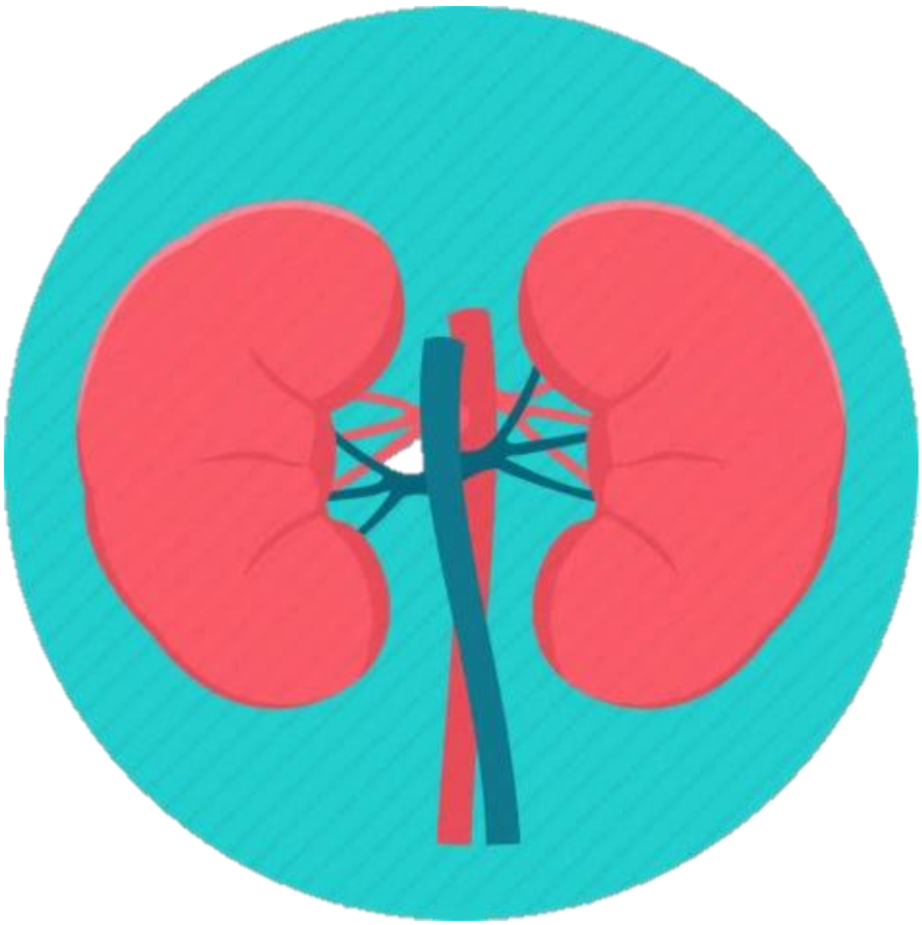
Lecture (5-6)

Renal Transport



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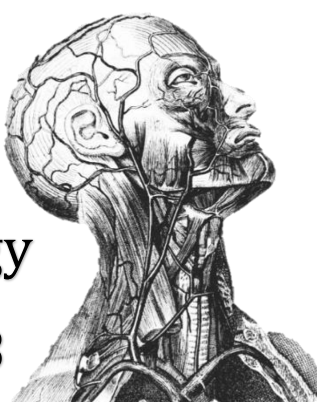
Physiology

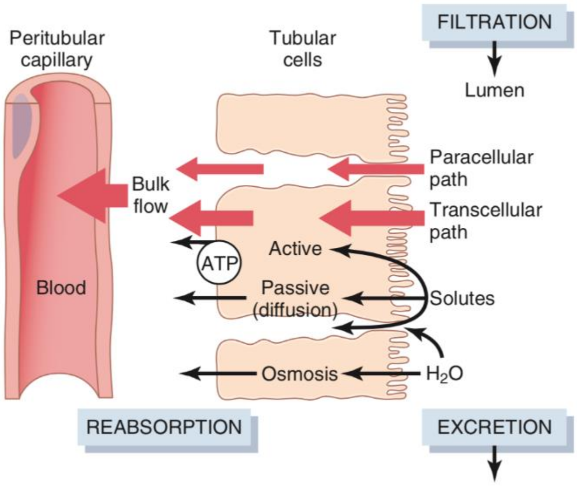
MED438



Tubular Transport:

- **Tubular reabsorption** is the **active** reabsorption of substances from the glomerular filtrate into peritubular capillary blood
- Most reabsorption occurs in the **PCT** because of highly metabolic cells, extensive brush border and an abundance of mitochondria
- **Tubular secretion** is the **active** secretion of substances from the peritubular capillaries to the renal tubules

- Glomerular filtration is non-selective whereas **tubular reabsorption is highly selective.**

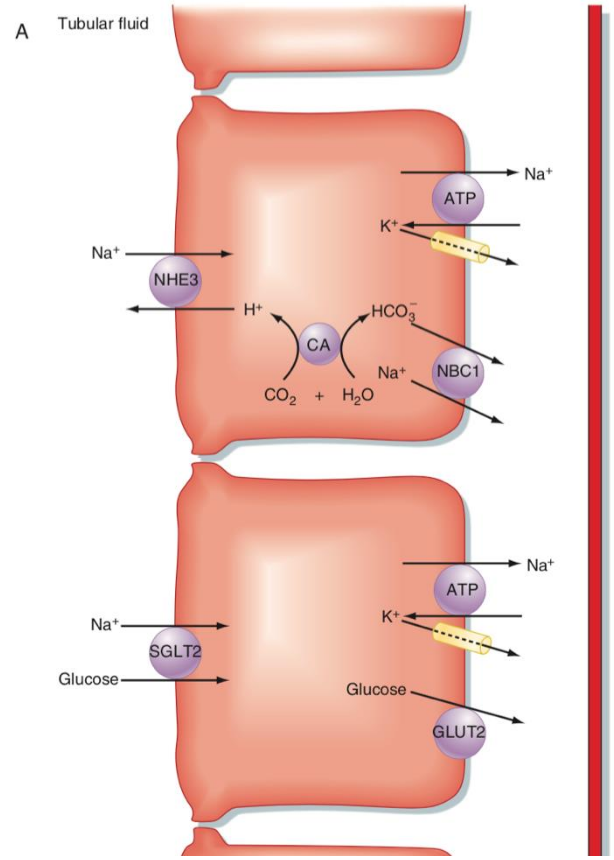


Reabsorption is a 2 step process:

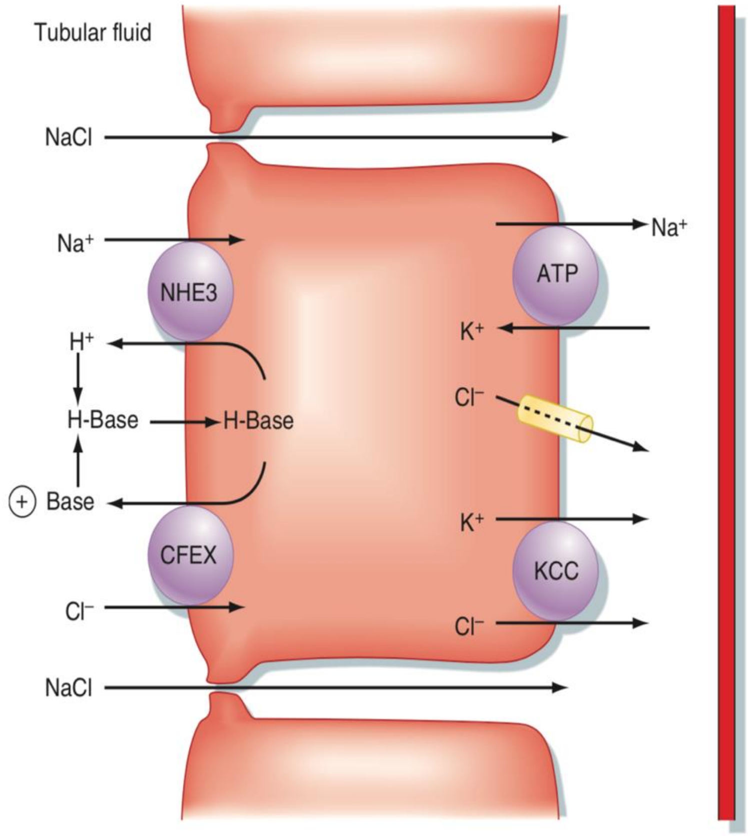
- First: transport of substance from the tubular lumen to the IF
  - ➔ Transport can be **active** (require ATP, against electrochemical gradient) or **passive** (water solutes like like Cl-Urea)
    - o Active transport can be **primary** (direct use of ATP) or **secondary** (indirect use)
  - ➔ Occur through **paracellular** (between cells) or **transcellular** (through the cell) routes
- Second: transport from IF to blood by ultrafiltration or bulk flow due to osmotic and hydrostatic forces

PCT Reabsorption

Early



Late



Basolateral membrane:

- Na/K pump (primary active)
- ($3Na^+$ out $2k^+$ into the cell)→ low $[Na^+]i$ (this gradient favours Na^+ entry across the apical membrane via transporter proteins)
  ➔ Driving osmotic force

Apical membrane (secondary active):

- **NHE (Na/H exchanger)**
- **Na/Glucose symporter**
- Na/Amino acid, lactate, phosphate symporter

Basolateral membrane:

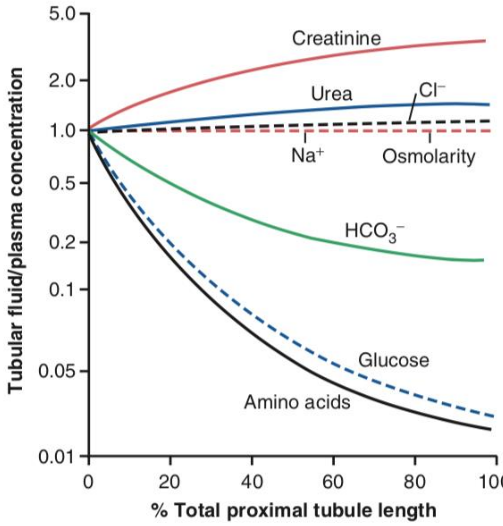
- Na/K pump (primary active)
  → driving osmotic force
- K/Cl cotransport

Apical membrane (secondary active):

- **NHE (Na/H exchanger)**
- **Cl/anion exchanger** (transcellular)
- NaCl diffusion (paracellular)

➔ **Cl replaces the organic molecules in late PCT due to the lack of organic molecules**

Water Reabsorption



- Water diffuse passively in transcellular and paracellular routes
- This diffusion is driven by the osmotic change due to Na^+ active diffusion
- Water osmosis balance the osmolality changes

Protein Reabsorption

- Minimal amount of proteins are reabsorbed through endocytosis
- Small proteins are intact
- Larger proteins are degraded by lysosomes
- Excess protein filtration will result in **proteinuria**, or protein in urine

Bicarbonate Reabsorption

- Bicarbonate cannot be reabsorbed directly instead it's reabsorbed as CO_2

1. In the lumen:

$$H^+ + HCO_3^- \rightarrow H_2CO_3$$

2. Extracellular Carbonic Anhydrase:

$$H_2CO_3 \rightarrow CO_2 + H_2O$$

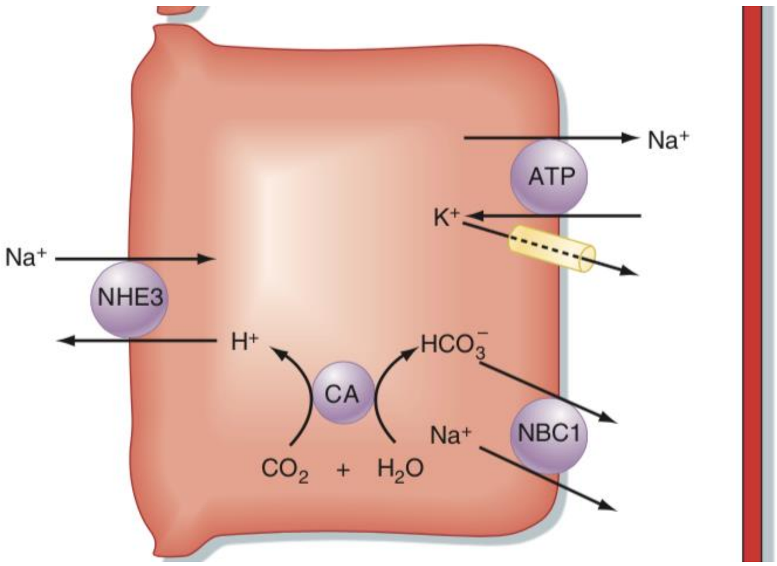
3. CO_2 is rapidly reabsorbed (lipophilic)
4. Intracellular Carbonic Anhydrase

$$CO_2 + H_2O \rightarrow H_2CO_3$$

5. Rapid dissociation:

$$H_2CO_3 \rightarrow H^+ + HCO_3^-$$

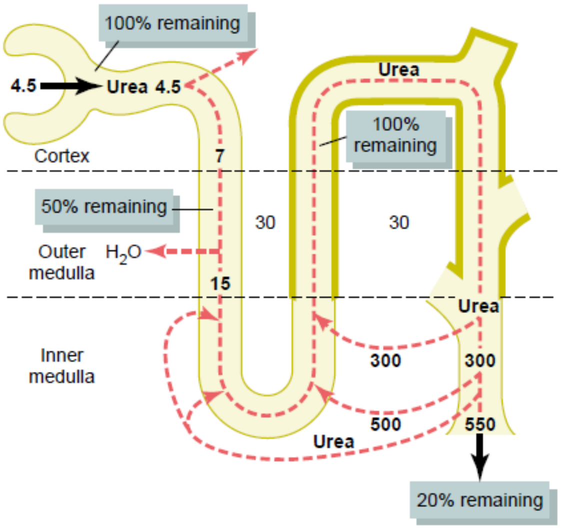
6. Bicarbonate is reabsorbed passively to the IF



Factors Affecting HCO_3^- reabsorption:

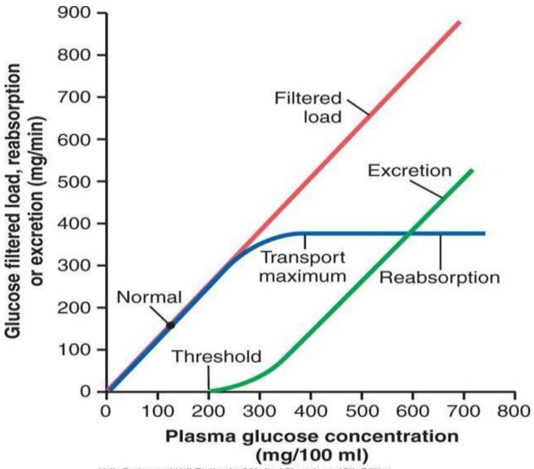
- Arterial P_{CO2} - Plasma $[K^+]$ - Plasma $[Cl^-]$ - Plasma aldosterone

Urea Reabsorption



- Normal level of plasma urea is 2.5-6.5 mM/L
- Urea is reabsorbed in two places:
  1. Second half of PCT
  2. Medullary CD **if ADH is present**
- Due to water reabsorption in the first half urea conc. Increase thus diffuse passively

Transport Maximum for Glucose **(important)**



- in normal conditions , as blood glucose level increase to certain limits (up to 150 mg/100 ml), the filtration load increase, and the glucose reabsorption increase
- in diabetic patients (blood glucose > 375) , the Na/glucose carriers are saturated (reach the **transport maximum**) , and the excess glucose execrated in urine , hence the diabetic patients have glucosuria.
- **threshold** reaches when some nephrons become saturated (glucose level >200) and glucose start to execrated in urine , but **the transport maximum** when all nephrons carriers are saturated

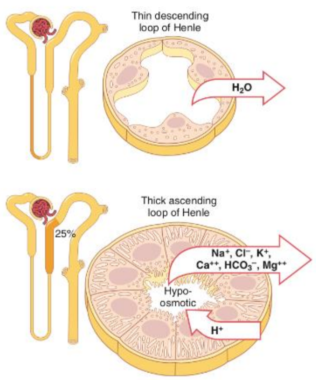
GUYTON P.341: Note that this appearance of glucose in the urine (at the threshold) occurs before the transport maximum is reached. One reason for the difference between threshold and transport maximum is that not all nephrons have the same transport maximum for glucose, and some of the nephrons therefore begin to excrete glucose before others have reached their transport maximum.

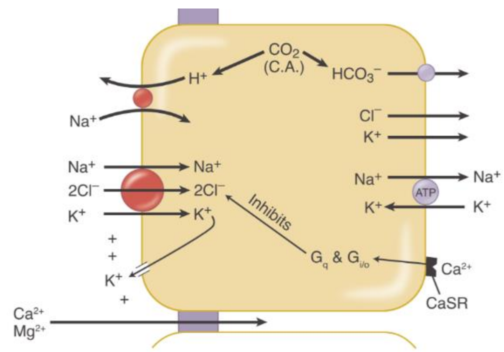
PCT Secretion

- Not all substances are filtered in the glomerulus
- Some substances are secreted later on because they were **bounded to plasma protein** during filtration
- But they're all secreted from the capillaries to the tubular fluid **actively**

Organic Anions	Organic Cations
Endogenous	Endogenous
• **Bile salts** • **cAMP** • Urate/Oxalate • Vitamins	• **Creatinine** • **Epinephrine** • **Norepinephrine** • Dopamine
Exogenous	Exogenous
• **NSAIDs** • **Penicillin** • **PAH** • Acetazolamide • Furosemide	• **Morphine** • Atropine • Amiloride • Procainamide

Loop of Henle





Thick ascending LoH

Descending LoH:

- Descending part is permeable to water (20%) and NOT permeable to solutes

Ascending LoH:

- Ascending part is permeable to solutes and NOT permeable to water
- Thin ascending part is passive
- **Thick** ascending part is active **(25% of solutes gets reabsorbed)**

➔ **50% is Transcellular:**

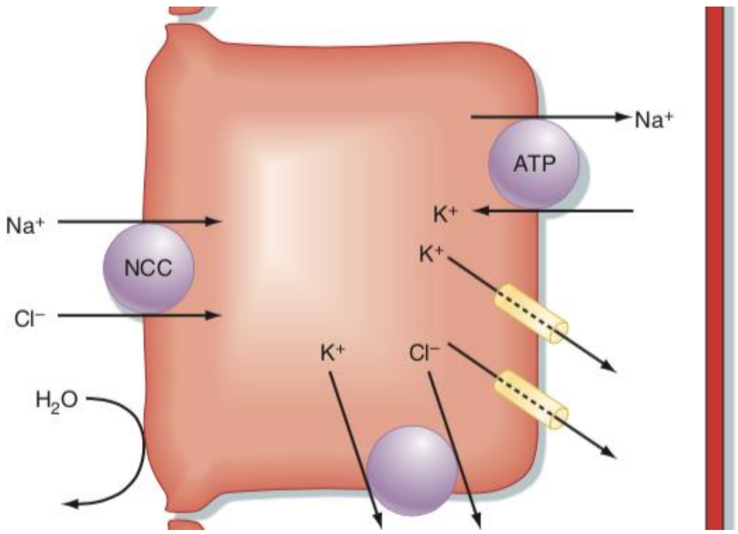
- $Na^+/2Cl^-/K^+$ co-transporter
- NHE

➔ **50% is Paracellular:**

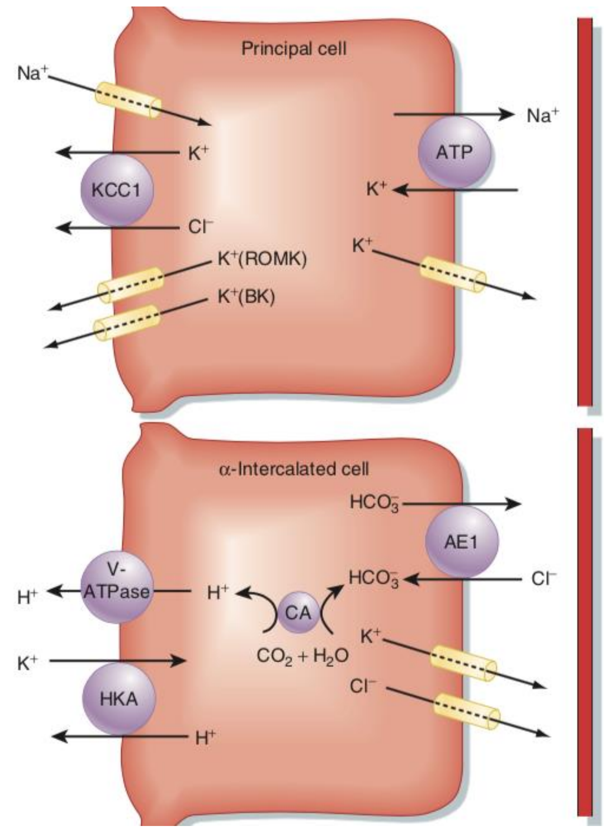
- Na^+, Cl^-, Ca^{++}, Mg^{++}
- Caused by the positive charge in the lumen resulting from K^+ escaping back to the lumen

DCT & Collecting Duct

Early (Diluting segment)



Late & CD



Basolateral membrane:

- Na/K pump (primary active)
  - ➔ Driving osmotic force
- Cl diffuse passively

Apical membrane (secondary active):

- Na/Cl cotransporter
- Water is **impermeable**

Principal Cells (Water balance/controlled by aldosterone)

- ENaC reabsorb Na^+
- K^+ secretion
- Water **permeable** if ADH is present

(⇑ADH → Open aquaporins → reabsorbtion)

α- Intercalated Cells (Acid/Base balance)

- H^+/K^+-ATPase

Aldosterone will increase the number of the following proteins:

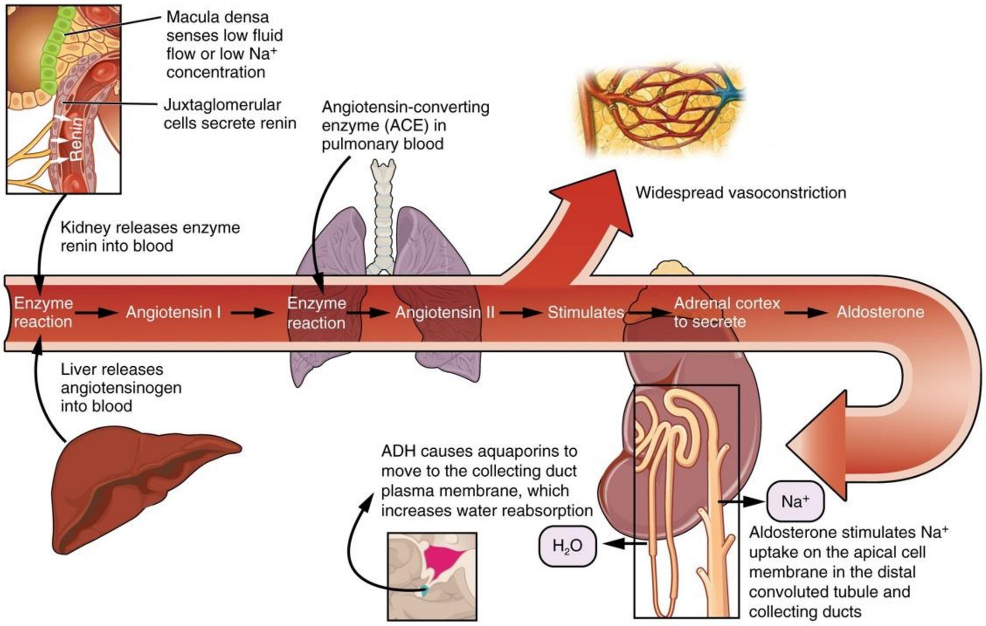
- Na^+/K^+ pump
- ENaC
- Na/Cl cotransport

Regulation of Tubular Reabsorption

- **Glomerulotubular balance** is a phenomenon where an increase in GFR will increase tubular reabsorption steadily
- So, increase in tubular load will increase tubular reabsorption

2 factors govern tubular reabsorption

1. Physical forces: hydrostatic and osmotic pressure
2. Hormonal and neural mechanisms: RAAS, ADH , ANP and sympathetic activity



Factors affecting Na^+ Reabsorption

1. GFR: ⥣ filtration of Na^+ → Macula densa is stimulated
2. Aldosterone: ⥣ Na^+ **reabsorption**
3. Estrogen: ⥣ Na^+ **reabsorption**
4. Natriuretic hormone: ⥣ Na^+ **excretion** (increase in blood volume stimulate ANP)
5. Osmotic diuresis: ⥣ Na^+ **excretion**
6. Diuretics: ⥣ Na^+ **excretion**
7. Poorly reabsorbed anions → Na^+ retention

- **Physical forces :**

Hydrostatic pressure (oppose reabsorption)		Colloid pressure (favor reabsorption)	
BP	Resistance	Filtration fraction (FF)	Plasma proteins
Increase BP >> increase GFR >> more plasma filtered >> decrease peritubular hydrostatic P >> increase reabsorption	If efferent is constricted >> decrease plasma flow >> decrease peritubular capillary hydrostatic P >> increase reabsorption	Increase FF >> proteins are more concentrated in Peritubular capillary >> increase in oncotic pressure >> increase reabsorption	Increase PP >> increase oncotic P >> increase reabsorption

Potassium Regulation

- **Potassium is an important substance in regulating:**
  1. Cell volume
  2. Acid/base status
  3. Cell growth
  4. Membrane potential (repolarization)
- Potassium is mainly in the ICF (98%), Only **2%** is in the ECF = **3.5-4.8 mmol/L**
- ⇓ EC K^+ → diffusion out of the cell → hyperpolarized
- ⇑ EC K^+ → diffusion in to the cell → partially depolarized
- Potassium is mainly ingested through diet and stored mainly in muscles

It's distributed and regulated through:

1. Internal distribution (cellular shift) – **the 1st line defense** - : regulate EC K^+
2. Renal excretion: regulate total body K^+

Internal Distribution of Potassium

Factors that affect potassium distribution	
⇓ Plasma K⁺ (⇑ uptake by cells)	⇑ Plasma K⁺ (⇓ uptake by cells)
Insulin	Exercise
Adrenaline (after meals/exercise)	⇑ EC Osmolality (due to water osmosis)
Aldosterone	Cell lysis (release cellular content)
Alkalosis	Acidosis

How do these factors affect K⁺ distribution between ICF and ECF?
Guyton P390

Renal Handling of Potassium

- 90% of potassium is reabsorbed in PCT & TAL **(obligatory reabsorption)**
- 10% of potassium enters into the distal nephrons **(regulatory reabsorption)**

➔ If K⁺ intake is low → only 3% of filtered load will be excreted

➔ If K⁺ intake is high → 10-15% of filtered load will be excreted

A- Proximal Convoluted Tubules

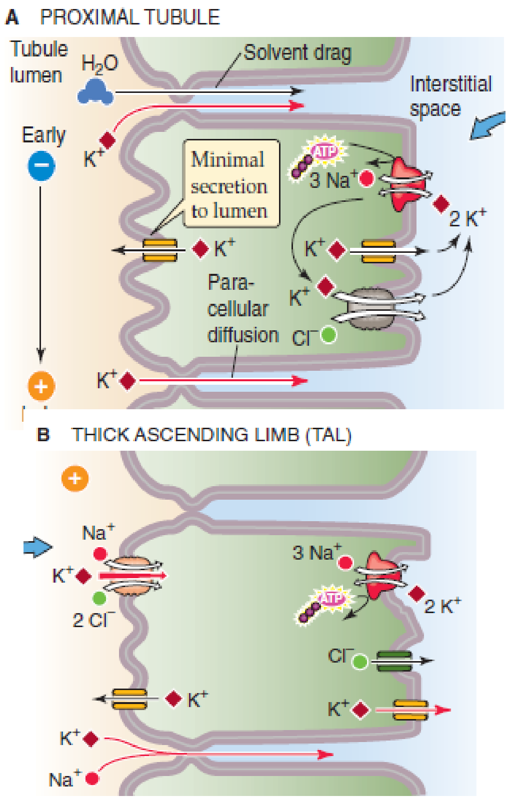
- K⁺ gets reabsorbed passively due to water osmosis (**solvent drag**)

B- Thick Ascending Loop of Henle

By secondary active transport K⁺ gets reabsorbed using Na⁺/2Cl⁻/K⁺ symportER (Apical triple transporter NKCC2)

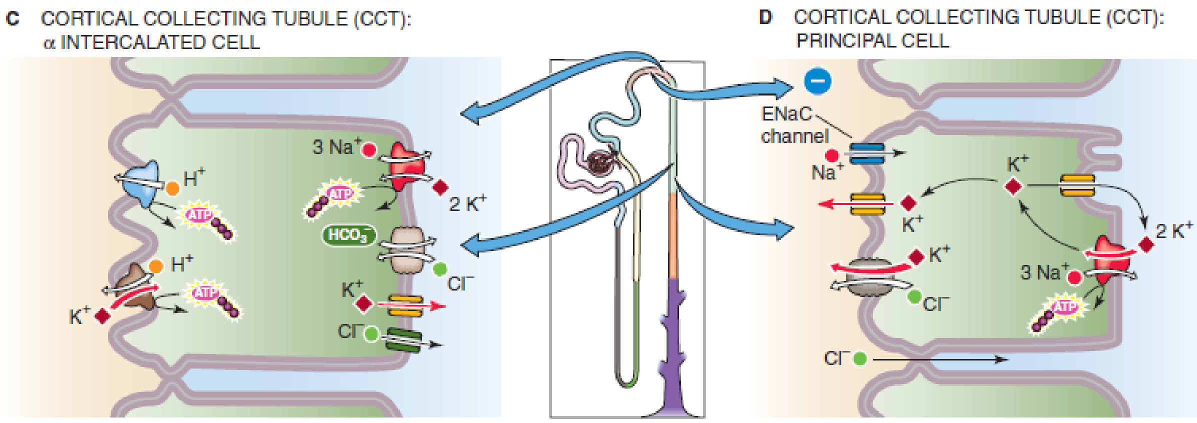
C- α-Intercalated Cells

- K⁺ gets reabsorbed
- H⁺ gets secreted



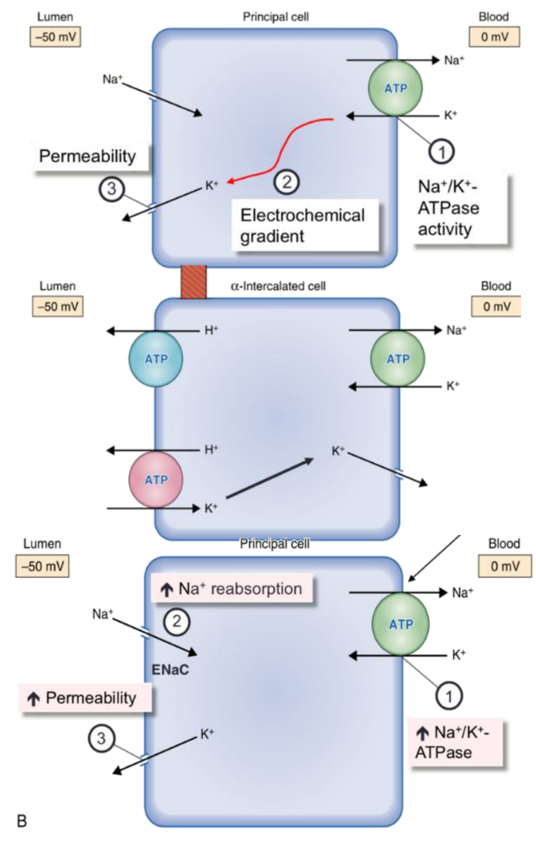
D- Principal Cells

- Na^+ and water are reabsorbed
- K^+ gets secreted



K+ Balance Mechanisms

- Major factors and hormones influencing K^+ excretion **(favored action)**



Homeostatic: Keep K^+ balance constant

1. Plasma [K^+]: ⇑ K^+ excretion

- Example: **Hyperkalemia**
  - Stimulate Na/K pump
  - ⇑ K^+ permeability (apical)
  - ⇑ aldosterone
- Opposite for Hypokalemia

2. Aldosterone: ⇑ K^+ excretion

- Released as a result of renin release
  - ⇑ Na/K pump
  - ⇑ K^+ permeability (apical)
  - ⇑ ENaC
  - ⇑ **Aldosterone → Conn's syndrome** ⇓ **Aldosterone → Addison's disease**

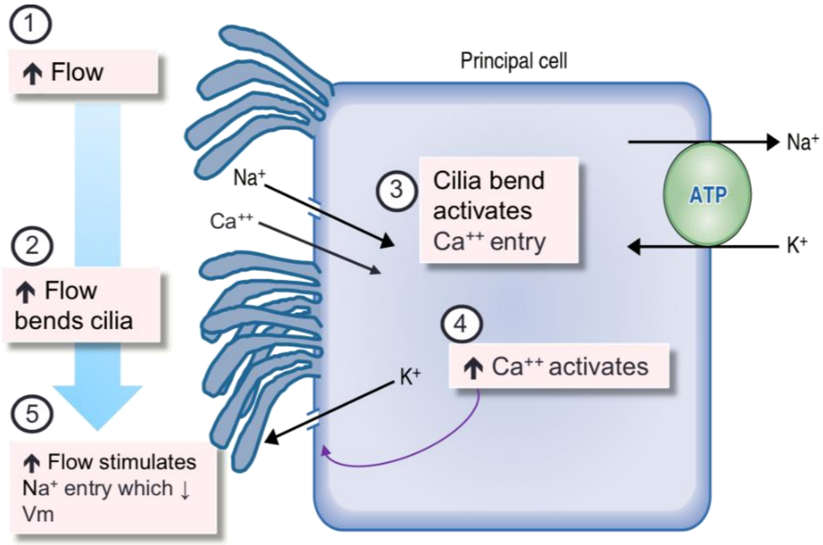
How does the body protect against hyperkalemia after each meal? Guyton 389

Increased intake of K increases aldosterone, which also increases its cell uptake. Insulin has a similar effect as well.

Pathophysiological: displace K^+ balance **(unfavored action)**

1. Diuresis: ⇑ K^+ excretion

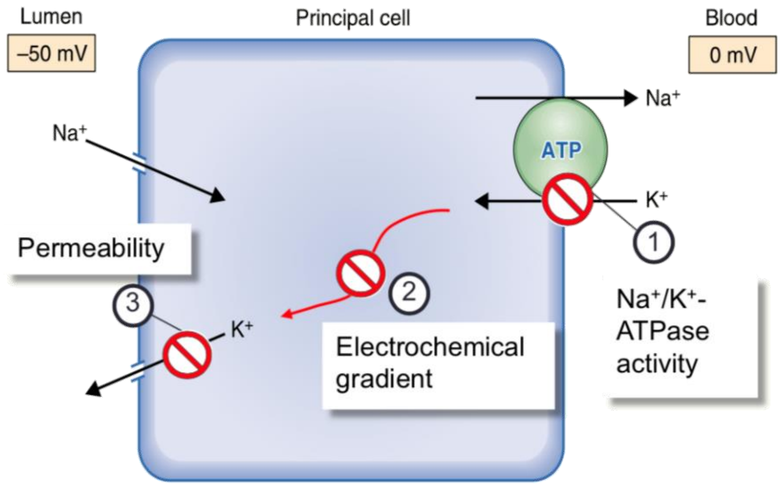
- Bending of cilia due to urine flow
- Activation Ca^{++} channels (mechanical)
- Ca^{++} entry will promote:
  - → K^+ excretion
  - → Na^+ reabsorption
  - → ⇑ K^+ uptake by Na/K pump



2. Acid-Base balance

- **Acidosis**
  - Na/K pump is inhibited
  - K^+ channels (apical) are inhibited
  - Hyperkalemia

- **Alkalosis**
  - Na/K pump is stimulated
  - K+ channels (apical) are stimulated
  - Hypokalemia



Effects of acidosis on K^+ secretion

Quiz

1. **In the presence of ADH, water is mostly reabsorbed in?**

   A. Cortical collecting duct
   B. Medullary collecting duct
   C. Proximal convoluted tubule
   D. Distal convoluted tubule

2. **Which of the following substances is maximally reabsorbed in the PCT?**

   A. Bicarbonate
   B. Sodium
   C. Glucose
   D. Potassium

3. **Which of the following represents water reabsorption in the PCT?**

   A. 15%
   B. 67%
   C. 25%
   D. 83%

4. **Which part of the nephron regulates K^+ reabsorption?**

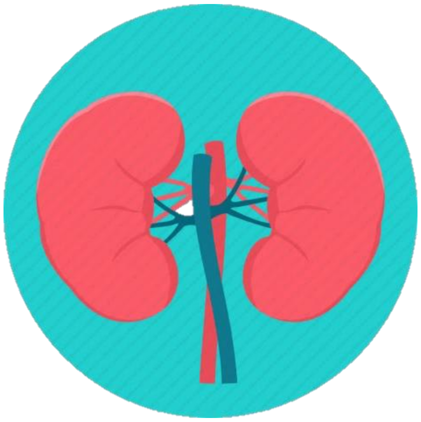
   A. Proximal convoluted tubules
   B. Thick ascending loop of henle
   C. Early distal convoluted tubules
   D. Collecting ducts

5. **Which of the following hormones increases K^+ levels in the urine**

   A. Vasopressin
   B. Aldosterone
   C. Insulin
   D. Epinephrine

Answers: C, C, B, D, B

Thank You



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