YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 3 - Physiology

Lec. Title : Sodium Chloride Regulation

**Written By : Sawsan Radi
Rahma Marie**

If you come by any mistake , please kindly report it to
shaghafbatch@gmail.com

Renal regulation of sodium and chloride

هاد رابط الكتاب بتقدروا تشوفوه لأنه الدكتورة كثير مختصرة نقاط
https://drive.google.com/file/d/1hEIQEnk8b_ZNqsHtybavkwCNMJL2prZr/view?usp=drivesdk
هاي المحاضرة بتبدأ من صفحة 274
مع العلم إنه التفريغ شمل النقاط المذكورة في السلايدز من الكتاب والريكورد
دعواتكم، كل الحُبّ

- The formation of urine involves three basic processes:
- (1) **ultrafiltration** of plasma by the glomerulus,
- (2**) reabsorption** of water and solutes from the ultrafiltrate
- (3) **secretion** of selected solutes into tubular fluid.

- Although an average of 115 to 180 L/day in women and 130 to 200 L/day in men of essentially protein-free fluid is filtered by the human glomeruli each day, **less than 1% of the filtered** water and sodium chloride (NaCl) and variable amounts of other solutes **are excreted in urine**
- **Reabsorption** of NaCl and water represents the major function of nephrons. Approximately 25,000 mEq/day of Na+ and 179 L/day of water are reabsorbed by the renal tubules

Single nephron terminology

- **Tubular fluid (TF) is urine** at any point along the nephron.

- **Plasma (P) is systemic plasma.** It is considered to be constant.

1. **TF/P_x ratio**

- compares the concentration of a substance in tubular fluid at any point along the nephron with the concentration in plasma.
- There will be 3 possible results: (1, <1, >1)

I. If **TF/P_x = 1.0:** then [x] in tubular fluids is **identical** to the [x] in plasma. that **can have 2 meanings**

- there has been **no reabsorption of the substance/ yet**

- **Ex: Na^+ is freely filtered** in **Bowman space** (before any reabsorption or secretion has taken place to modify the tubular fluid), so the filtrate should be identical to the plasma concentration…
- The **generalization** can be made that ***for any freely filtered substance, $[TF/P]_x$ is 1.0 in Bowman's space***

- reabsorption of the substance has been **exactly proportional to** the reabsorption of water.

- **Ex:** at the end of the proximal tubule, **reabsorption** of the solute has **occurred**, but **reabsorption of water has occurred** in **exactly the same proportion**. the **concentration** of the solute in tubular fluid **does not change.**
- in the case of Na+ in the proximal tubule: **Na+ is reabsorbed**, but **$[TF/P]_{Na+}$ remains 1.0 along the entire proximal tubule** because there is proportionality of Na+ and water reabsorption.

II. If **TF/P < 1.0: only one meaning**

- reabsorption of the substance has been **greater than the reabsorption of water** and the **concentration in tubular fluid is less than that in plasma**.
- **Ex**: if $TF/P_{Na+} = 0.8$, then **the [Na^+] in tubular fluid is 80% of the [Na^+] in plasma.**

III. If **TF/P > 1.0: 2 meanings**

- **reabsorption** of the substance has **been less than the reabsorption of water**
- **there has been secretion** of the substance, causing its concentration to increase **above** that in plasma.

- All small solutes (sodium, potassium etc) are freely filtered across the glomerular capillaries. So their TF/P = 1.0.

2. TF/P_{inulin}

- is used as a marker for water reabsorption along the nephron.
- inulin is **filtered freely** across glomerular capillaries, it is **neither reabsorbed nor secreted**. Thus the concentration of inulin in tubular fluid is not affected by its own reabsorption or secretion, and it is only **affected by the volume of water present (as water is reabsorbed,** inulin concentration of tubular fluid **increases)**
- **Ex: $[TF/P]_{inulin}$ = 2.0.** this means that the tubular fluid inulin concentration **is twice** the plasma inulin concentration. **Water must have been reabsorbed** in earlier portions of the nephron **to cause the tubular fluid inulin concentration to double.** But how much water have been reabsorbed?

$$\text{Fraction of filtered } H_2O \text{ reabsorbed} = 1 - \frac{1}{[TF/P]_{inulin}}$$

- **from the equation :** (1 − 1/2). if 50% of the filtered water has been reabsorbed, the TF/P_{inulin} = 2.0**.**
- For another example, if TF/P_{inulin} = 3.0, then 67% of the filtered water has been reabsorbed (i.e., 1 − 1/3).

3. $[TF/P]_x/[TF/P]_{inulin}$ ratio:

- This double ratio gives the **fraction of the filtered load remaining at any point along the nephron.**

- **For correcting $[TF/P]_x$ for water reabsorption.** In other words, it can be known with certainty whether a substance has been reabsorbed, secreted, or not transported at all.

- **For example,** From the earlier discussion, recall that at the end of the proximal tubule [TF P] . Na+ = 1 0, which led to confusion about whether Na+ was reabsorbed in the proximal tubule.
- But, if $[TF/P]_{Na+}/[TF/P]_{inulin}$ = 0.3 at the end of the proximal tubule, then 30% of the filtered Na^+ remains in the tubular fluid and 70% has been reabsorbed into the blood. (also 70% of water has been reabsorbed)

General information about Na^+ reabsorption

- **Na^+ is freely filtered** across the glomerular capillaries; therefore, the [Na^+] in the tubular fluid of Bowman space equals that in plasma (i.e., TF/P_{Na+} = 1.0).
- Na^+ is reabsorbed along the entire nephron, and very little is excreted in urine (<1% of the filtered load).
- **The amount of Na^+ excreted in urine must be exactly equal to daily intake (**called Na^+ balance)
- To excrete daily untake, kidney excretes 1% of filtered load
- **Ex:** an average Na+ intake of 150 mEq/day, to maintain Na+ balance, excretion should be 150 mEq/day, which is less than 1% of the filtered load. (If GFR is 180 L/day and plasma Na+ concentration is 140 mEq/L, then the filtered load of Na+ is 25,200 mEq/day. Excretion of 150 mEq/day, therefore, is 0.6% of the filtered load [150 mEq/day divided by 25,200 mEq/day],
- The percentage of reabsorbtion of Na^+ is not the same along the nephron (the next slide shows that)
- late distal convoluted tubule and collecting duct are the sites of action of the Na_+-regulating hormone **aldosterone** & they and are **responsible for the fine-tuning of Na_+reabsorption**

Sodium reabsorption along the nephron

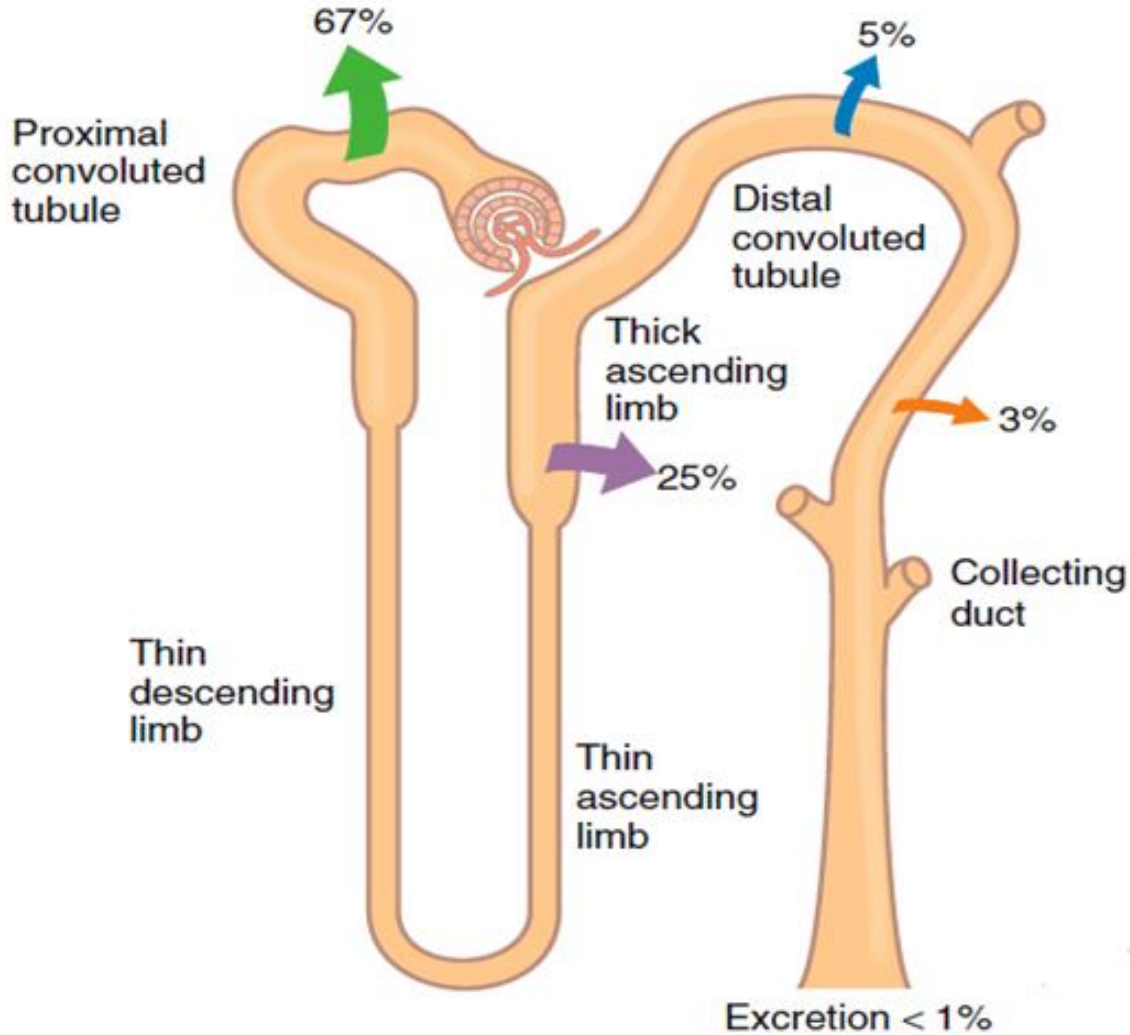


FIGURE 5.7 Na^+ handling along the nephron. *Arrows* indicate reabsorption of Na^+. *Numbers* indicate the percentage of the filtered load of Na^+ that is reabsorbed or excreted.

1. Proximal tubules

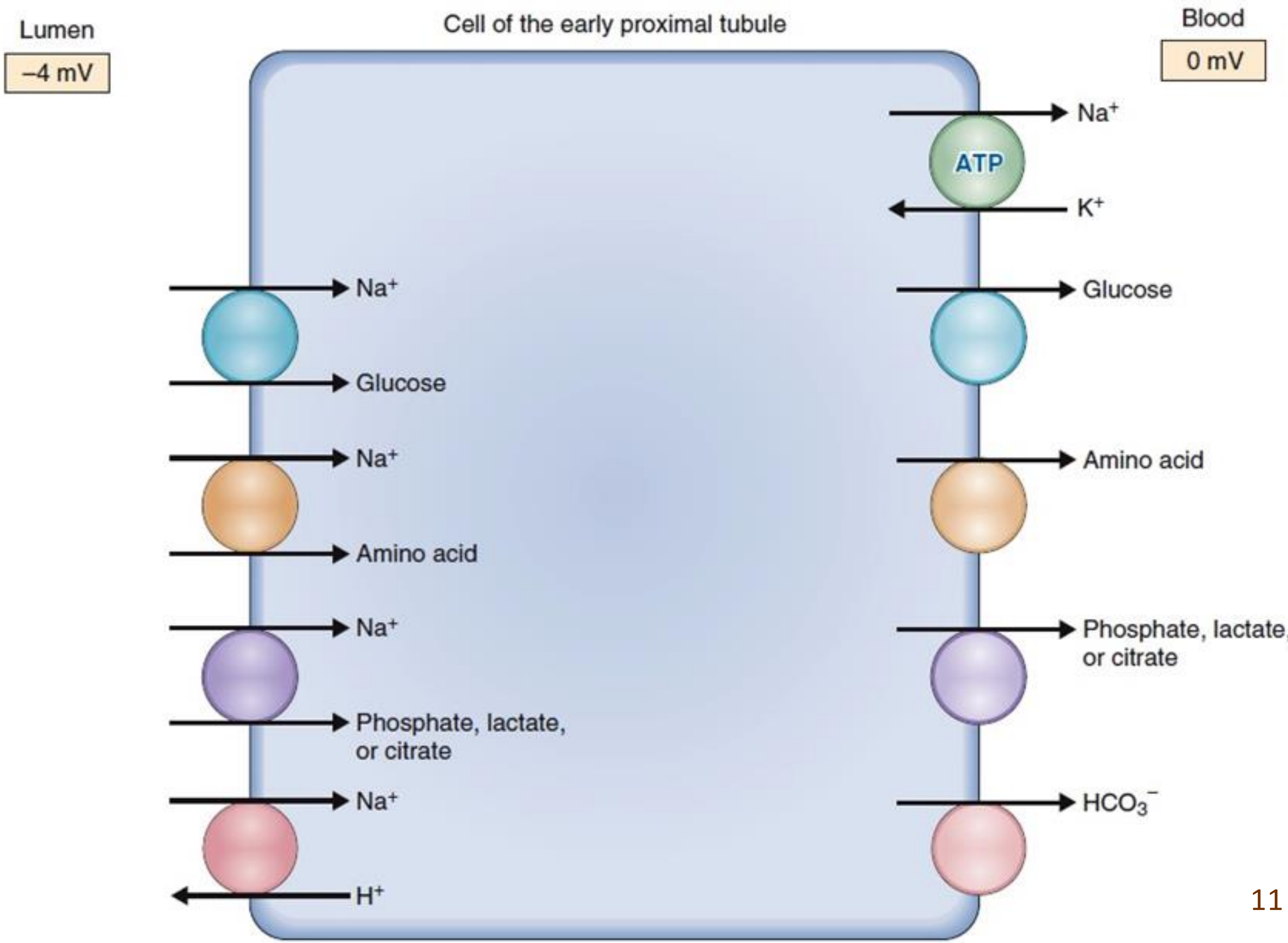
- **Reabsorb two-thirds, or 67%, of the filtered Na^+ and H_2O,** more than any other part of the nephron.
- Is the site of **glomerulotubular balance (**a mechanism for coupling reabsorption to the GFR)**.**
- The tight coupling between **Na^+** & **water** is called **isosmotic.** The reabsorption of Na^+ and H_2O in the proximal tubule is exactly proportional.

  Therefore, both TF/P_{Na+} and TF/P_{osm} = 1.0.

- consists of :

- an **early proximal** convoluted tubule (**Na_+ is reabsorbed primarily with HCO_3^- and organic solutes)**
- **late proximal** convoluted tubule (**Na+ is reabsorbed primarily with Cl−, but without organic solutes).**

Early proximal tubules



Early proximal tubules

- Na^+ is reabsorbed by **cotransport (the solutes move in the same direction)** with glucose (SGLT), amino acids, phosphate, and lactate.

  These cotransport processes account for the reabsorption of all of the filtered glucose and amino acids (100% reabsorbed).

- The **Na^+** moves into the cell **down** its electrochemical gradients, giving energy for the movement of **other** solutes into the cell **against** their electrochemical gradients.

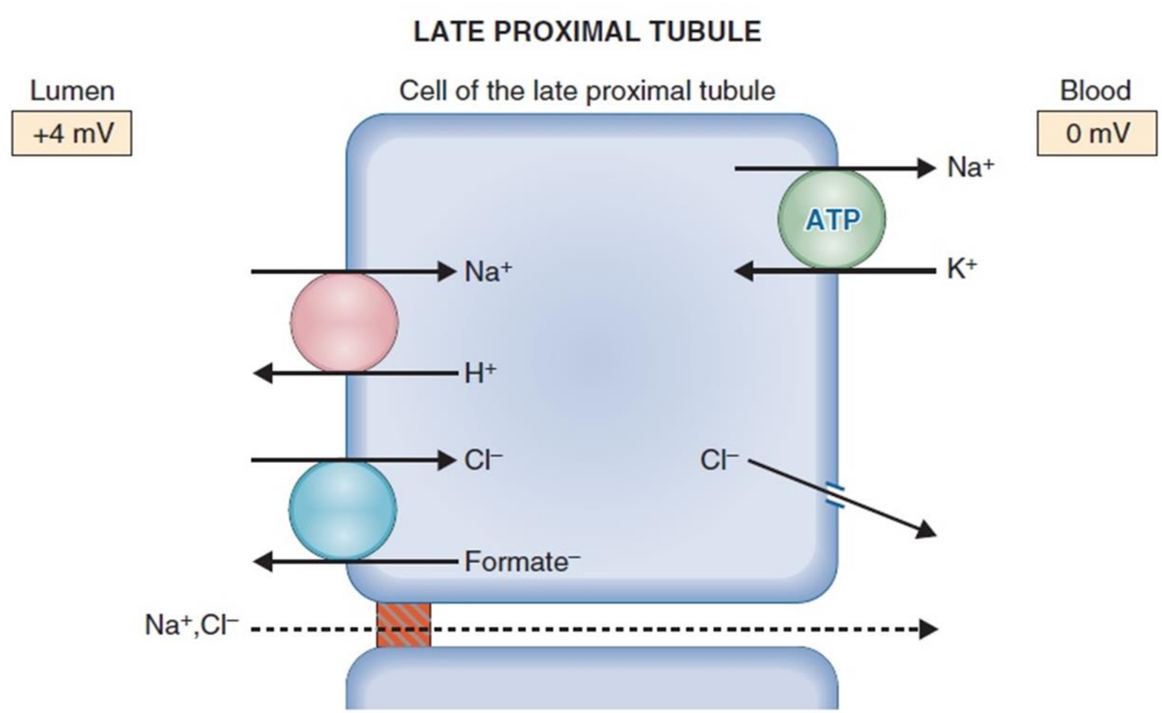
- Na^+ is also reabsorbed by **countertransport (the solutes move in the different directions)** via Na^+–H^+ exchange, which is linked directly to the reabsorption of filtered $HCO3^-$.(85% reabsorbed)

- There is a **lumen-negative** potential difference across the cells of the early proximal tubule, which is created by

- **Na_+-glucose and Na_+-amino acid cotransport**. These transporters bring **net positive charge into the cell** and leave negative charge in the lumen.
- The other transporters are electroneutral (e.g., Na_+-H_+exchange) and therefore **do not contribute to the transepithelial potential difference**.

Late proximal tubule

- All of the filtered glucose and amino acids, and most of the filtered $HCO3^-$ **have already been completely removed** from the tubular fluid by reabsorption in the early proximal tubule.
- In the late proximal tubule, **Cl^- concentration is high**, because (1) **$HCO3^-$** has been **preferentially reabsorbed** in the early proximal tubule (2) **water is isosmotically** reabsorbed → the **tubular fluid [Cl^-]increases** and becomes **higher** than **the [Cl^-]of the glomerular** filtrate and of blood.
- **Cl^- is reabsorbed with Na^+.**
- **Please read the book, page 280 for more details**

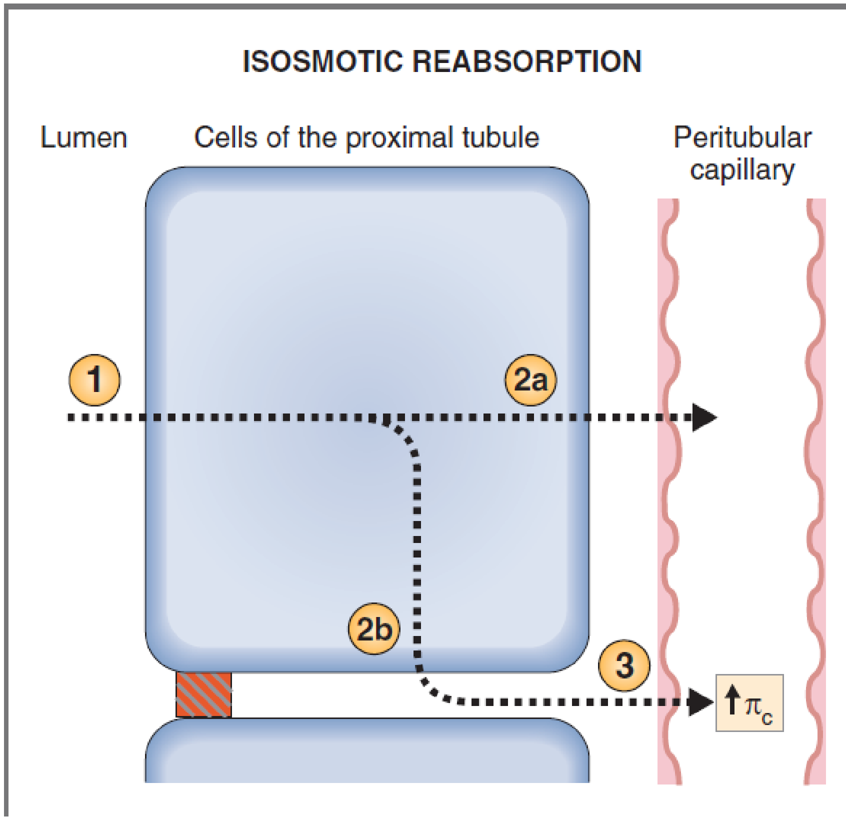


Isosmotic reabsorption

- $[TF/P]_{Na+}$ and $[TF/P]_{osmolarity}$ = 1.0 along the entire proximal tubule (discussed).
- **Mechanism of isosmotic reabsorption:**

- **Solute** reabsorption is the **primary event**, and water follows passively.

- 1. Na+ enters the cell across the luminal membrane . Because the luminal membrane is permeable to water, **water follows** the solute to maintain isosmolarity.
- 2. Na+ is pumped out of the cell by the Na+-K+ ATPase , which is located in the peritubular or basolateral membranes. (“Basal” refers to the cell membranes facing the peritubular capillary [2a] , and “lateral” refers to the cell membranes facing the lateral intercellular spaces between cells [2b].) As Na+ is pumped out of the cell , water again follows passively.

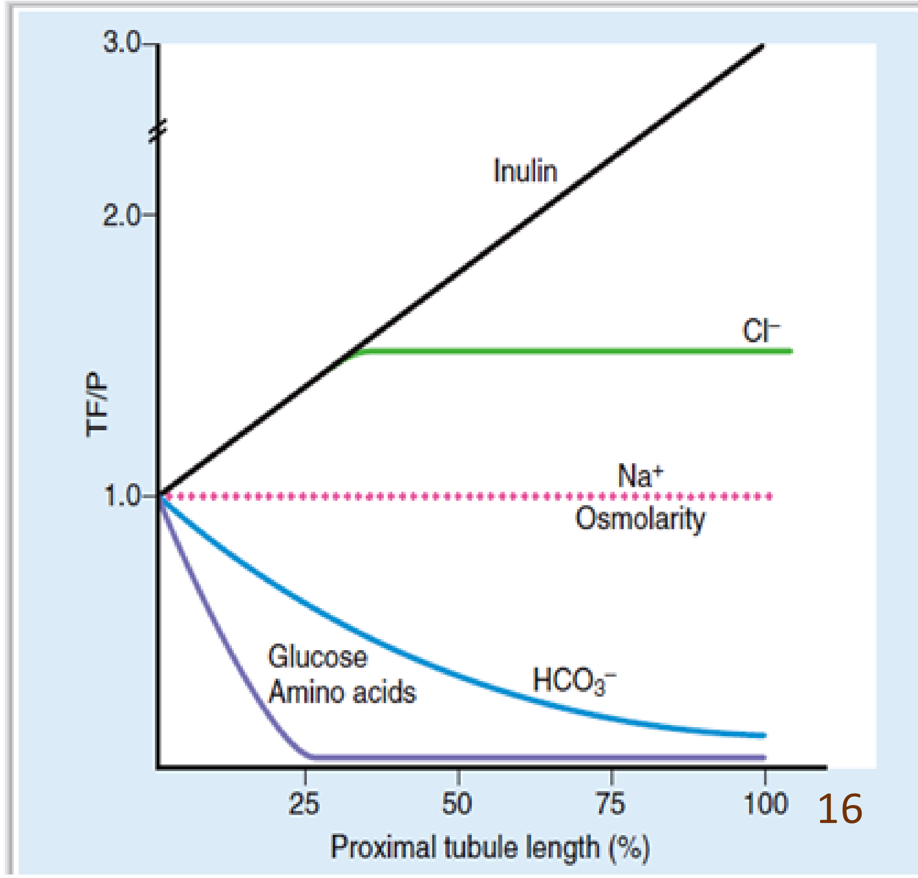


- 3. The **lateral intercellular space** is an important route for reabsorption of solute and water. Isosmotic fluid accumulates in these spaces between the proximal tubule cells. This isosmotic fluid in the spaces is then acted upon by **Starling forces** in the peritubular capillary. The major Starling force driving reabsorption is the **high oncotic pressure (πc)** of peritubular capillary blood. Recall that glomerular filtration elevates the protein concentration (and πc) of the glomerular capillary blood; this blood leaves glomerular capillaries to become the peritubular capillary blood. The high π_c is then a pressure favoring reabsorption of isosmotic fluid.

TF/P ratios along the proximal tubule

- At the end of reabsorption in the proximal tubule, what happens to the TF/P sodium? The value stays at **1.0 at the sodium moves osmotically.**
- What happens to TF/P inulin? The value **increases** as inulin is not reabsorbed, only water is. The TF/P inulin value becomes more concentrated and **the ratio goes over 1.0**.

- The **chloride in the beginning** of the proximal tubule is **no reabsorbed**. But its **TF/P value is over 1.0** according to the curve. This shows that *chloride reabsorption is less than water*. Chloride is not proportionally reabsorbed with water.
- The **bicarbonate** TF/P value **at the end** of the proximal tubule is **almost 0**. This is because **I t is reabsorbed more than water is.** The same thing happens with **glucose and amino acids**. All 3 are fully reabsorbed.



Glomerulotubular balance in the proximal tubule

- Maintains **constant fractional reabsorption** (two-thirds, or 67%) of the filtered Na^+ and H_2O.
- If GFR increases →the filtered load of Na^+ also increases.
  - **Without** a change in reabsorption, this increase in GFR would lead to **increased Na^+ excretion**.
- This loss in **Na^+ doesn't occur**, because of the protective mechanism of glomerulotubular balance
- However, glomerulotubular balance functions such that **Na^+ reabsorption also will increase**, ensuring that a **constant fraction** is reabsorbed.
- Increases in GFR and filtration fraction cause the **protein concentration and πc (oncotic pressure of starling law) of peritubular capillary** blood to **increase** → increase in fluid reabsorption.

- Thus, there is matching of filtration and reabsorption, or glomerulotubular balance.

- If the reabsorption is not balanced and **sodium reabsorption excessively increases** , diuretics can be given.
- For more details please read the book page 282

Effects of ECF volume on proximal tubular reabsorption

- *ECF volume* ***contraction increases*** *reabsorption.* Volume contraction **increases peritubular capillary protein** concentration. As a result there is increase in π_c (force favors reabsorption) and decreases peritubular capillary P_c (force against reabsorption)→ increase in fractional reabsorption of isosmotic fluids → **increase in proximal tubular reabsorption.**

- ex: **Diarrhea** causes ECF contraction **without** change in osmolarity. Contraction of **proteins** and **hydrostatic pressure** change which **favors reabsorption**. The ECF contraction produces **protective mechanism** as the kidneys try to reabsorb water and solutes **to minimize dehydration**.

<u>Effects of ECF volume on proximal tubular reabsorption</u>

- *ECF volume* ***expansion decreases*** *reabsorption.* Volume expansion **decreases** peritubular capillary **protein** concentration (by dilution) . The **π_c decreased, and P_c increased →decrease in proximal tubular reabsorption.**

- portion of the fluid that would have been reabsorbed instead **leaks back into the lumen of the tubule** (across the tight junction) and is excreted.

- **ex: When giving an isotonic normal saline. We cause an expansion and reabsorption decreases.**

2. Loop of Henle: a. Thin Descending Limb and Thin Ascending Limb

- The **thin descending limb** is permeable to **water** and small solutes, such as **NaCl** and **urea.**
  - In countercurrent multiplication, **water moves out** of the thin descending limb, **solutes move into** the thin descending limb, and the **tubular fluid** becomes progressively ***hyperosmotic*** as it flows down the descending limb.

- The **thin ascending** limb also is permeable to **NaCl,** but it is ***impermeable*** to **water.**
  - During countercurrent multiplication, **solute moves out** of the thin ascending limb **without water** and the **tubular fluid** becomes progressively ***hyposmotic*** as it flows up the ascending limb.

b. Thick ascending limb of the loop of Henle

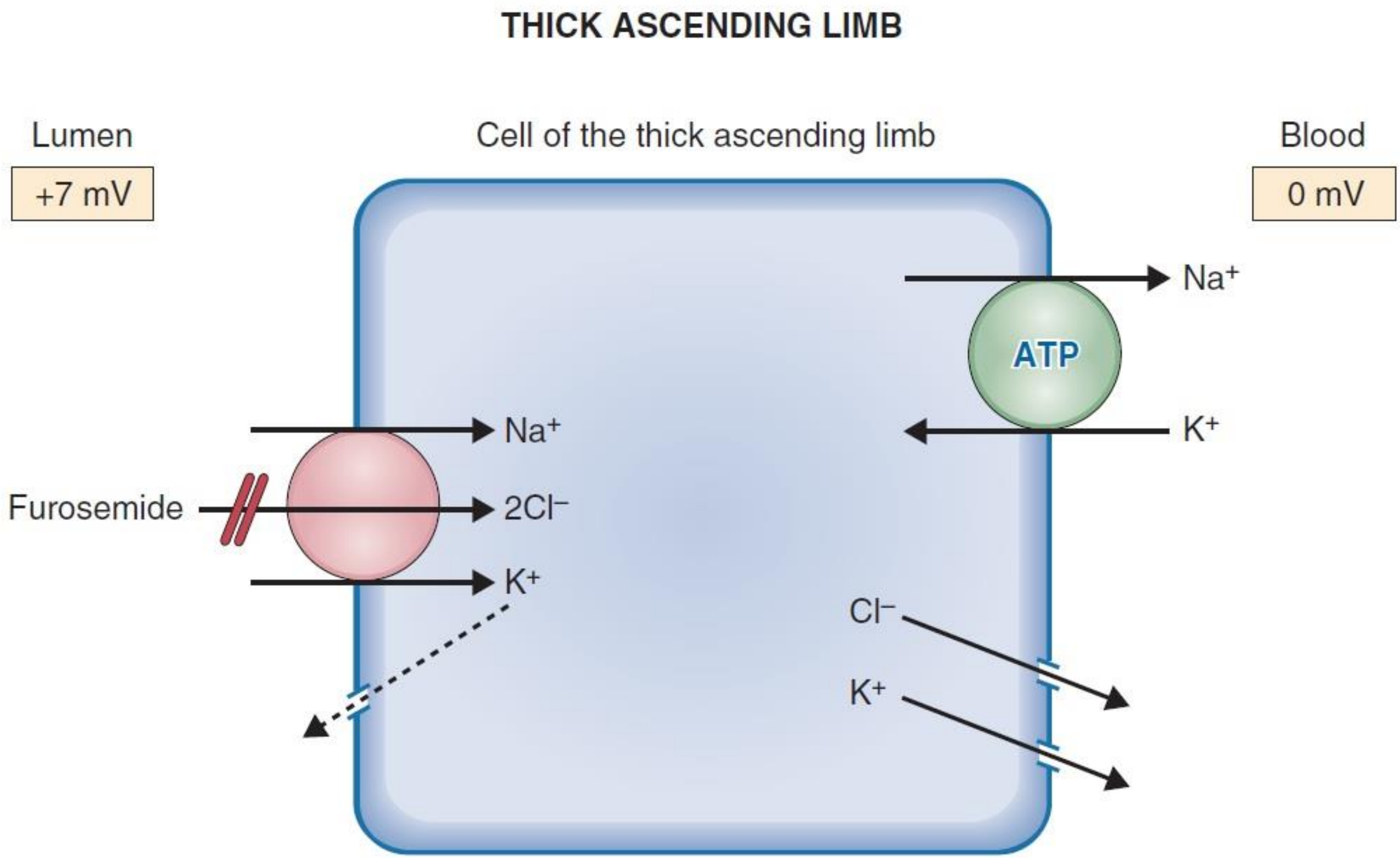
- **Reabsorbs 25% of the filtered Na^+.**
- Reabsorption mechanism in thick ascending limb is **load dependent**.
  - The **more Na^+** is delivered to the thick ascending tubule, **the more it reabsorbs.**
- Contains a **Na^+–K^+–2Cl^- cotransporter in the luminal membrane** *(active transport).also* ***called NKCC2.***
- The energy for the cotransporter is derived from the familiar **Na^+ gradient**, which is maintained by the Na^+-K^+ ATPase in the basolateral membranes.
- Na^+, K^+ *& 2Cl^- enter on the cotransporter and Na^+ is extruded from the cell by* **Na^+-K^+ ATPase** *, K^+ & 2Cl^-* ***diffuse*** *through channels on basolateral mem.*
- The cotransporter results in a **lumen-positive potential difference** (driving the reabsorption of divalent cations mg^{+2} & Ca^{+2})**.** Although the Na^+–K^+–2Cl^- cotransporter appears to be electroneutral, some K^+ diffuses back into the lumen, making the lumen electrically positive.

b. Thick ascending limb of the loop of Henle

- Thick ascending limb is **impermeable to water** → NaCl is reabsorbed without water.
  - **tubular fluid [Na^+]** and **tubular fluid osmolarity** ***decrease*** to less than their concentrations in plasma (i.e., **TF/P_{Na+} and TF/P_{osm} < 1.0**) → so it's called **diluting segment.**
- **Furosemide** is a loop diuretic that works on this cotransporter.

- It binds to the **chloride binding site** and **stops the movement of transporter completely.** This stops sodium reabsorption and helps with hypertension. (25% of **Na^+** remained in the tubule → 25% of water will be excreted)

b. Thick ascending limb of the loop of Henle



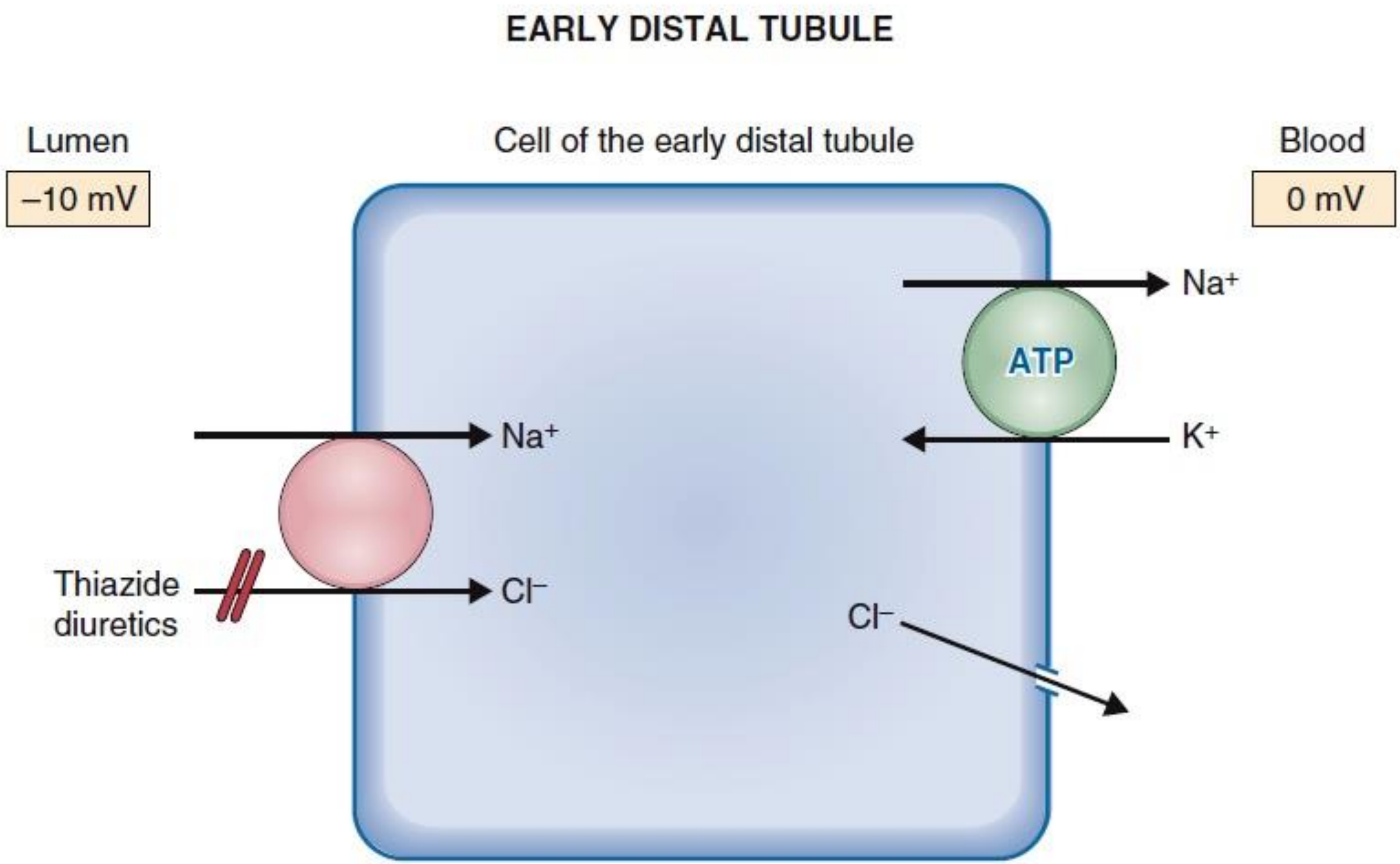
3. Distal tubule and collecting duct

- Together **reabsorb 8% of the filtered Na^+.**
- Reabsorption is **load dependent.**

A. Early distal tubule:

- reabsorbs NaCl by a **Na^+–Cl^- cotransporter** in the luminal membrane.
- Is **impermeable to water,** as is the thick ascending limb. Thus, reabsorption of NaCl occurs without water, which further dilutes the tubular fluid.
  - Is called the **cortical diluting segment.**
- **Thiazide diuretics work on the sodium chloride cotransporter**. For hypertension, it is given before Furosemide. For malignant hypertension, Furosemide is given.

Early distal tubule



B. Late distal tubule and collecting duct

- have two cell types:

Principal cells & α-Intercalated cells

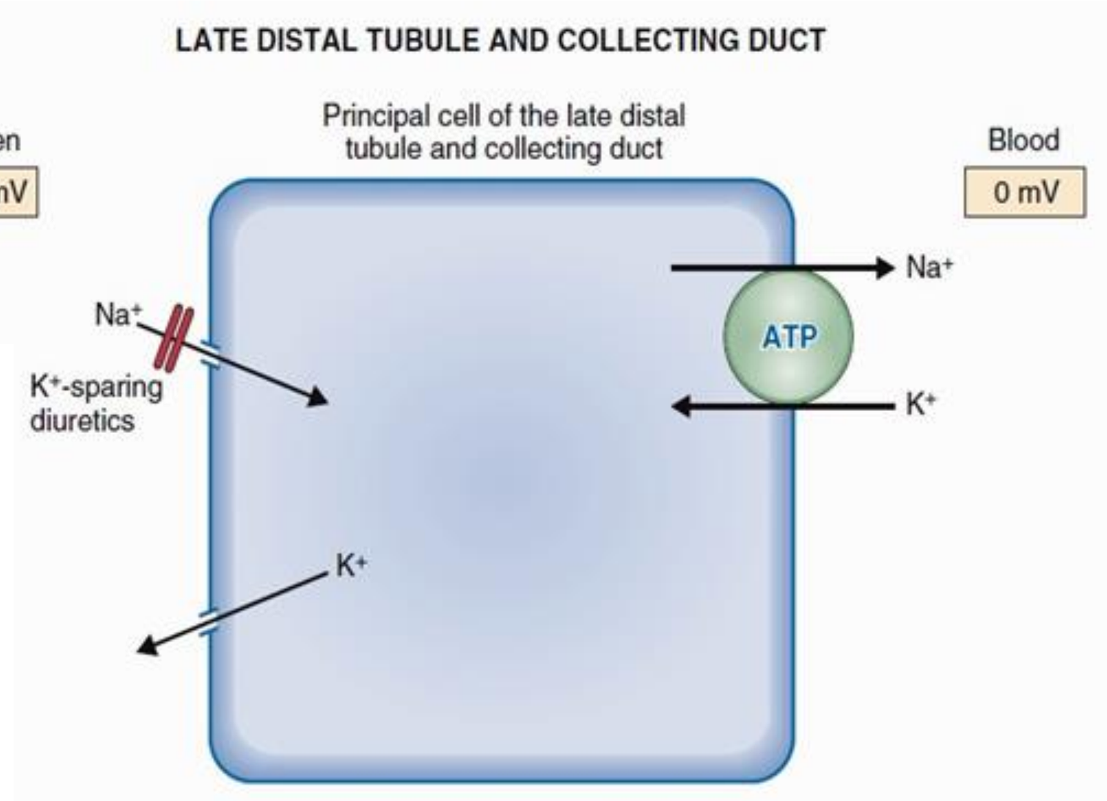
- Reabsorb only 3% of filtered Na^+
- **Principal cells:**
- reabsorb Na^+ and H_2O and secrete K^+.and Hormonally regulated:

- **Aldosterone increases Its Na^+ reabsorption and increases K^+ secretion.**
- About **2% of overall Na^+ reabsorption** is affected by aldosterone.
- **Antidiuretic hormone (ADH) increases H_2O permeability** by directing the **insertion of H_2O channels (Aquaporin 2/ AQP2 and 4)** in the luminal membrane. In the absence of ADH, the principal cells are virtually impermeable to water.

- **α-Intercalated cells:**

- **secrete H+** by an H+-adenosine triphosphatase (ATPase), which is **stimulated by aldosterone**.
- **reabsorb K+ by an H+, K+-ATPase.**

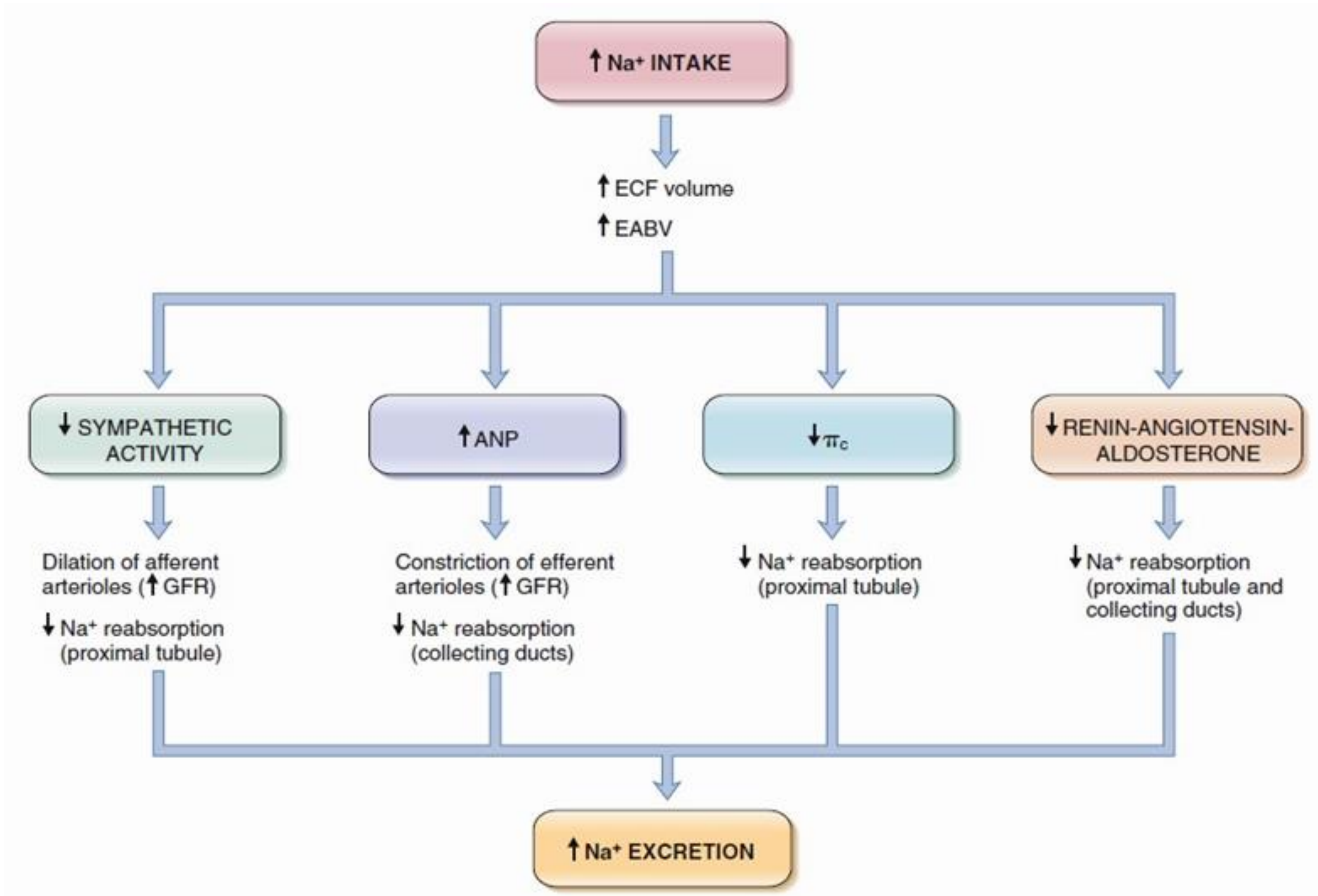
Principal cells



Na^{+} diffuses down electrochemical gradient through *epithelial Na^{+} channels* (ENaC)

- Na+ reabsorption by the principal cells is **inhibited by the K+-sparing diuretics** (e.g., amiloride, triamterene, spironolactone).
- **Spironolactone**, a steroid and **aldosterone-antagonist**.
- **Amiloride** and triamterene bind to the luminal membrane Na+ channels and **inhibit the aldosterone** induced increase in Na+ reabsorption

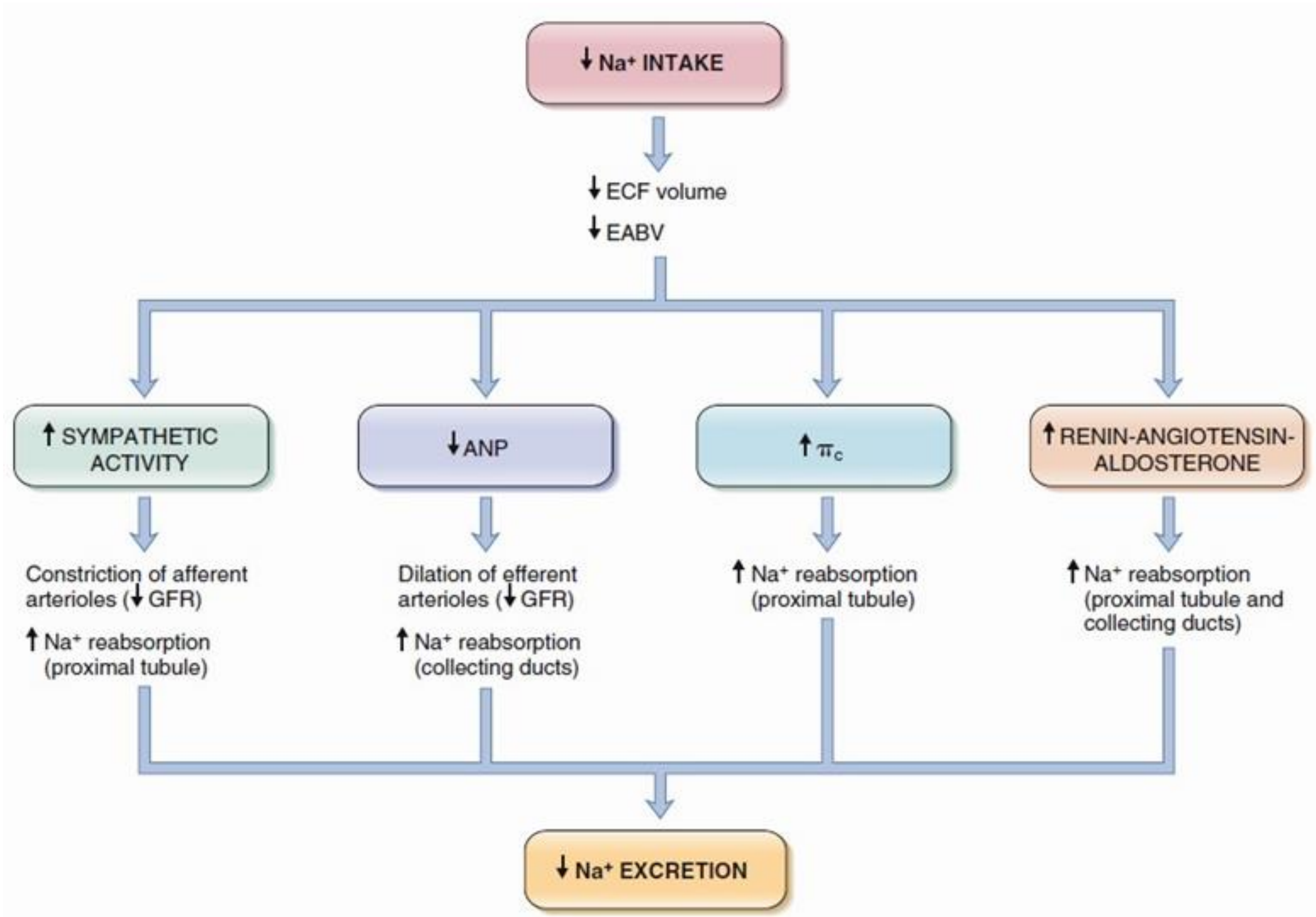
Regulation of Na^+ balance



ANP, Atriopeptin; EABV, effective arterial blood volume; ECF, extracellular fluid; GFR, glomerular filtration rate; πc, peritubular capillary oncotic pressure.

Regulation of Na^+ balance:

please after reading the next slide, read the book pages 286 - 288



- Na+ and its associated anions Cl− and HCO3− are the major solutes of ECF. In turn, the amount of Na+ in the ECF determines the ECF volume.

1. Sympathetic nerve activity:

- Sympathetic activity is activated by the **baroreceptor** mechanism in response to a decrease in arterial pressure and causes **vaso-constriction of afferent arterioles and increased proximal tubule Na+ reabsorption**.
- Activate **NH3 exchanger (indirectly)** which increases **Na^+** excretion & decreases reabsorption

2. **Atriopeptin (ANP):**

- Causes **vasodilation of afferent** arterioles, **vasoconstriction of efferent** arterioles, **increased GFR**, and decreased Na+ reabsorption in the late distal tubule and collecting ducts.

3. **Starling forces in peritubular capillaries:**

- increases in ECF volume dilute πc and inhibit proximal tubule Na+ reabsorption; decreases in ECF volume concentrate πc and stimulate proximal tubule Na+ reabsorption.

4. **Renin-angiotensin-aldosterone system:**

- **angiotensin II stimulates Na+ reabsorption** in the proximal tubule (Na+_H+ exchange), and **aldosterone stimulates Na+ reabsorption** in the late distal tubule and the collecting duct.

TABLE 6.7 Summary of the Functions of the Major Nephron Segments

Segment/Cell Type	Major Functions	Cellular Mechanisms	Hormone Actions	Diuretic Actions
Early Proximal Tubule	Isosmotic reabsorption of solute and water	Na^+-glucose, Na^+-amino acid, Na^+-phosphate cotransport	PTH inhibits Na^+-phosphate cotransport	Osmotic diuretics
		Na^+-H^+ exchange	Angiotensin II stimulates Na^+-H^+ exchange	Carbonic anhydrase inhibitors
Late Proximal Tubule	Isosmotic reabsorption of solute and water	NaCl reabsorption driven by Cl^- gradient	—	Osmotic diuretics
Thick Ascending Limb of the Loop of Henle	Reabsorption of NaCl without water Dilution of tubular fluid Single effect of countercurrent multiplication Reabsorption of Ca^{2+} and Mg^{2+} driven by lumen-positive potential	Na^+-K^+-$2Cl^-$ cotransport	ADH stimulates Na^+-K^+-$2Cl^-$ cotransport	Loop diuretics
Early Distal Tubule	Reabsorption of NaCl without water Dilution of tubular fluid	Na^+-Cl^- cotransport	PTH stimulates Ca^{2+} reabsorption	Thiazide diuretics
Late Distal Tubule and Collecting Ducts (principal cells)	Reabsorption of NaCl	Na^+ channels (ENaC)	Aldosterone stimulates Na^+ reabsorption	K^+-sparing diuretics
	K^+ secretion	K^+ channels	Aldosterone stimulates K^+ secretion	
	Variable water reabsorption	AQP2 water channels	ADH stimulates water reabsorption	
Late Distal Tubule and Collecting Ducts (α-intercalated cells)	Reabsorption of K^+	H^+-K^+ ATPase	—	—
	Secretion of H^+	H^+ ATPase	Aldosterone simulates H^+ secretion	K^+-sparing diuretics

ADH, Antidiuretic hormone; *PTH*, parathyroid hormone; *ENaC*, epithelial Na^+ channels; *AQP2*, aquaporin 2.