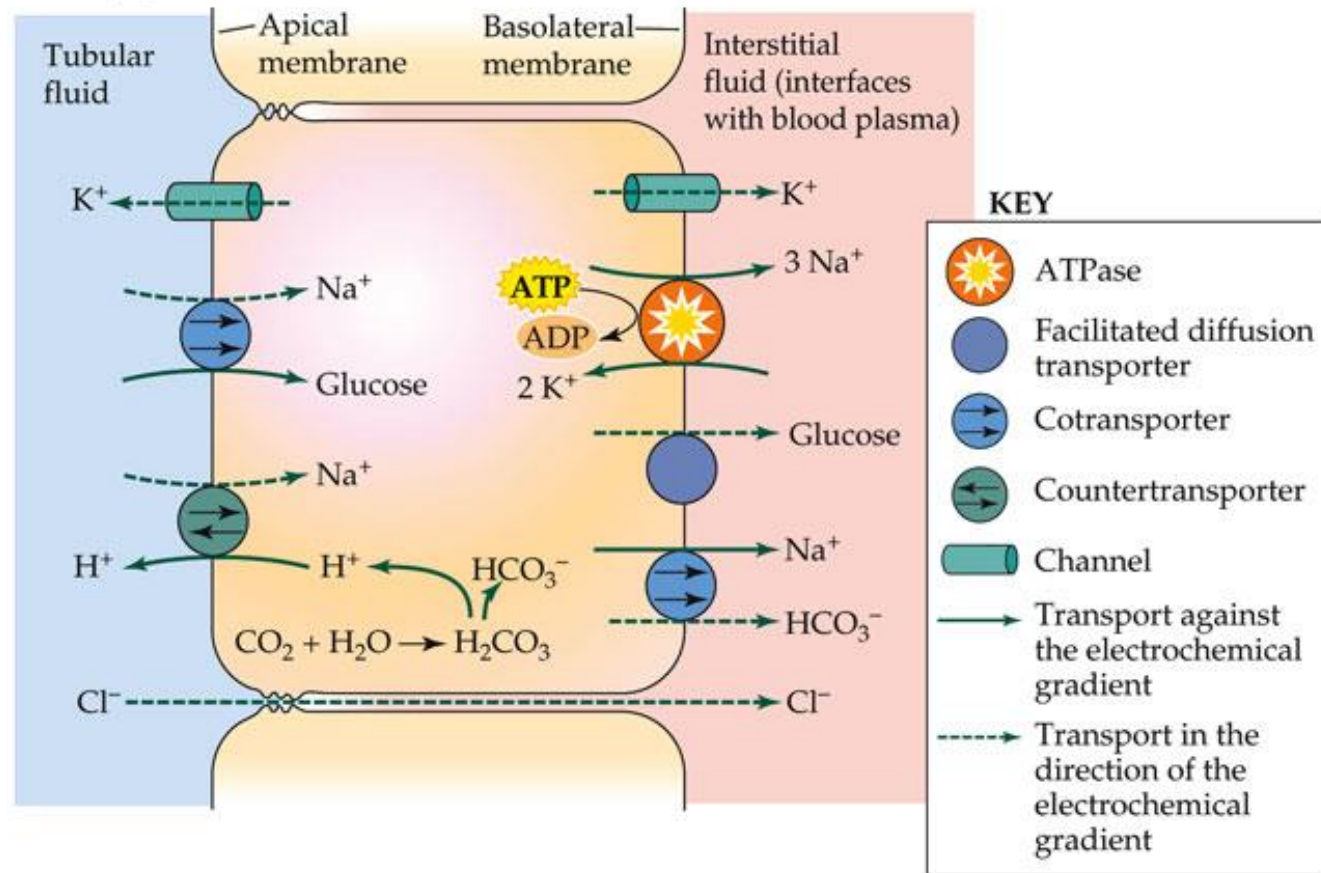


Results in low  $[\text{Na}^+]_i$



This gradient favours  $\text{Na}^+$  entry across the apical membrane via transporter proteins

(a) Early proximal convoluted tubule

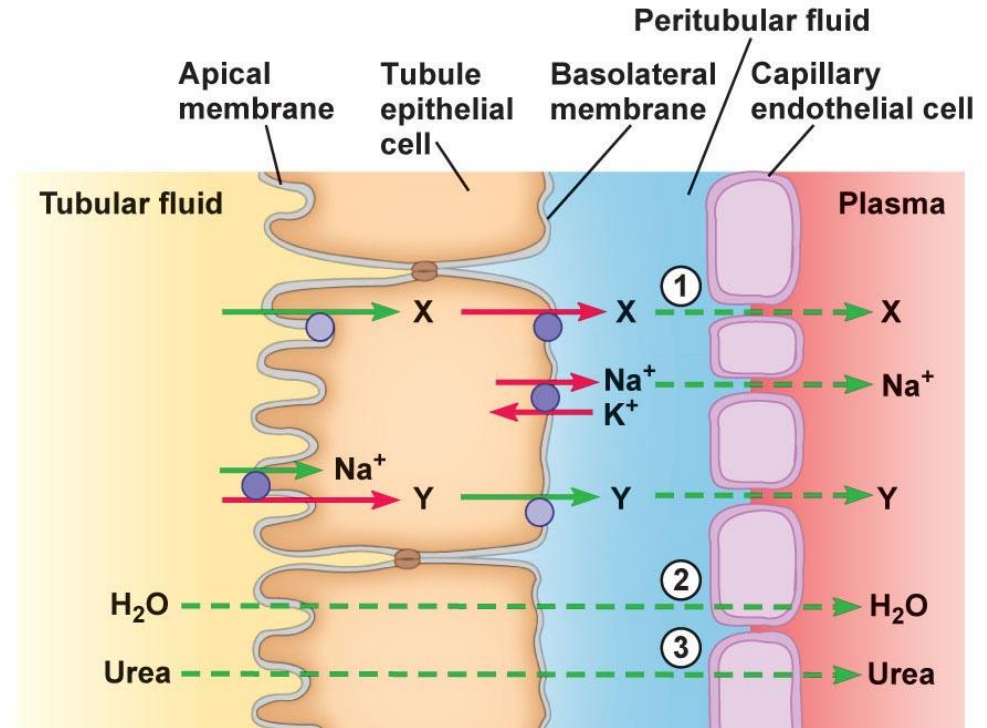


# How Does the Proximal Tubule Reabsorb Water?

**Water is reabsorbed through both;**

- Paracellular path
- Transcellular path

Transcellular movement is facilitated by the presence of **water channels (AQP1)**



## Steps for water and urea reabsorption:

- ① Solutes (Na<sup>+</sup>, X, Y) are actively reabsorbed, increasing the osmolarity of peritubular fluid and plasma.
- ② Water is reabsorbed by osmosis.
- ③ Urea (permeating solute) is reabsorbed passively.

# Differences in Sodium Reabsorption Along PT

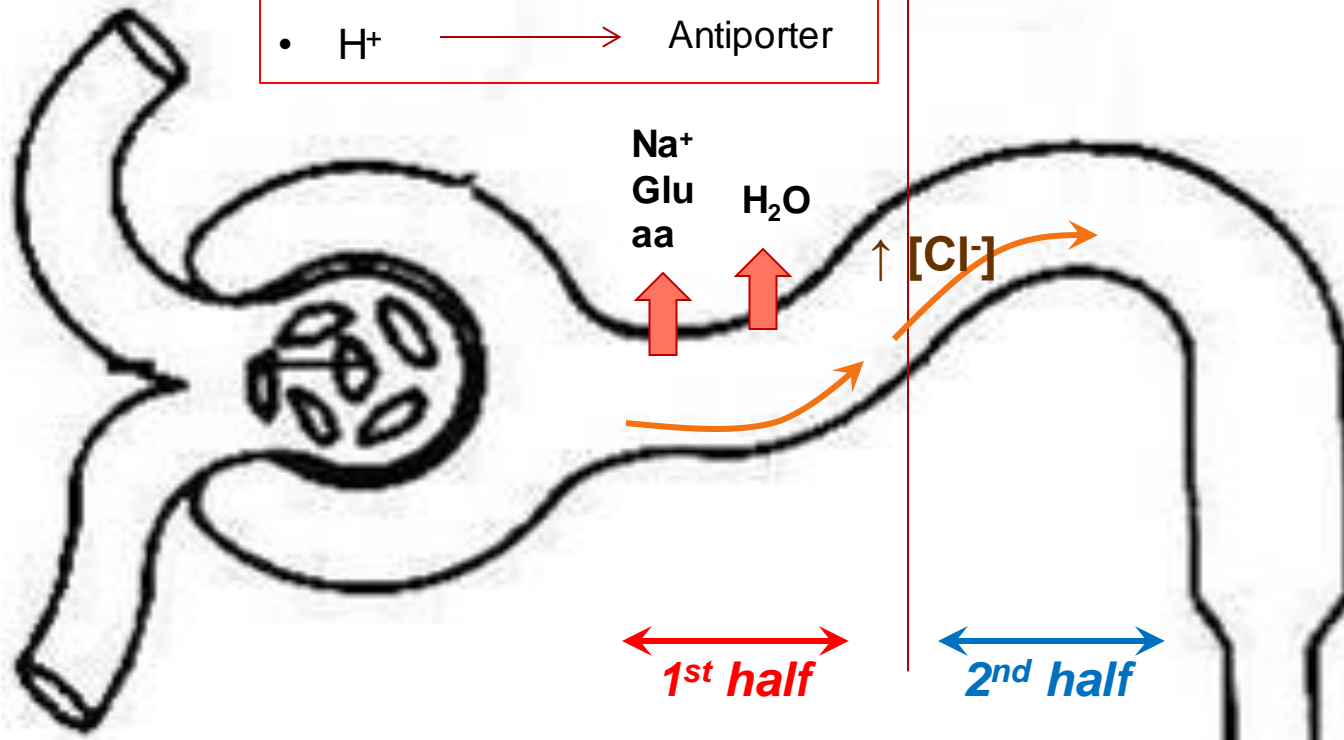
***Na<sup>+</sup> reabsorption is coupled to that of;***

- Glucose.
  - Amino acids.
  - Lactate.
  - Phosphate
- } Symporters
- H<sup>+</sup> → Antiporter

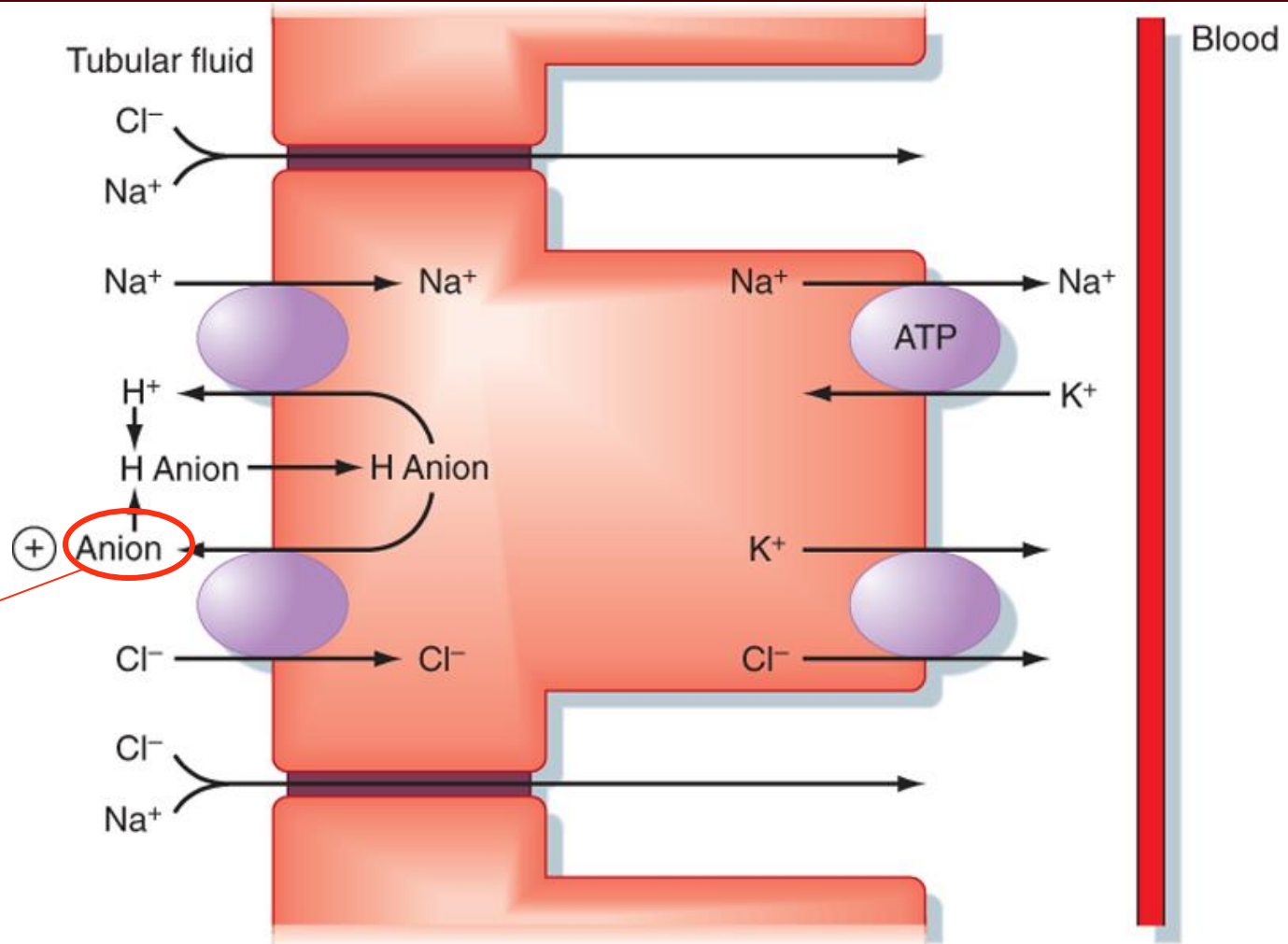
***Na<sup>+</sup> reabsorption is mainly coupled to that of;***

- Cl<sup>-</sup>

***Why??***



# Sodium Chloride Reabsorption in the 2<sup>nd</sup> Half of PT



e.g.  
Formate  
Oxalate  
Sulfate

# How Does the Proximal Tubule Secrete Hydrogen Ions?

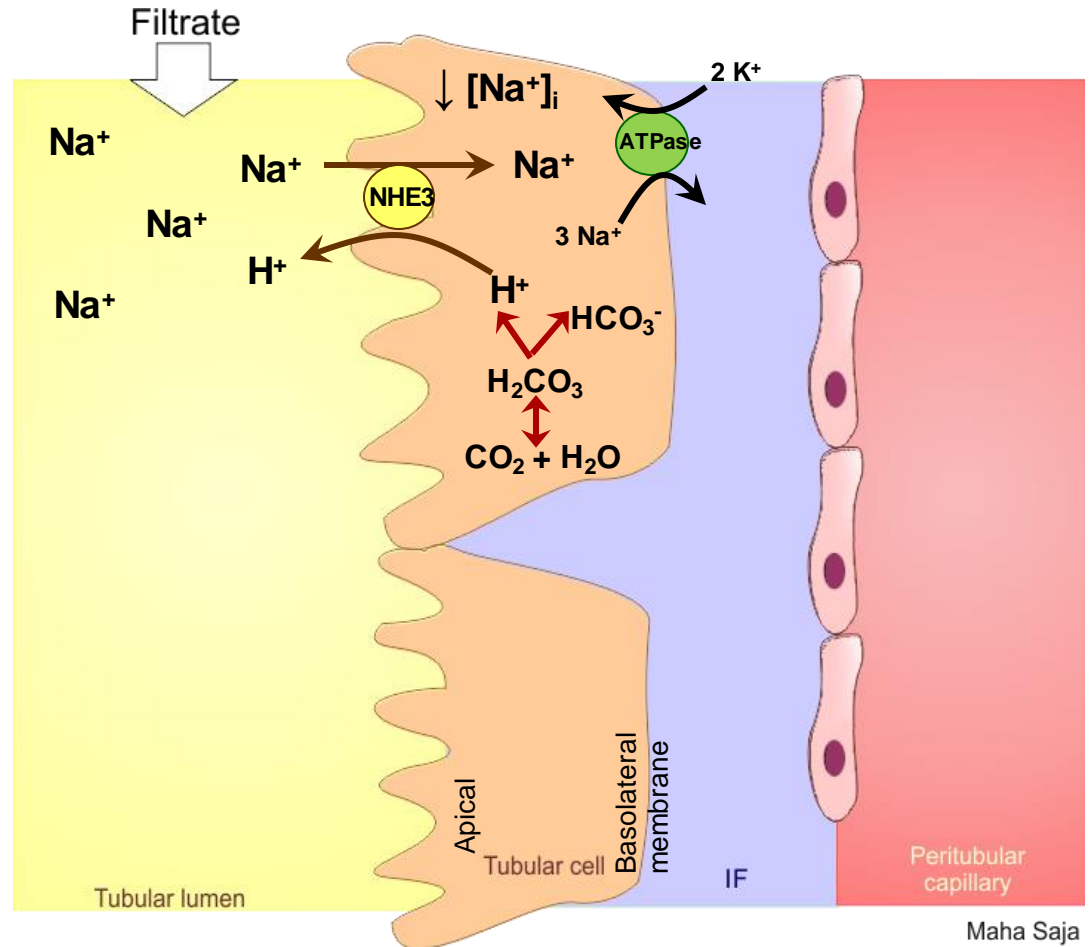
Basolateral  $\text{Na}^+\text{-K}^+$  ATPase pumps  $3\text{Na}^+$  out and  $2\text{K}^+$  into the cell



Results in low  $[\text{Na}^+]_i$



This gradient favours passive entry of  $\text{Na}^+$  into the tubular cell across the apical membrane via NHE in exchange with  $\text{H}^+$ .



# Organic Anion/Cation Secretion

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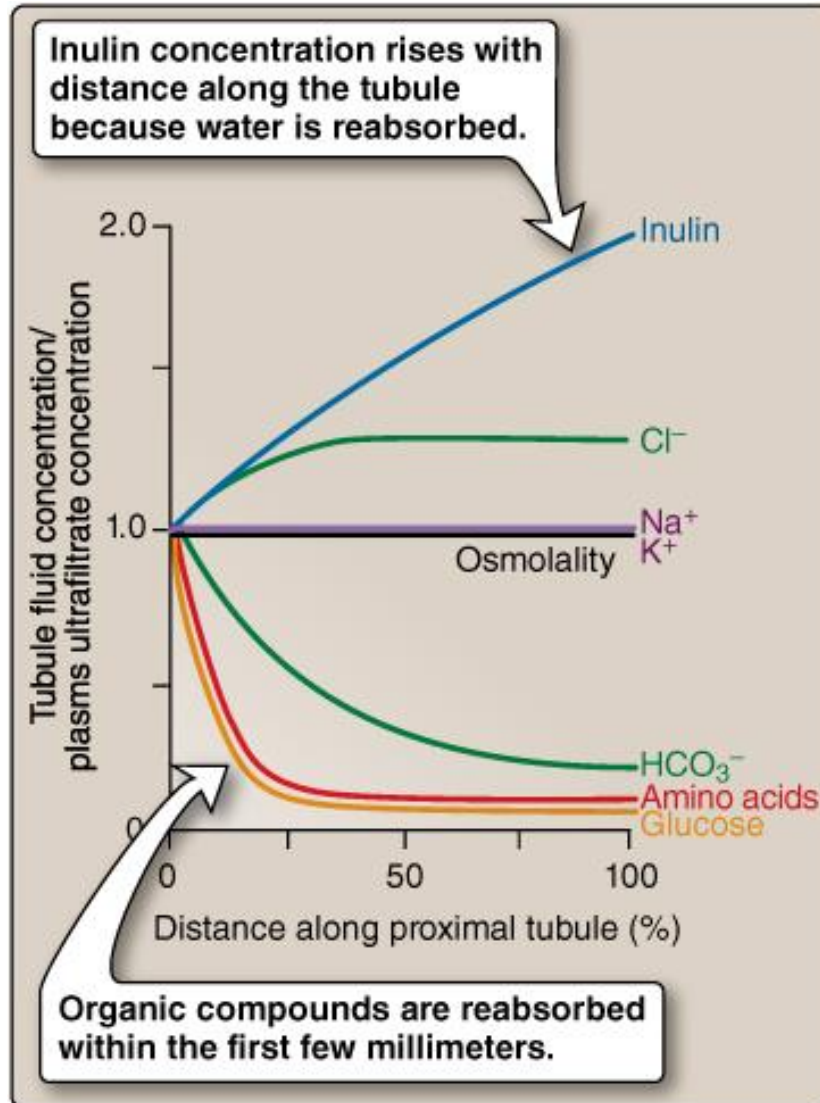
## Organic Anions

- Endogenous:
  - Bile salts.
  - Oxalate.
  - Urate.
  - Vitamins (ascorbate, folate).
- Exogenous:
  - Acetazolamide.
  - Furosemide.
  - Salicylates.
  - Penicillin.

## Organic cations

- Endogenous;
  - Creatinine.
  - Dopamine.
  - Epinephrine.
  - Norepinephrine.
- Exogenous;
  - Atropine.
  - Morphine.
  - Amiloride.
  - Procainamide.

# Summary of PCT Filtrate Modification

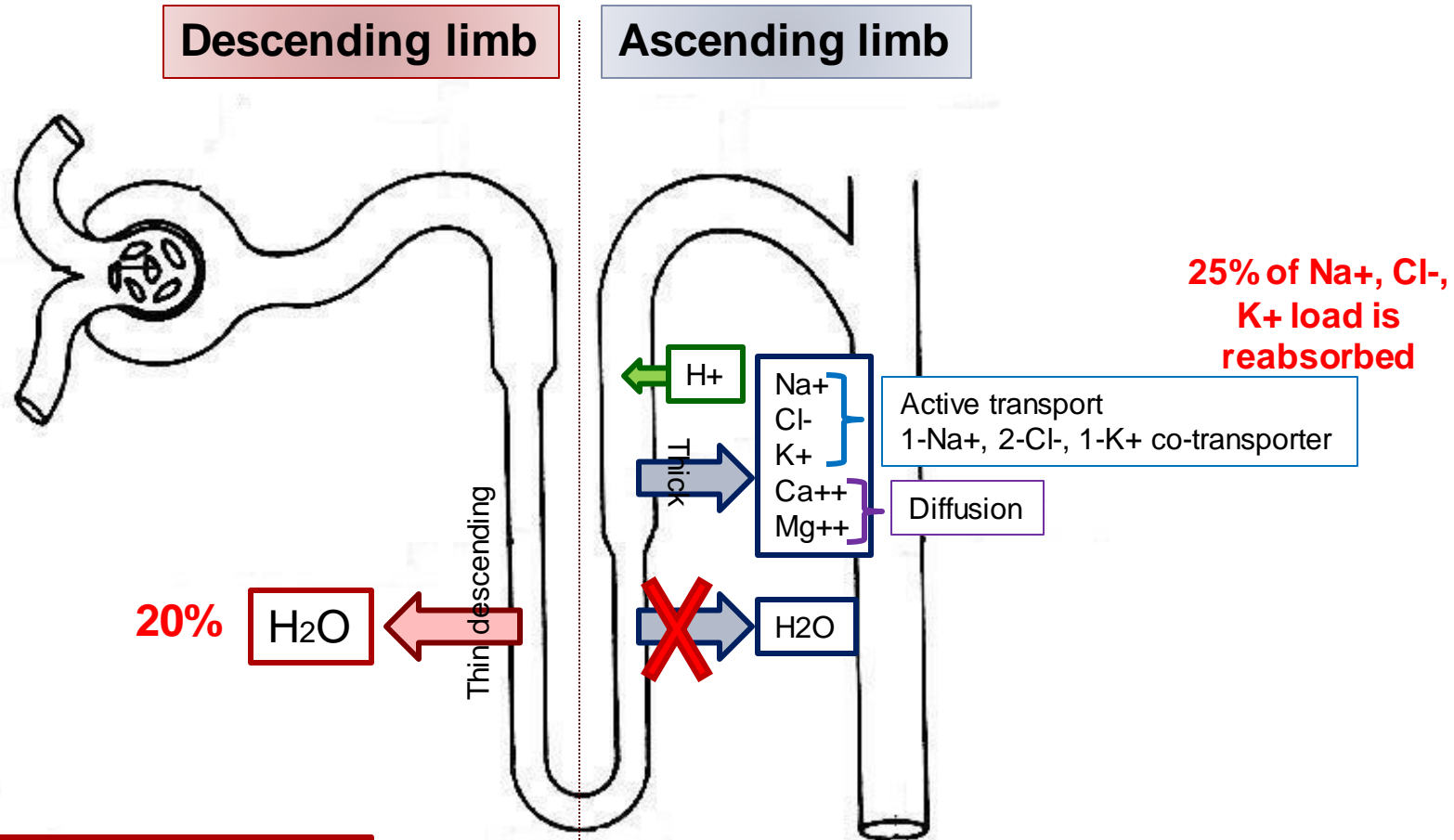




# LOOP OF HENLE

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# Loop of Henle



- Highly permeable to water
- Moderate permeability to solutes

- **Impermeable** to water
- Reabsorption of solutes in the thick segment

# Transport Mechanisms in the TAL

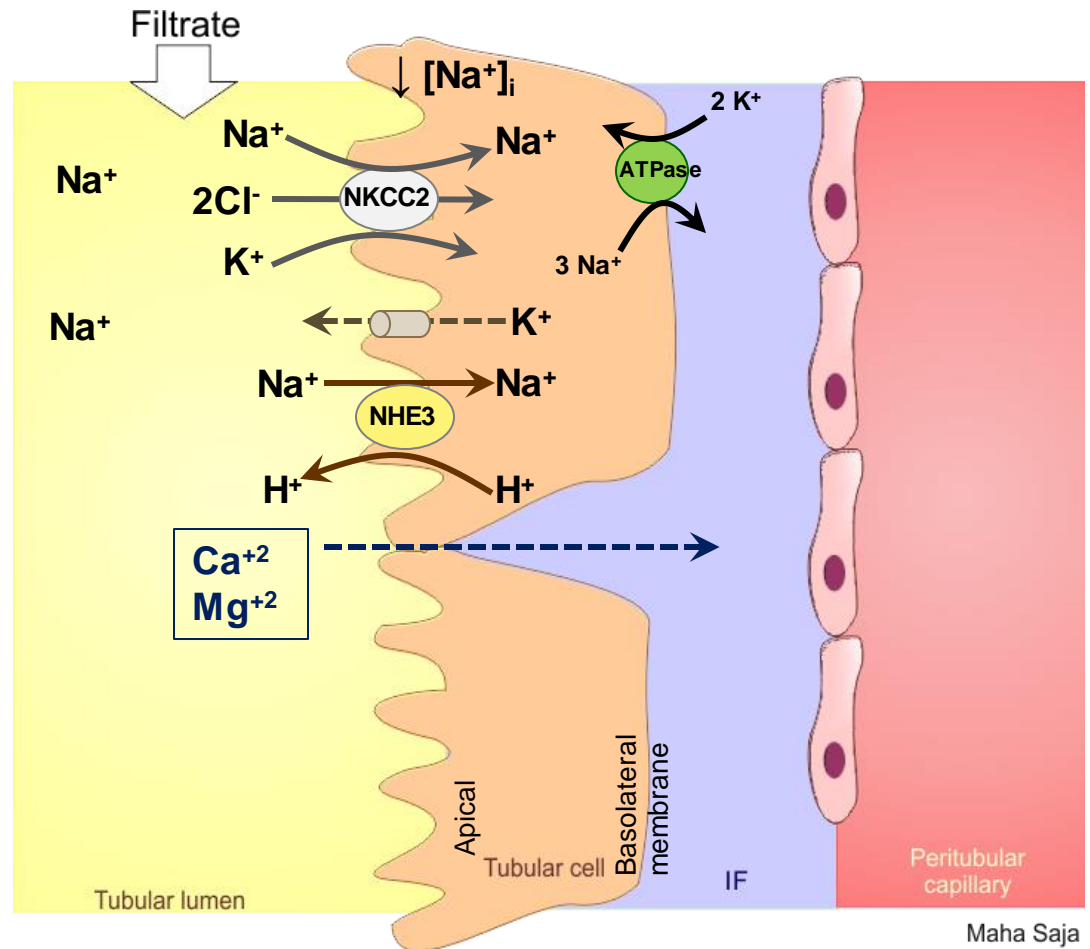
Basolateral  $\text{Na}^+\text{-K}^+$  ATPase pumps  $3\text{Na}^+$  out and  $2\text{K}^+$  into the cell



Results in low  $[\text{Na}^+]_i$



This gradient favours passive entry of  $\text{Na}^+$  into the tubular cell across the apical membrane via NKCC2 along with  $\text{Cl}^-$  &  $\text{K}^+$ .



**Loop diuretics block NKCC2**

# **DISTAL TUBULE & COLLECTING DUCT**

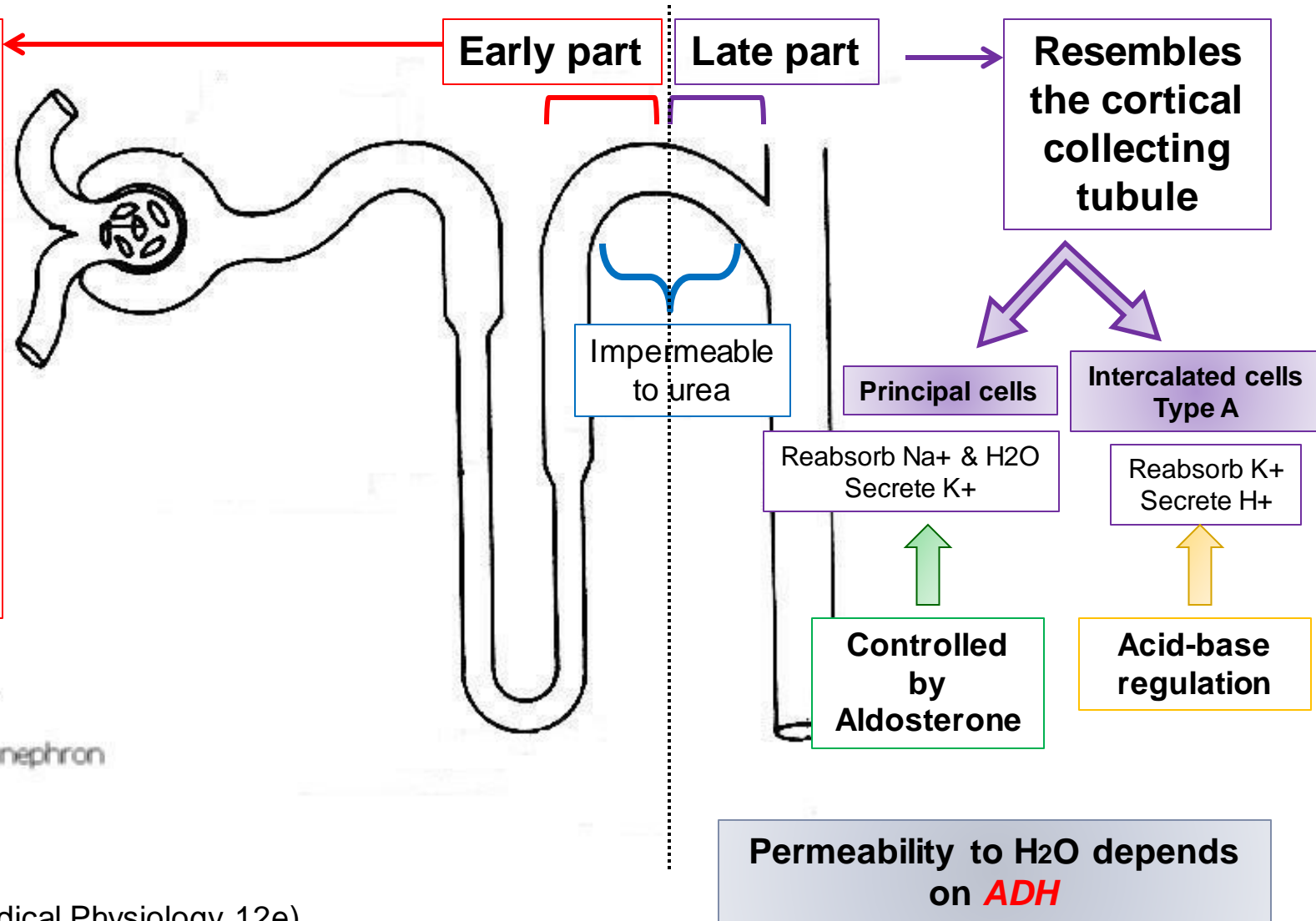
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# Transport Across the Distal Tubule

Resembles the thick ascending loop of Henle

Known as *the diluting segment*

Reabsorbs 5% of NaCl



# Transport Mechanisms in the Early DT

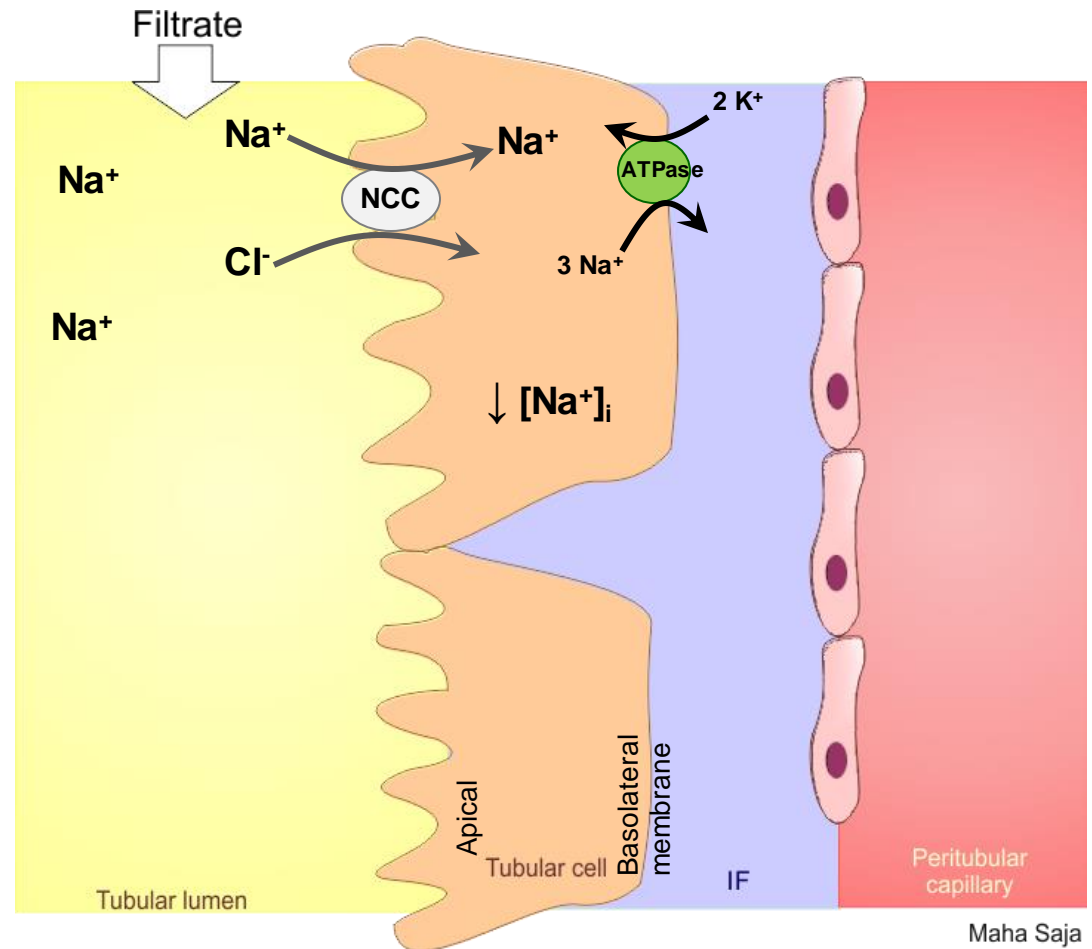
Basolateral  $\text{Na}^+\text{-K}^+$   
ATPase pumps  
 $3\text{Na}^+$  out and  $2\text{K}^+$   
into the cell



Results in low  $[\text{Na}^+]_i$

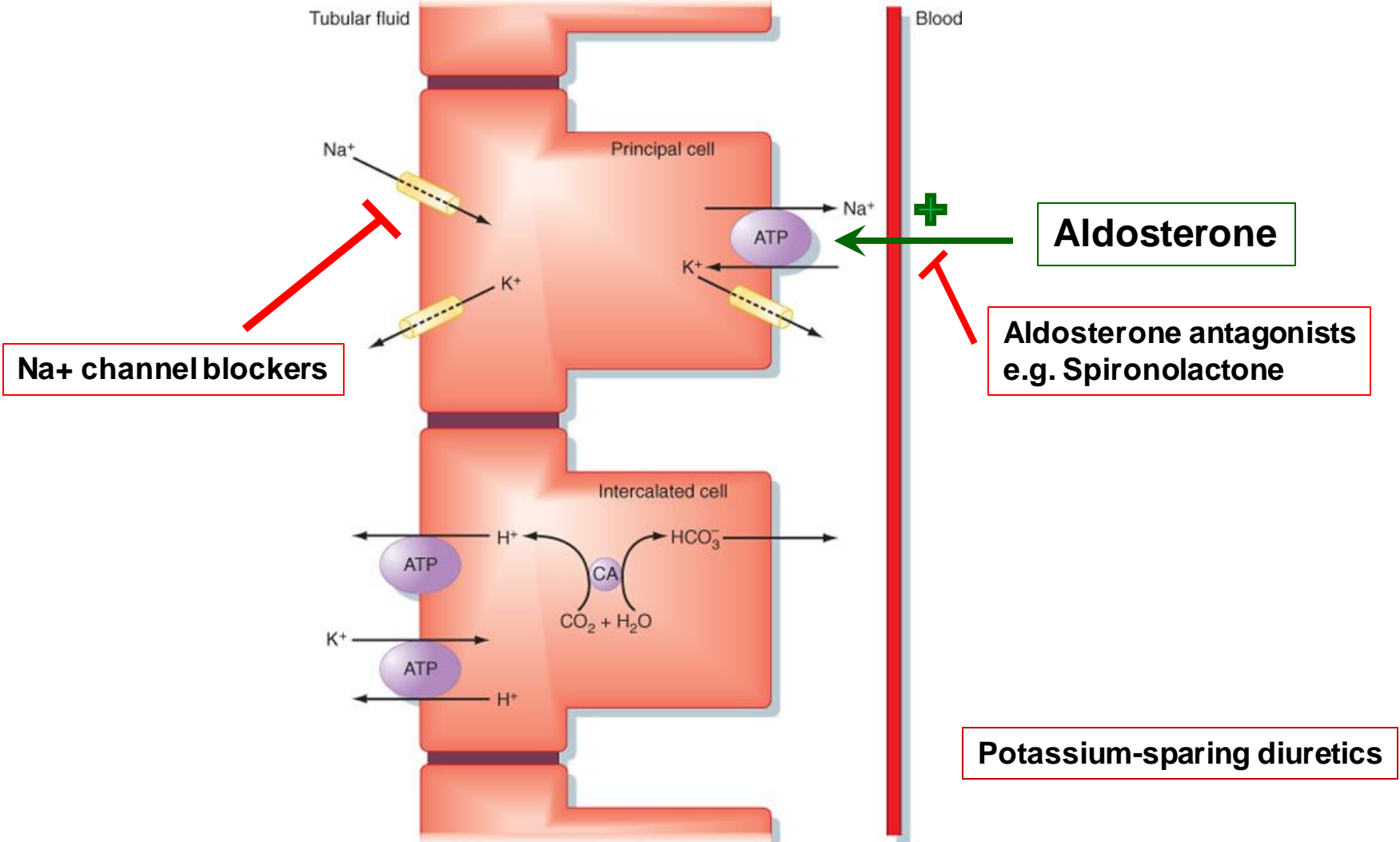


This gradient  
favours passive  
entry of  $\text{Na}^+$  into the  
tubular cell across  
the apical  
membrane via NCC  
along with  $\text{Cl}^-$ .



**Thiazide diuretics block NCC**

# Late Distal Tubule & Collecting Tubule



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.  
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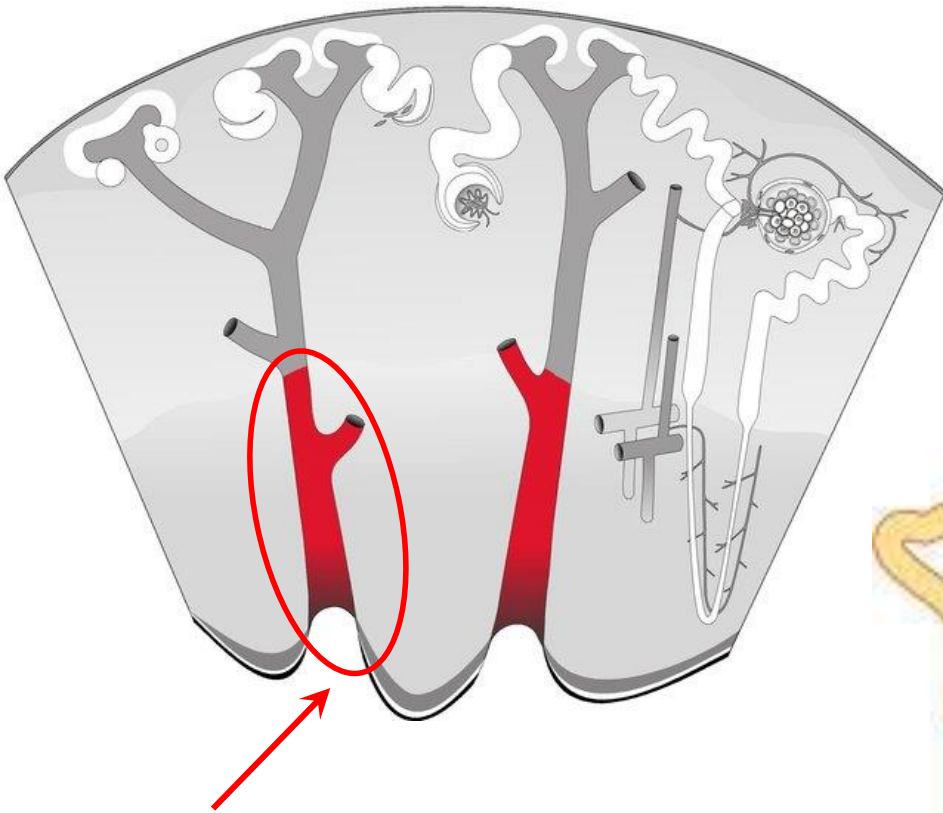
# Medullary Collecting Duct

Reabsorbs  $\approx 3\%$  of filtered  $\text{Na}^+$

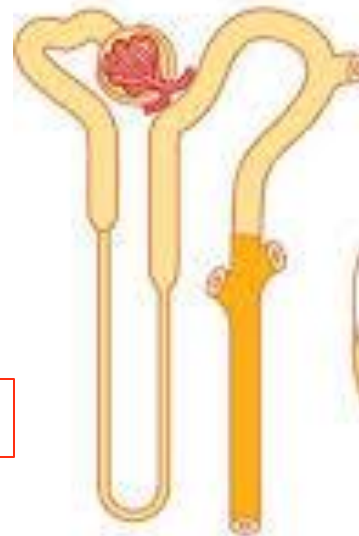
Permeability to water is under ADH control

Permeable to urea

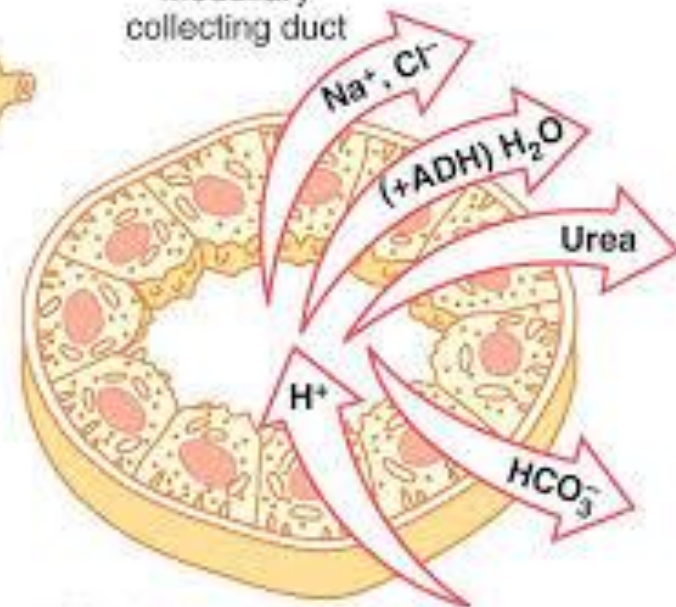
Secrete  $\text{H}^+$



Reabsorbs  $\approx 3\%$  of filtered  $\text{Na}^+$

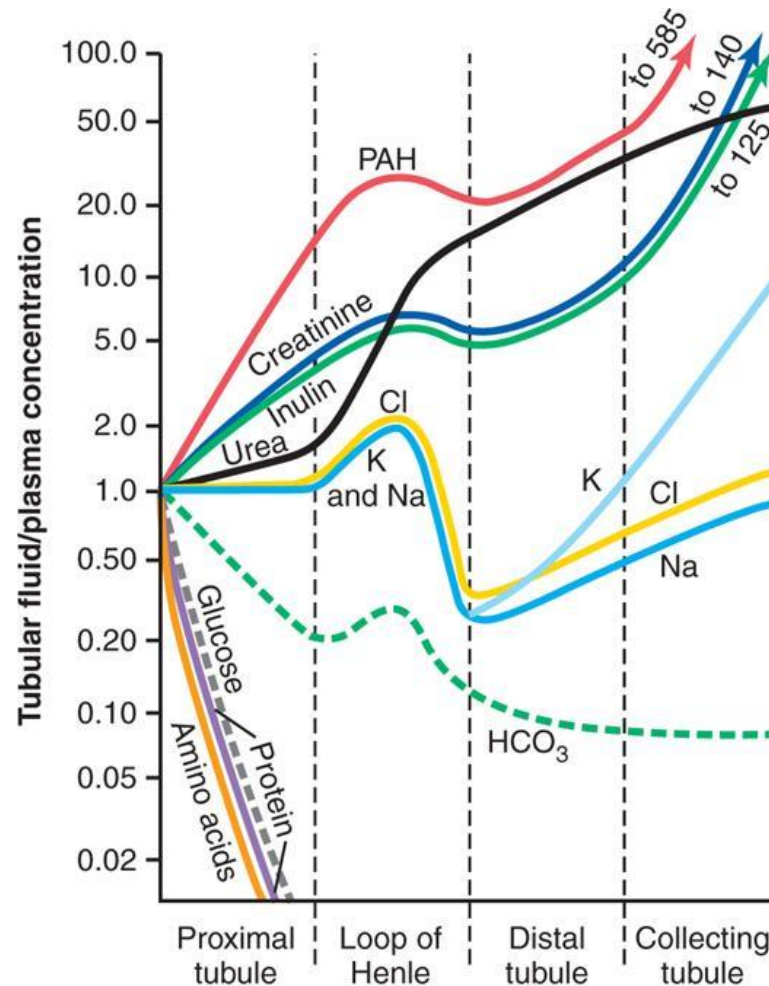


Medullary collecting duct





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

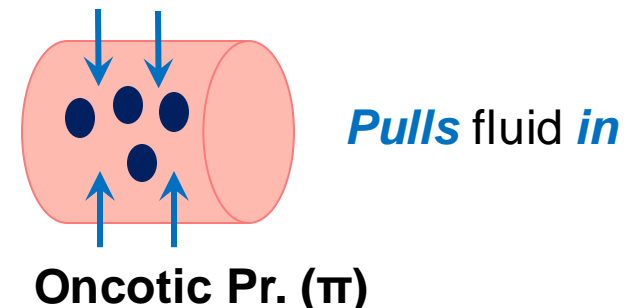
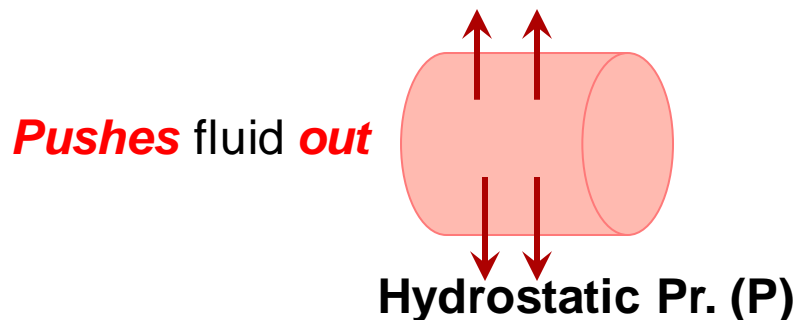


# REGULATION OF TUBULAR REABSORPTION

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# Regulation of Tubular Reabsorption

- **Regulation of tubular reabsorption depends on:**
  1. Physical forces that govern reabsorption.
  2. 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?**



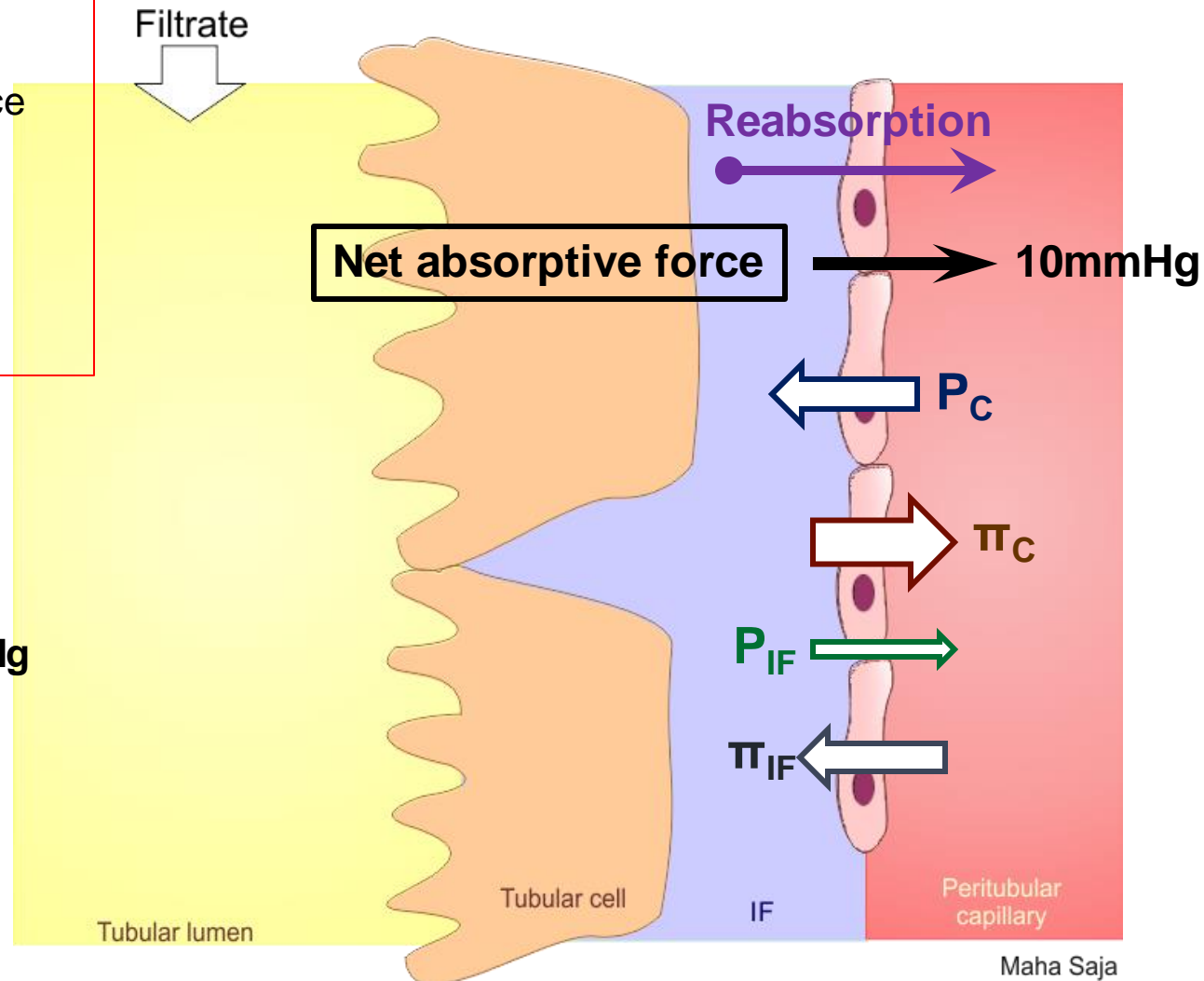
# Physical Forces that Govern Tubular Reabsorption

$P_C$  is influenced by:

- ABP.
- Aff & Eff arteriolar resistance

$\pi_C$  is influenced by:

- FF.
- Systemic plasma colloid osmotic pr.



## Reabsorption

**Favouring** | **Opposing**

$\pi_C = 32$

$P_C = 13\text{mmHg}$

$P_{IF} = 6$

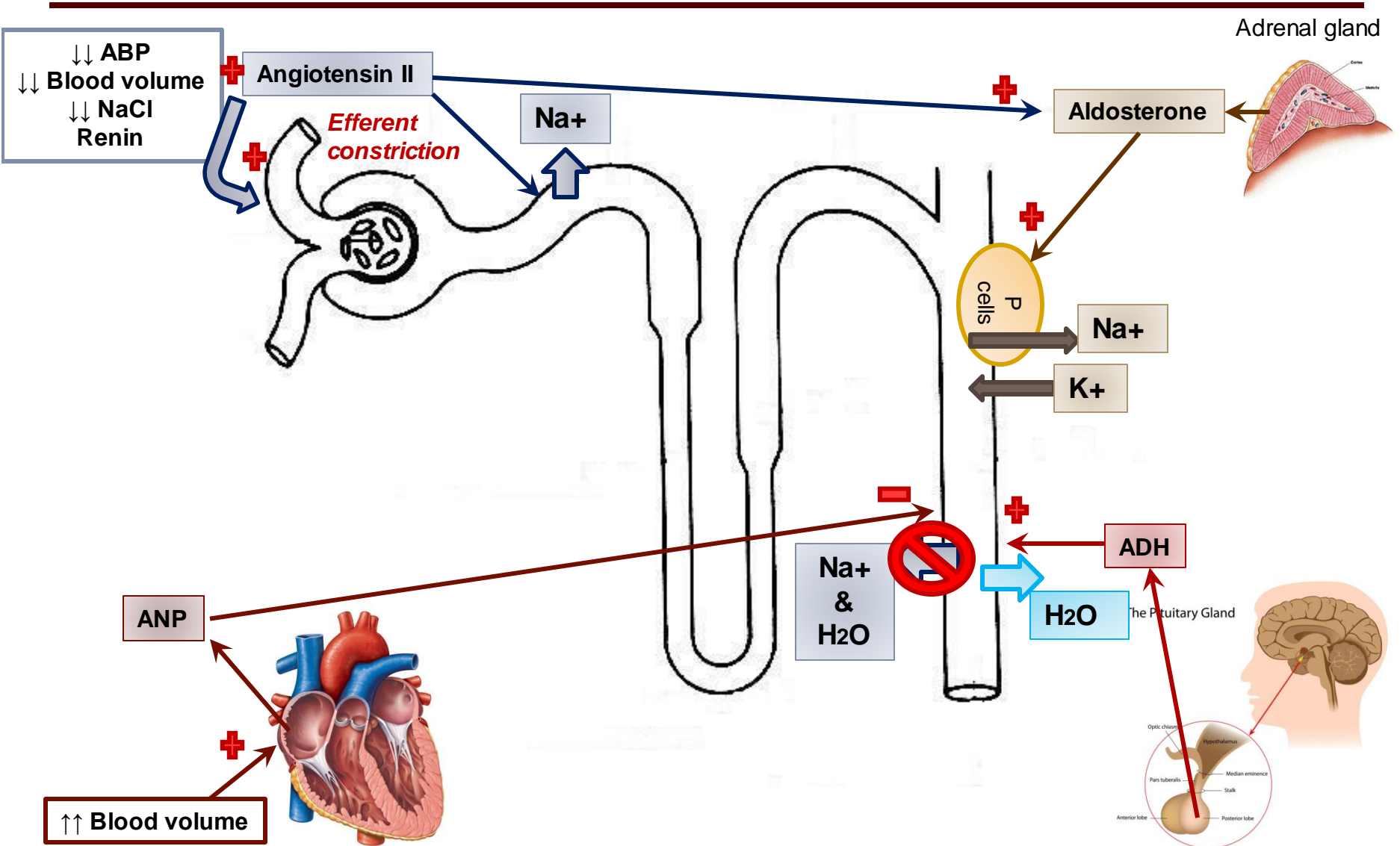
$\pi_{IF} = 15$

38

>

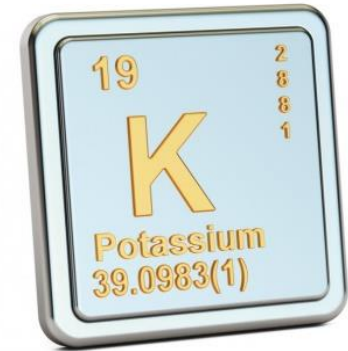
28

# Hormonal Regulation of Tubular Reabsorption



# REGULATION OF POTASSIUM

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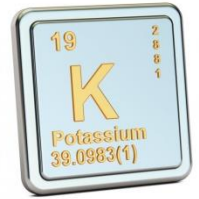
# Potassium

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- One of the most abundant cations in the body.
- 98% in ICF and 2% in ECF.
- $[K^+]_i > [K^+]_o \rightarrow 150 \text{ mEq/L} > 3.5\text{-}5 \text{ mEq/L}$ .
- ***Why is  $K^+$  important?***
  - ✓ Cell volume regulation.
  - ✓ Cell pH regulation.
  - ✓ Resting membrane potential.
  - ✓ Cardiac and neuronal activity.

# The Importance of Regulating K<sup>+</sup>



**Table 37-1** Physiological Role of K<sup>+</sup> Ions

## A. Roles of Intracellular K<sup>+</sup>

Cell-volume maintenance

Net loss of K<sup>+</sup> → cell shrinkage  
Net gain of K<sup>+</sup> → cell swelling

Intracellular pH regulation

Net loss of K<sup>+</sup> → cell acidosis  
Net gain of K<sup>+</sup> → cell alkalosis

Cell enzyme functions

K<sup>+</sup> dependence of enzymes (e.g., some ATPases, succinic dehydrogenase)

DNA/protein synthesis, growth

Lack of K<sup>+</sup> → reduction of protein synthesis, stunted growth

## B. Roles of Transmembrane [K<sup>+</sup>] Ratio

Resting cell membrane potential

Reduced [K<sup>+</sup>]<sub>i</sub>/[K<sup>+</sup>]<sub>o</sub> → membrane depolarization  
Increased [K<sup>+</sup>]<sub>i</sub>/[K<sup>+</sup>]<sub>o</sub> → membrane hyperpolarization

Neuromuscular activity

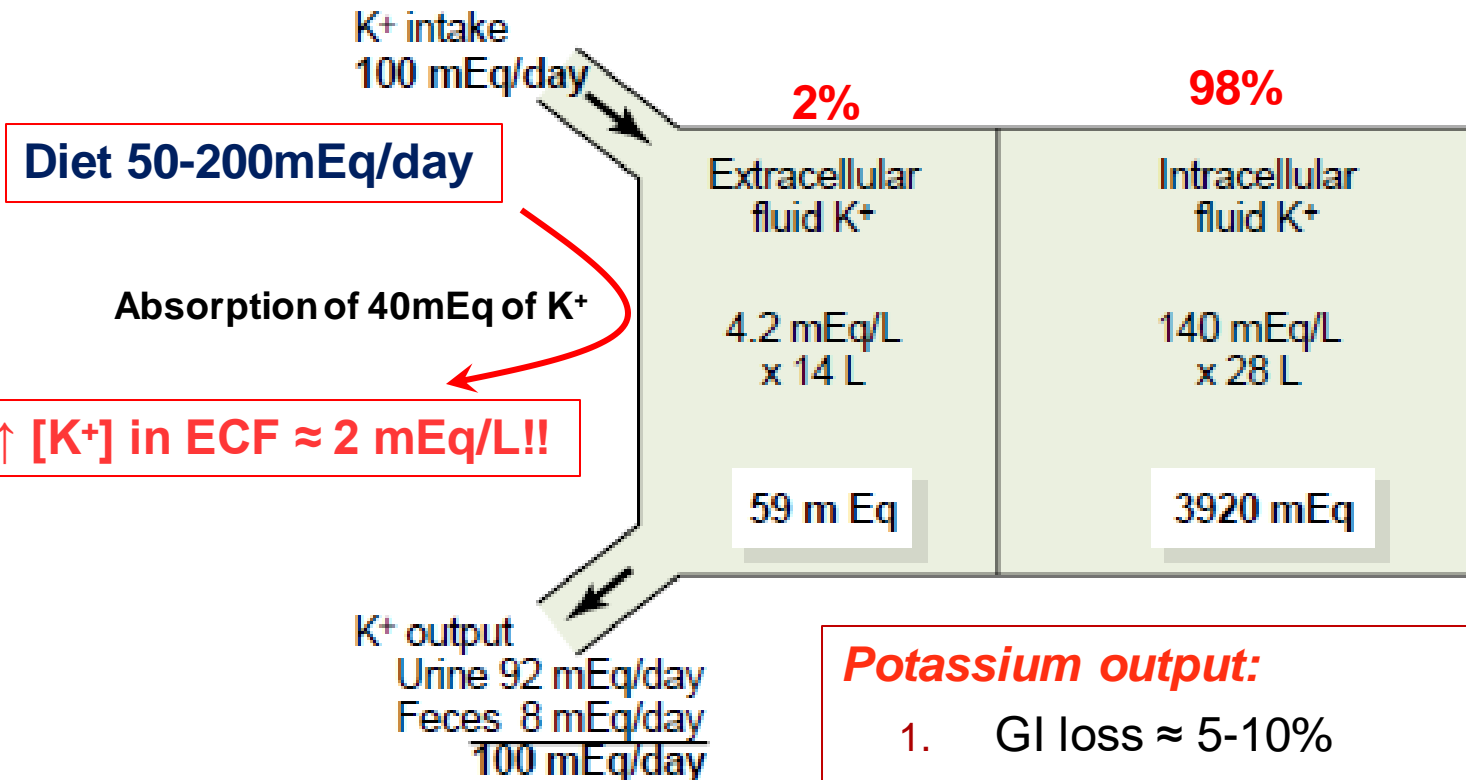
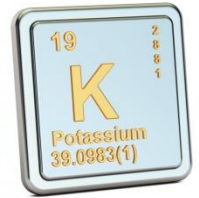
Low plasma K<sup>+</sup>: muscle weakness, muscle paralysis, intestinal distention, respiratory failure  
High plasma K<sup>+</sup>: increased muscle excitability; later, muscle weakness (paralysis)

Cardiac activity

Low plasma K<sup>+</sup>: slowed conduction of pacemaker activity, arrhythmias  
High plasma K<sup>+</sup>: conduction disturbances, ventricular arrhythmias, and ventricular fibrillation



# Potassium Homeostasis



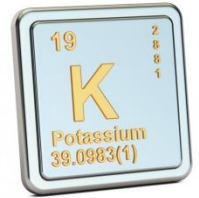
*How does the body protect against this risk of hyperkalemia following each meal?*

- Potassium output:**
1. GI loss ≈ 5-10%
  2. Renal excretion ≈ 90-95%.

**Figure 29-1**

Normal potassium intake, distribution of potassium in the body fluids, and potassium output from the body.

# Body Defense Against $K^+$ Abnormalities



## 1<sup>st</sup> line of defence

### Cellular shift

Redistribution of  $K^+$  between ICF and ECF.

- ↑↑ ECF [ $K^+$ ] → shift  $K^+$  into the cells
- ↓↓ ECF [ $K^+$ ] → shift  $K^+$  out of the cells.

***What are the factors altering  $K^+$  distribution between both compartments?***

### Renal excretion

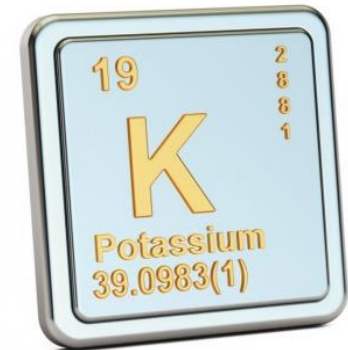
Depending on  $K^+$  body status, the kidney may;

- ↑↑ excretion of  $K^+$
- ↓↓ excretion of  $K^+$

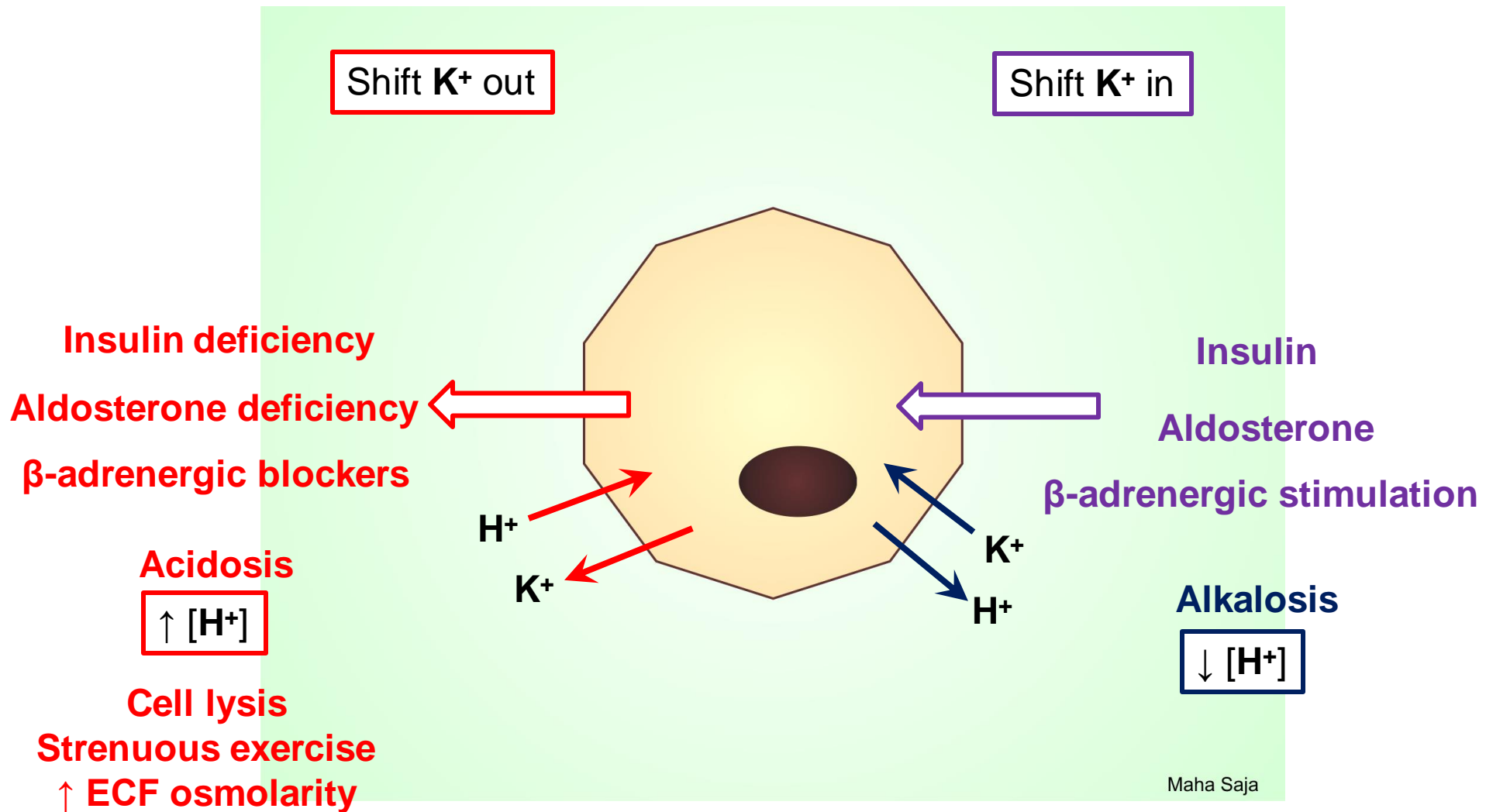
***How does the kidney achieve that?***

# CELLULAR SHIFT

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# Factors That Can Shift $K^+$ In and Out of Cells



# Factors Affecting K<sup>+</sup> Distribution Between ICF and ECF

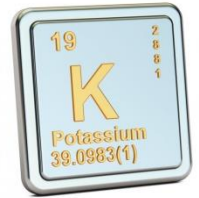


Table 29-1

## Factors That Can Alter Potassium Distribution Between the Intra- and Extracellular Fluid

### Factors That Shift K<sup>+</sup> into Cells (Decrease Extracellular [K<sup>+</sup>])

- Insulin
- Aldosterone
- $\beta$ -adrenergic stimulation
- Alkalosis

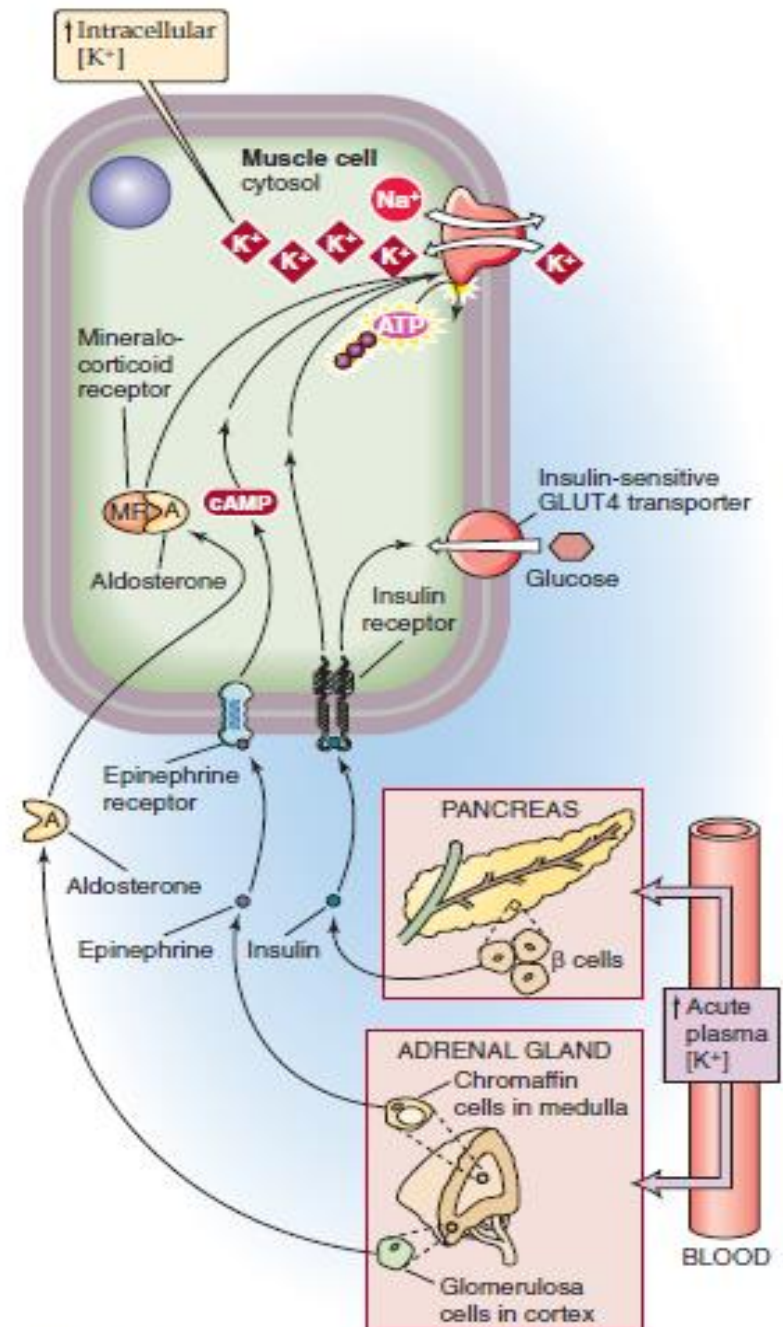
### Factors That Shift K<sup>+</sup> Out of Cells (Increase Extracellular [K<sup>+</sup>])

- Insulin deficiency (diabetes mellitus)
- Aldosterone deficiency (Addison's disease)
- $\beta$ -adrenergic blockade
- Acidosis
- Cell lysis
- Strenuous exercise
- Increased extracellular fluid osmolarity

## Physiologic factors affecting $K^+$ distribution between ICF and ECF:

- Help regulate plasma  $[K^+]$ : keep plasma  $[K^+]$  constant.

- Aldosterone.
- Insulin.
- Epinephrine.



**Figure 37-3**  $K^+$  uptake into cells in response to high plasma  $[K^+]$ .

# Pathophysiologic Factors Affecting $K^+$ Distribution Between ICF and ECF

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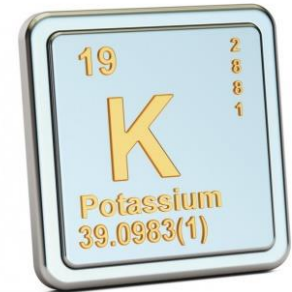


- Acid base disturbance.
- Change in plasma osmolality.
- Cell lysis.
- Exercise.

***How do these factors affect  $K^+$  distribution between ICF and ECF compartments?***

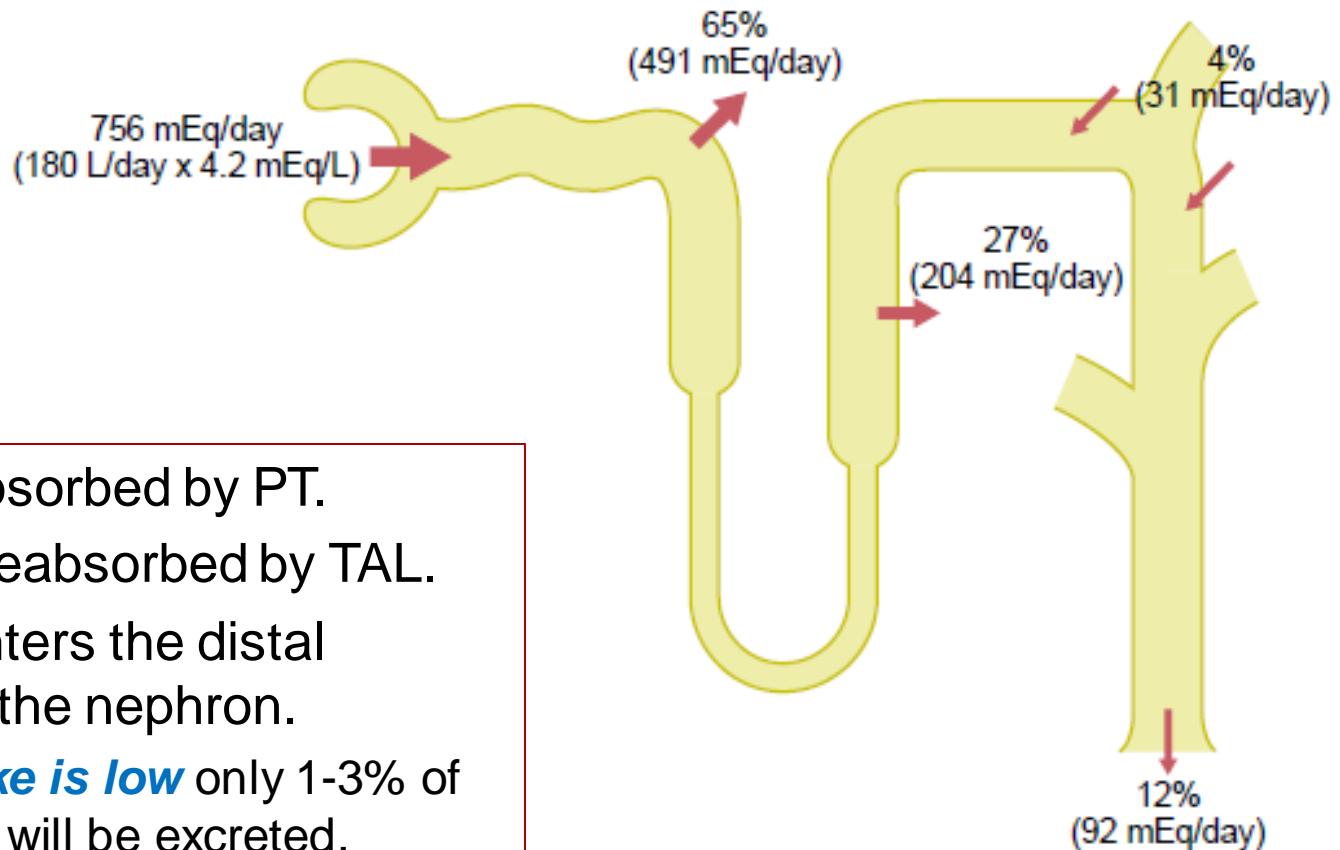
# RENAL POTASSIUM EXCRETION

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# Renal Potassium Handling



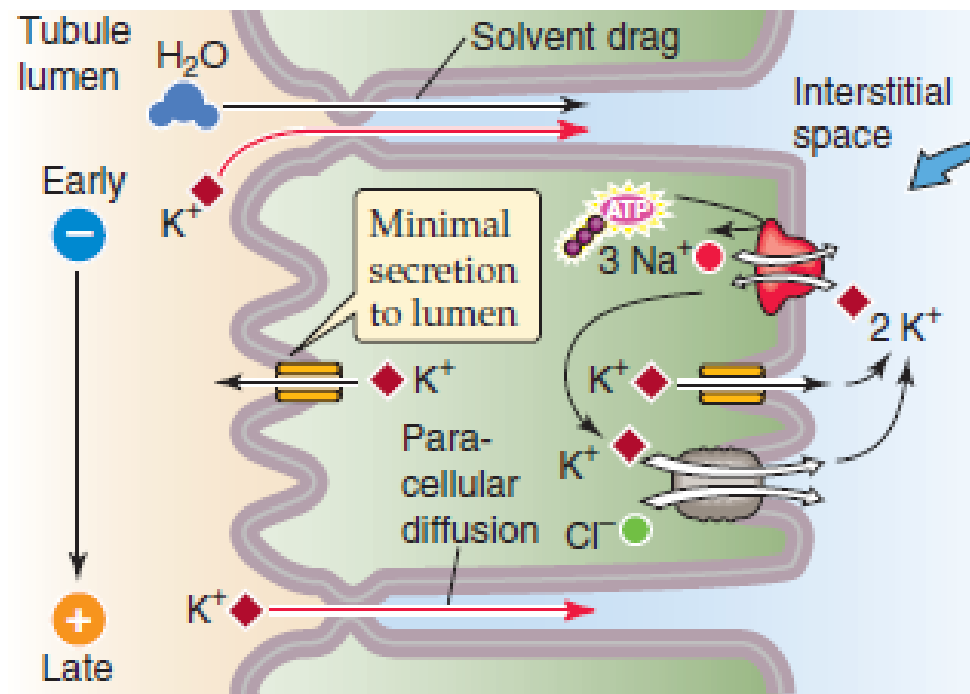
- $\approx 65\%$  reabsorbed by PT.
- $\approx 25\text{-}30\%$  reabsorbed by TAL.
- $\approx 5\text{-}10\%$  enters the distal portions of the nephron.
  - **If  $K^+$  intake is low** only 1-3% of filtered  $K^+$  will be excreted.
  - **If  $K^+$  intake is normal/high**, 10-15% of filtered  $K^+$  will be excreted

# Potassium Handling by the kidney

**In the PCT** →  $K^+$  reabsorption is a passive process.. **How?**

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

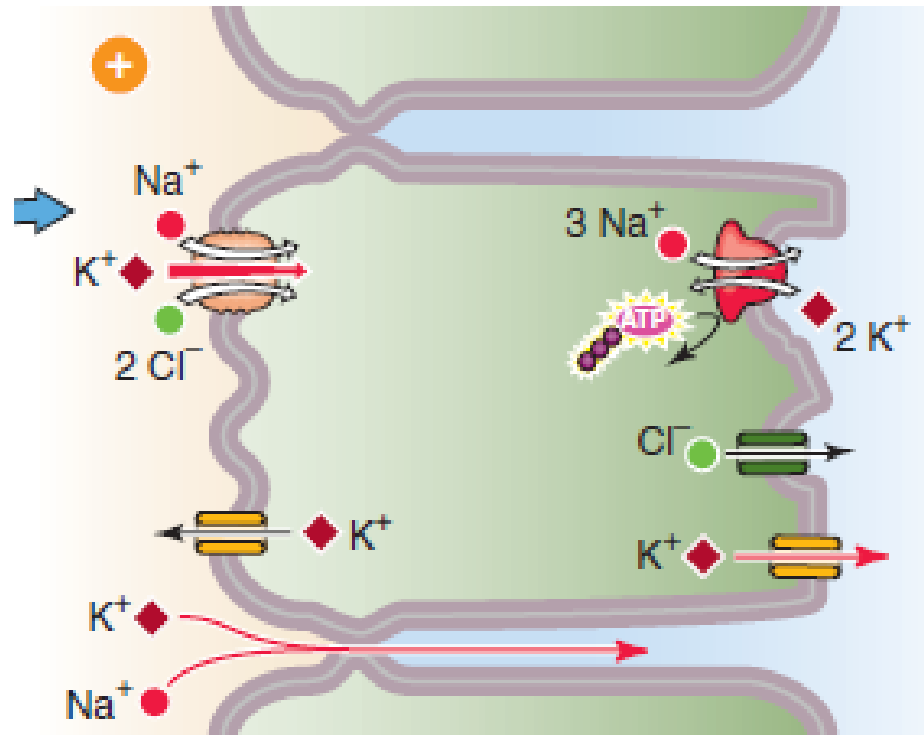
## A PROXIMAL TUBULE



# Potassium Handling by the TAL

By secondary active transport using the apical triple transporter (NKCC2).

B THICK ASCENDING LIMB (TAL)

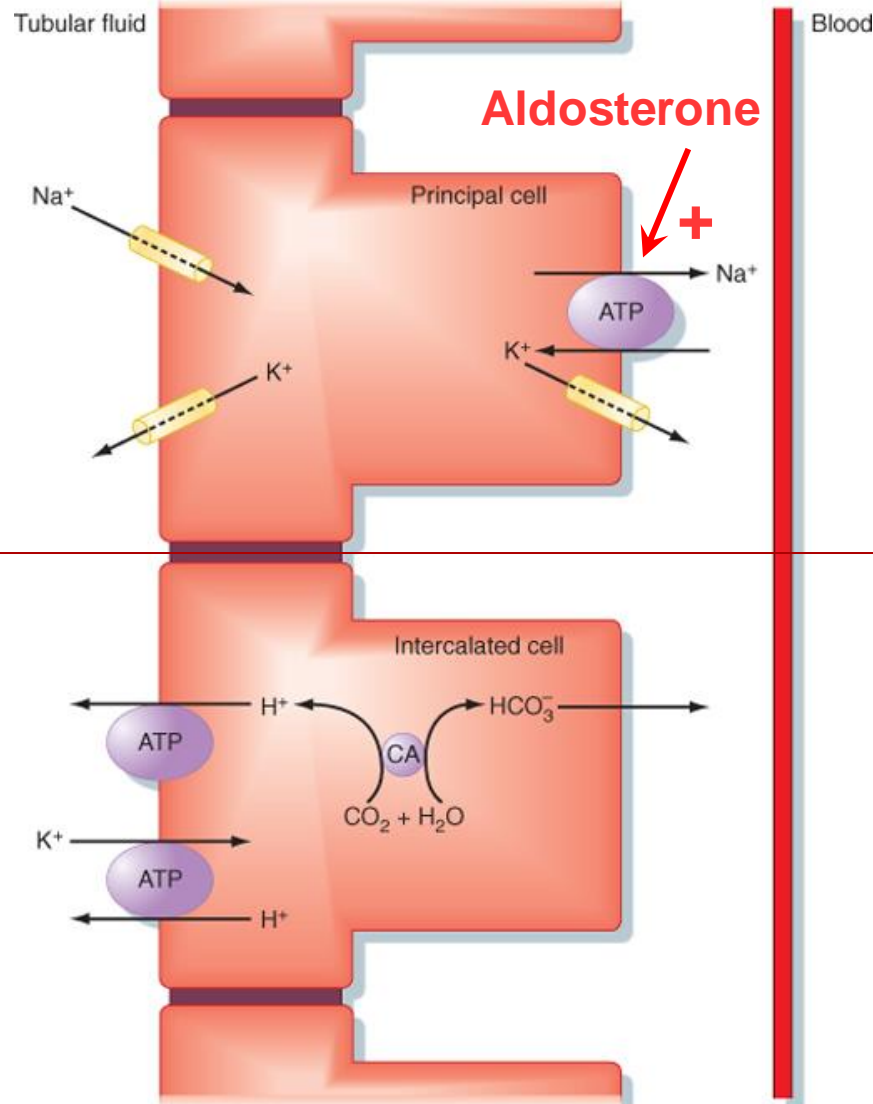


# Potassium Handling by the Distal Portions of the Nephron

**High  $K^+$  intake**  
→ ↑ secretion of  $K^+$ .

**Low  $K^+$  intake**  
→ ↓ secretion of  $K^+$ .

**In  $K^+$  depletion** →  
↑ reabsorption of  $K^+$ .



Principle cells

Reabsorb  $Na^+$   
and water &  
secrete  $K^+$

$\alpha$ -intercalated cells

Secrete  $H^+$  and  
reabsorb  $K^+$

# Factors Regulating Potassium Secretion

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Factors that *stimulate* potassium secretion:

1.  $\uparrow\uparrow$  ECF  $[K^+]$ .
2.  $\uparrow\uparrow$  aldosterone.
3.  $\uparrow\uparrow$  tubular flow rate.

Factors that *decrease* potassium secretion:

- Acidosis ( $\uparrow\uparrow [H^+]$ )

**THANK YOU**

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