YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 4 - Physiology

Lec. Title : Renal regulation of K, Ca, Mg and PO 4

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Renal regulation of K, Ca, Mg and PO_4

الدكتورة نوعًا ما مختصرة بعض المعلومات الموجودين في الكتاب ، لهيك بتقدروا تشوفوا الكتاب، على النسخة السادسة من صفحة 288 ل

التفريغ شامل للنقاط المذكورة في السلايدز من الكتاب والريكورد بس بنأكّد لو حاب تشوف الزيادة ارجع للكتاب ،ولو حسينا في شي مهم بنكتب رقم صفحته لحتى تشوفوه ..

دعواتكم، كلّ الحُبّ...

K^+ balance

- Most of the body's K^+ **(98%) is located in the ICF.**
- maintenance of potassium (K^+) balance is **essential for the normal function of excitable tissues** (e.g., nerve, skeletal muscle, cardiac muscle).

- ICF K^+ concentration (150 mEq/L) is much higher than the ECF concentration (4.5 mEq/L).
  - This large concentration gradient for K^+ is maintained by the **Na^+-K^+ ATPase** that is present in all cell membranes.

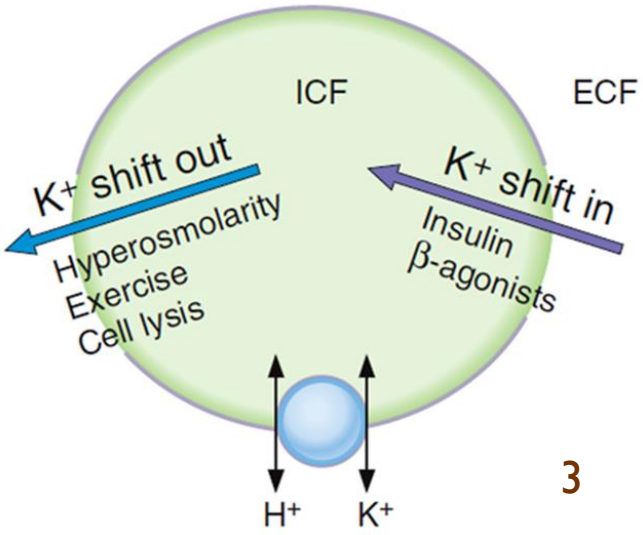
- One challenge to maintaining the low extracellular K+ concentration is the large amount of K+ present in the intracellular compartment. (needs internal balance)

- Another challenge is the **variation in dietary K+ intake** in humans: Dietary K+ can vary from as low as 50 mEq/day to as high as 150 mEq/day. **To maintain K+ balance**, urinary **excretion** of K+ must be **equal** to K+ **intake**. (needs external balance)

Internal K^+ balance

- A **small shift** of K^+ into or out of the cells can produce a **large change in the ECF** K^+ concentration.
  - A shift of K^+ **out of cells to ECF (blood),** causes **hyperkalemia**.
  - A shift of K^+ **into cells** causes **hypokalemia**.
- Factors affect internal K^+ balance:

1. **Insulin** *stimulates* K+ **uptake** into cells by **increasing** the activity of Na+-K+ ATPase. **ensures** that *ingested K+* ***does not*** *remain in the ECF* and *produce* ***hyperkalemia***(as cases of **Deficiency of insulin**, ex: **DM type I**)
2. *Osmolarity:* **Hyperosmolarity** (increased osmolarity of ECF) causes a shift of **K+ out of cells.** (water will flow from ICF to ECF because of the osmotic gradient. As water leaves the cells, the intracellular K+ concentration increases, which then drives the diffusion of K+ from ICF to ECF.)
3. **Cell lysis:** (breakdown of cell membranes) releases a large amount of K+ from the ICF and produces **hyperkalemia**.(Ex: burns, cancer chemo)



4.**adrenergic:**

- Activation of **β2-adrenergic receptors** by β2 agonists , by increasing the activity of the Na+-K+ ATPase, causes a shift of K+ into cells> (**hypokalemia)**
- activation of **α- adrenergic receptors** causes a shift of K+ out of cells and may produce **hyperkalemia**

5. **Exercise** causes a **K+ shift out** of cells; the depletion of cellular ATP stores **opens K+ channels** in the muscle cell membranes and *K+ moves out* of the cells down its electrochemical gradient

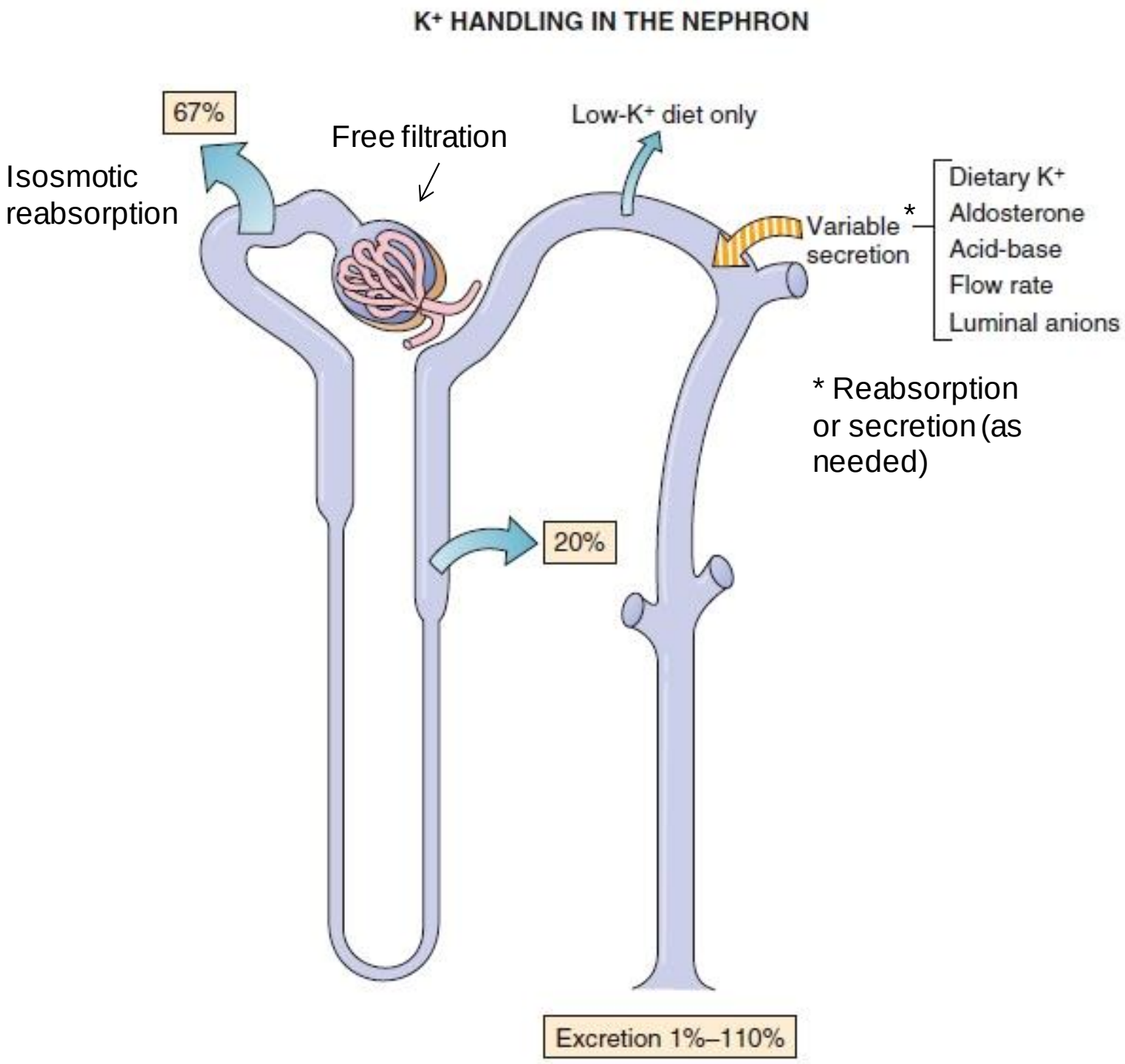
Usually, the **shift is small**…. a person treated with ***a β2-adrenergic*** **antagonist** (which independently produces a K+ shift out of cells), or in those with **impaired renal function** (in which K+ cannot be adequately excreted), strenuous exercise can result in **hyperkalemia.**

Causes of Shift of K^+ Out of Cells→Hyperkalemia	Causes of Shift of K^+ into Cells→Hypokalemia
Insulin deficiency	Insulin
β-Adrenergic antagonists	β-Adrenergic agonists
Acidosis (exchange of extracellular H^+ for intracellular K^+)	Alkalosis (exchange of intracellular H^+ for extracellular K^+)
Hyperosmolarity (H_2O flows out of the cell; K^+ diffuses out with H_2O)	Hyposmolarity (H_2O flows into the cell; K^+ diffuses in with H_2O)
Inhibitors of Na^+–K^+ pump (e.g., digitalis) (when pump is blocked, K^+ is not taken up into cells)	
Exercise	
Cell lysis	

External K^+ balance

- Dietary K^+ intake in humans is highly **variable.**
- To maintain K^+ balance, urinary **excretion** of K^+ must **be equal** to K^+ **intake.**
  - Thus on a daily basis, urinary excretion of K^+ must be *capable of varying from 50 to 150 mEq/day.*
- To accomplish this, K^+ is handled in the kidneys by a combination of **filtration, reabsorption,** and **secretion** mechanisms

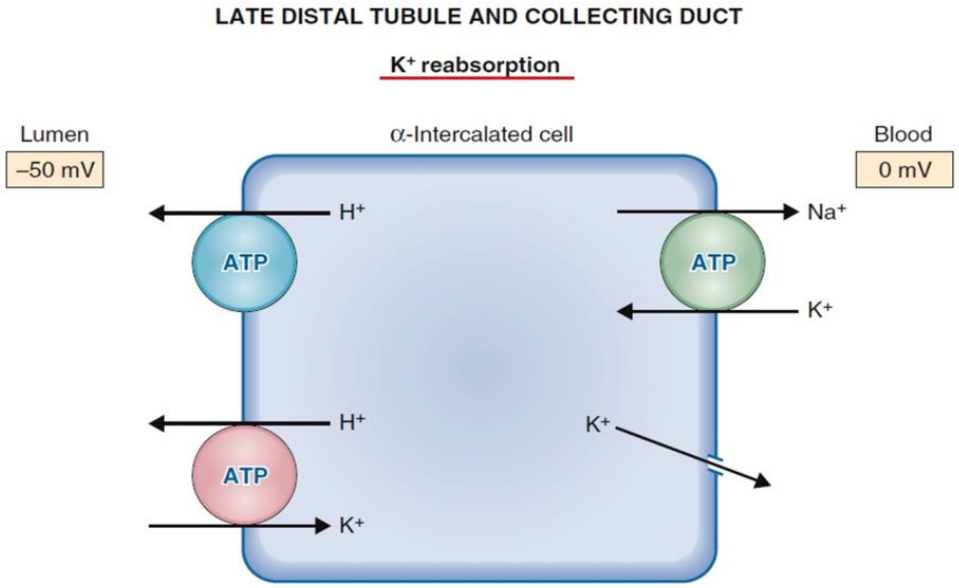
1. **Filtration.** K^+ is **not** bound to plasma proteins and is **freely filtered** across the glomerular capillaries. TF/P potassium in the beginning of filtration = 1.0
2. **proximal convoluted tubule** reabsorbs about **67% of the filtered load** of K^+ as part of the isosmotic fluid reabsorption
3. **Thick ascending limb** of the loop of Henle Reabsorbs **20% of the filtered K^+….** K^+ enters the cells of the thick ascending limb via the **Na^+-K^+-$2Cl^-$ cotransporter** and then **leaves** the cell along either of two possible routes: K^+ may ***diffuse*** across *the basolateral membrane* ***through K^+ channels***, to be reabsorbed, or K^+ may ***diffuse back into the lumen***, which does not result in reabsorption.


K+ HANDLING IN THE NEPHRON
67%
Isosmotic reabsorption
Free filtration
Low-K+ diet only
Variable secretion
*
Dietary K+
Aldosterone
Acid-base
Flow rate
Luminal anions
* Reabsorption or secretion (as needed)
20%
Excretion 1%–110%

External K^+ balance

4. **Distal tubule and collecting duct** Either reabsorb or secrete K^+, **depending on dietary K^+ intake**.

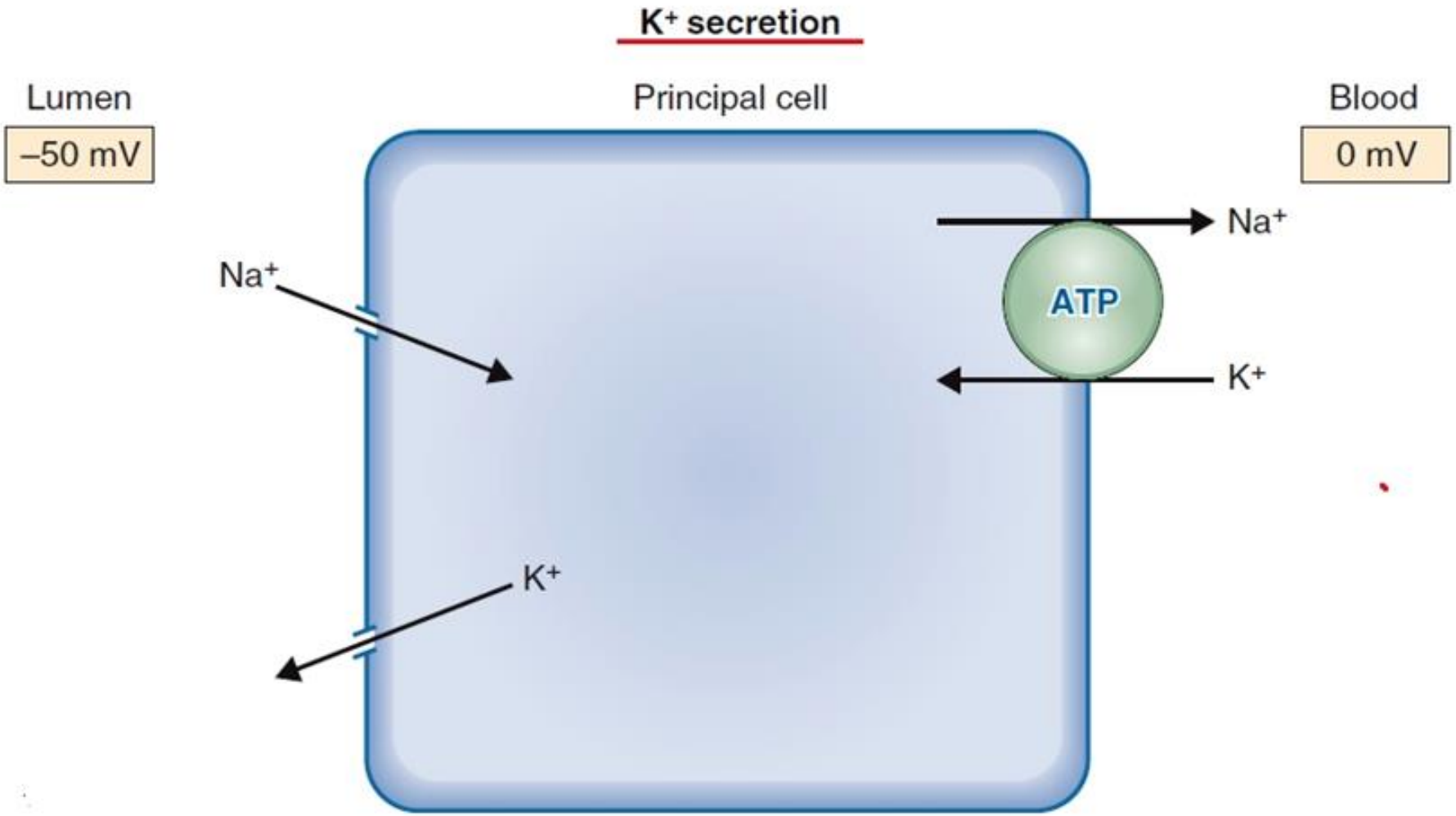
- **Reabsorption of K^+**
  - involves an **H^+_K^+-ATPase** in the **luminal** membrane of the ***α-intercalated cells*** (*primary active transport).*
  - pumps **H+ from the cell** to the lumen and **simultaneously** pumps **K^+ from the lumen** into the cell. **K^+ then diffuses from the cell** *into blood* (is reabsorbed) ***via K^+ channels.***
  - Occurs only on a **low-K^+ diet (K^+ depletion).** Under these conditions, K^+ **excretion** can be as *low as 1% of the filtered load* because the kidney conserves as much K^+ as possible.



4. Distal tubule and collecting duct

- **Secretion of K^+**
  - occurs in the ***principal cells*. (**Principle cells also reabsorb NaCl**.)**
  - is **variable** and accounts for the wide range of urinary K^+ excretion.
  - depends on factors such as *dietary K^+, aldosterone levels, acid-base status, and urine flow rate*.
  - At the **basolateral membrane** of the principal cell, **K+ is actively transported into the cell (from blood)** by **the Na^+_K^+ pump** → maintains a **high intracellular K+ concentration.**
  - At the luminal membrane, K^+ is **passively secreted** *into the lumen* through **K^+ channels**
  - The magnitude of this passive secretion is **determined by: the chemical and electrical driving forces on K^+ across the luminal membrane.**
  - Factor that **increases** the magnitude of the **electrochemical gradient** for K^+ *across the luminal membrane* will **increase K^+ secretion**

LATE DISTAL TUBULE AND COLLECTING DUCT



Factors that change K^+ secretion

table Changes in Distal K^+ Secretion

Causes of Increased Distal K^+ Secretion	Causes of Decreased Distal K^+ Secretion
High-K^+ diet	Low-K^+ diet
Hyperaldosteronism	Hypoaldosteronism
Alkalosis	Acidosis
Thiazide diuretics	K^+-sparing diuretics
Loop diuretics	
Luminal anions	

1. Dietary K+:

- A diet high in K^+ increases K^+ secretion, and a diet low in K^+ decreases K^+ secretion.
- On a **high-K^+ diet,** intracellular K^+ increases (including principal cells), so that the driving force for K^+ secretion also increases.
- On a **low-K^+ diet,** intracellular K^+ decreases so that the driving force for K^+ secretion decreases. Also, the α-intercalated cells are stimulated to reabsorb K^+ by the H^+, K^+-ATPase.

2. Aldosterone

- **Increases K^+ secretion.**

1. Induces the **synthesis** of luminal membrane ***Na^+ channels*** → **increased Na^+ entry into the cells** across the luminal membrane → more **Na^+ available for the Na^+-K^+ ATPase** → more **Na^+ is pumped out (to blood)** → more K^+ is pumped into the cell (from the blood).
2. **Increases the quantity of Na^+–K^+ pumps → increases K^+ uptake** into the principal cells (from the blood).

➢ **increase** the **intracellular K^+ concentration** and the **driving force for K^+ secretion.**

3. increases the number of luminal membrane **K+ channels→ increase secretion**

- **Hyperaldosteronism** increases K^+ secretion and causes **hypokalemia.**
- **Hypoaldosteronism** decreases K^+ secretion and causes **hyperkalemia.**

- Please read page 294 from the book for more details

3. Acid-base

- Effectively, **H^+ and K^+ exchange** for each other across the **basolateral** cell membrane **of the principal cells**.

- **Alkalosis increases K^+ secretion.** The blood contains too little H^+, therefore, **H^+ leaves the cell** across the basolateral membrane (**to** the blood) **and K^+ enters the cell** to maintain **electroneutrality** (**from** the blood)→ the *intracellular K^+ concentration* and the *driving force for K^+ secretion* **increase**. → **hypokalemia**

- **Acidosis decreases K^+ secretion.** The blood contains excess H^+ →**H^+ enters the cell** across the basolateral membrane (to the blood). and **K^+ leaves the cell** (from the blood). **to** maintain **electroneutrality** → the *intracellular K^+ concentration* and the *driving force for K^+ secretion* **decrease**. →**hyperkalemia**

4. Diuretics

- **loop diuretics** and the **thiazide diuretics,** cause **increased K+ excretion** or **kaliuresis.**
  - Diuretics that increase **flow rate** through the distal tubule and collecting ducts (e.g., **thiazide diuretics, loop diuretics)** cause dilution of the luminal K^+ concentration**, increasing the driving force** for K^+ secretion. Also, as a result of increased K^+ secretion, these diuretics cause **hypokalemia.**
  - **loop diuretics** (but not thiazide diuretics) also cause increased K+ excretion by **inhibiting Na+-K+-2Cl– cotransport** and, as a result, **K+ reabsorption** in the thick ascending limb **inhibited too**.
- **K+-sparing diuretics decrease K+ secretion**

- *Spironolactone* is an **antagonist of aldosterone**; triamterene and **amiloride act directly on the principal cells.**
- The most important use of the K^+-sparing diuretics is in *combination with thiazide or loop diuretics* **to offset (reduce) urinary K^+ losses**.
- If used alone, they cause **hyperkalemia.**

For more details read the book, page 295

6. Luminal anions

- **Excess anions** (e.g., $HCO3^-$) in the lumen cause an **increase in K^+ secretion** by **increasing the electronegativity** of the lumen and **increasing the driving force** for K^+ secretion.

Renal regulation of phosphate

- **85% of the filtered phosphate is reabsorbed** in the proximal tubule by a **Na^+-phosphate cotransporter** in the luminal membrane → saturable and has a T_m. (similar to glucose)>
- Phosphate has a ph almost equivalent to plasma (6-7.4). So **Excreted phosphate** acts as a ph **buffer for urine**….. called **titratable acid**
- Because **distal segments** of the nephron do not reabsorb phosphate, **15% of the filtered load is excreted in urine**.
- Parathyroid hormone **(PTH) inhibits** phosphate **reabsorption:**

- PTH binds to a basolateral receptor in the proximal tubule → activates **adenylate cyclase** → **↑cAMP** → *series of **Protein Kinases** activated* → ***Inhibition Na+_phosphate cotransport*** → PTH causes **phosphaturia** and **increased urinary cAMP**.
- **defect** in the receptor, Gs protein, or adenylyl cyclase complex causes an inherited disorder **called pseudohypoparathyroidism**

Renal regulation of calcium

- **For more details please read the book ,page296-297**

- **Sixty percent of the plasma Ca^{2+} is filtered** across the glomerular capillaries …**Why?** This is because a **percentage is bound to plasma protein**s.

- In **proximal tubules**, 67% of Ca^{2+} is **passively** reabsorbed → Ca^{2+} reabsorption is tightly coupled to Na^{+} reabsorption.

- **The thick ascending limb** reabsorbs **25% of the filtered Ca2+.**

- This occurs along a **paracellular route** and is **tightly coupled to Na+** reabsorption. → depends on the **lumen-positive potential difference**, which is generated by the Na+-K+-2Cl– cotransporter.
- This lumen-positive potential normally drives the reabsorption of divalent cations such as Ca2+, as positive charge repels positive charge.

- Together, the distal tubule and collecting duct reabsorb 8% of the filtered Ca2+ by an active process and not in relation with Na+ reabsorption.
- The channels that is **responsible for the active transport** of calcium to the distal tubule are **TRBV5 and 6** and vitamin D enhances the **transcription** of the channels. Channels that **move calcium from the cell to the blood** are **NCX1 channels**. So vitamin D enhances calcium **reabsorption**.
- **PTH increases Ca2+ reabsorption** via a basolateral receptor , **activation of adenylate cyclase and generation of cAMP**.
- **The Loop diuretics** (e.g., furosemide) cause increased urinary Ca^{2+} excretion.
- Loop diuretics cause **hypocalcemia** as they cause calcium excretion after **stopping Na-K-2Cl cotransporter**.

- **Thiazide diuretics increase Ca2+ reabsorption** in the early distal tubule and therefore **decrease Ca2+ excretion** (while **they inhibit Na+ reabsorption).**

Magnesium (Mg^{2+})

- **For more details please read the book ,page297-298**
- Is **reabsorbed** in the proximal tubule, thick ascending limb of the loop of Henle, and distal tubule (95%).
- In the **thick ascending limb** (the major site for Mg^{2+} reabsorption), **Mg^{2+} and Ca^{2+} compete for reabsorption**; therefore:
  - **hypercalcemia** causes an **increase in Mg^{2+} excretion** (by inhibiting Mg^{2+} reabsorption).
  - **hypermagnesemia** causes an **increase in Ca^{2+} excretion** (by inhibiting Ca^{2+} reabsorption).