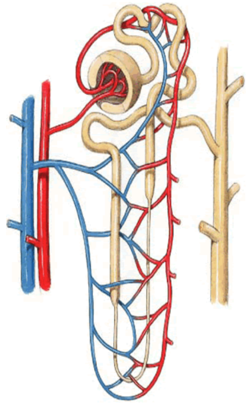

TUBULAR PROCESSING OF FILTRATE

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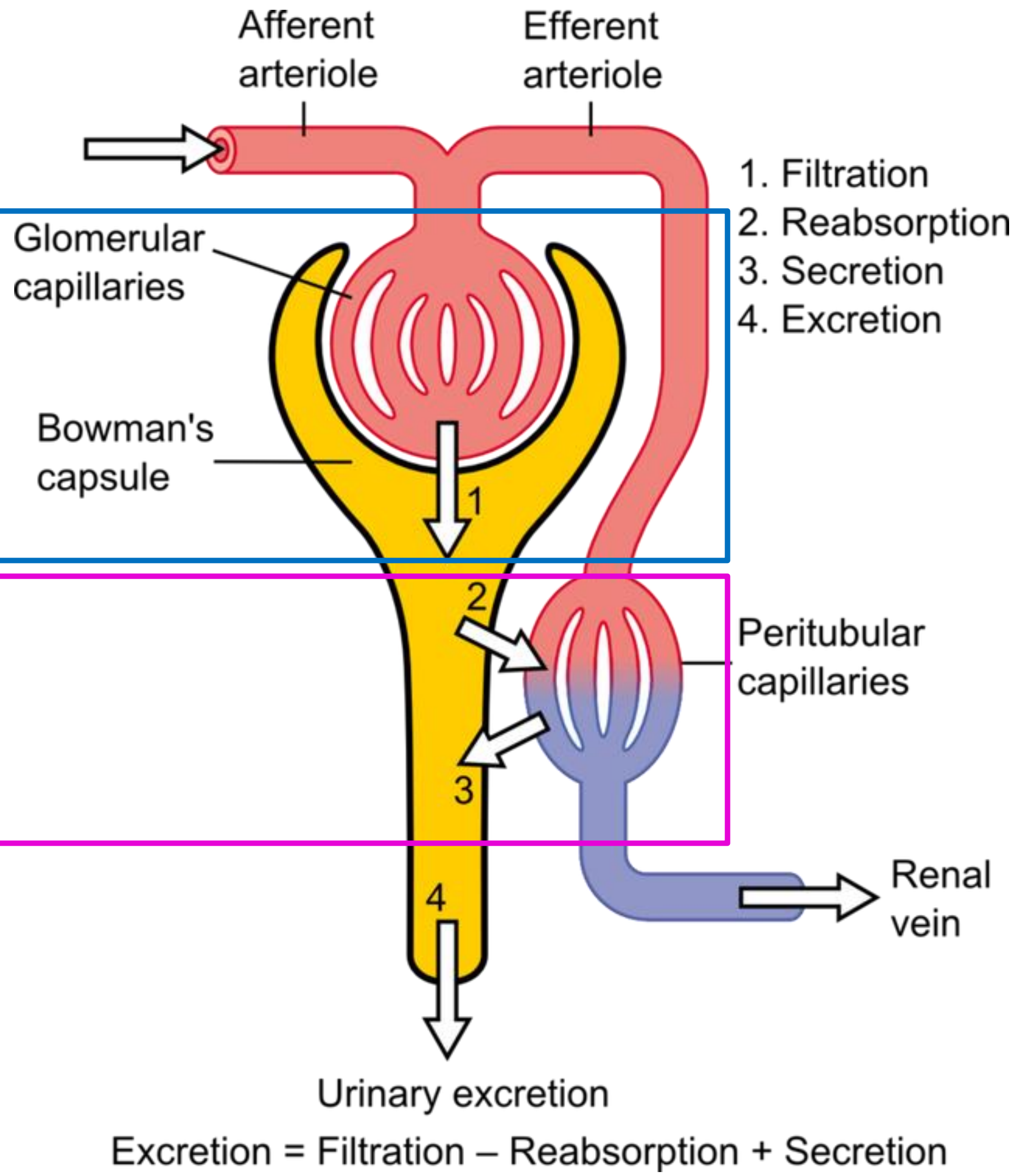
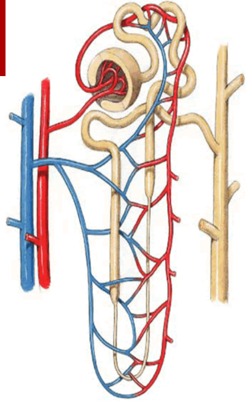
Objectives

- 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.

What did we discuss so far?

What are we going to discuss in this lecture?





Contents

- The mechanisms of tubular transport through the different parts of the nephron.

- Tubular reabsorption and tubular secretion.

- Regulation of tubular processing.

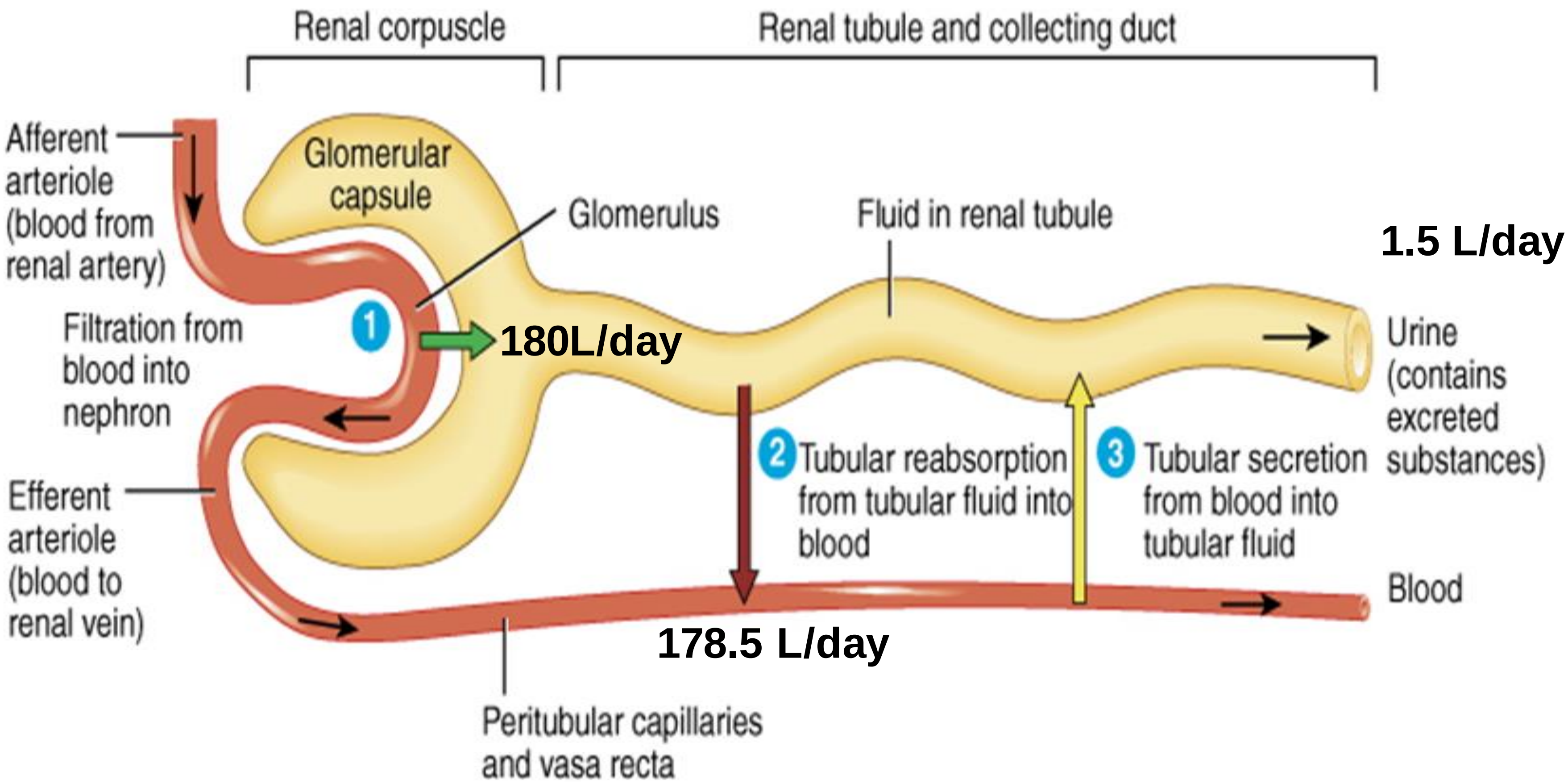
Introduction

<u>From the previous lecture,</u>

- 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

- 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

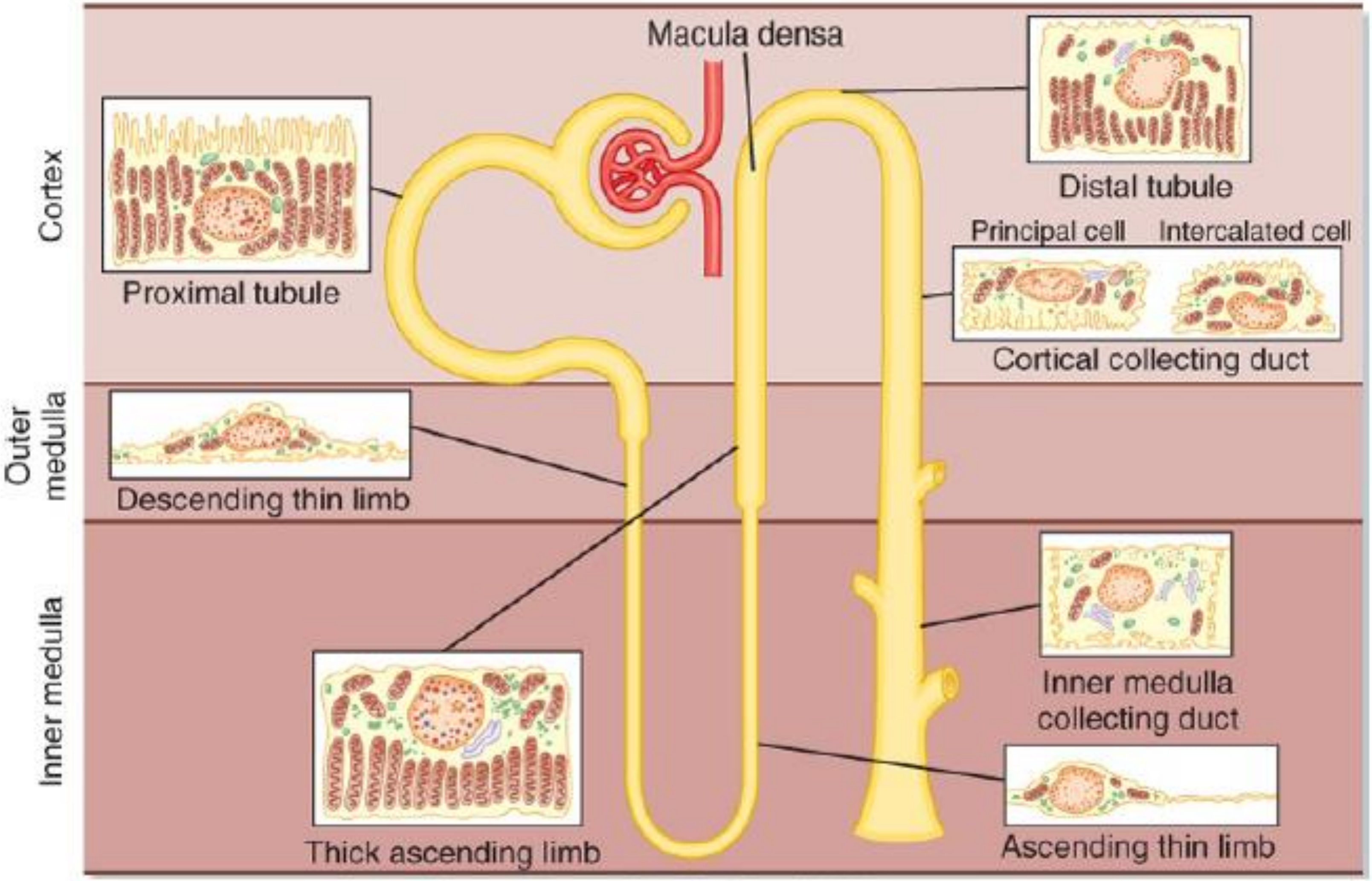


Figure 32-3 Diagram of a nephron, including the cellular ultra-structure.

TUBULAR REABSORPTION & SECRETION

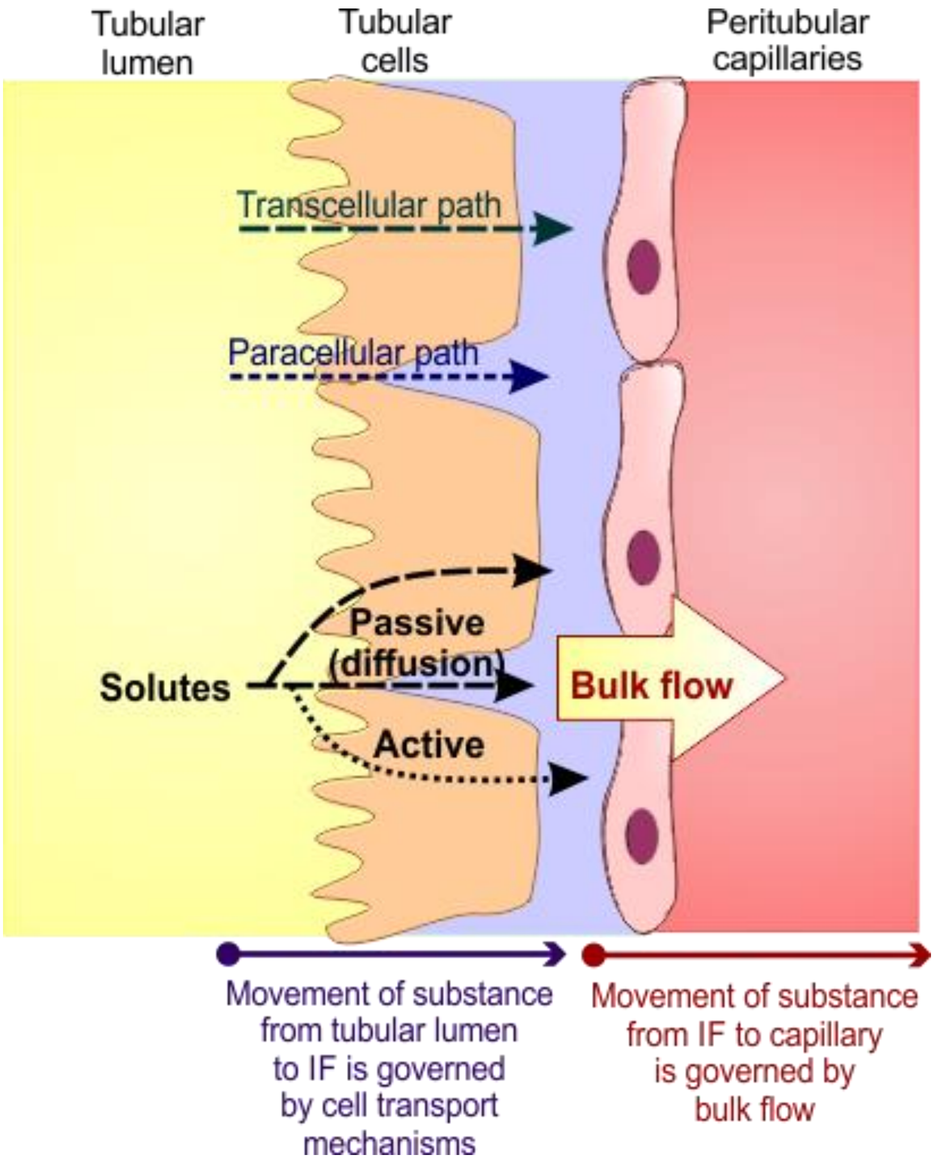
How Does the Nephron Reabsorb Substances

- ***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+-K+ 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.

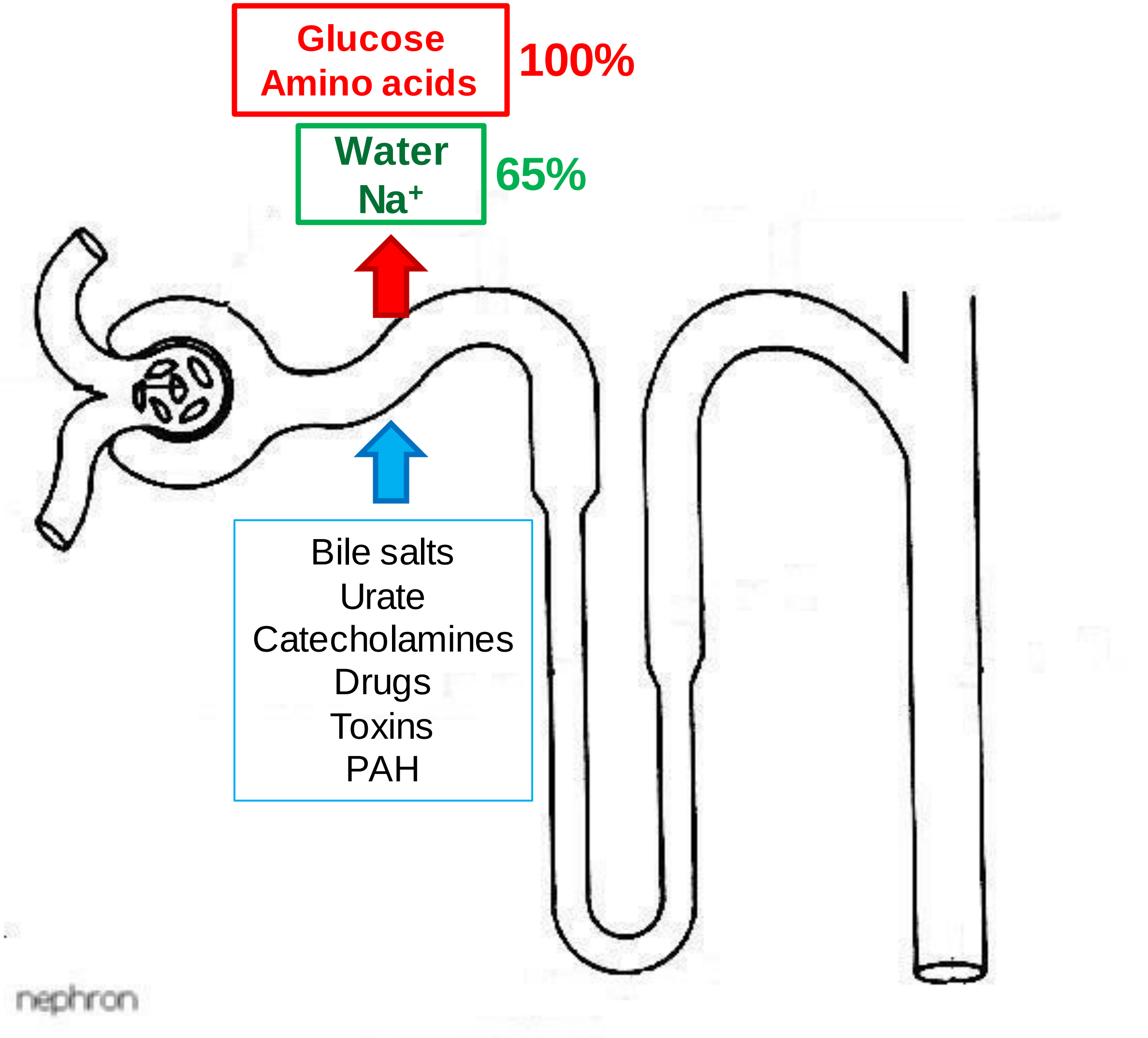
Passive diffusion Osmosis

Water
Solutes like Cl-
Urea

TUBULAR REABSORPTION IN EACH PART OF THE NEPHRON

Proximal Tubule

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

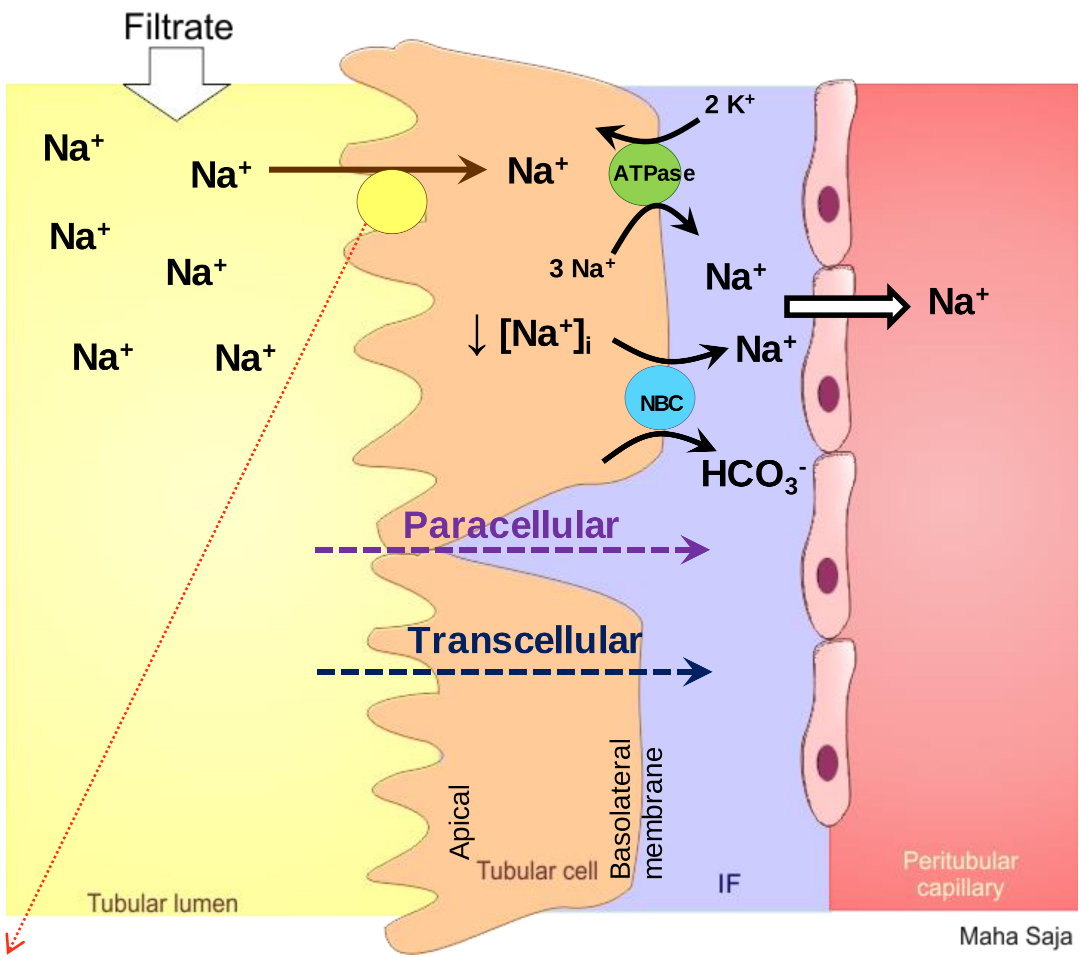


How Does the Proximal Tubule Reabsorb Sodium (Na^+)?

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 transporter proteins



Many types of transporter proteins;

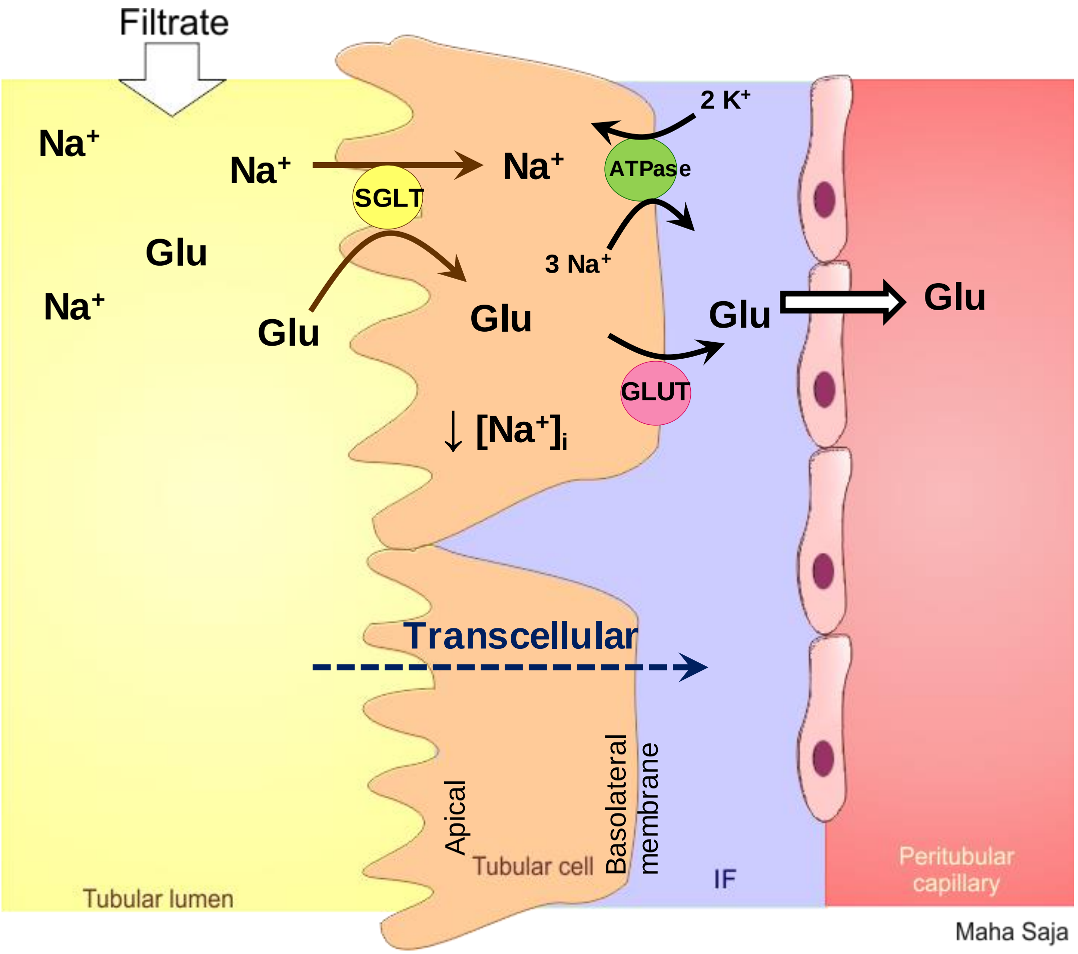
- Co-transporters.
- Exchangers (counter-transporters).

How Does the Proximal Tubule Reabsorb Glucose?

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 SGLT carrying glucose with it.



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

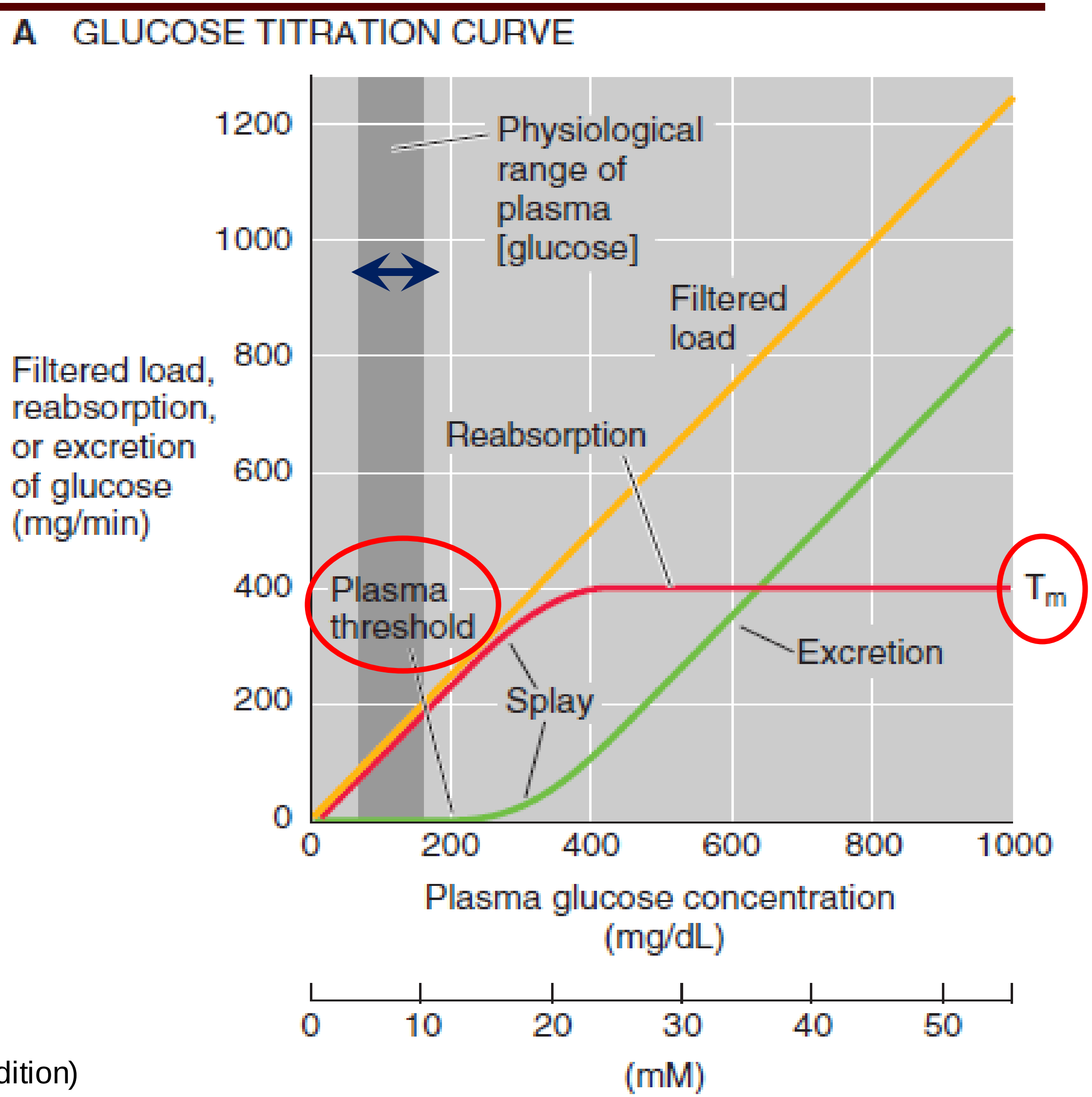
The Relationship Between Plasma [Glucose] and its Urine Excretion

What are the features of this glucose titration curve?

What is the plasma threshold of glucose?

What is meant by transport maximum (Tm)? Why does it occur?

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



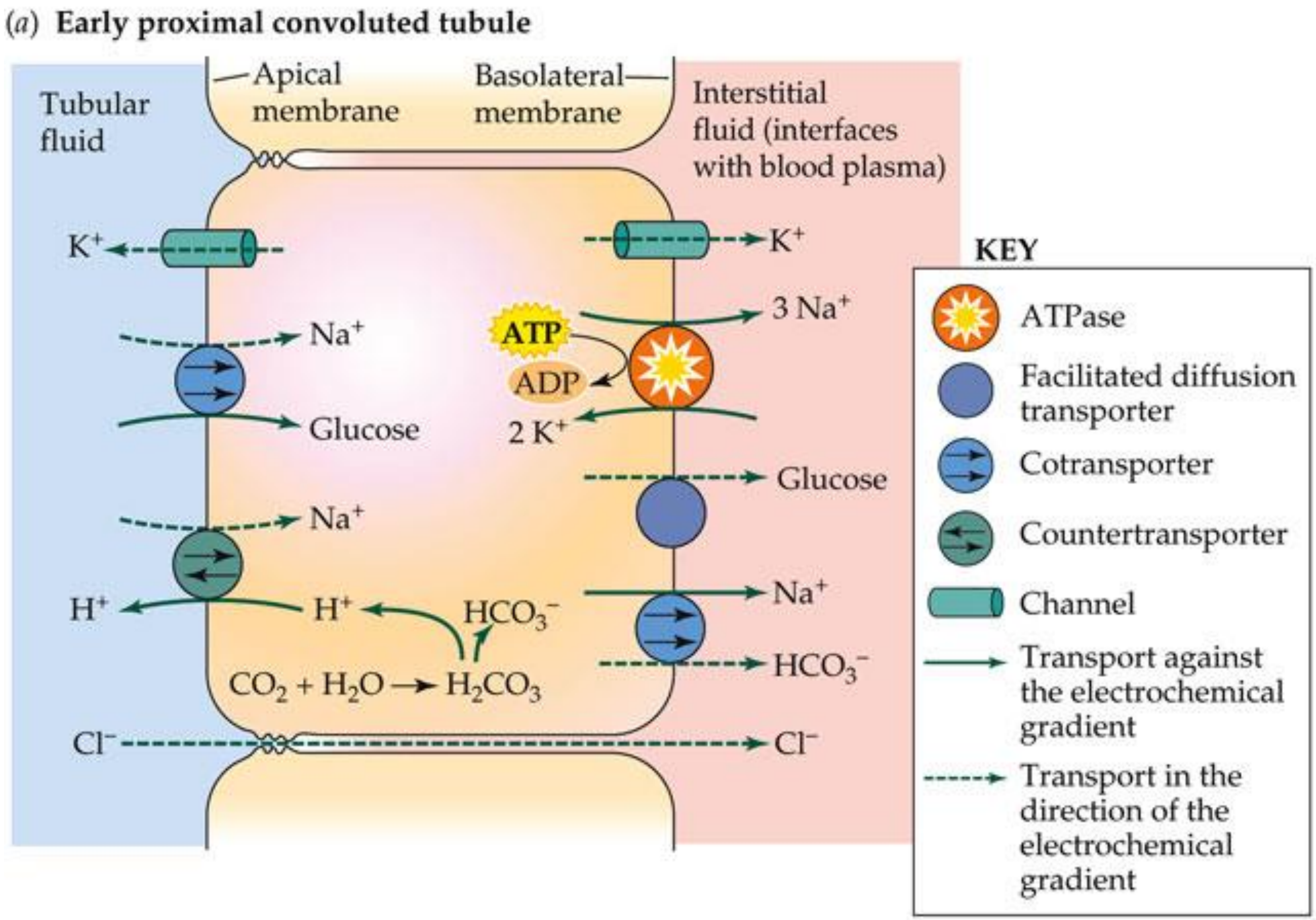
(Boron & Boulpaep. Medical Physiology. Updated edition)

Summary of PT Transport Mechanisms

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

Results in low $[Na^+]i$

This gradient favours Na^+ entry across the apical membrane via transporter proteins



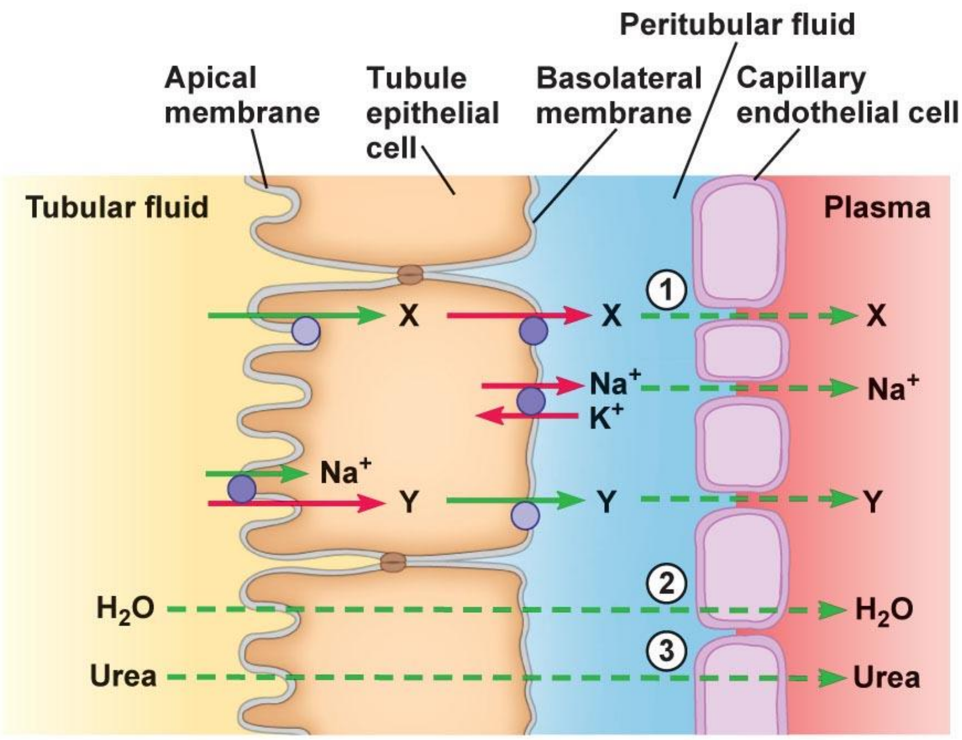
Animal Physiology 2e, **Figure 28.16 (Part 1)**

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^+, 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^+ reabsorption is coupled to that of;

- Glucose.
- Amino acids.
- Lactate.
- Phosphate

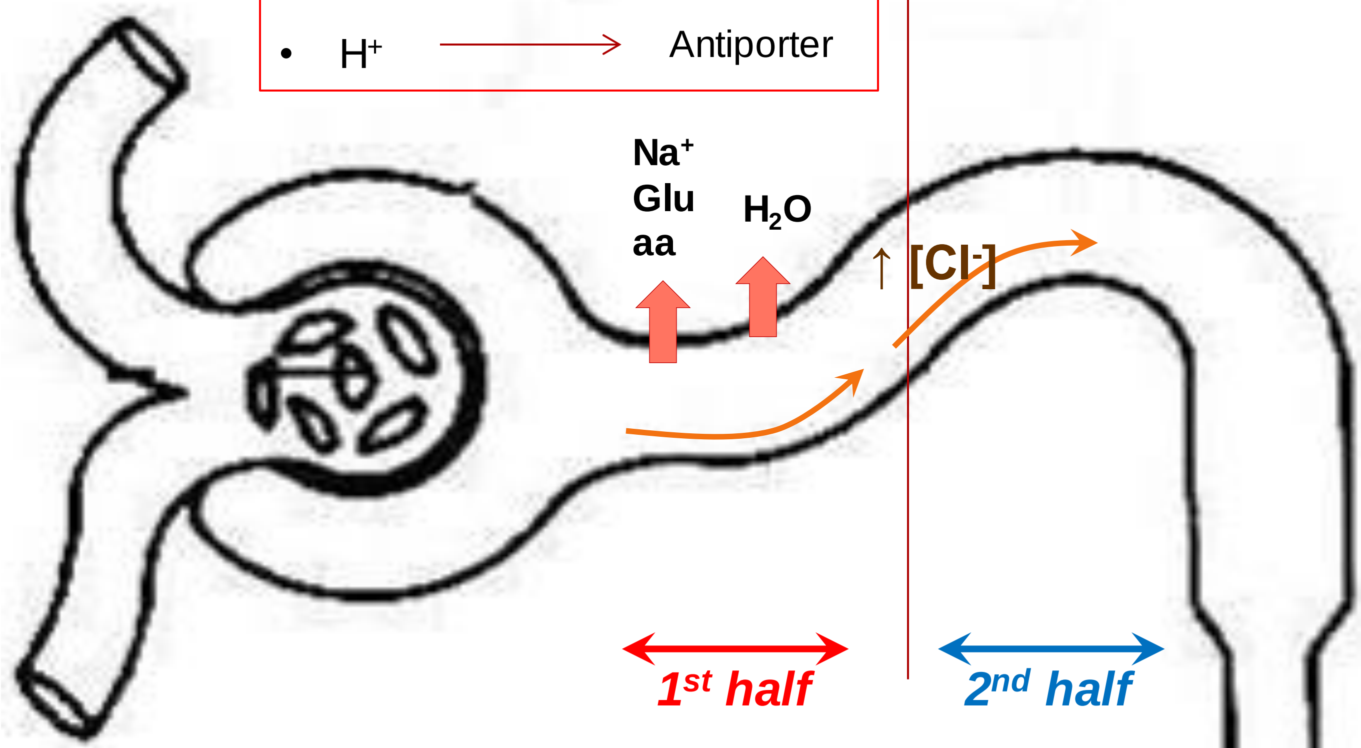
} Symporters

- H^+ → Antiporter

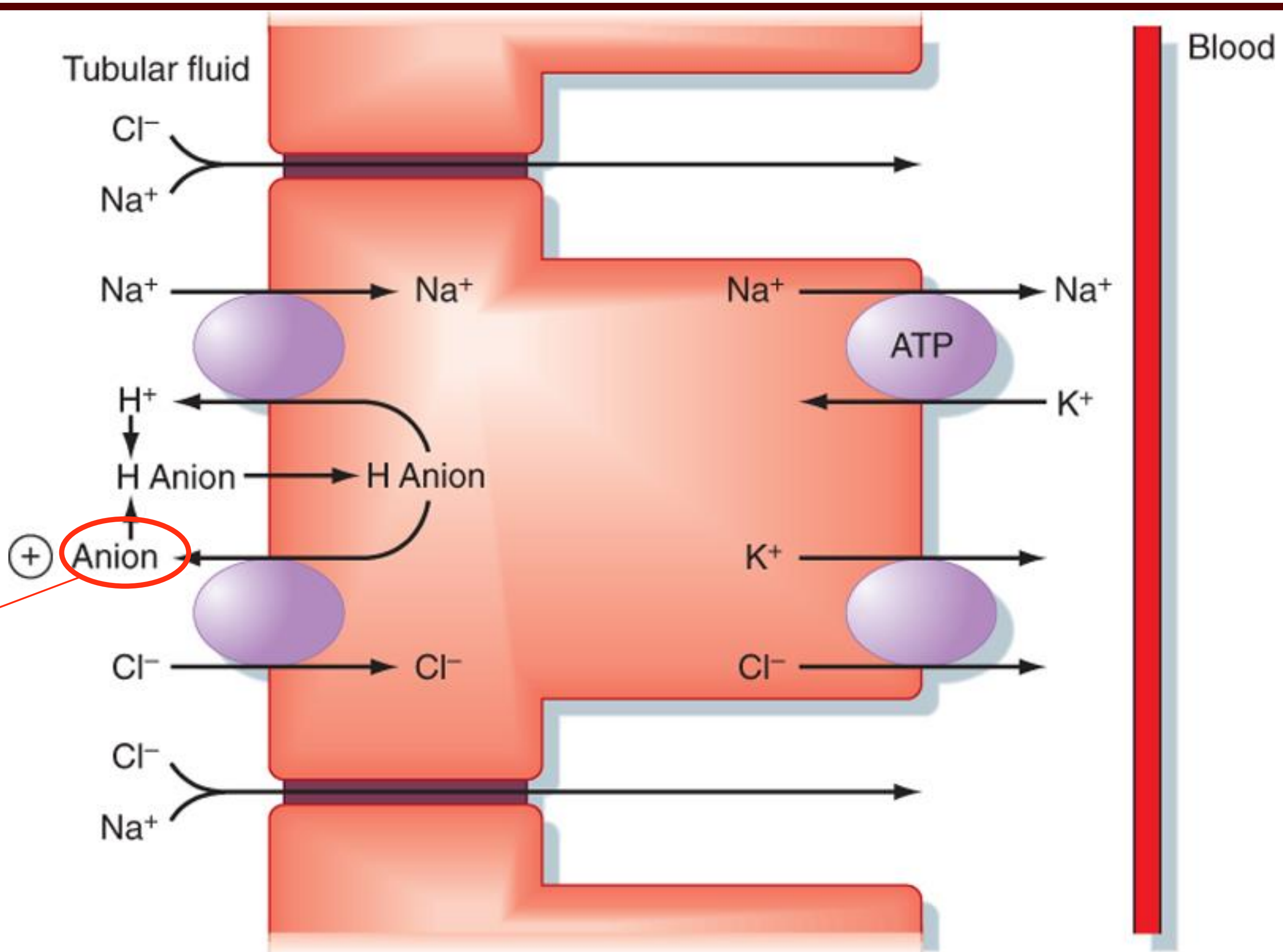
Na^+ reabsorption is mainly coupled to that of;

- Cl^-

Why??



Sodium Chloride Reabsorption in the 2nd Half of PT



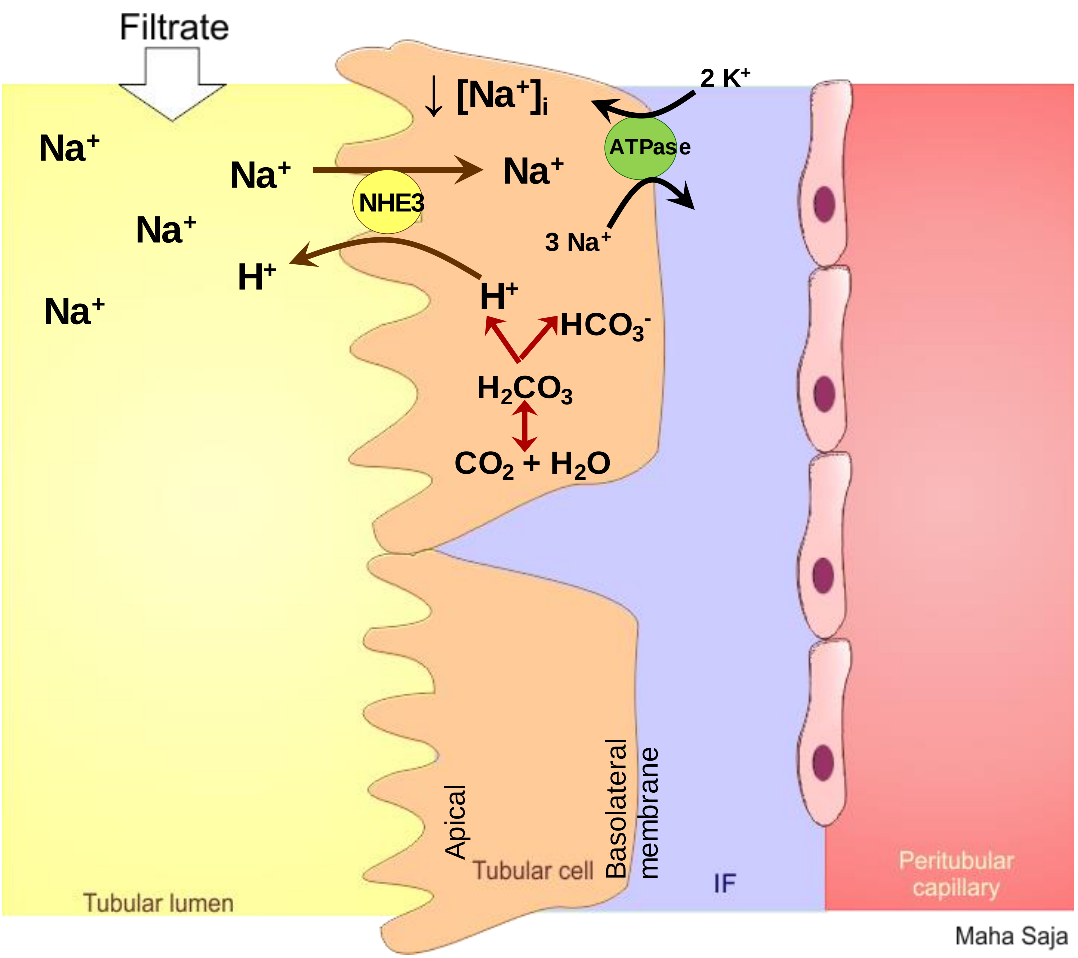
e.g.
Formate
Oxalate
Sulfate

How Does the Proximal Tubule Secrete Hydrogen Ions?

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

Results in low $[Na^+]i$

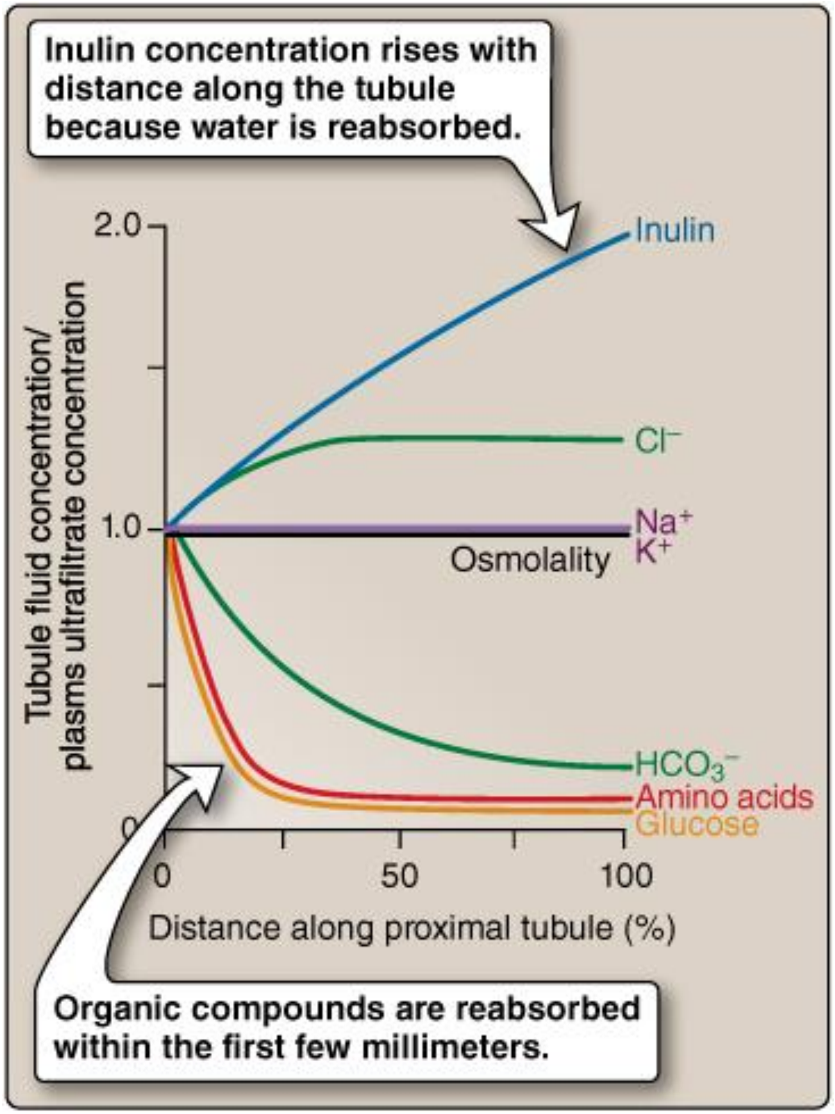
This gradient favours passive entry of Na^+ into the tubular cell across the apical membrane via NHE in exchange with H^+.



Organic Anion/Cation Secretion

Organic Anions	Organic cations
• Endogenous: • Bile salts. • Oxalate. • Urate. • Vitamins (ascorbate, folate). • Exogenous: • Acetazolamide. • Furosemide. • Salicylates. • Penicillin.	• Endogenous; • Creatinine. • Dopamine. • Epinephrine. • Norepinephrine. • Exogenous; • Atropine. • Morphine. • Amiloride. • Procainamide.

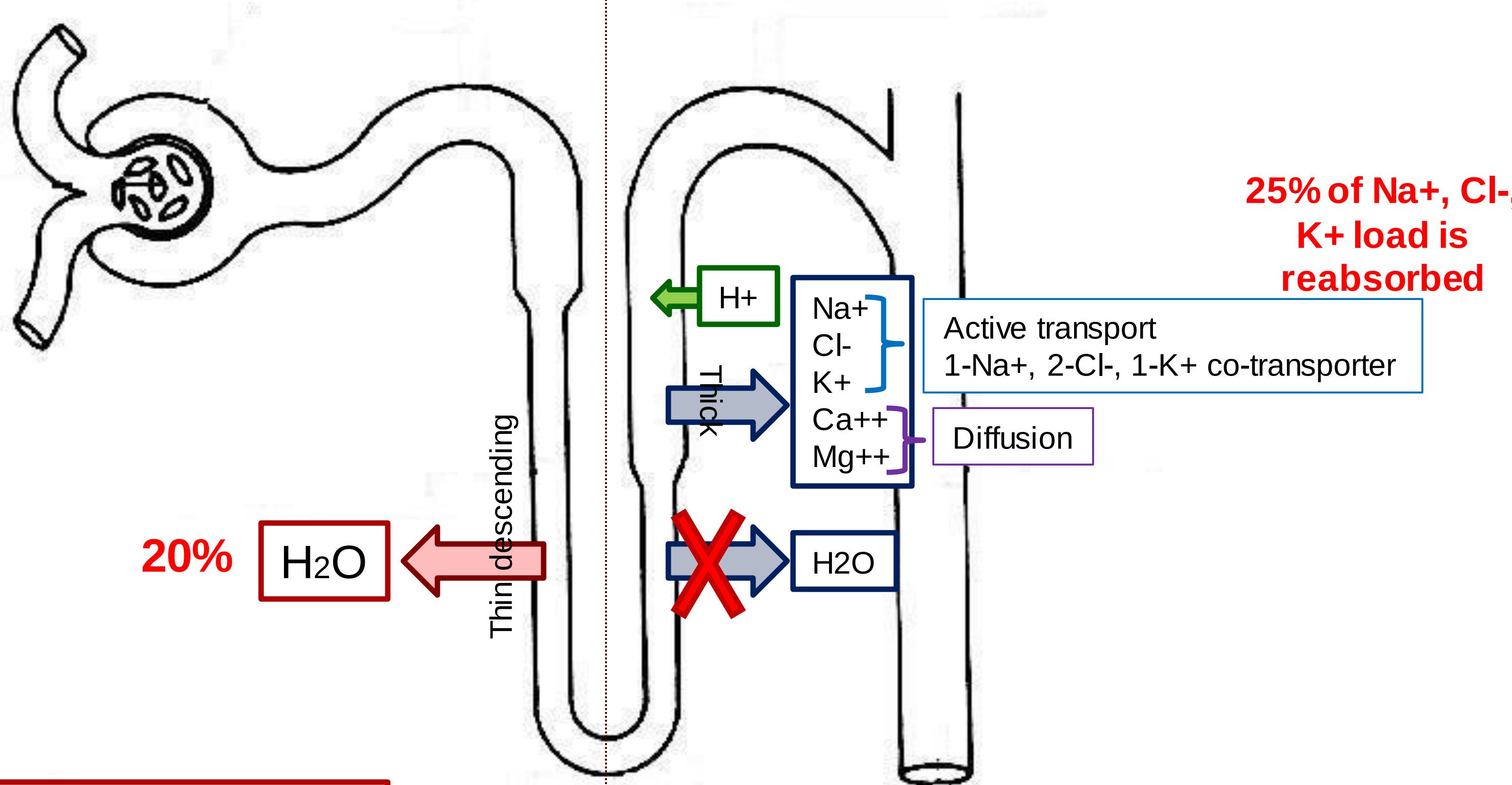
Summary of PCT Filtrate Modification



LOOP OF HENLE

Loop of Henle

Descending limb | **Ascending limb**



- Highly permeable to water
- Moderate permeability to solutes

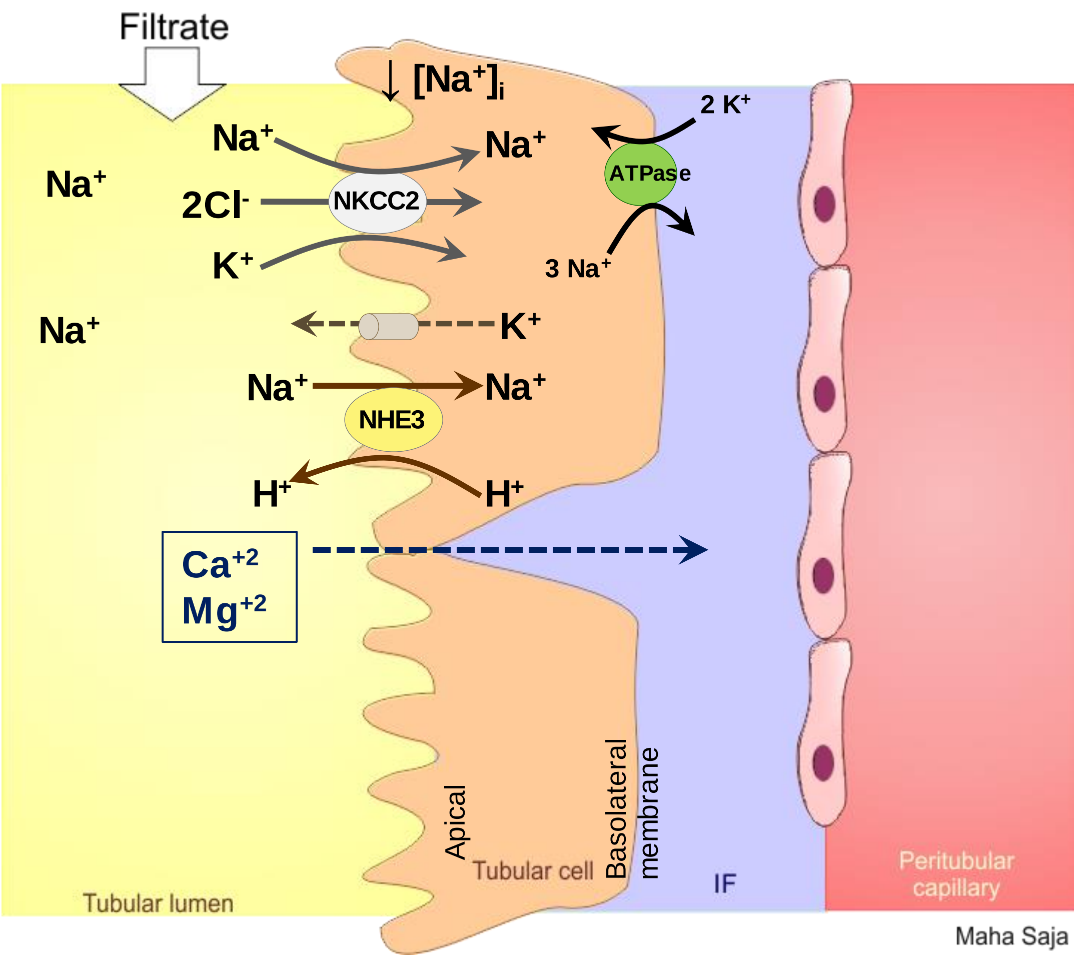
- *Impermeable* to water
- Reabsorption of solutes in the thick segment

Transport Mechanisms in the TAL

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 NKCC2 along with Cl^- & K^+.



Loop diuretics block NKCC2

DISTAL TUBULE & COLLECTING DUCT

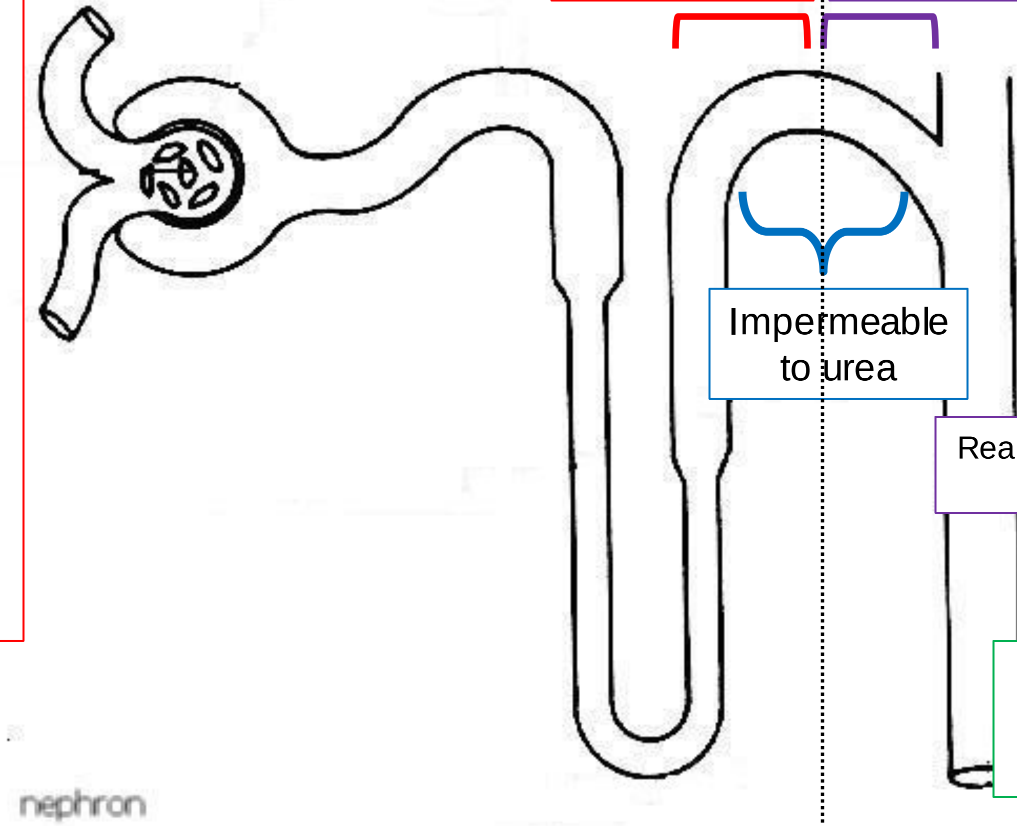
Transport Across the Distal Tubule

Resembles the thick ascending loop of Henle

Known as *the diluting segment*

Reabsorbs 5% of NaCl

Early part | **Late part**



Impermeable to urea

Resembles the cortical collecting tubule

Principal cells

Reabsorb Na+ & H2O
Secrete K+

Controlled by Aldosterone

Intercalated cells Type A

Reabsorb K+
Secrete H+

Acid-base regulation

Permeability to H_2O depends on *ADH*

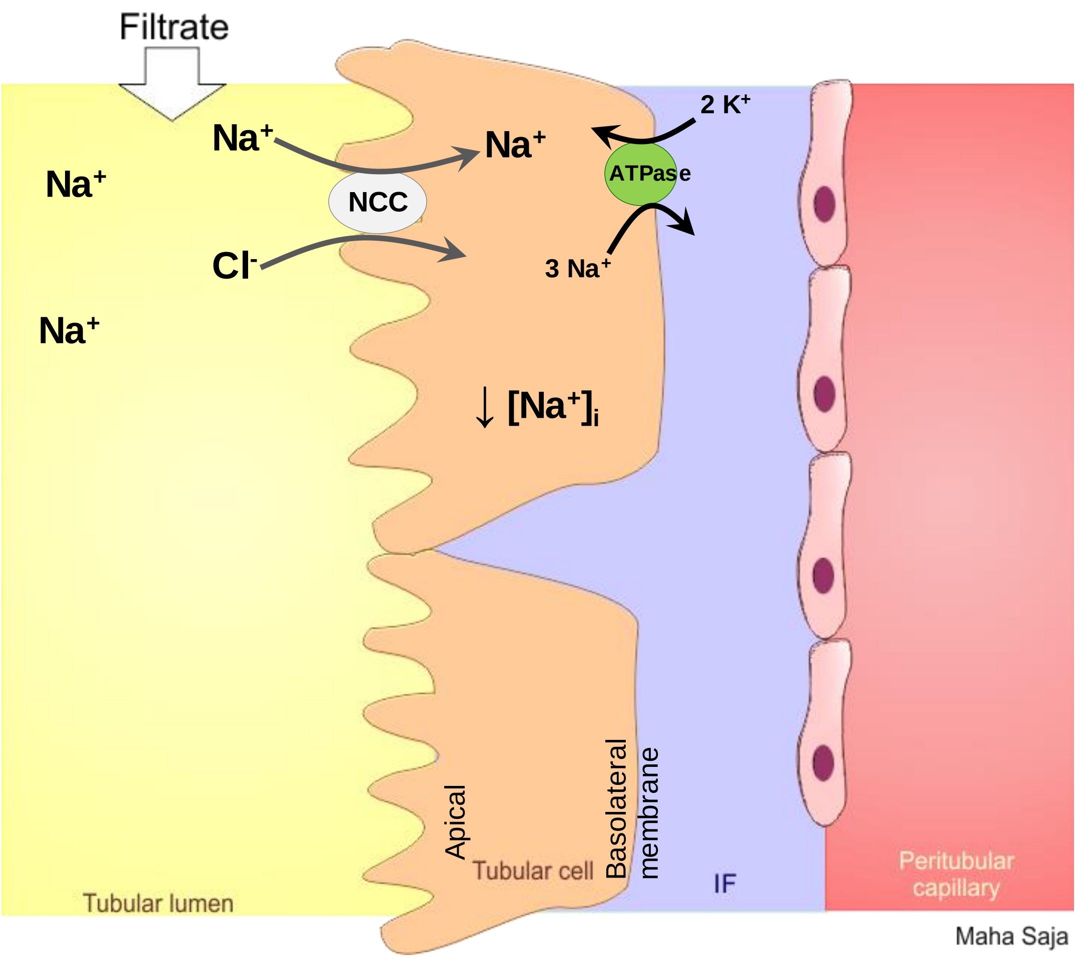
(Guyton & Hall Medical Physiology, 12e)

Transport Mechanisms in the Early DT

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

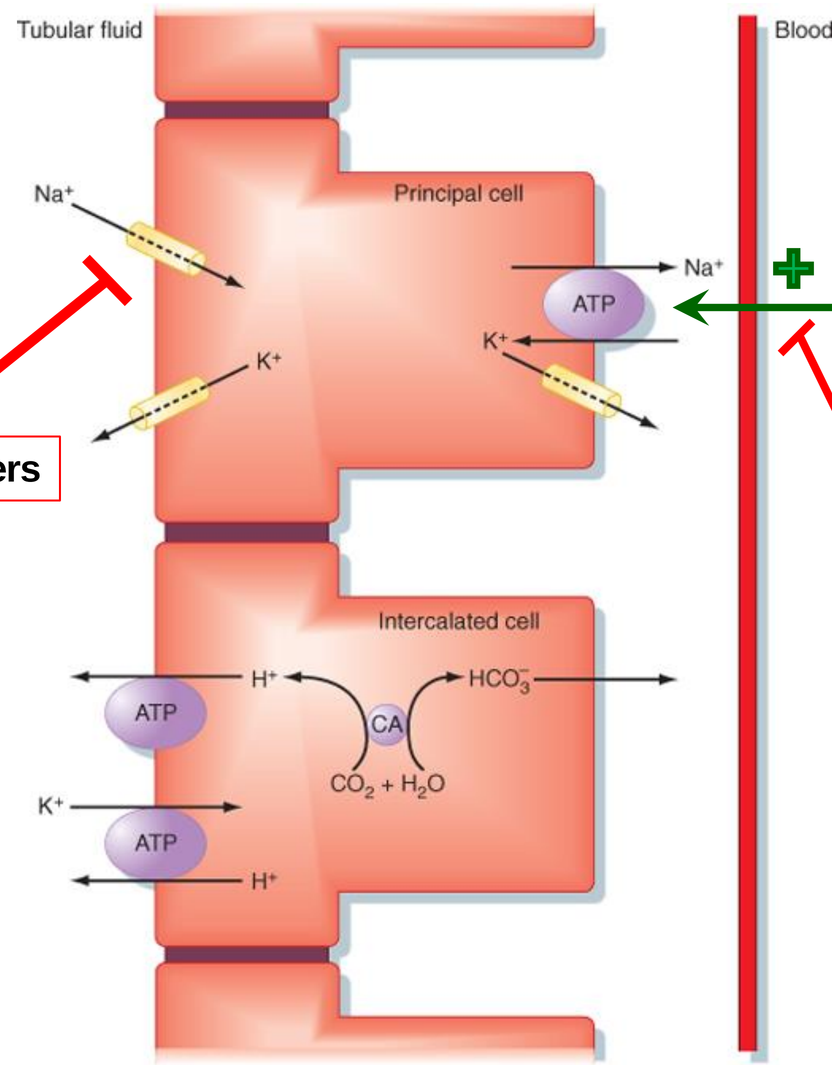
Results in low $[Na^+]i$

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



Thiazide diuretics block NCC

Late Distal Tubule & Collecting Tubule



Aldosterone

Aldosterone antagonists
e.g. Spironolactone

Na+ channel blockers

Potassium-sparing diuretics

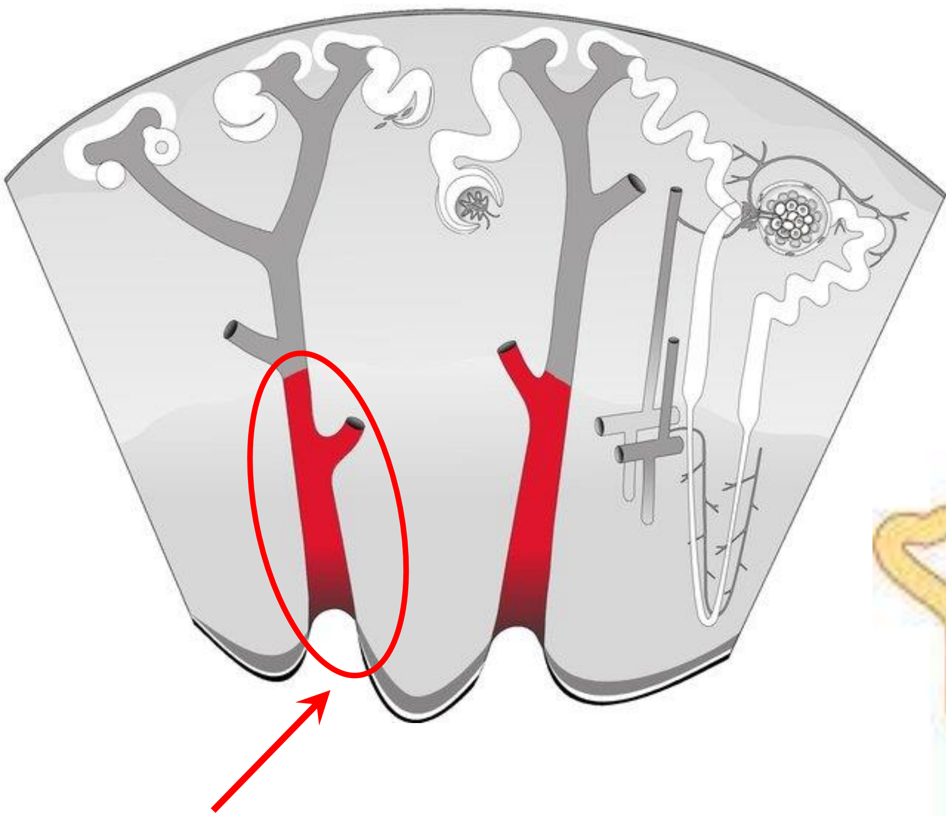
Medullary Collecting Duct

Reabsorbs ≈ 3% of filtered Na^+

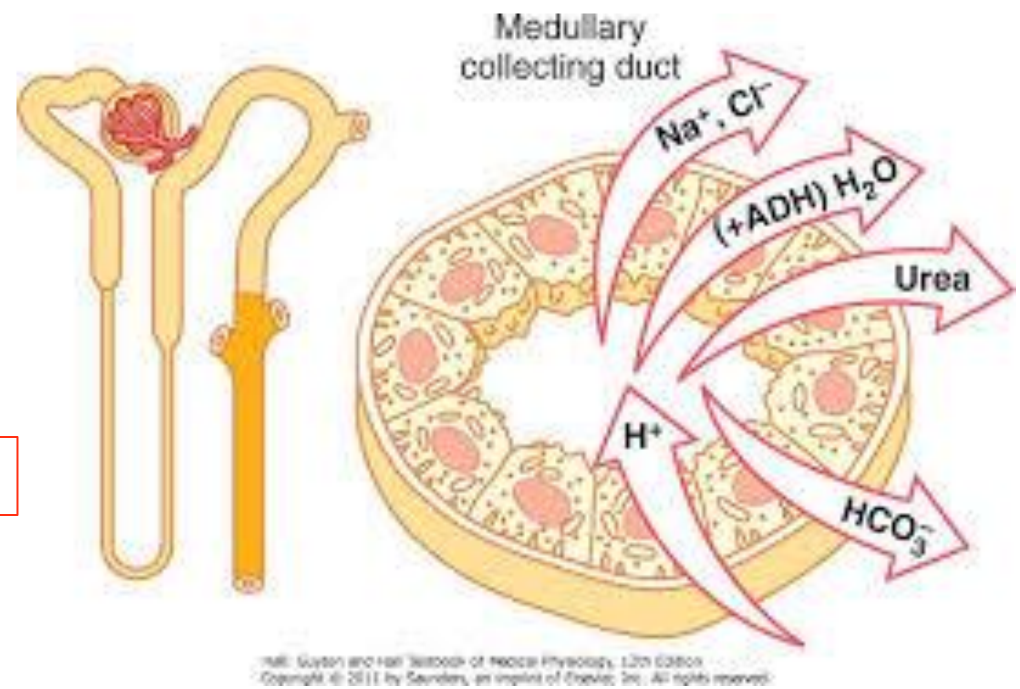
Permeability to water is under ADH control

Permeable to urea

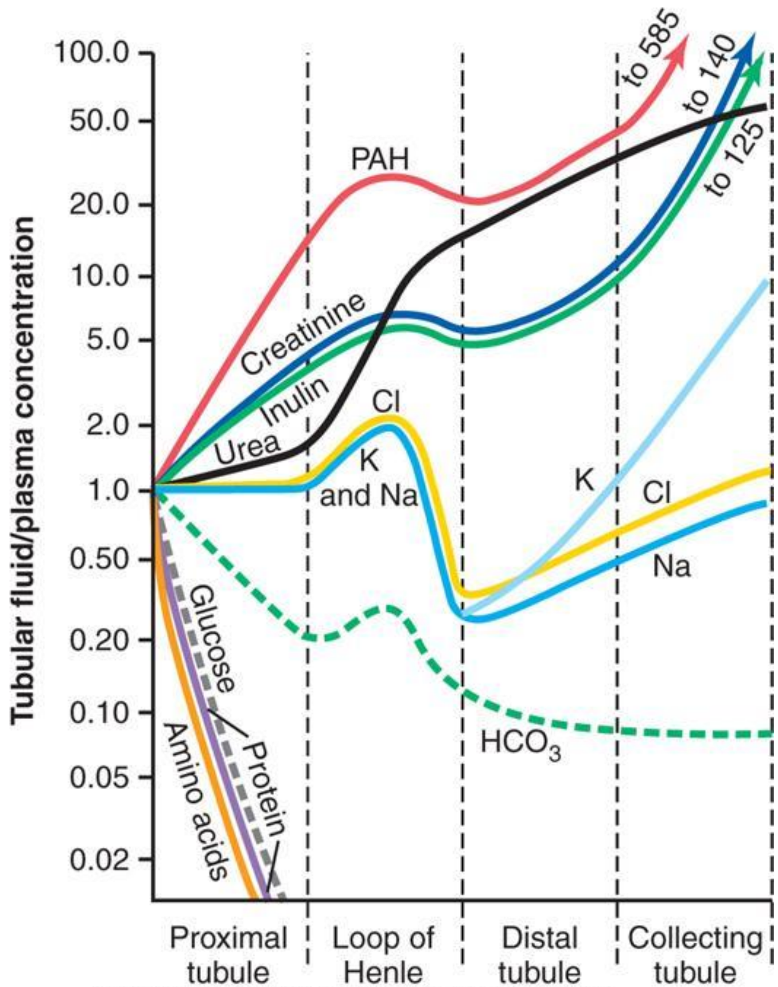
Secrete H+



Reabsorbs ≈ 3% of filtered Na^+



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



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

REGULATION OF TUBULAR REABSORPTION

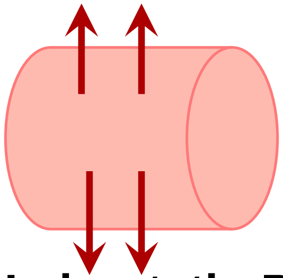
Regulation of Tubular Reabsorption

- ***Regulation of tubular reabsorption depends on***:
  1. Physical forces that govern reabsorption.
  2. Hormonal and neural mechanisms.

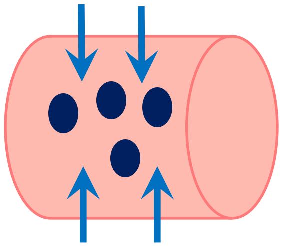
- Tubules can increase their reabsorption in response to increased tubular load → ***glomerulo-tubular balance.***

- ***What are the physical forces that govern tubular reabsorption?***

Pushes fluid ***out***



Hydrostatic Pr. (P)



Pulls fluid ***in***

Oncotic Pr. (π)

Physical Forces that Govern Tubular Reabsorption

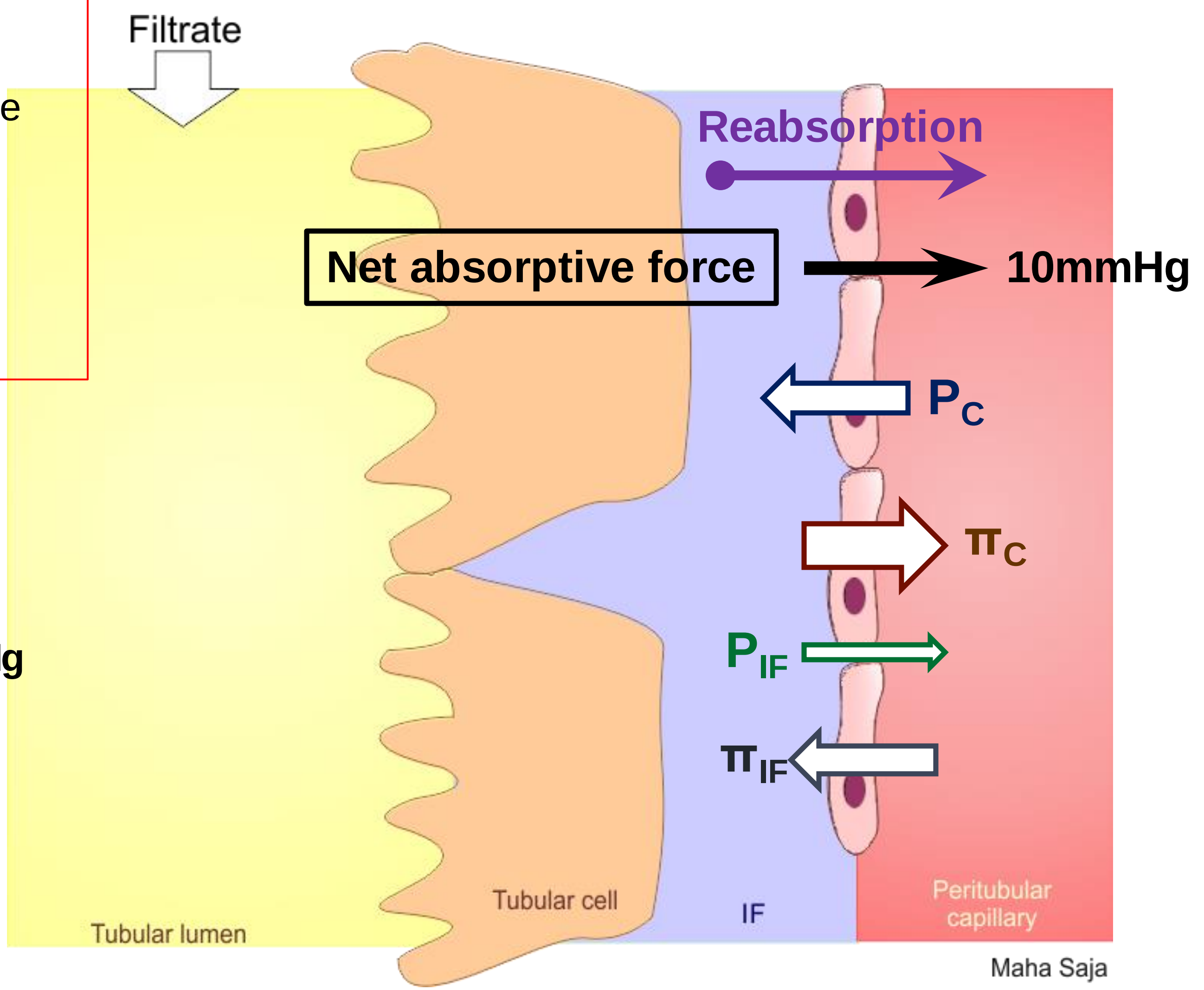
P_C is influenced by:
- ABP.
- Aff & Eff arteriolar resistance

π_C is influenced by:
- FF.
- Systemic plasma colloid osmotic pr.

Reabsorption

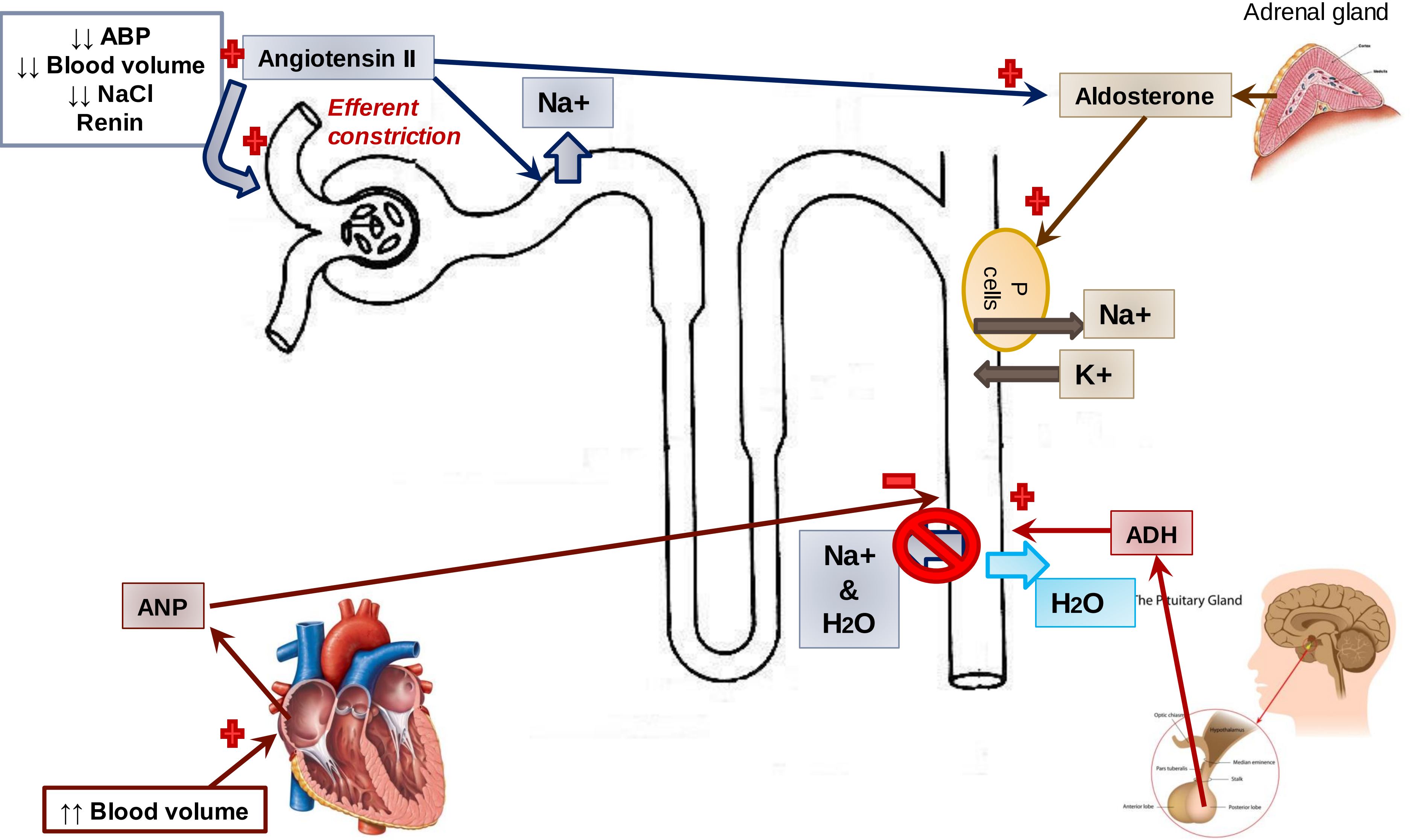
Favouring	***Opposing***
π_C = 32	**P_C = 13mmHg**
P_{IF} = 6	**π_{IF} = 15**
38	**28**

38 > 28

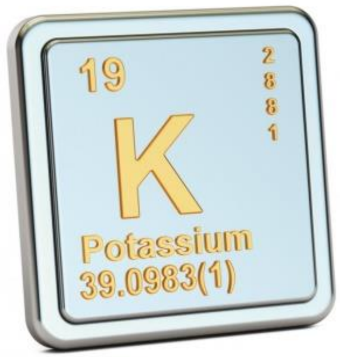


(Guyton & Hall Medical Physiology, 12e)

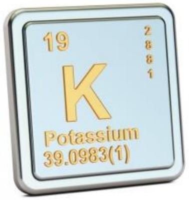
Hormonal Regulation of Tubular Reabsorption



REGULATION OF POTASSIUM



Potassium



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

The Importance of Regulating K^+

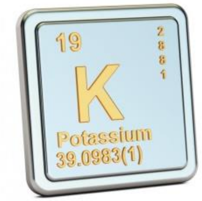
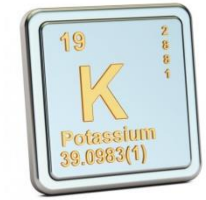


Table 37-1 Physiological Role of K^+ Ions

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

(Boron & Boulpaep. Medical Physiology)

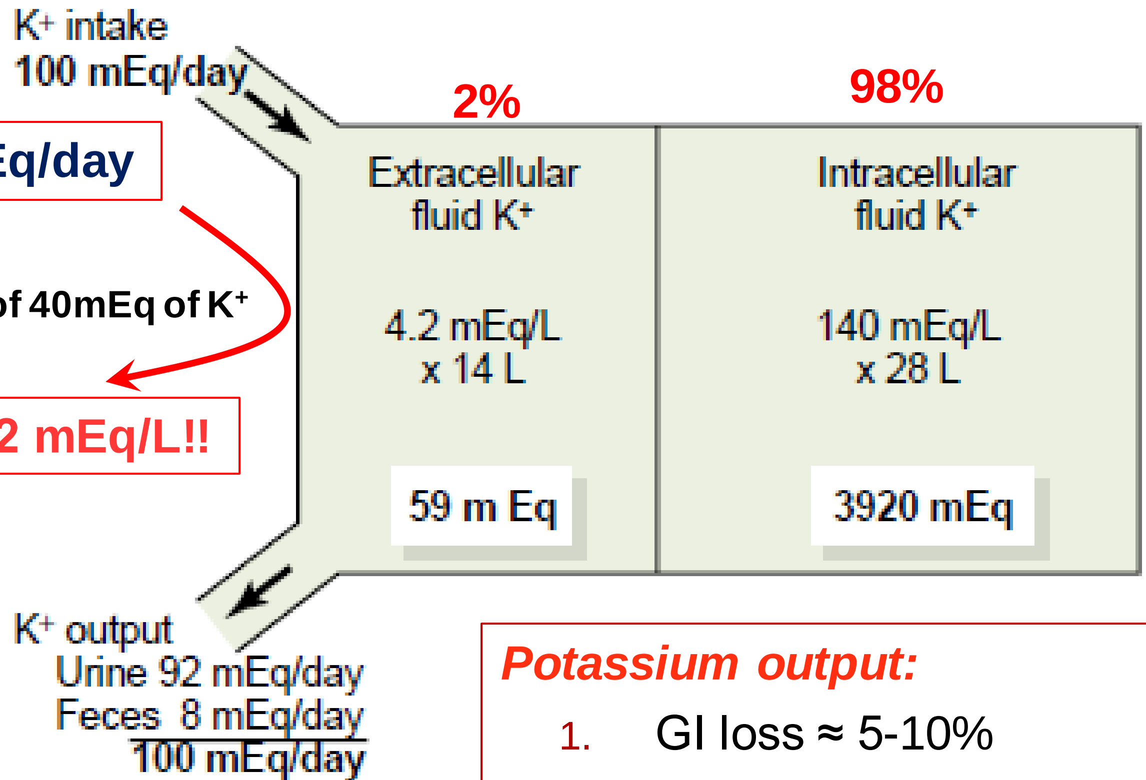
Potassium Homeostasis



Diet 50-200mEq/day

Absorption of 40mEq of K^+

↑ $[K^+]$ in ECF ≈ 2 mEq/L!!



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

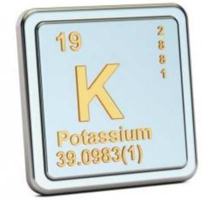
Potassium output:

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^{st} 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?

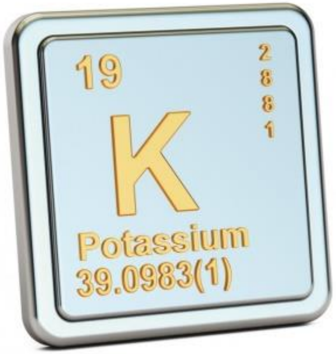
Renal excretion

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

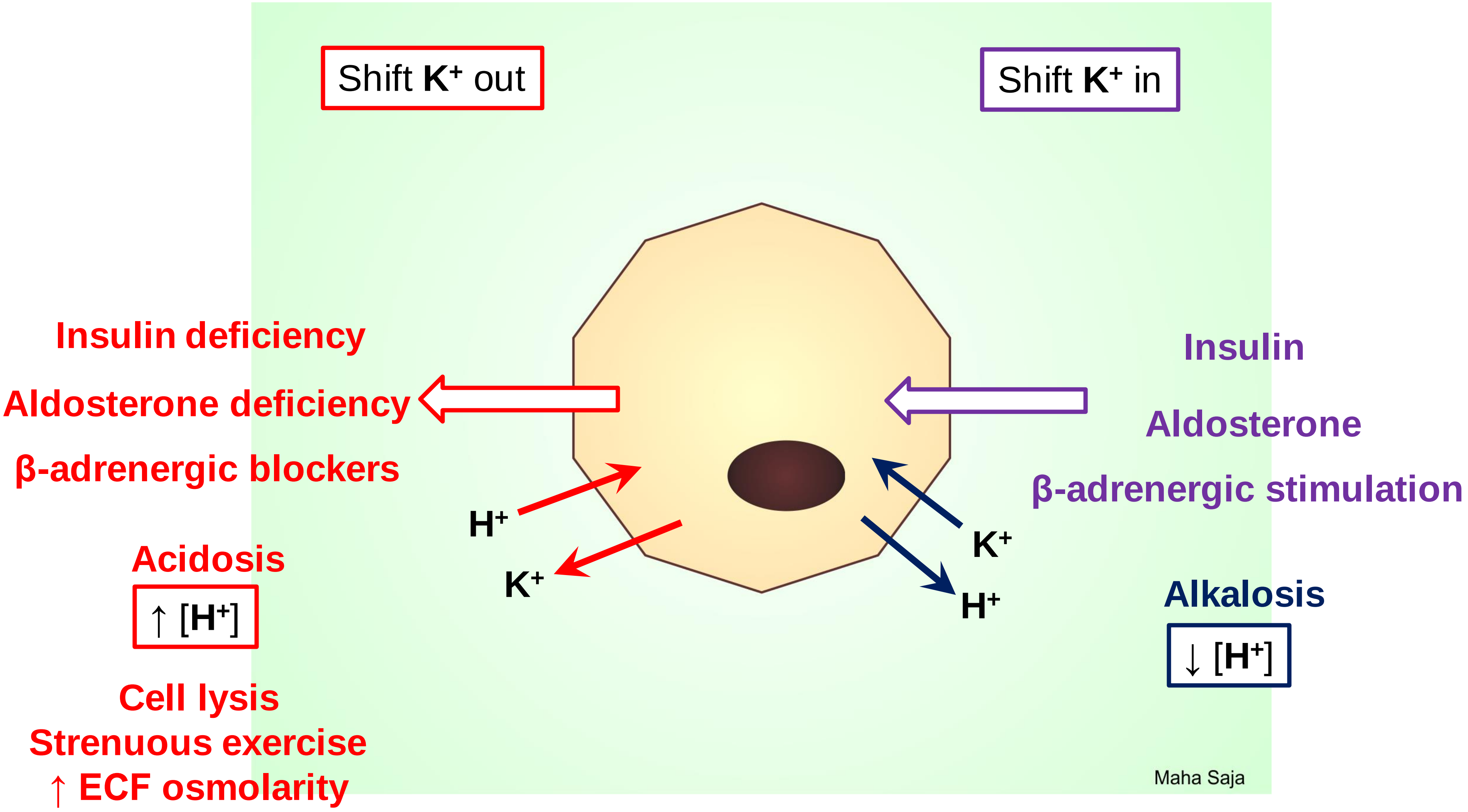
↑↑ excretion of K^+
↓↓ excretion of K^+

How does the kidney achieve that?

CELLULAR SHIFT



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



Factors Affecting K^+ Distribution Between ICF and ECF

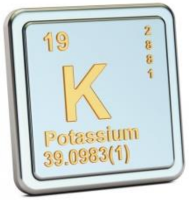


Table 29–1

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

Factors That Shift K^+ into Cells (Decrease Extracellular $[K^+]$)	Factors That Shift K^+ Out of Cells (Increase Extracellular $[K^+]$)
• Insulin	• Insulin deficiency (diabetes mellitus)
• Aldosterone	• Aldosterone deficiency (Addison's disease)
• β-adrenergic stimulation	• β-adrenergic blockade
• Alkalosis	• Acidosis
	• Cell lysis
	• Strenuous exercise
	• Increased extracellular fluid osmolarity

(Guyton & Hall Medical Physiology, 12e)

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

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

(Boron & Boulpaep Medical Physiology-updated edition)

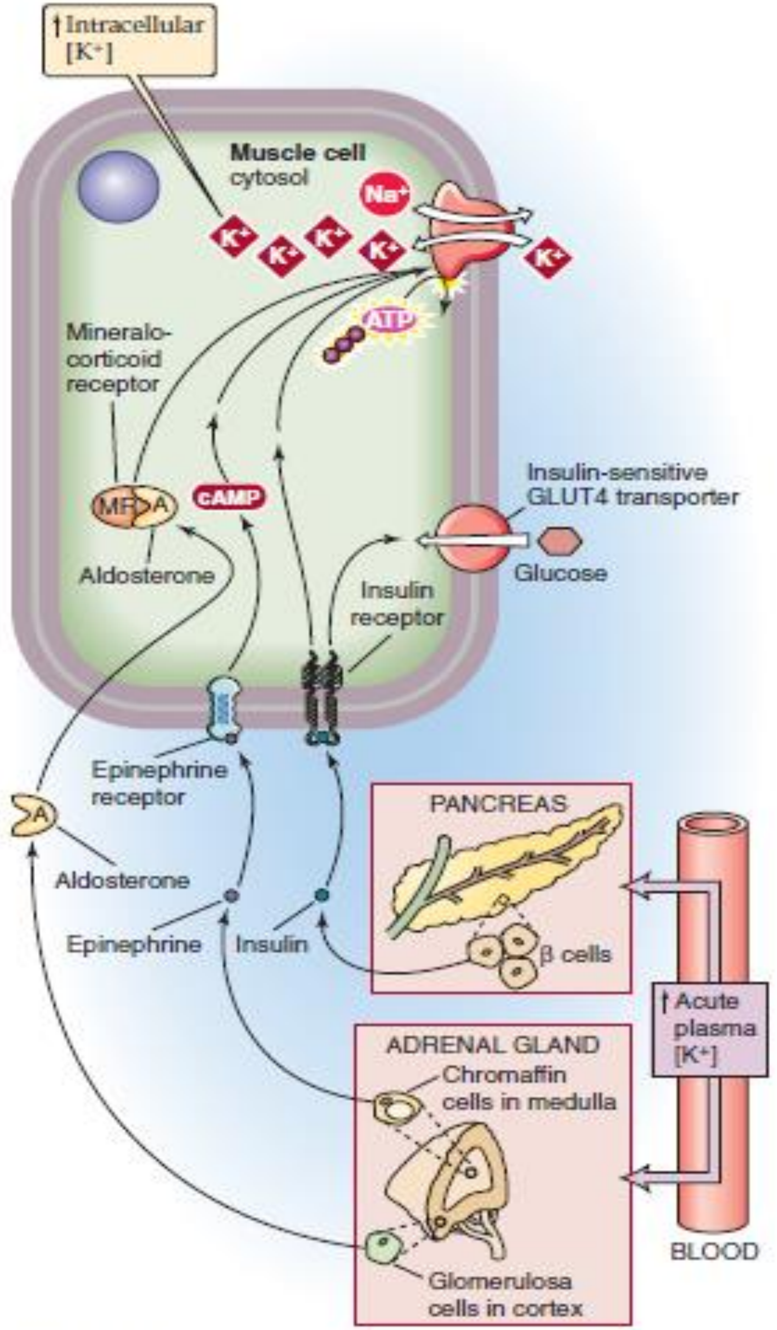
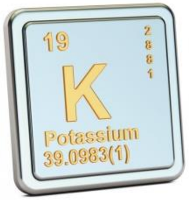


Figure 37-3 K+ uptake into cells in response to high plasma [K+].

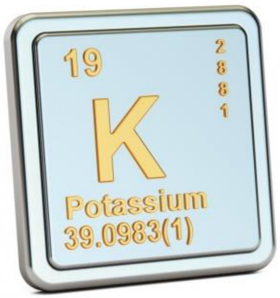
Pathophysiologic Factors Affecting K^+ Distribution Between ICF and ECF



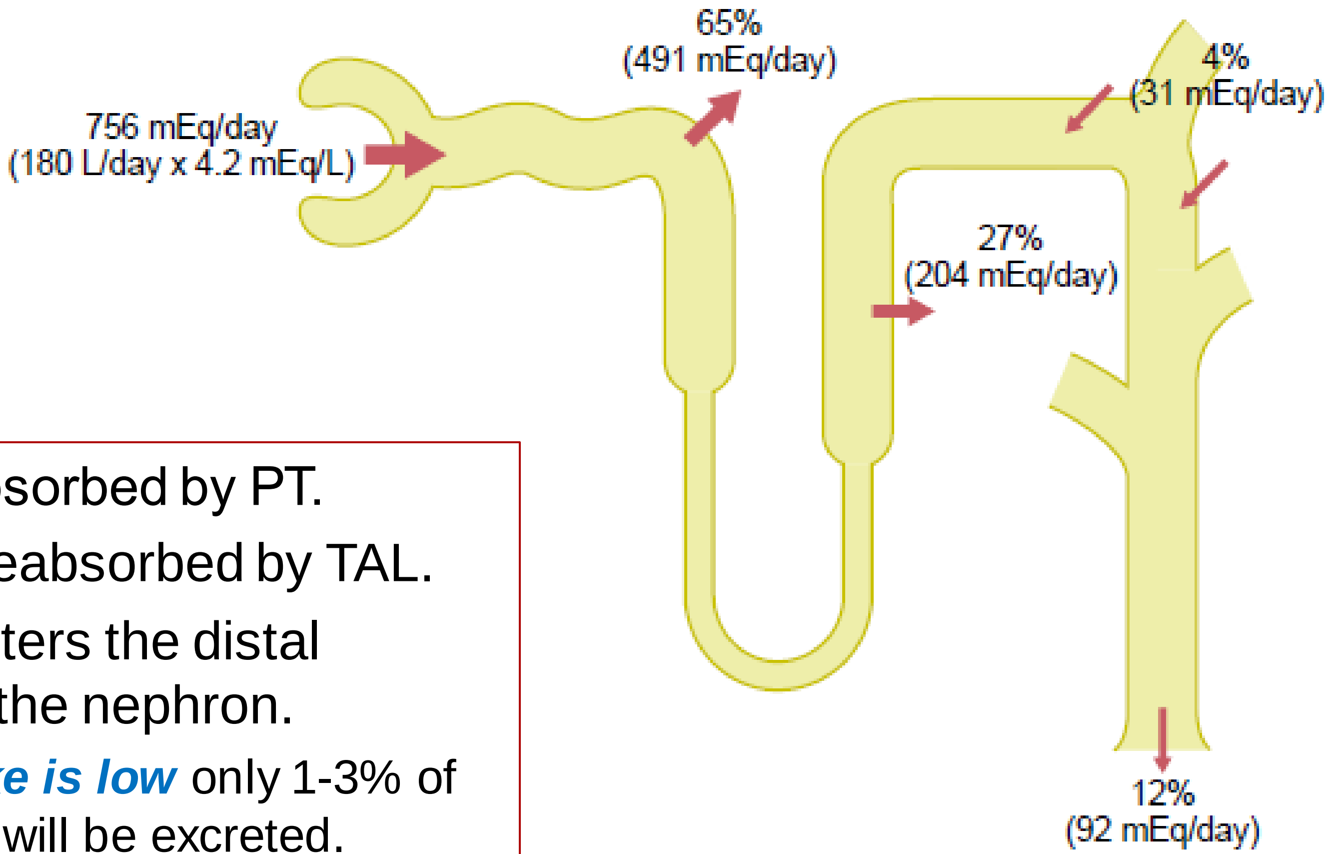
- Acid base disturbance.
- Change in plasma osmolality.
- Cell lysis.
- Exercise.

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

RENAL POTASSIUM EXCRETION



Renal Potassium Handling

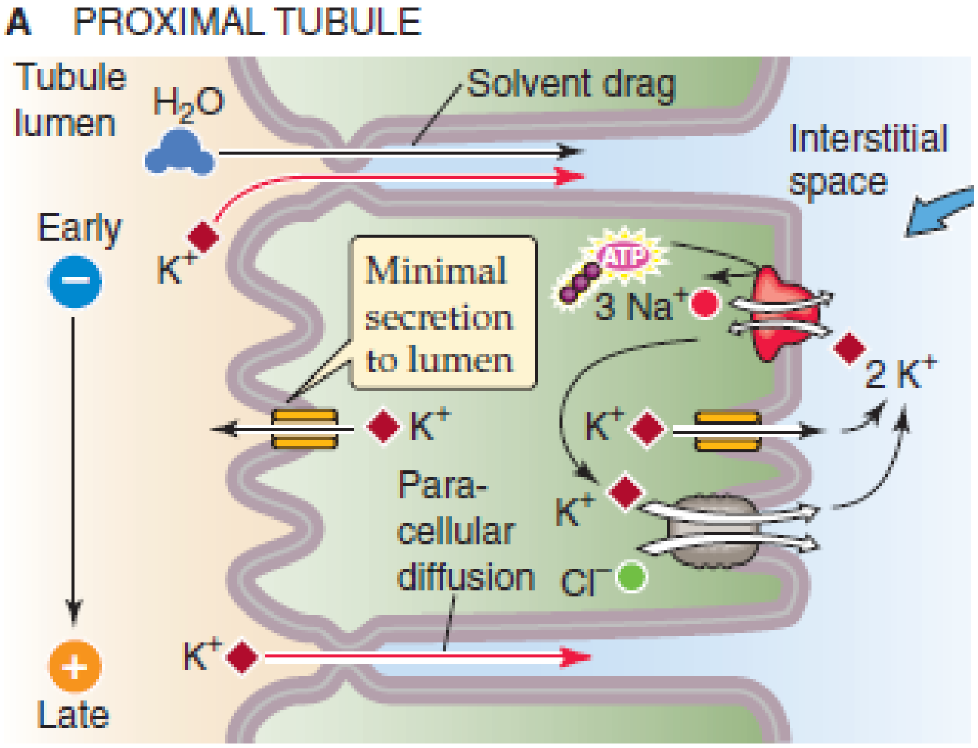


- ≈ 65% reabsorbed by PT.
- ≈ 25-30% reabsorbed by TAL.
- ≈ 5-10% enters the distal portions of the nephron.
  - ***If K^+ intake is low*** only 1-3% of filtered K^+ will be excreted.
  - ***If K^+ intake is normal/high***, 10-15% of filtered K^+ will be excreted

Potassium Handling by the kidney

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

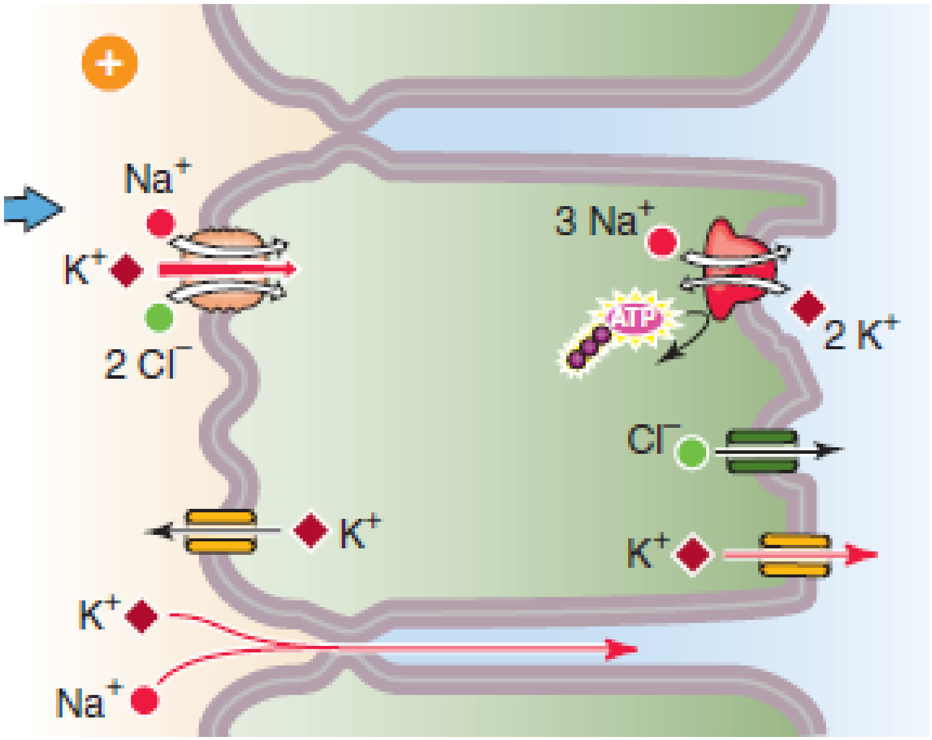
Water reabsorption through the paracellular route drags K^+ with it (***solvent drag***).



Potassium Handling by the TAL

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

B THICK ASCENDING LIMB (TAL)

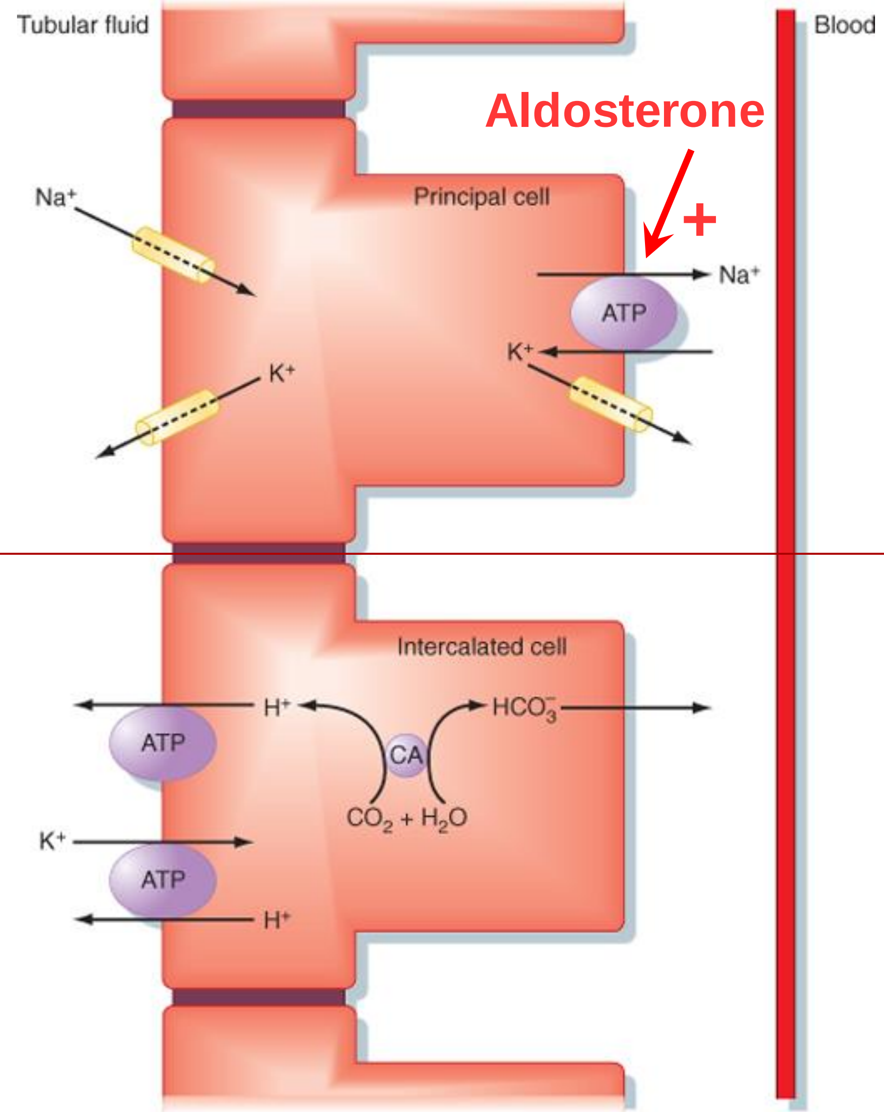


Potassium Handling by the Distal Portions of the Nephron

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

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

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



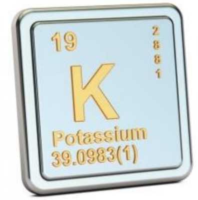
Principle cells

Reabsorb Na^+ and water & secrete K^+

α-intercalated cells

Secrete H^+ and reabsorb K^+

Factors Regulating Potassium Secretion



Factors that ***stimulate*** potassium secretion:

1. ↑↑ ECF [$\mathbf{K}^+$].
2. ↑↑ aldosterone.
3. ↑↑ tubular flow rate.

Factors that ***decrease*** potassium secretion:

- Acidosis (↑↑ [$\mathbf{H}^+$])

THANK YOU