

# Renální fyziologie

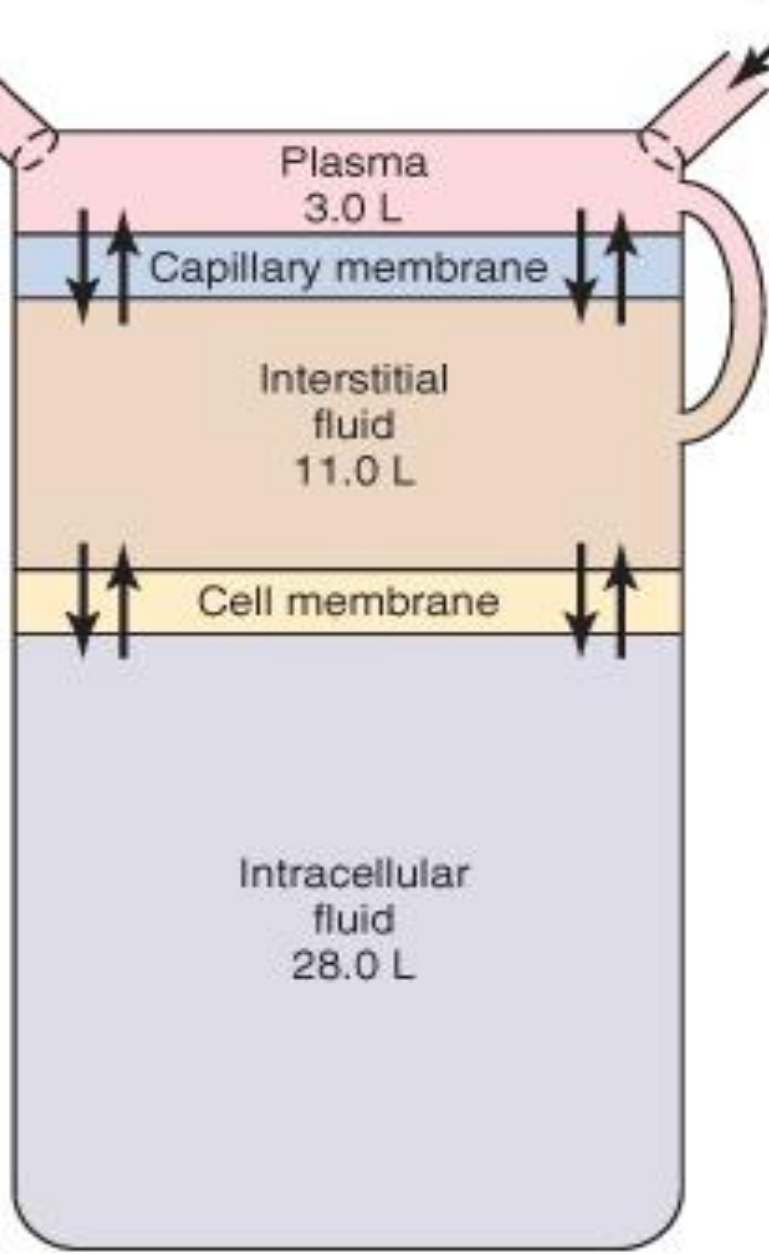
Prof. MUDr. Luděk Červenka, CSc.

**OUTPUT**

- Kidneys
- Lungs
- Feces
- Sweat
- Skin

**INTAKE**

Extracellular fluid (14.0 L)



Lymphatics

Plasma  
3.0 L

Capillary membrane

Interstitial fluid  
11.0 L

Cell membrane

Intracellular fluid  
28.0 L

## Daily intake and output of water (ml/day)

**Normal**

**Maximum**

### Intake

Fluid ingested

3 100

infinity

From metabolism

300

**Total intake**

**3 400**

### Output

Insensible – skin

350

5 000

Insensible – lungs

350 (vapor pressure 47 mmHg)

850

Sweat

150

5 000

Feces

100

7 000

Urine

2 400

infinity

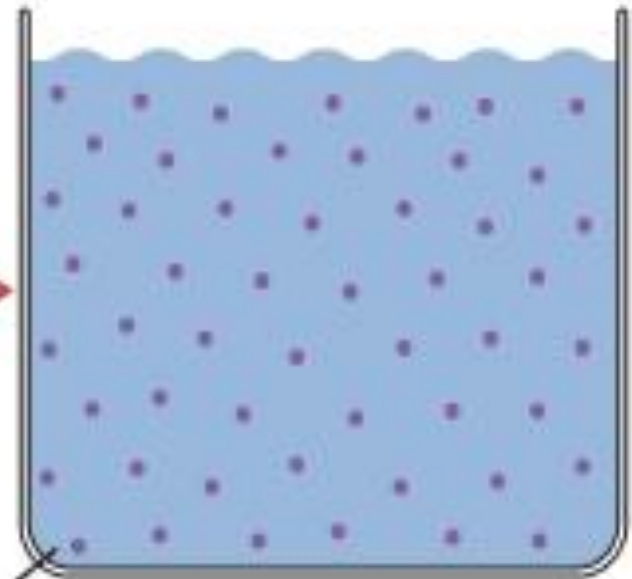
**Total output**

**3 400**



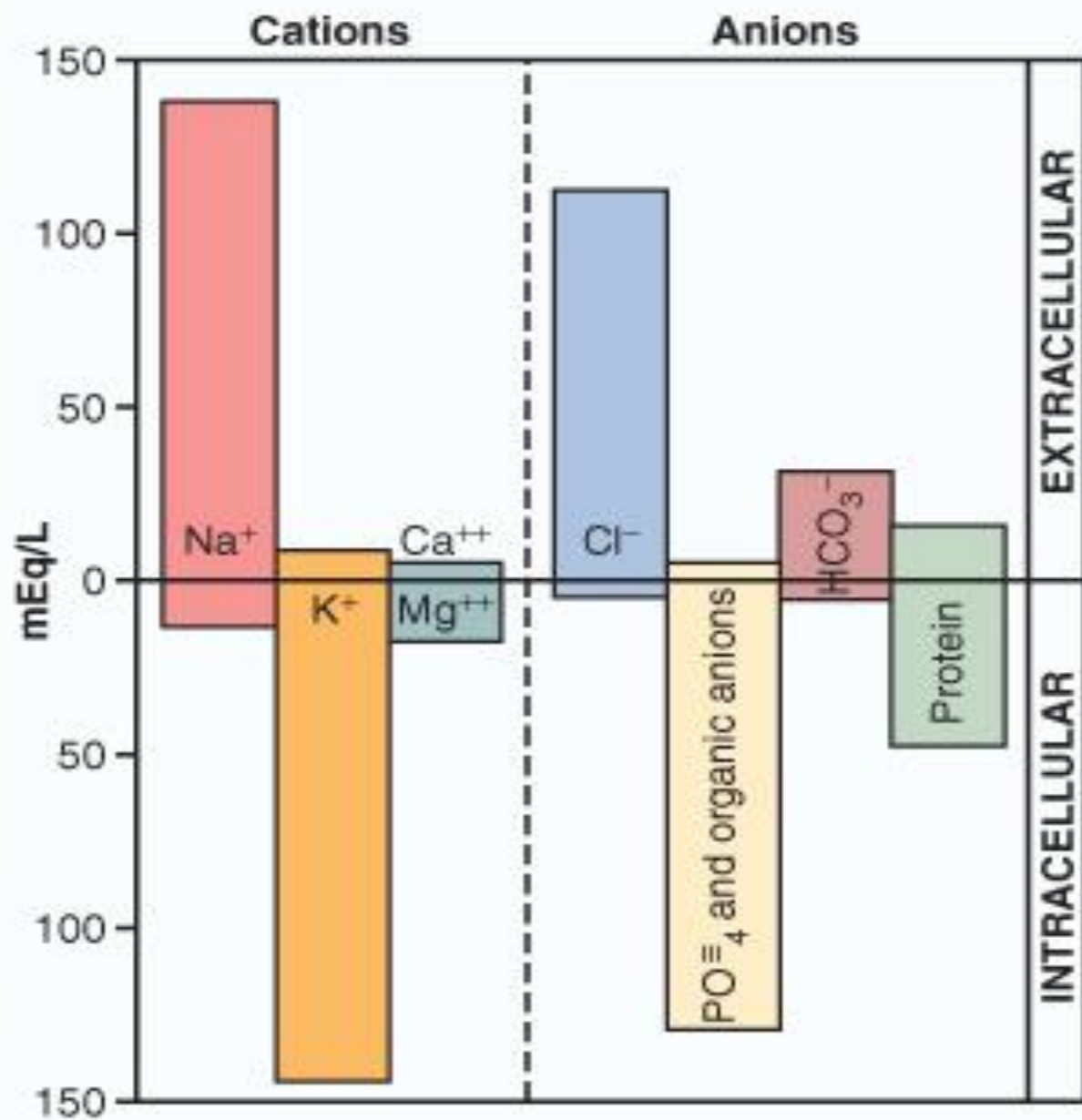
Indicator Mass A = Volume A x Concentration A

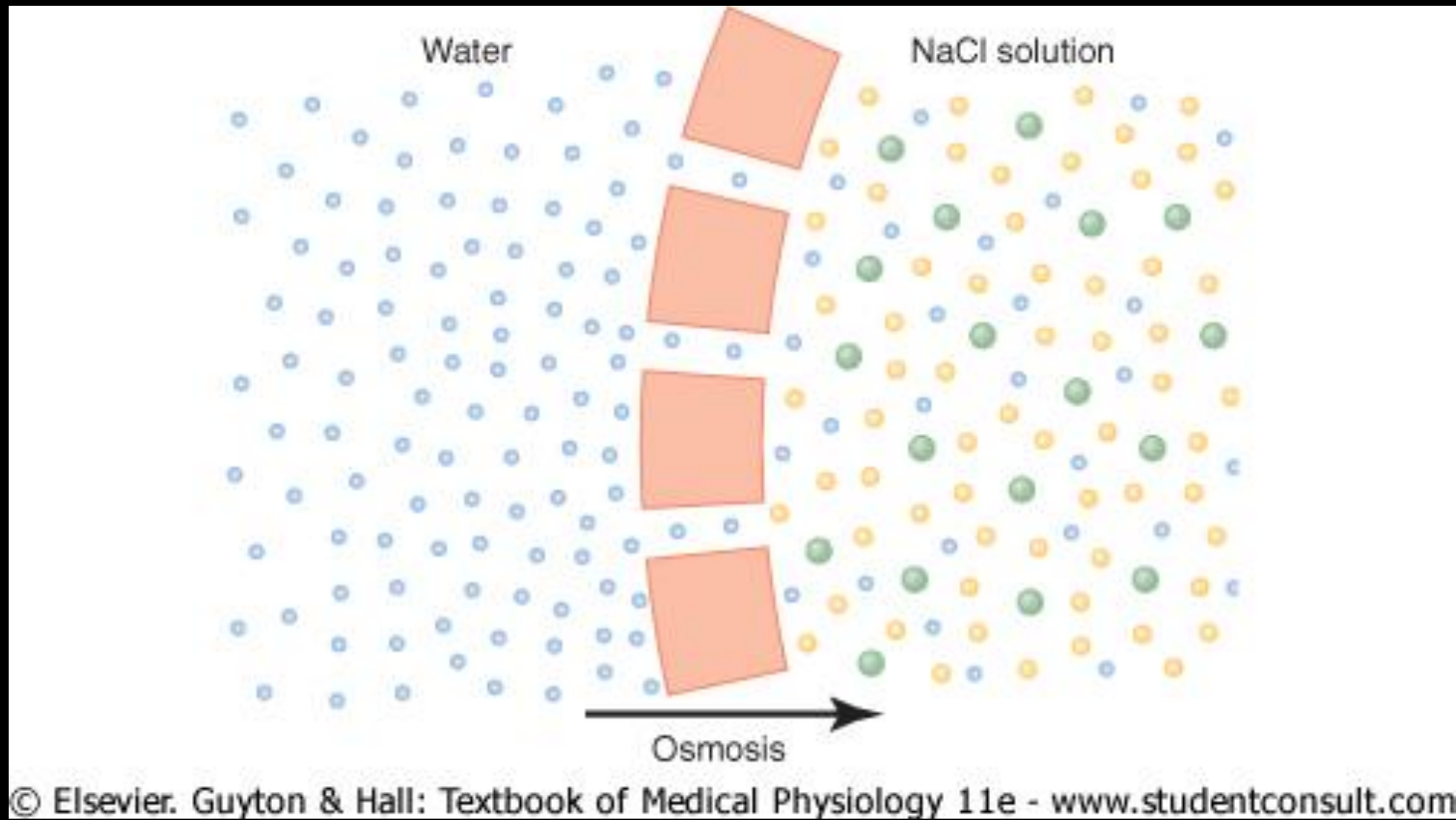
Indicator Mass A = Indicator Mass B



Indicator Mass B = Volume B x Concentration B

Volume B = Indicator Mass B / Concentration B





**Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration**

# Importance of Number of Osmotic Particles in Determining Osmotic Pressure

Osmotic pressure is determined by the *number* of particles per volume of fluid, not by the *mass* of the particles.

each particle in a solution, regardless of its mass, exerts, on average the same amount of pressure against the membrane.

$$k = \frac{m \cdot v^2}{2}$$

k = kinetic energy

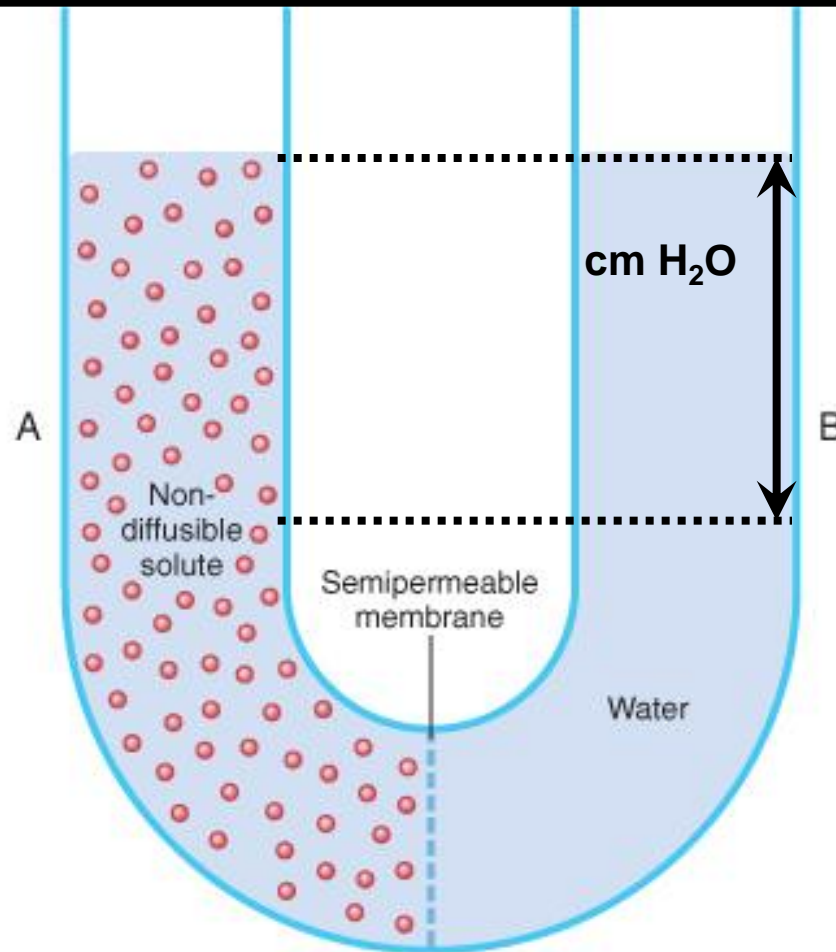
m = mass

v = velocity

Therefore, 1 mole of glucose in each liter has a concentration of 1 osm/L (even if 180 g/mol)  
1 mole of sodium chloride has an osmolar concentration of 2 osm/L (even if 58.5 g/mol)  
Thus, the term **osmole** refers to the number of osmotically active particles in a solution rather than to the molar concentration.

**Osmolality** = when concentration is expressed as *osmoles per kilogram of water*

**Osmolarity** = is expressed as *osmoles per liter of solution*



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The exact amount of pressure required to stop osmosis is called the *osmotic pressure* of the solution.



## Relation of Osmolality to Osmotic Pressure

A concentration of 1 osmole/L will cause 19 300 mmHg osmotic pressure

1 milliosmole/L is equivalent to 19.3 mmHg

Physiologically body fluids 300 mOsm/L = 5790 mmHg total osmotic pressure

Corrected osmolar activity (*osmotic coefficient*) = 0.93

The reason for this correction is that cations and anions exert interionic attraction, which can cause a slight decrease in the osmotic „activity“ of the dissolved substance

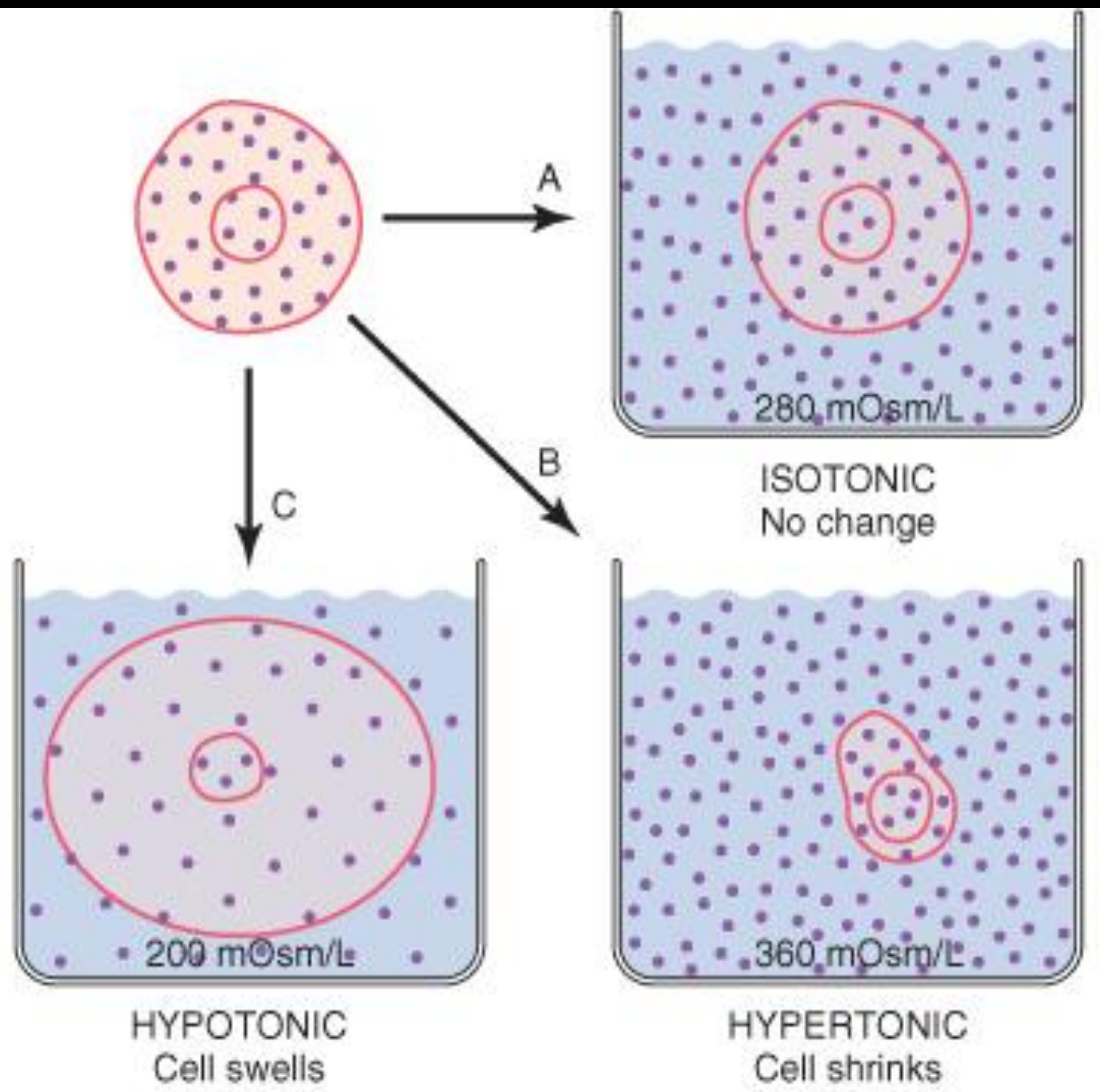
### Calculation of the Osmolarity and Osmotic Pressure of a Solution (by using van't Hoff's law)

0.9 % NaCl = 9 g NaCl per liter. Molecular weight of sodium chloride is 58.5 g/mol, the molarity of solution is 9 g/L divided by 58.5 g/mol = 0.154 mol/L.

The osmolarity is  $2 \times 0.154 = 0.308$  osm/L = 308 mOsm/L

$308 \text{ mOsm/L} \times 0.93$  (osmotic coefficient) = 286 mOsm/L is the actual osmolarity of 0.9 % NaCl

|  | <b>Plasma (mOsm/L H<sub>2</sub>O)</b> | <b>Interstitial</b> | <b>Intracellular</b> |
|--|---------------------------------------|---------------------|----------------------|
| Na <sup>+</sup>  | 142                                   | 139                 | 14                   |
| K <sup>+</sup>   | 4.2                                   | 4                   | 140                  |
| Mg <sup>2+</sup>   | 1.3                                   | 1.2                 | 0                    |
| Cl <sup>-</sup>  | 108                                   | 108                 | 4                    |
| HCO <sub>3</sub> <sup>-</sup>  | 24                                    | 28.3                | 10                   |
| HPO <sub>4</sub> <sup>2-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> | 2                                     | 2                   | 11                   |
| SO <sub>4</sub> <sup>2-</sup>  | 0.5                                   | 0.5                 | 1                    |
| Amino acids  | 2                                     | 2                   | 8                    |
| Phosphocreatinine  |                                       |                     | 45                   |
| Carnosine  |                                       |                     | 14                   |
| Creatine   | 0.2                                   | 0.2                 | 9                    |
| Lactate  | 1.2                                   | 1.2                 | 1.5                  |
| Adenosine triphosphate   |                                       |                     | 5                    |
| Hexose monophosphate   |                                       |                     | 3.7                  |
| Glucose  | 5.6                                   | 5.6                 |                      |
| Protein  | 1.2                                   | 0.2                 | 4                    |
| Urea   | 4                                     | 4                   | 4                    |
| Others   | 4.8                                   | 3.9                 | 10                   |
| <b>Total mOsm/L</b>  | <b>301.8</b>                          | <b>300.8</b>        | <b>301.2</b>         |
| <b>Corrected osmolar activity</b>  | <b>282.0</b>                          | <b>281.0</b>        | <b>281.0</b>         |



## Calculations of Fluid Shifts and Osmolarities After Infusion of Hypertonic Saline

If 2 liters of a hypertonic 3.0 % NaCl solution are infused into the extracellular fluid compartment of a 70 kg patient whose initial plasma osmolarity is 280 mOsm/l, what would be the intracellular and extracellular fluid volumes and osmolarities after reaching osmotic equilibrium?

Assuming that extracellular fluid volume is 20 % and intracellular fluid volume 40 % of the body weight.

## Initial Conditions

|                     | Volume<br>(liters) | Concentration<br>(mOsm/l) | Total<br>(mOsm) |
|---------------------|--------------------|---------------------------|-----------------|
| Extracellular fluid | 14                 | 280                       | 3 920           |
| Intracellular fluid | 28                 | 280                       | 7 840           |
| Total body fluid    | 42                 | 280                       | 11 760          |

2 L of 3 % NaCl = 30 g NaCl per liter. Because the molecular weight is 58.5 g/mol.

This mean there is about 0.513 mole of NaCl per liter (30:58.5).

For 2 liters of solution this would be 1.026 mole (2 x 0.513).

Because 1 mole of NaCl equals 2 osmoles = 2 x 1.026 = 2.052 osmoles = 2 052 mOsm

## Instantaneous Effect of Adding 2 Liters of 3.0 % NaCl

|                     | Volume<br>(liters)  | Concentration<br>(mOsm/l) | Total<br>(mOsm)            |
|---------------------|---------------------|---------------------------|----------------------------|
| Extracellular fluid | <b>16</b><br>14 + 2 | <b>373</b><br>5972 : 16   | <b>5972</b><br>3920 + 2052 |
| Intracellular fluid | <b>28</b>           | <b>280</b>                | <b>7 840</b>               |
| Total body fluid    | <b>44</b>           | <b>no equilibrium</b>     | <b>13 812</b>              |

Final osmolarity after reaching equilibrium must be:  $13\ 812 : 44 = 313.9\ \text{mOsm/L}$

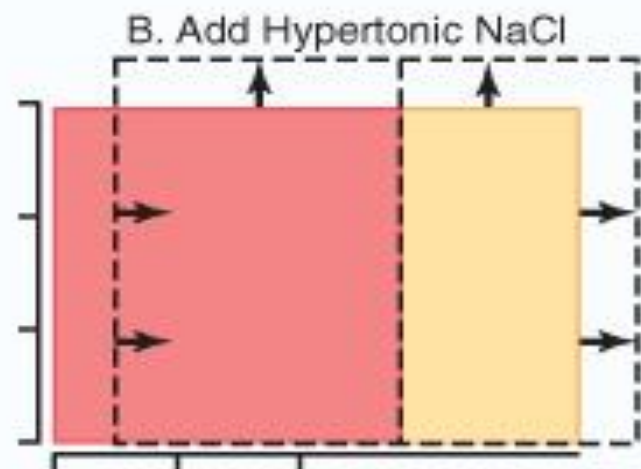
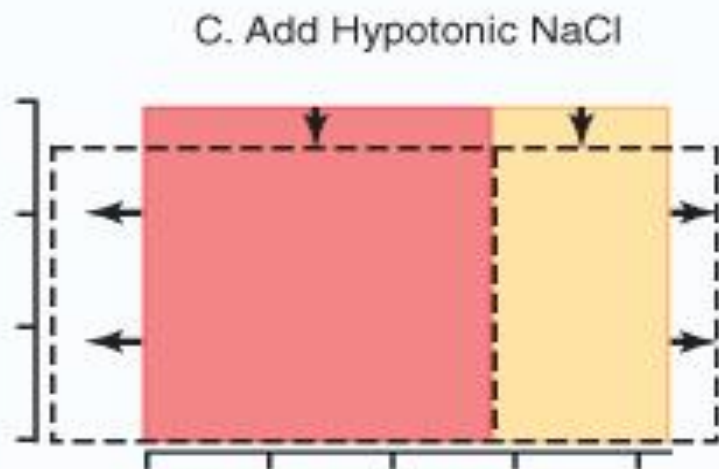
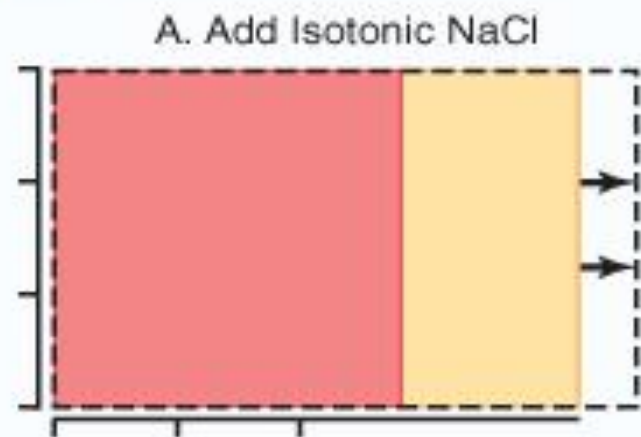
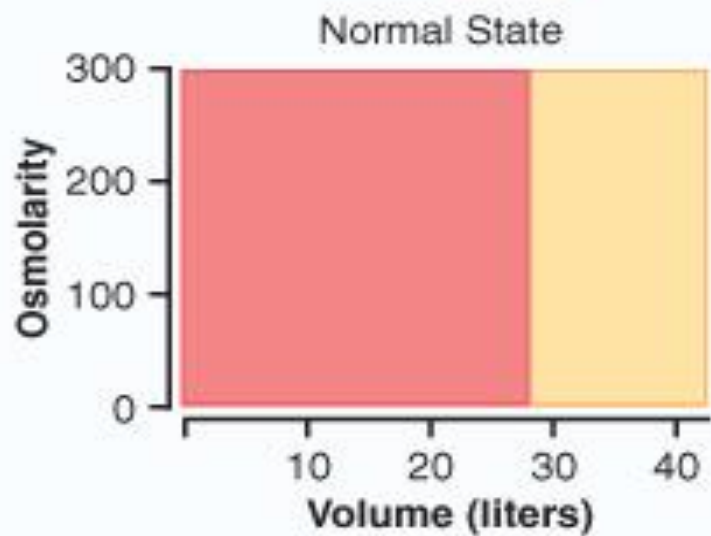
## Effect of Adding 2 Liters of 3.0 % NaCl after Osmotic Equilibrium

|                     | Volume<br>(liters)          | Concentration<br>(mOsm/l) | Total<br>(mOsm) |
|---------------------|-----------------------------|---------------------------|-----------------|
| Extracellular fluid | <b>19.02</b><br>5 972:313.9 | <b>313.9</b>              | <b>5 972</b>    |
| Intracellular fluid | <b>24.98</b><br>7 840:313.9 | <b>313.9</b>              | <b>7 840</b>    |
| Total body fluid    | <b>44</b><br>13 812:313.9   | <b>313.9</b>              | <b>13 812</b>   |

One can see that adding 2 liters of hypertonic NaCl solution causes more than a 5-liter increase in extracellular fluid volume ( $19.02 - 14 = 5.02$ ), while decreasing intracellular fluid volume by 3 liters ( $24.98 - 28 = -3.02$ ).

Intracellular fluid

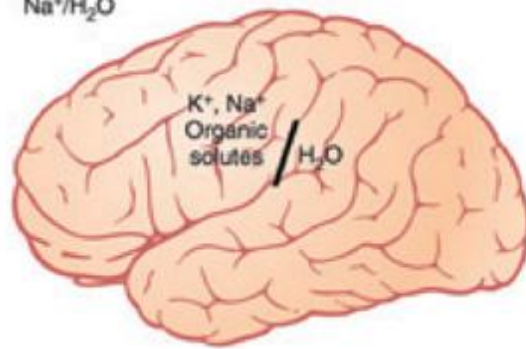
Extracellular fluid



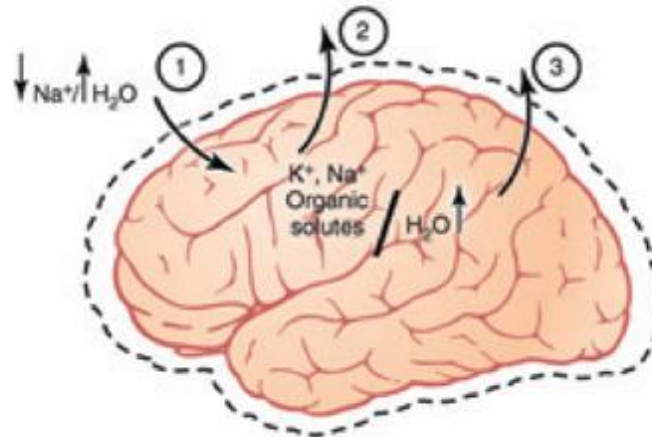


| <b>Abnormality</b>                       | <b>Cause</b>   | <b>Plasma Na<sup>+</sup> Concentration</b> | <b>ECFV</b> | <b>ICFV</b> |
|--|--|--|-------------|-------------|
| Hyponatremia<br>Dehydration              | Adrenal insufficiency<br>overuse of diuretics<br>vomiting and diarrhea | ↓  | ↓           | ↑           |
| <b>C</b> Hyponatremia<br>Overhydratation | Excess ADH (SIADH)   | ↓  | ↑           | ↑           |
| Hypernatremia<br>Dehydration             | Diabetes insipidus<br>excessive sweating<br>(without water intake)     | ↑  | ↓           | ↓           |
| Hypernatremia<br>Overhydration           | Cushing's disease<br>primary aldosteronism                             | ↑  | ↑           | ↓           |

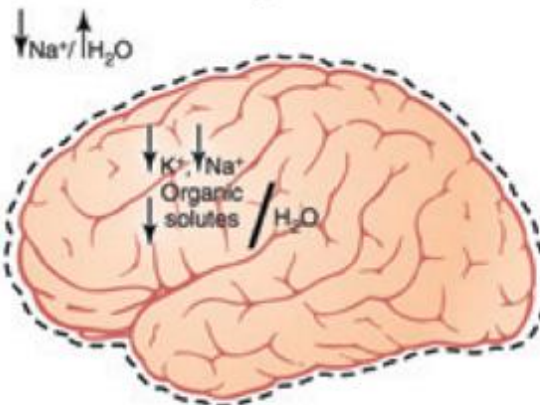
$\text{Na}^+/\text{H}_2\text{O}$



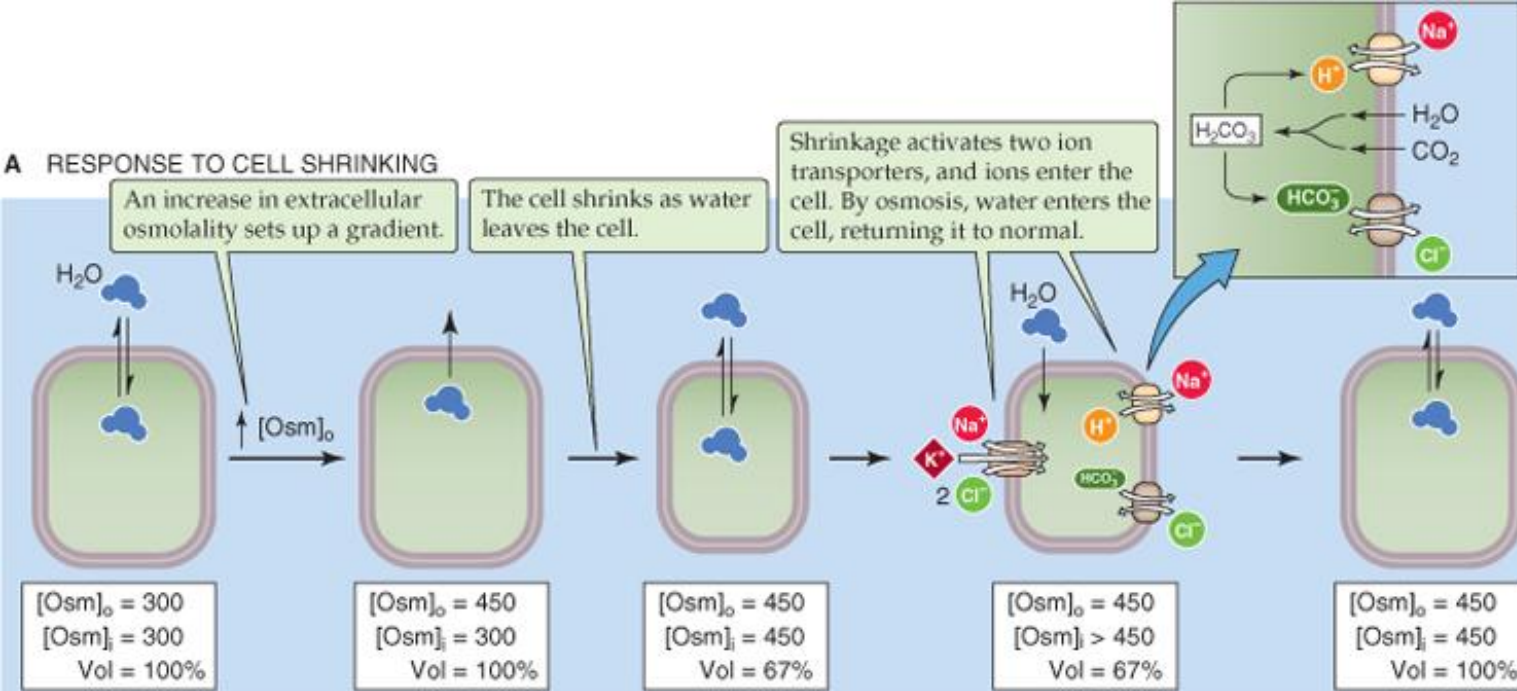
Normonatremia



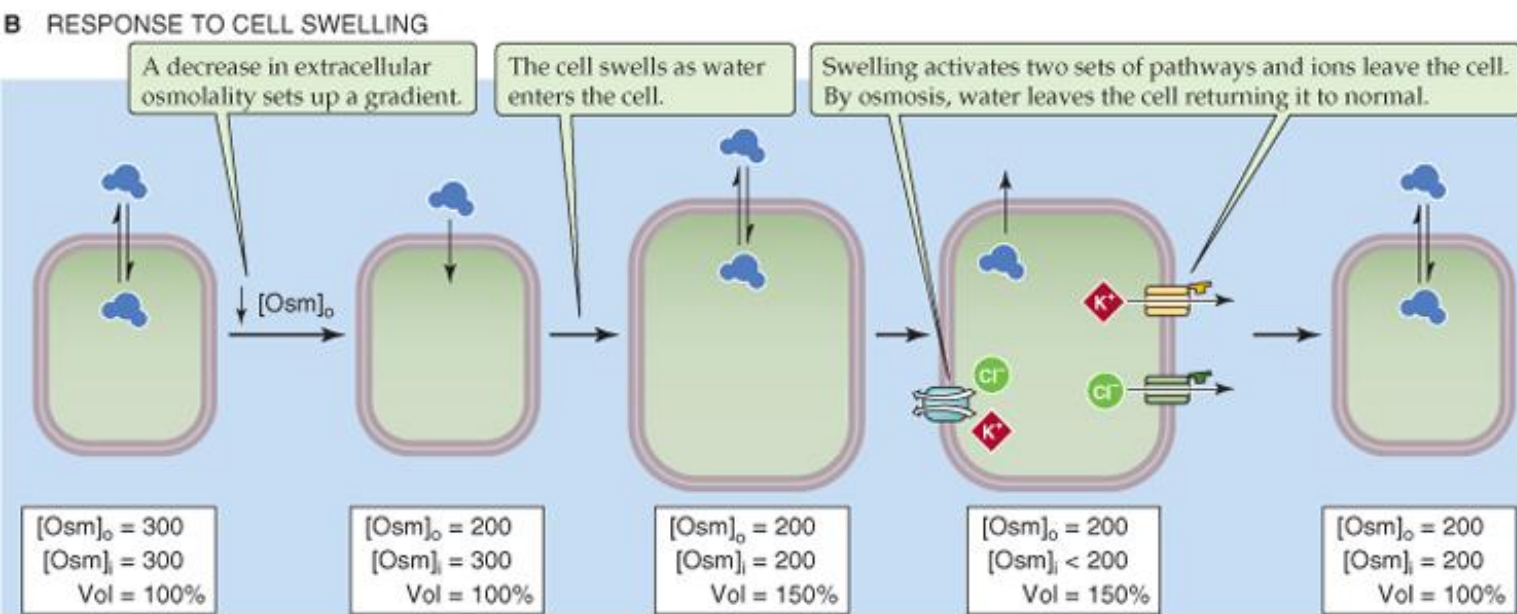
Acute hyponatremia



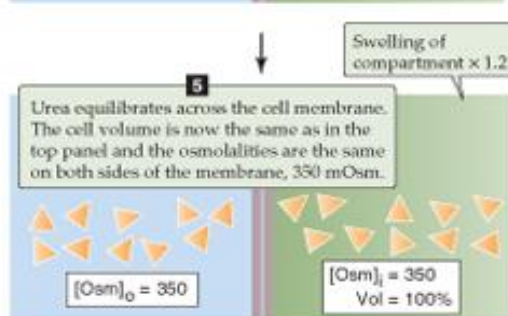
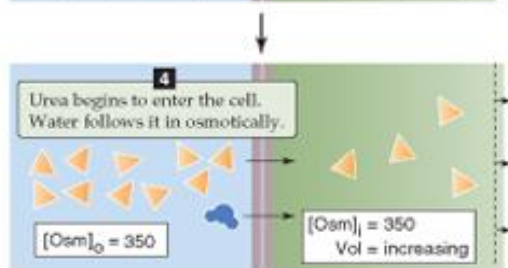
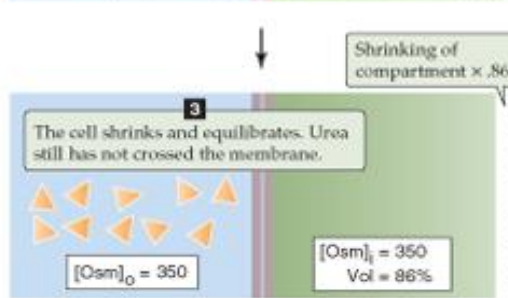
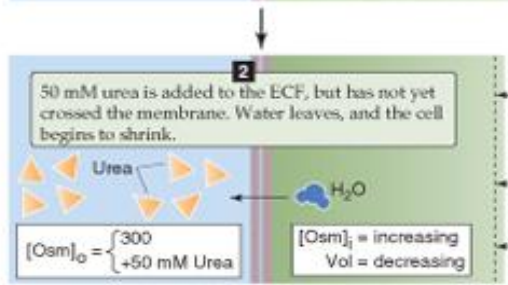
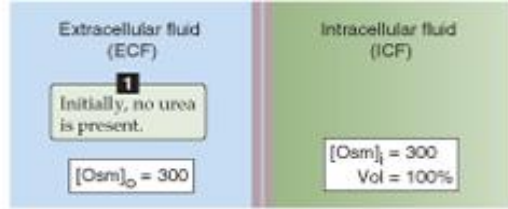
Chronic hyponatremia



**Regulatory volume increase (brain)**  
 (acute – salts)  
 (chronic – organic solutes - sorbitol)



**Regulatory volume decrease**

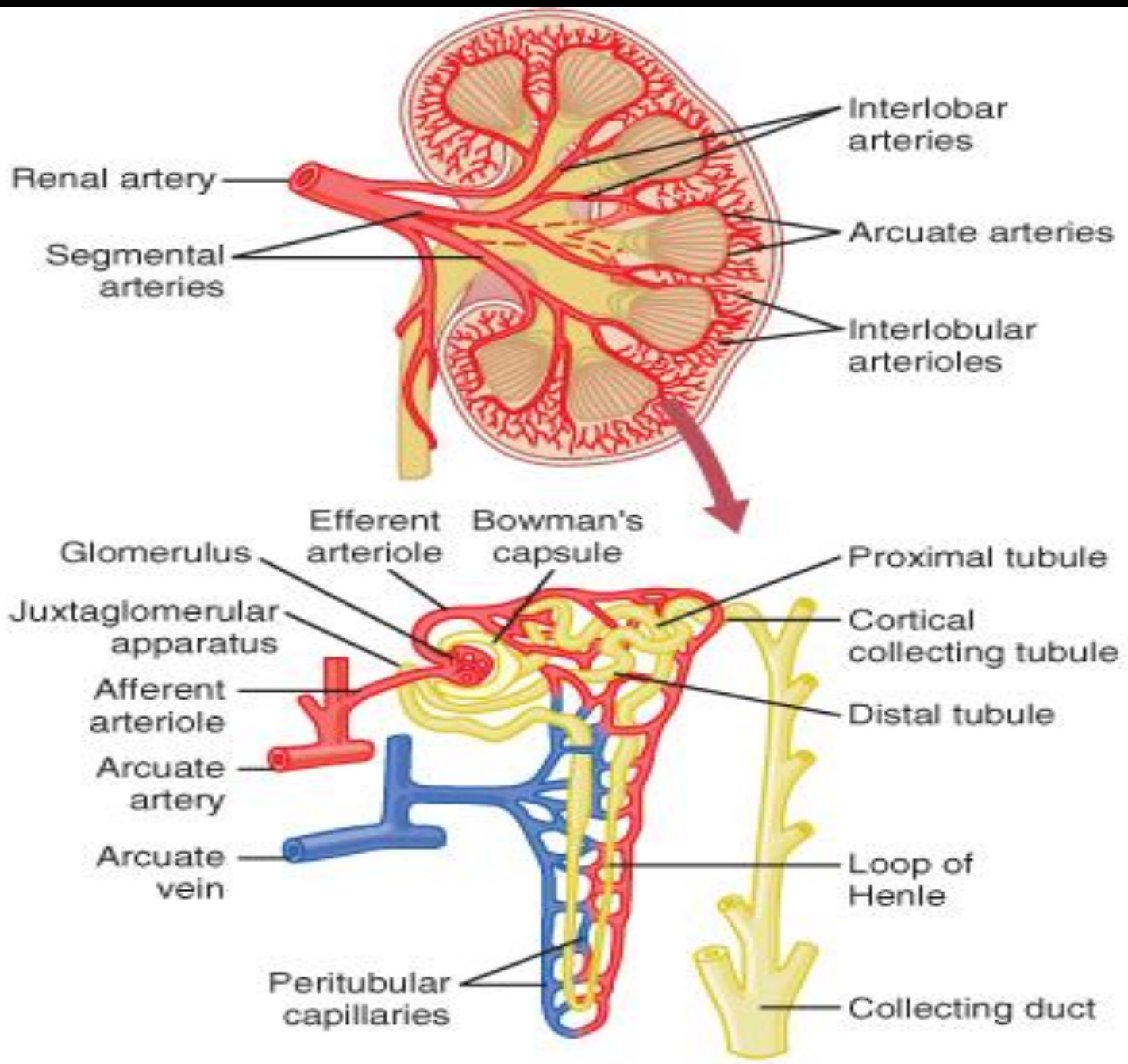


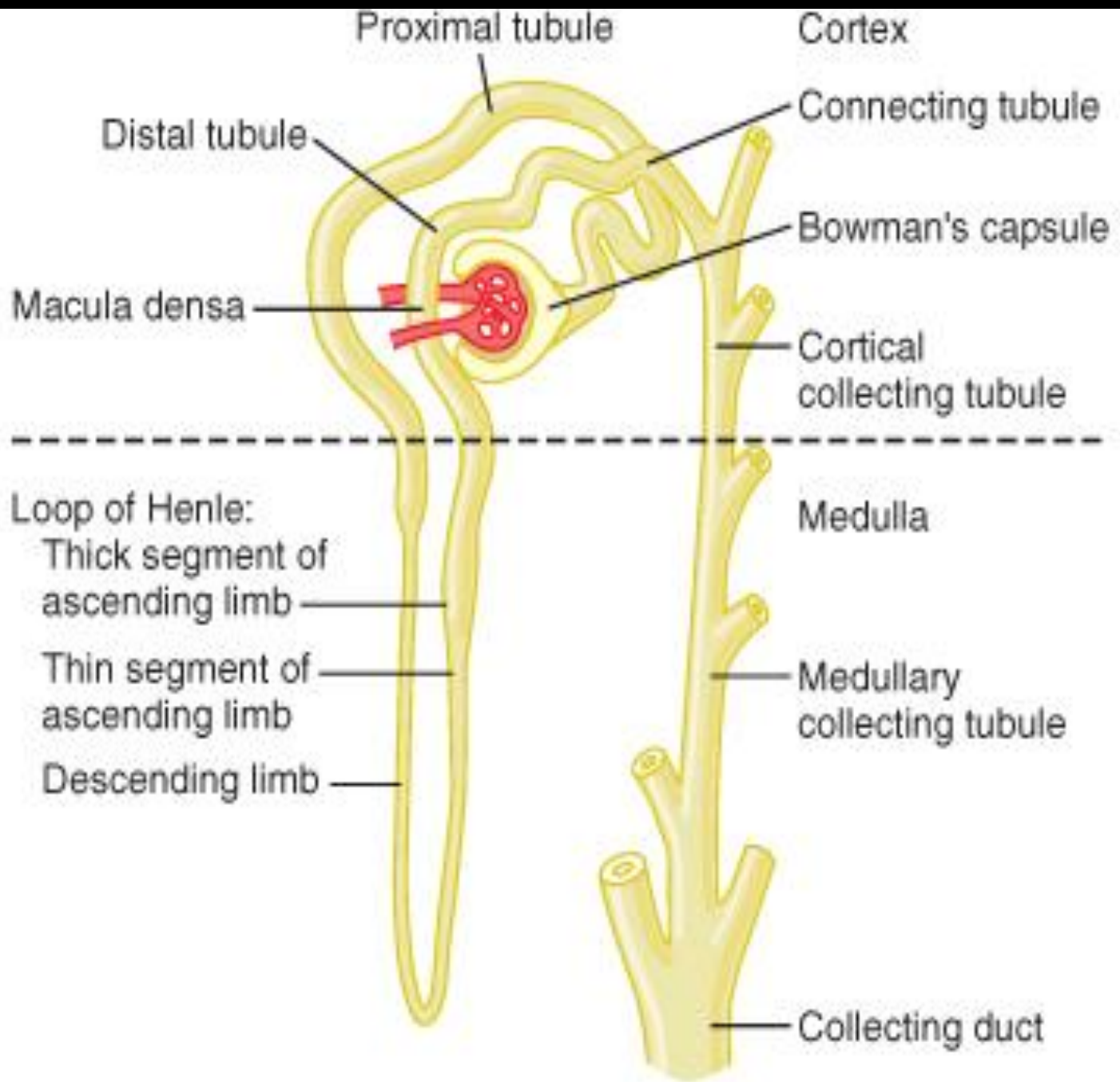
$$\text{Total osmolality (mOsm)} \cong 2 \cdot [\text{Na}^+] + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

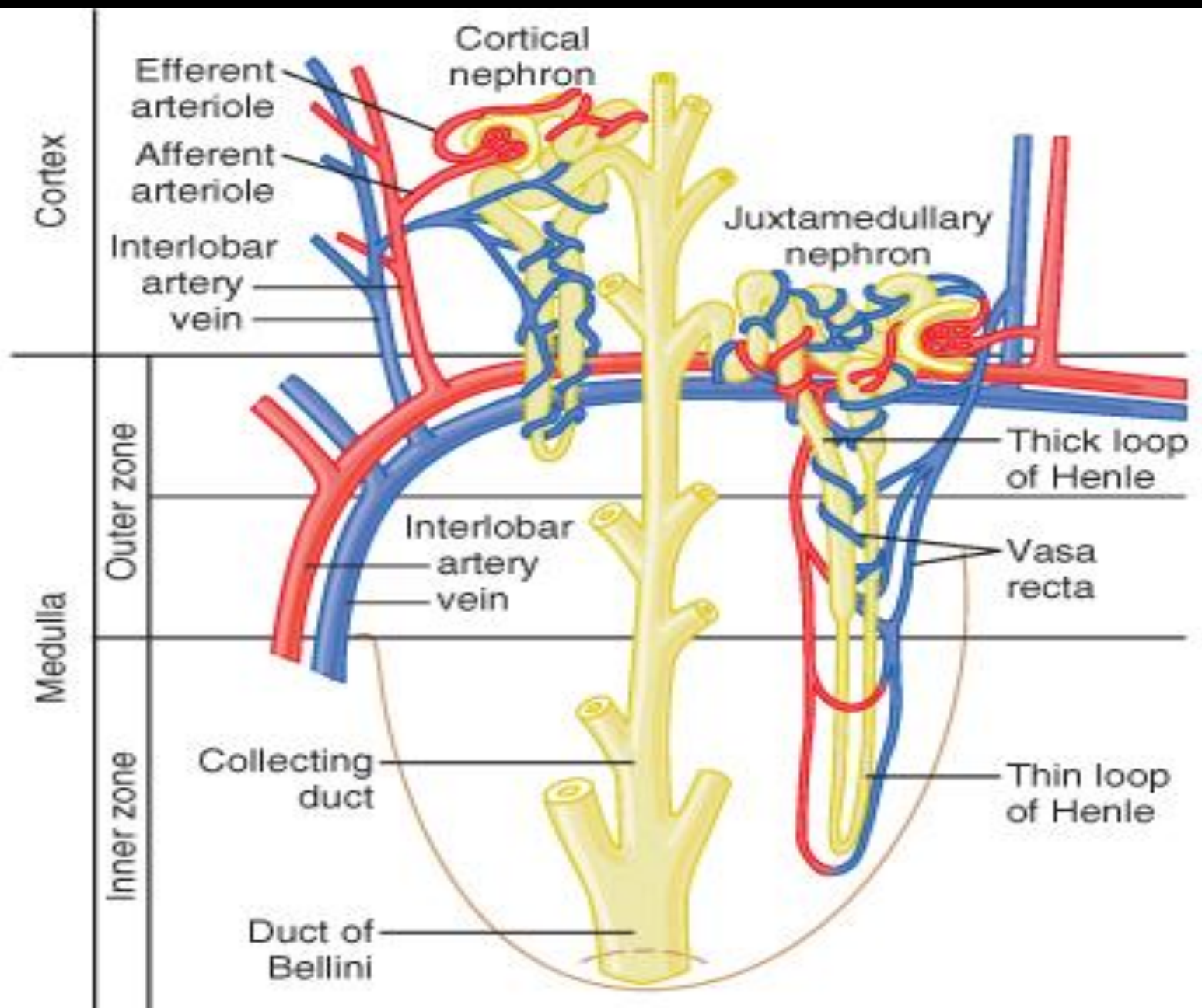
$$\text{Tonicity or effective osmolality (mOsm)} \cong 2 \cdot [\text{Na}^+] + \frac{\text{Glucose (mg/dL)}}{18} \quad (5-32)$$

## **Kidneys serve following functions:**

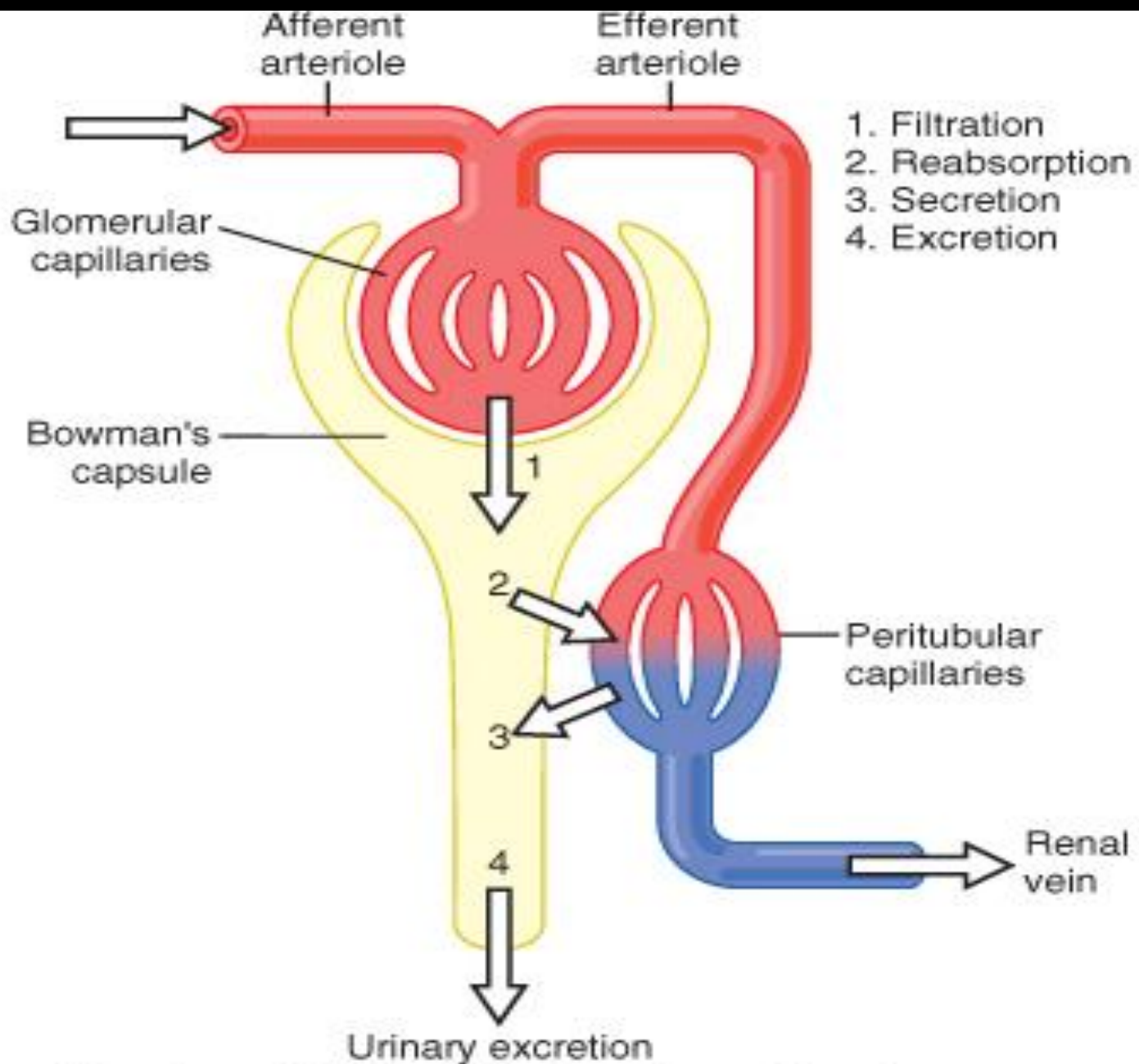
- 1. Excretion of metabolic waste products and foreign chemicals**
- 2. Regulation of water and electrolyte balance**
- 3. Regulation of body fluid osmolality**
- 4. Regulation of acid-base balance**
- 5. Metabolism of hormones**
- 6. Gluconeogenesis**





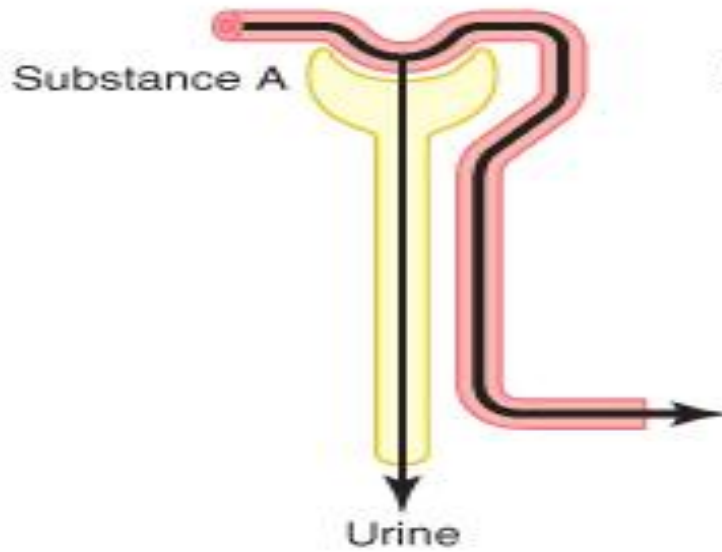




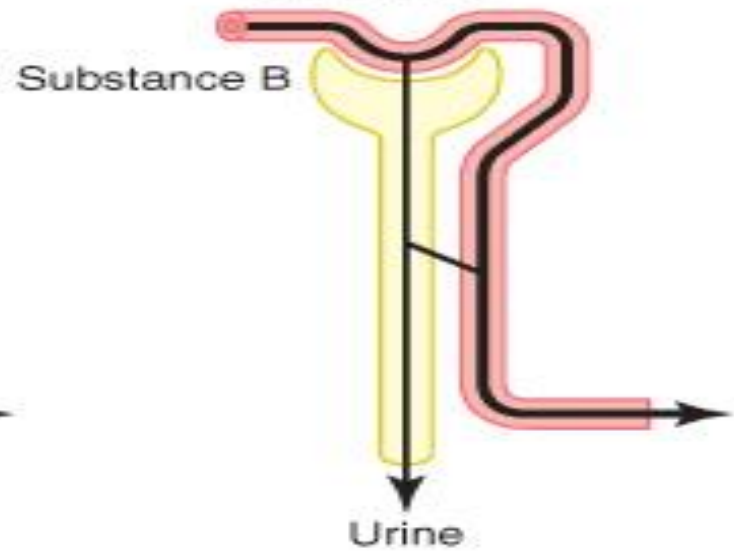


$$\text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion}$$

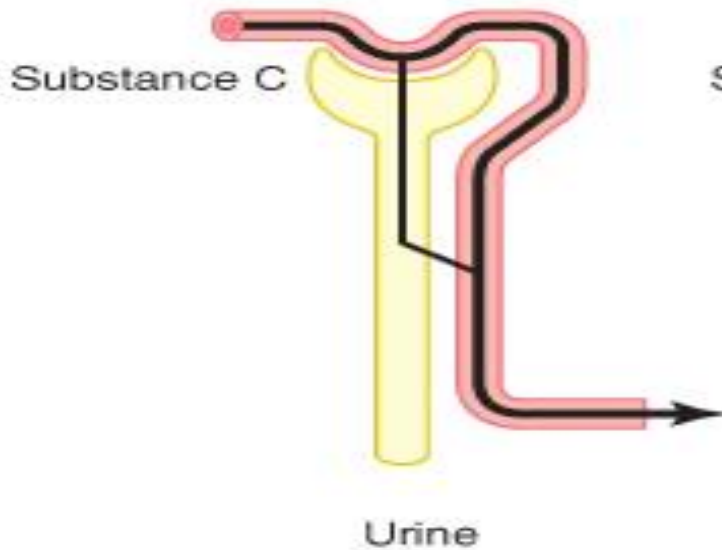
A. Filtration only



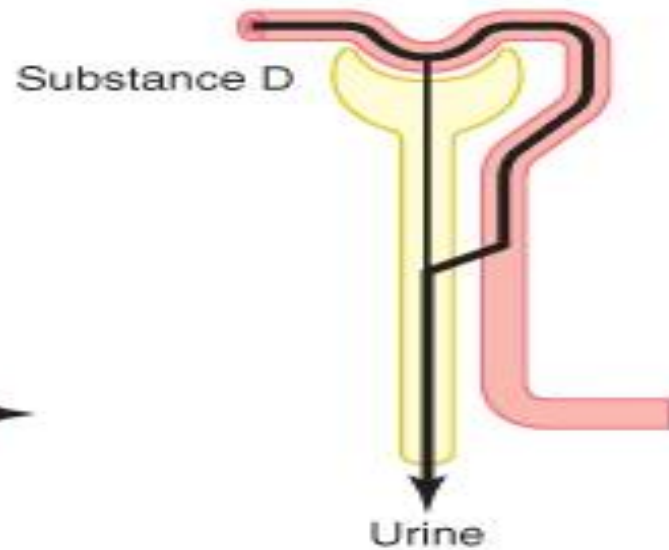
B. Filtration, partial reabsorption

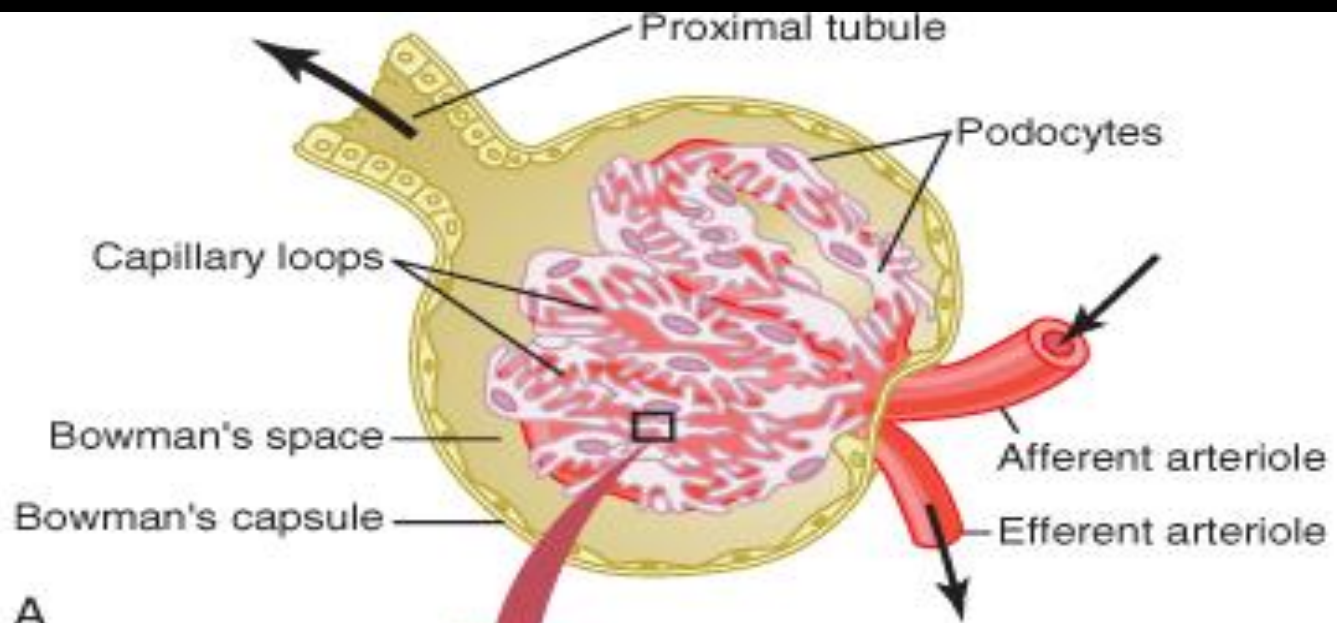


C. Filtration, complete reabsorption

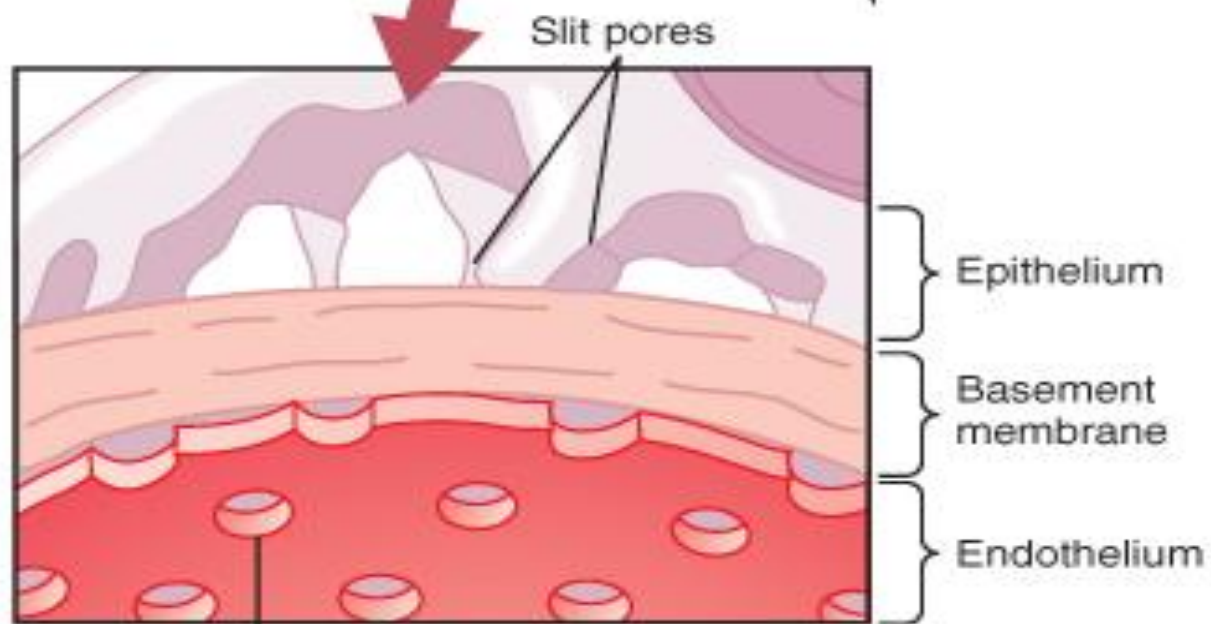


D. Filtration, secretion

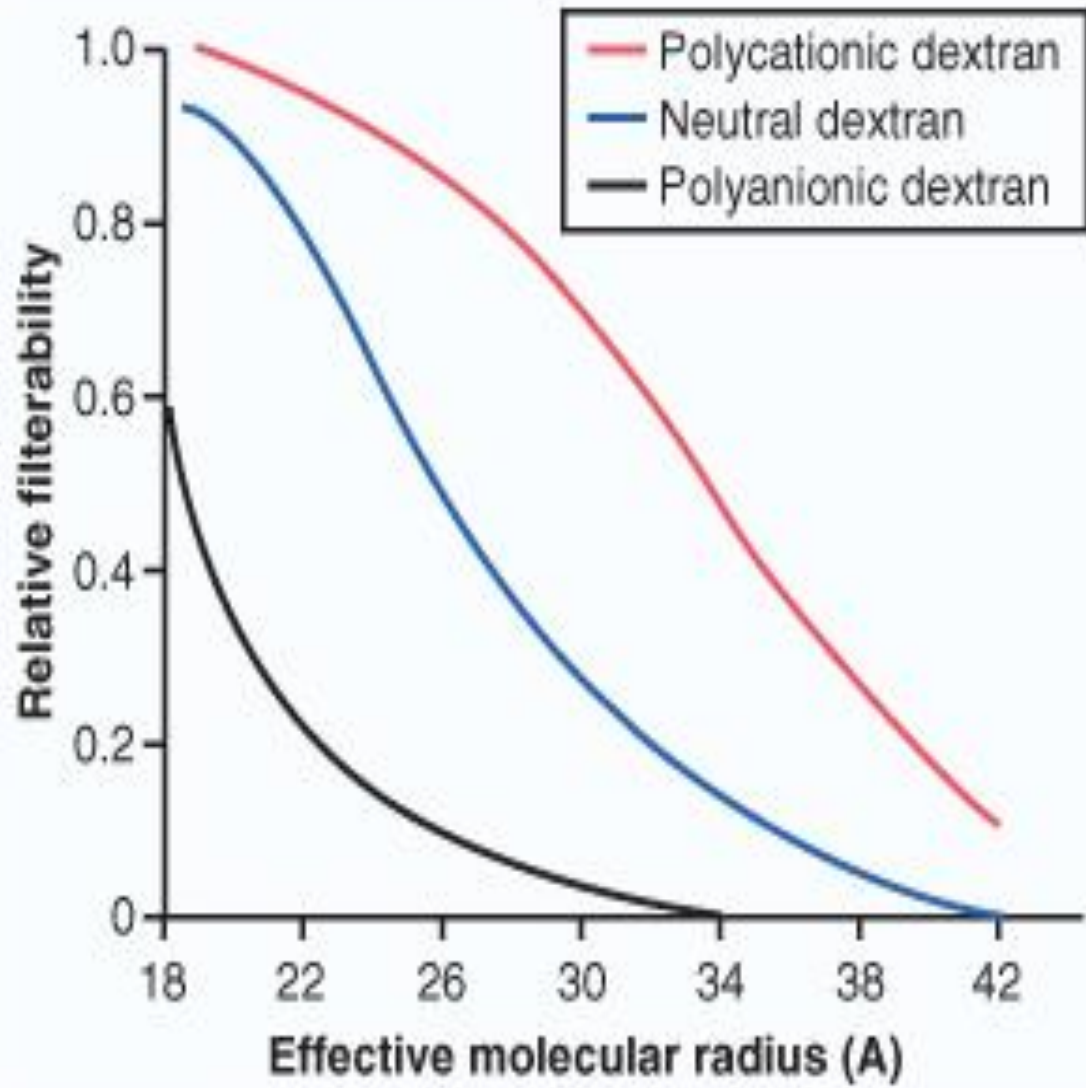


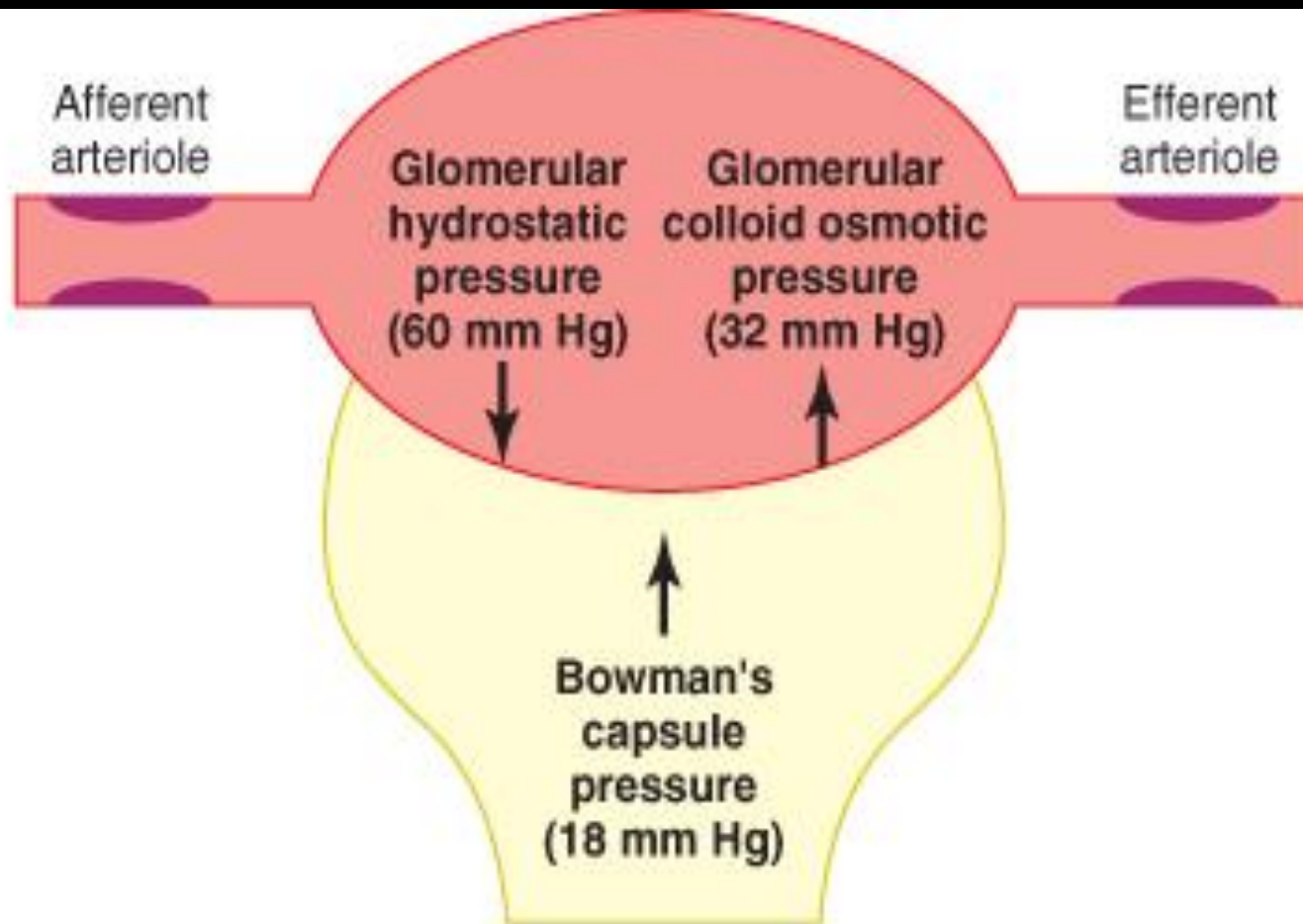


A

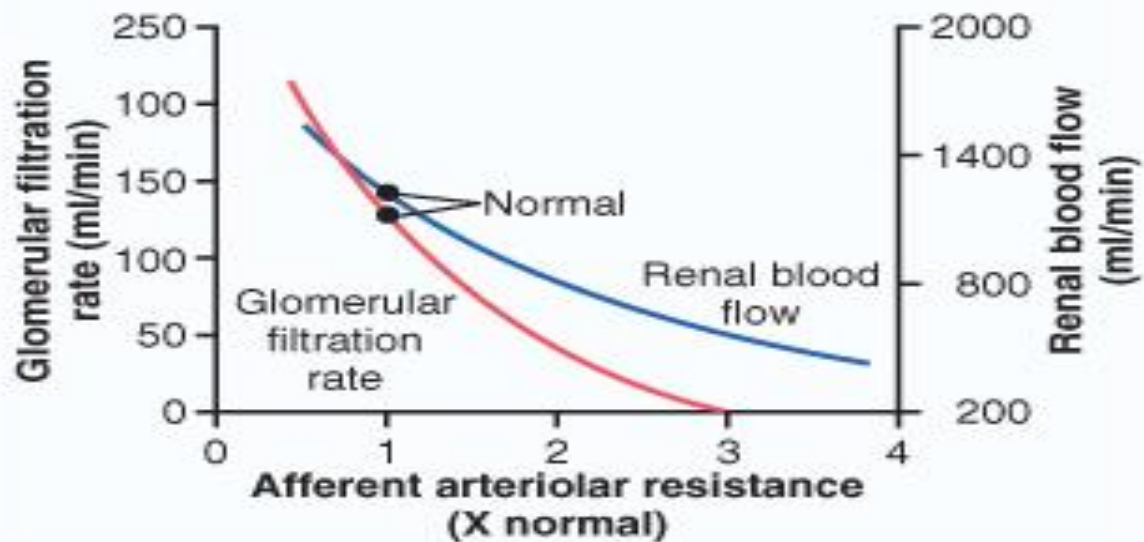
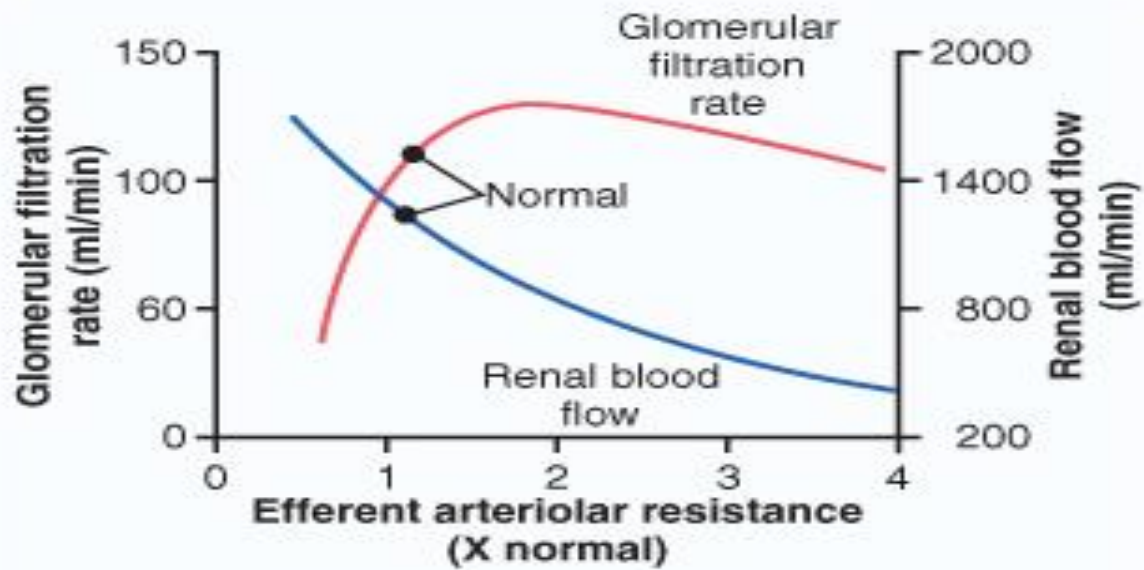


B





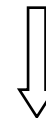
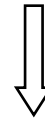
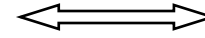
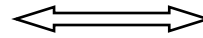
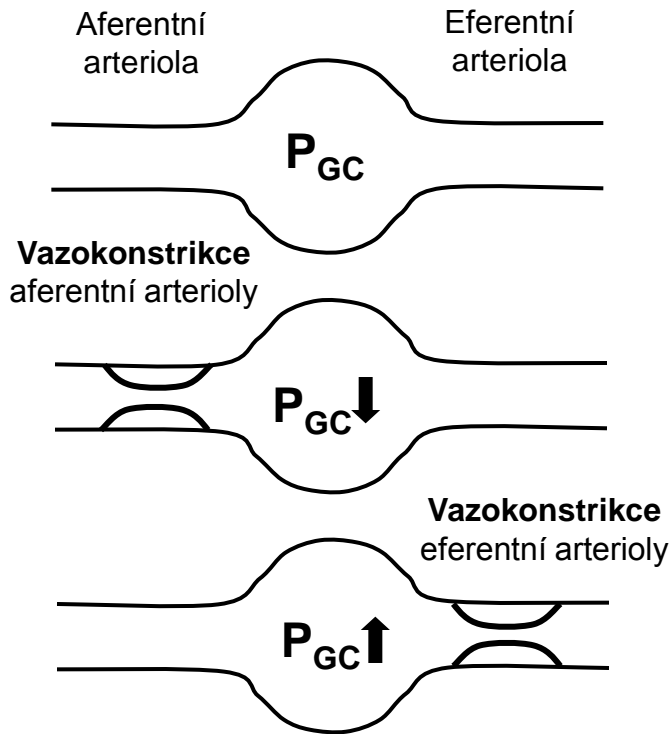
$$\text{Net filtration pressure (10 mm Hg)} = \text{Glomerular hydrostatic pressure (60 mm Hg)} - \text{Bowman's capsule pressure (18 mm Hg)} - \text{Glomerular oncotic pressure (32 mm Hg)}$$

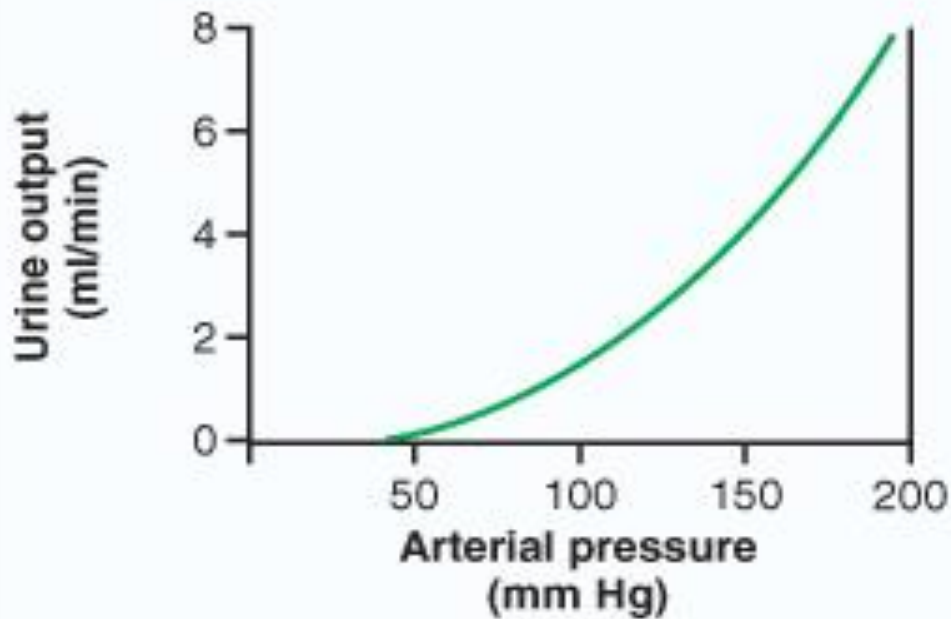
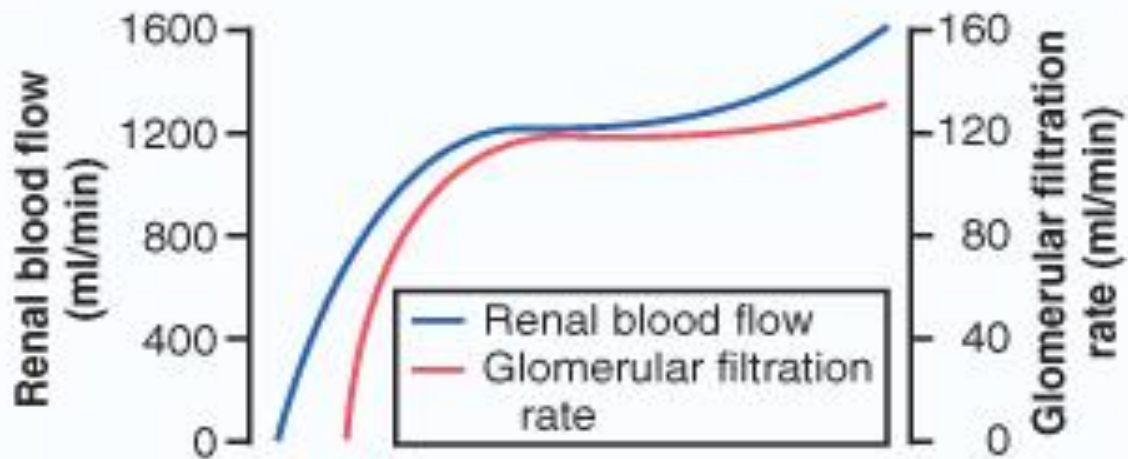


# GLOMERULÁRNÍ KAPILÁRY

GLOMERULÁRNÍ  
FILTRACE

PRŮTOK KRVE  
LEDVINAMI

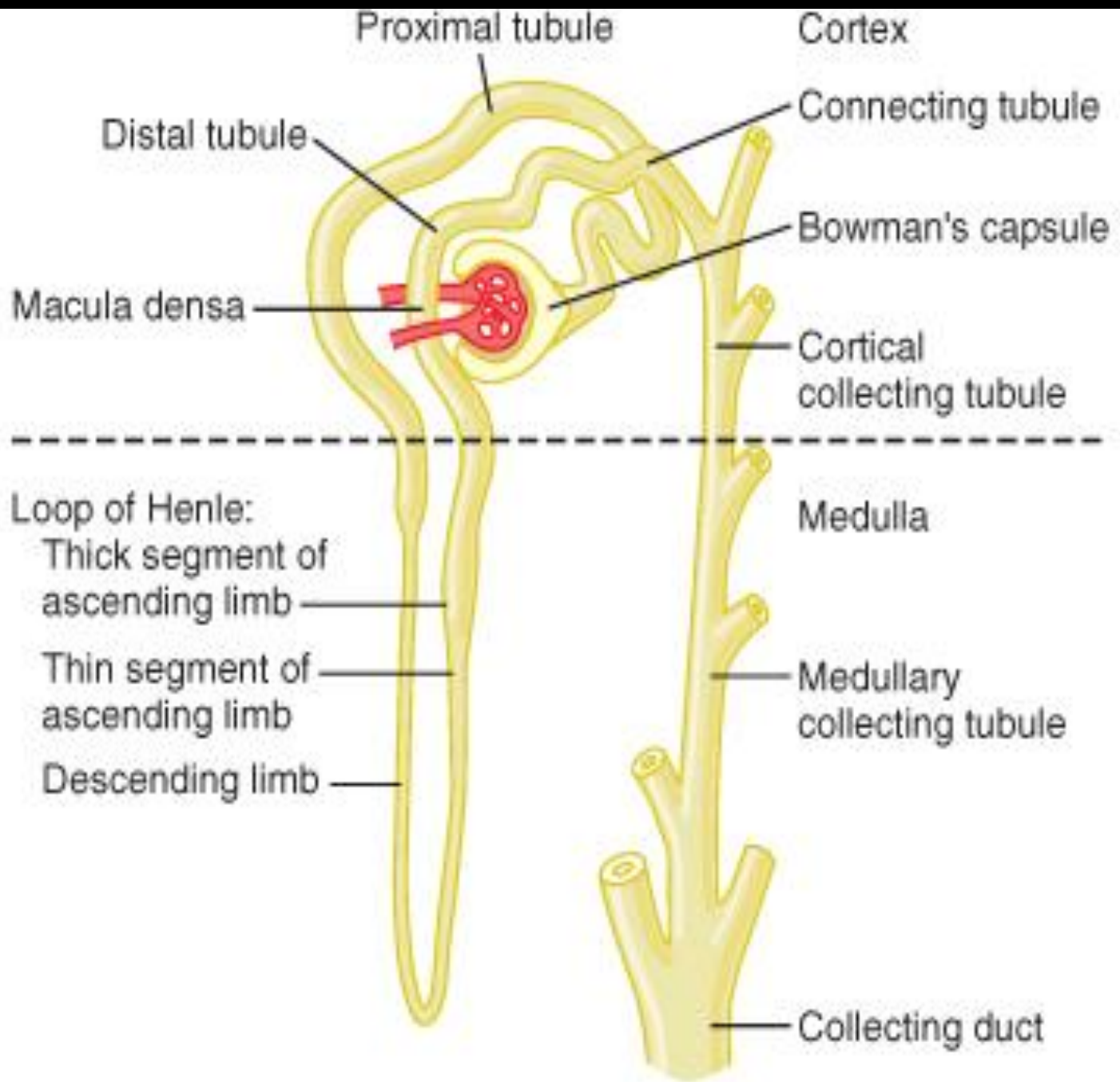


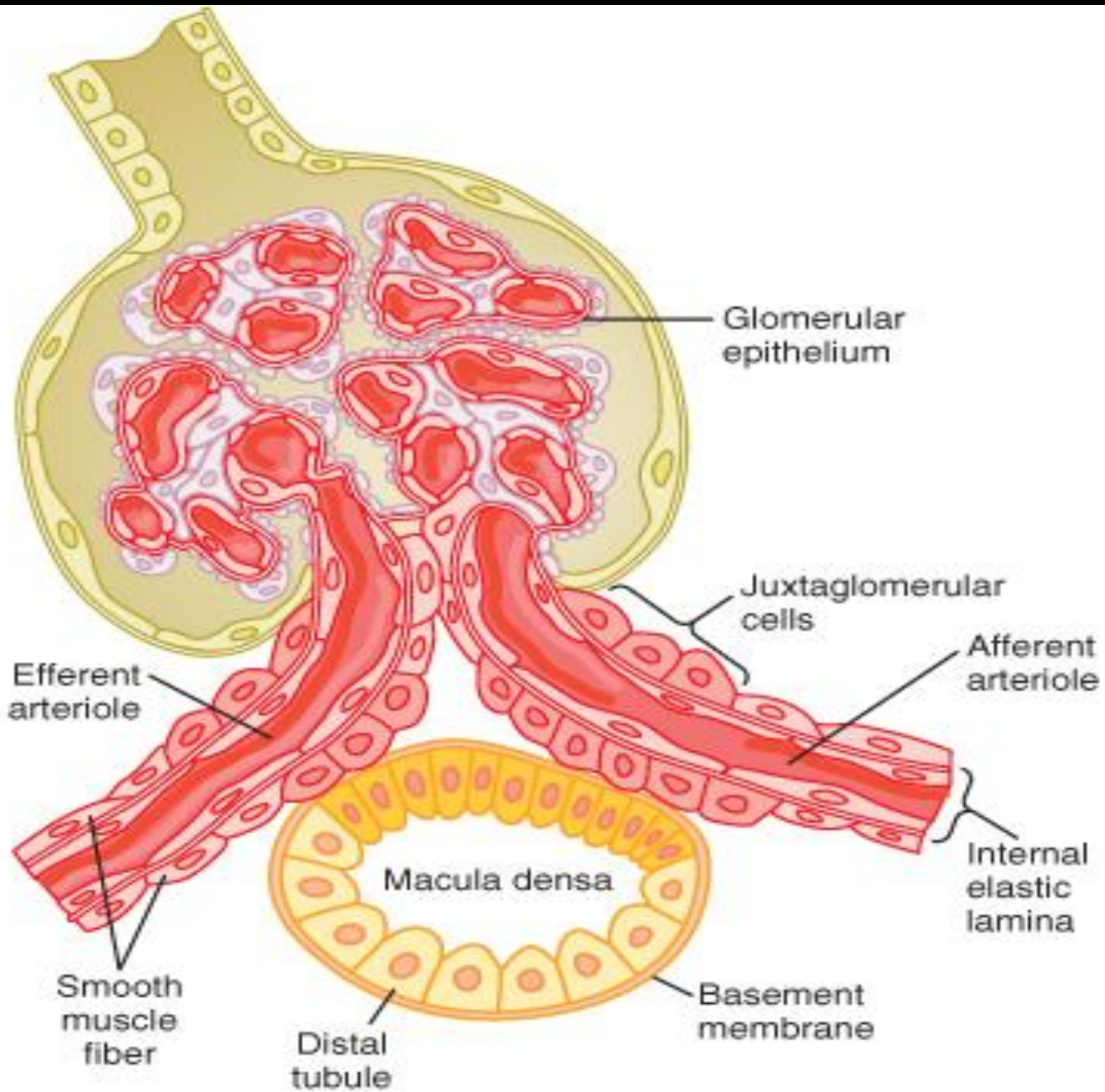


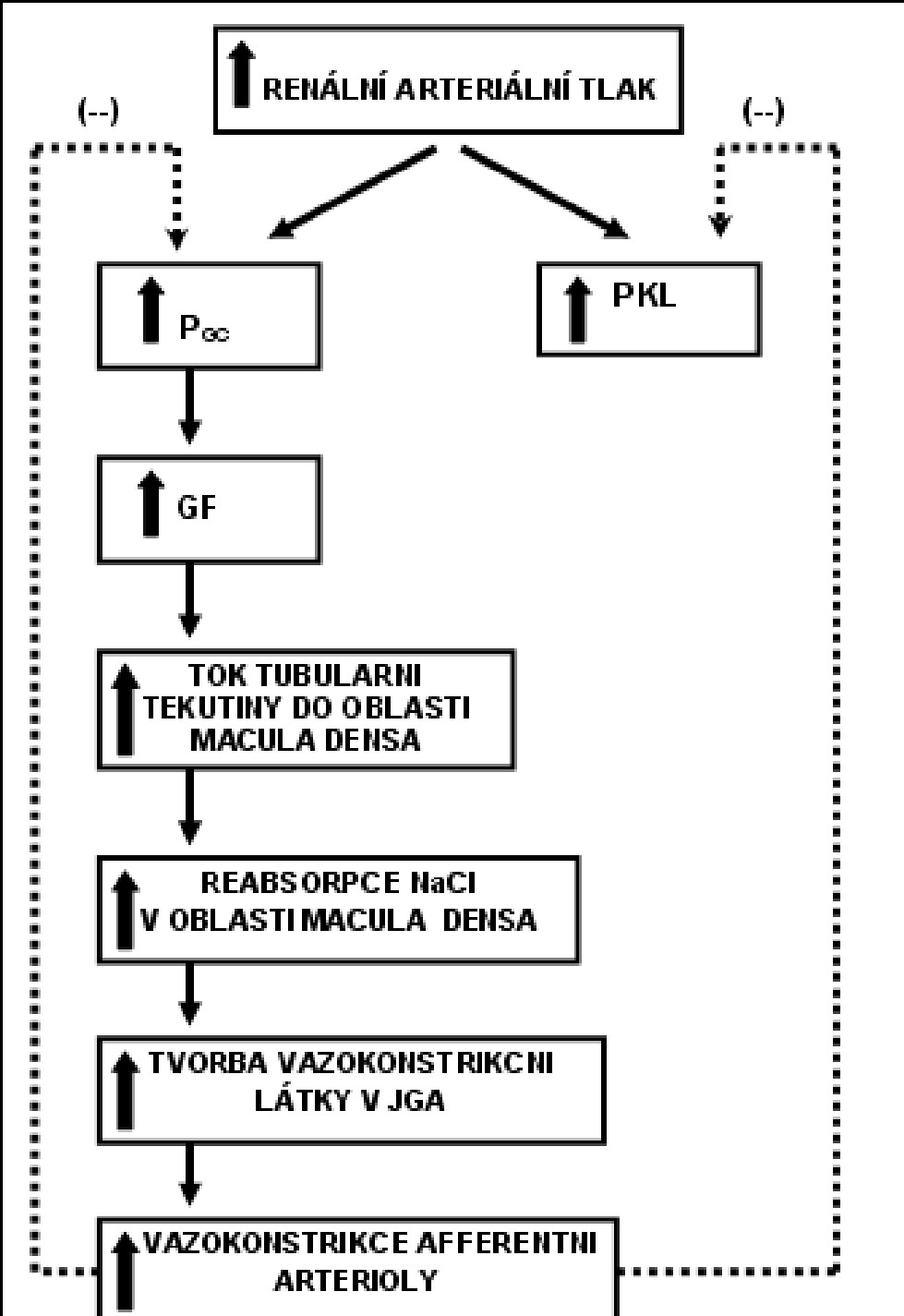


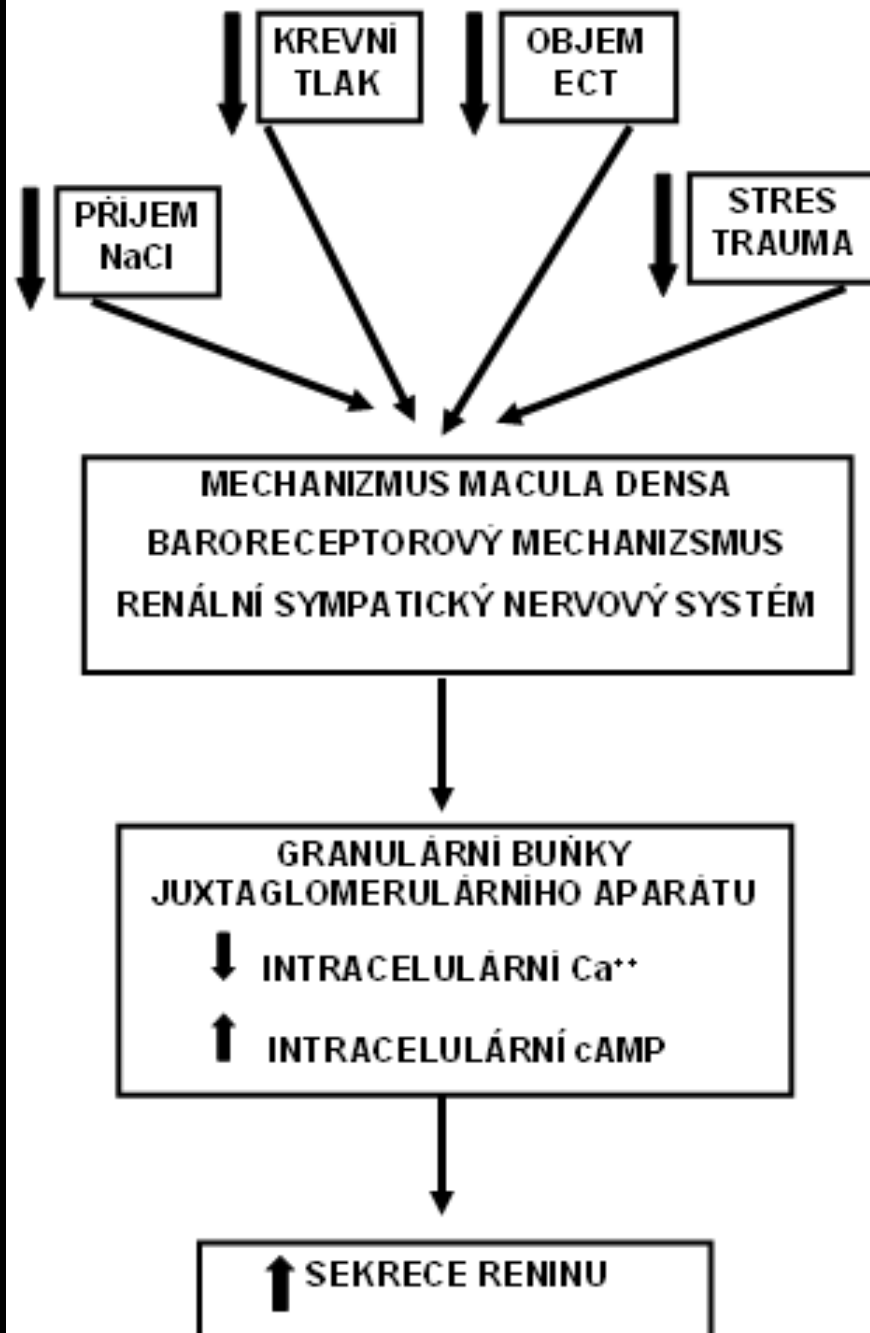
# **Autoregulation of Glomerular Filtration Rate and Renal Blood Flow**

- 1. Myogenic Mechanism**
- 2. Tubuloglomerular Feedback**









## **Use of Clearance Methods to Quantify Kidney Function**

***Renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time***

$$P_{\text{inulin}} = 1 \text{ mg/ml}$$

Amount filtered = Amount excreted

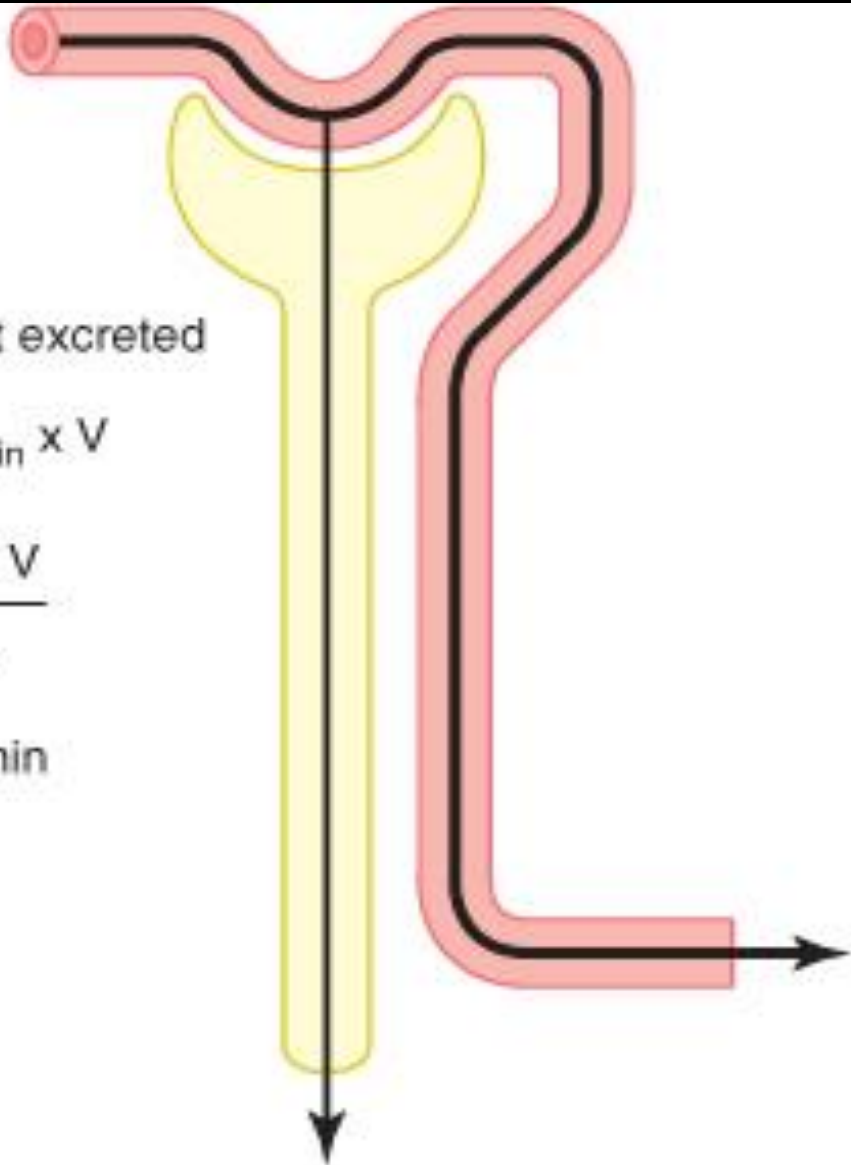
$$\text{GFR} \times P_{\text{inulin}} = U_{\text{inulin}} \times V$$

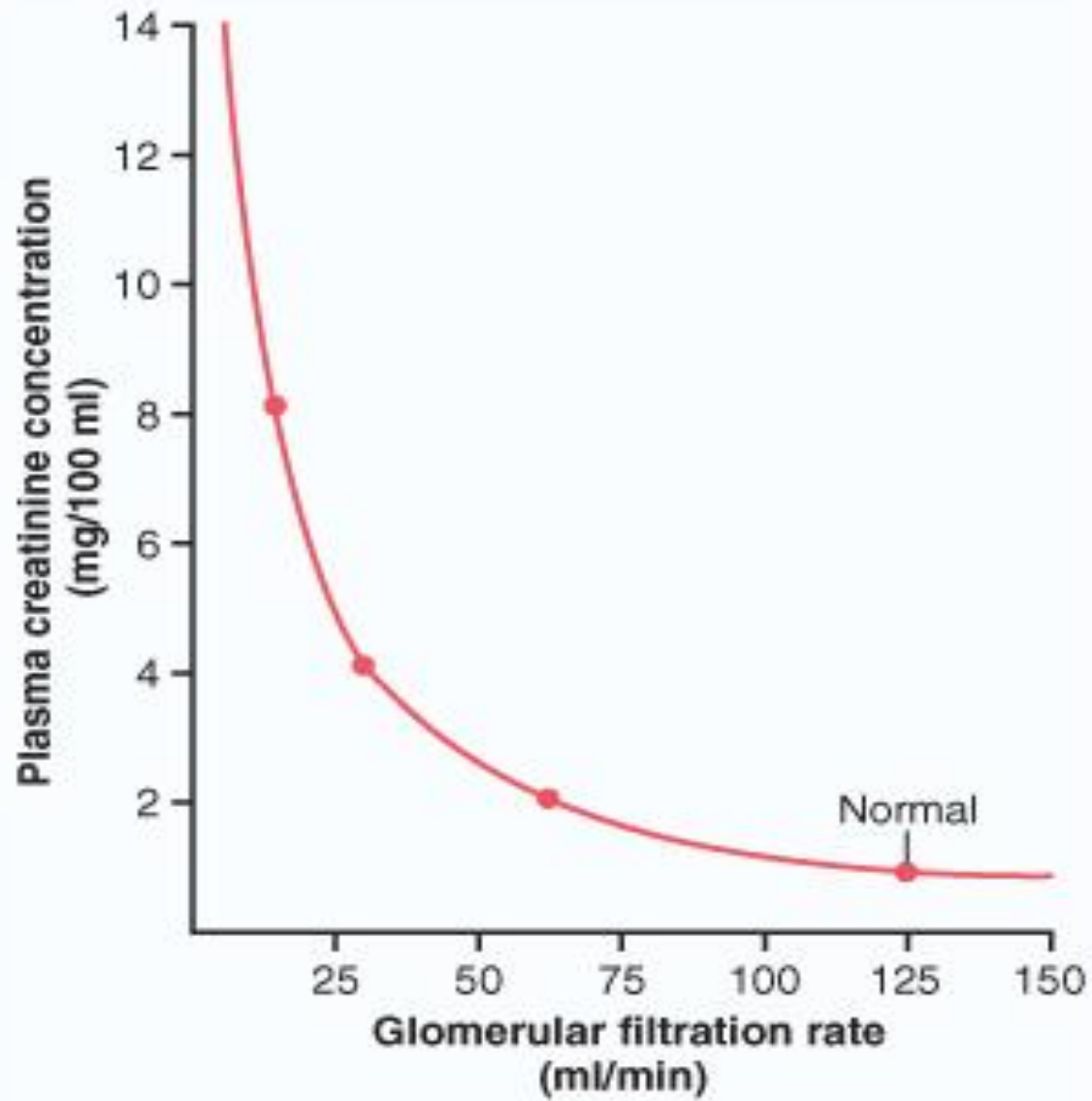
$$\text{GFR} = \frac{U_{\text{inulin}} \times V}{P_{\text{inulin}}}$$

$$\text{GFR} = 125 \text{ ml/min}$$

$$U_{\text{inulin}} = 125 \text{ mg/ml}$$

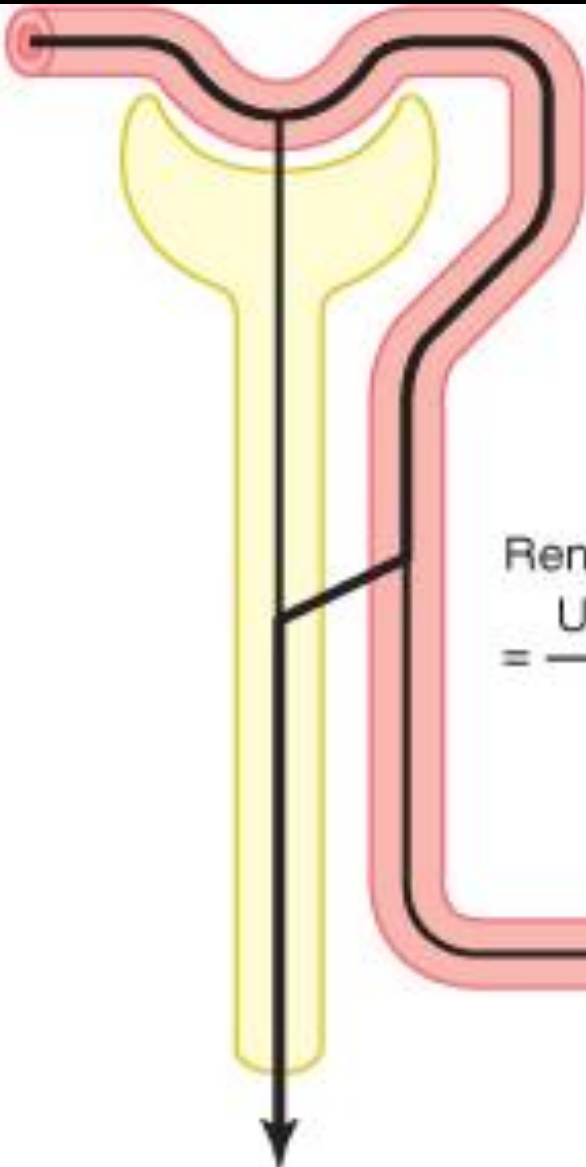
$$V = 1 \text{ ml/min}$$







$P_{PAH} = 0.01 \text{ mg/ml}$



Renal plasma flow

$$= \frac{U_{PAH} \times V}{P_{PAH}}$$

Renal venous  
PAH =  
0.001 mg/ml

$U_{PAH} = 5.85 \text{ mg/ml}$

$V = 1 \text{ ml/min}$

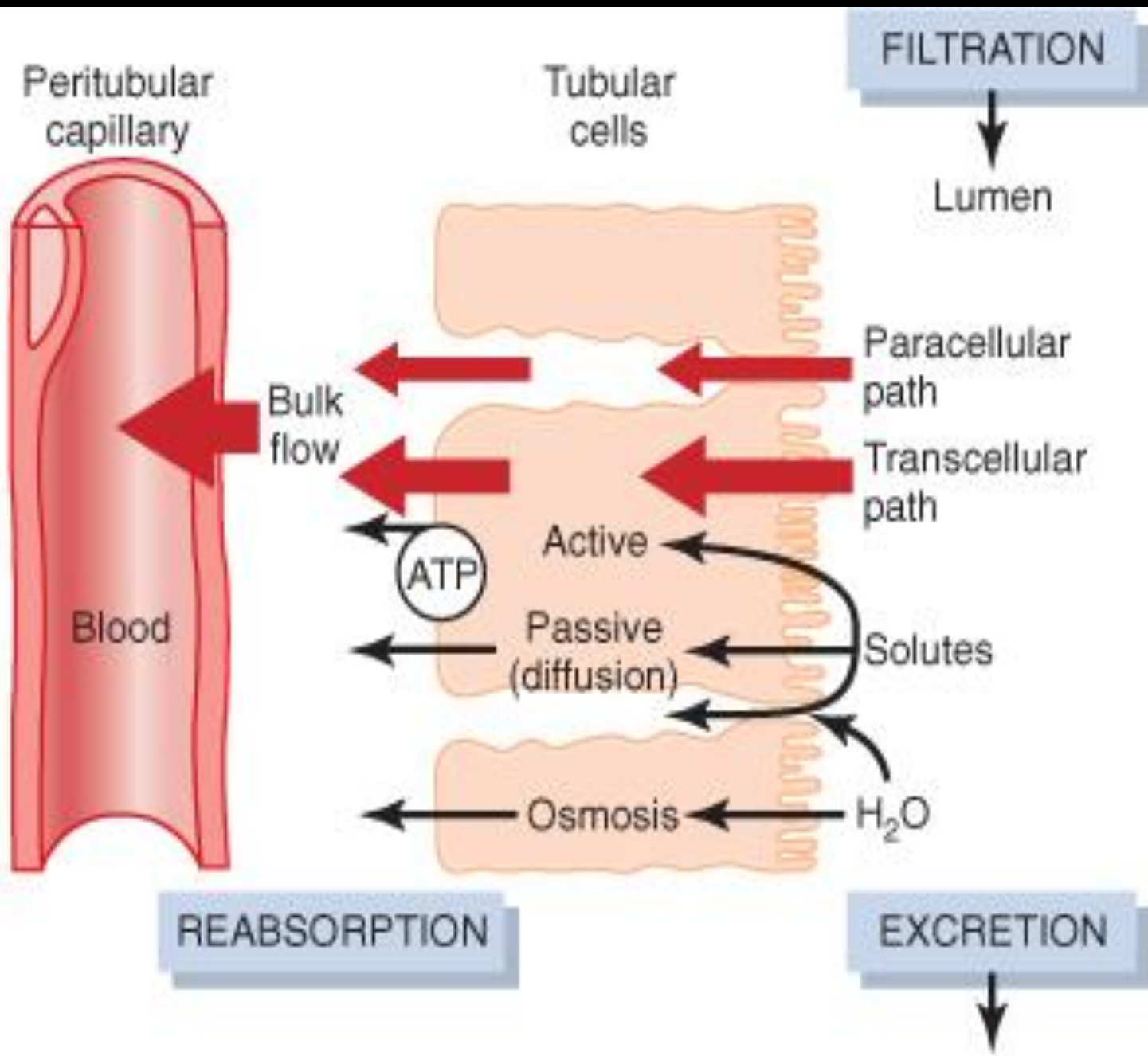
## **Tubular Processing of the Glomerular Filtrate**

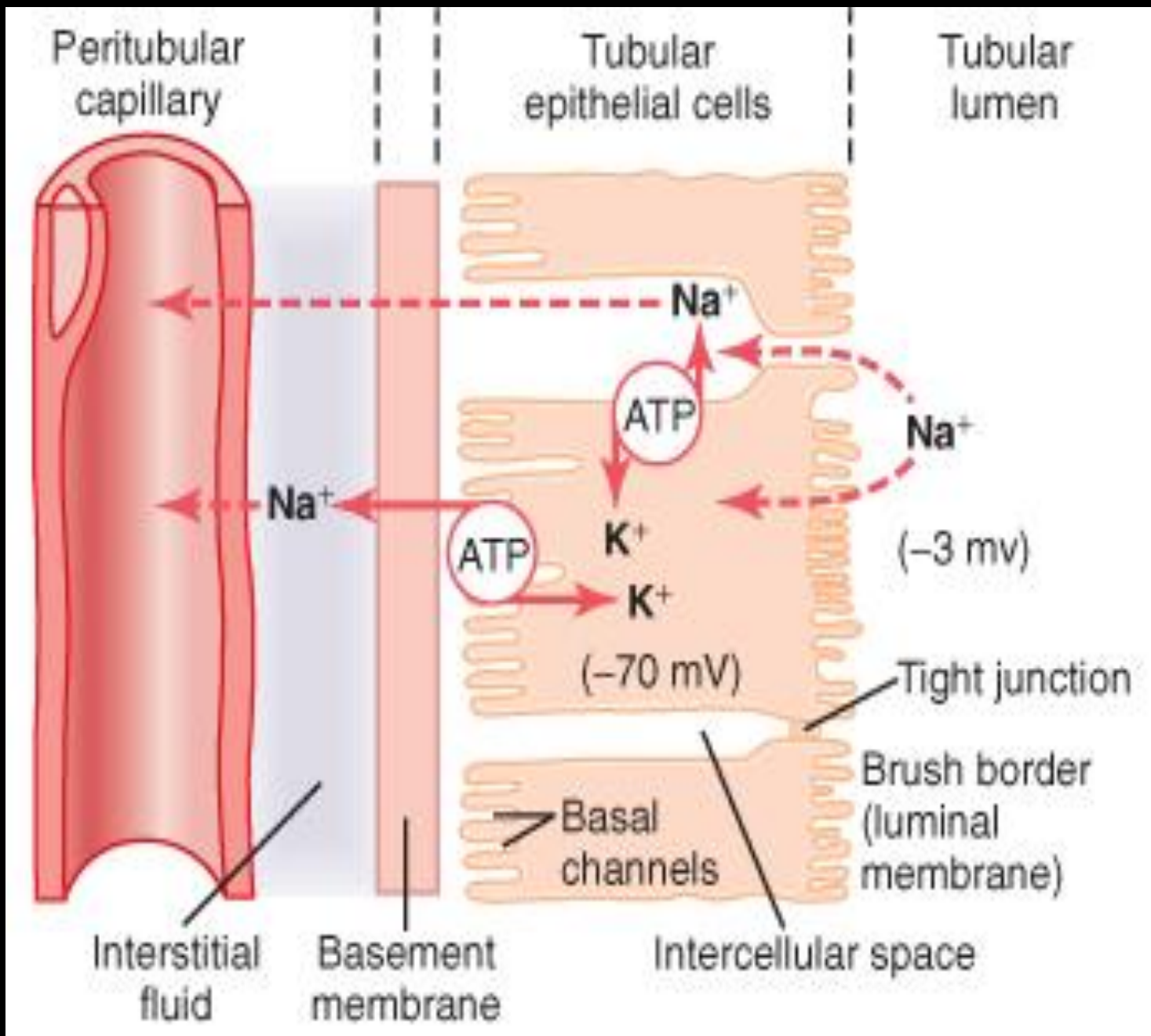
**Urinary excretion = Glomerular Filtration – Tubular reabsorption  
+ Tubular Secretion**

- 1. The processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion for many substances.**
- 2. Unlike glomerular filtration, tubular reabsorption is highly selective.**

## Filtration, Reabsorption and Excretion Rates of Different Substances by the Kidneys

|                        | Amount Filtered | Amount Reabsorbed | Amount Excreted | % of Filtered Load Reabsorbed |
|------------------------|-----------------|-------------------|-----------------|-------------------------------|
| Glucose (g/day)        | 180             | 180               | 0               | 100                           |
| Bicarbonate (mmol/day) | 4 320           | 4 318             | 2               | 99.9                          |
| Sodium (mmol/day)      | 25 560          | 25 410            | 150             | 99.4                          |
| Chloride (mmol/day)    | 19 440          | 19 260            | 180             | 99.1                          |
| Potassium (mmol/day)   | 756             | 664               | 92              | 87.8                          |
| Creatinine (g/day)     | 1.8             | 0                 | 1.8             | 0                             |



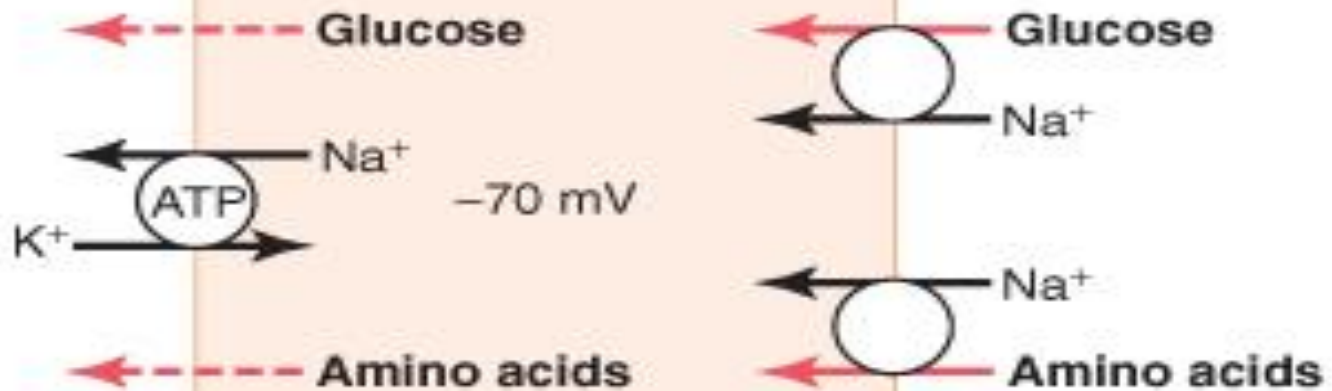


Interstitial fluid

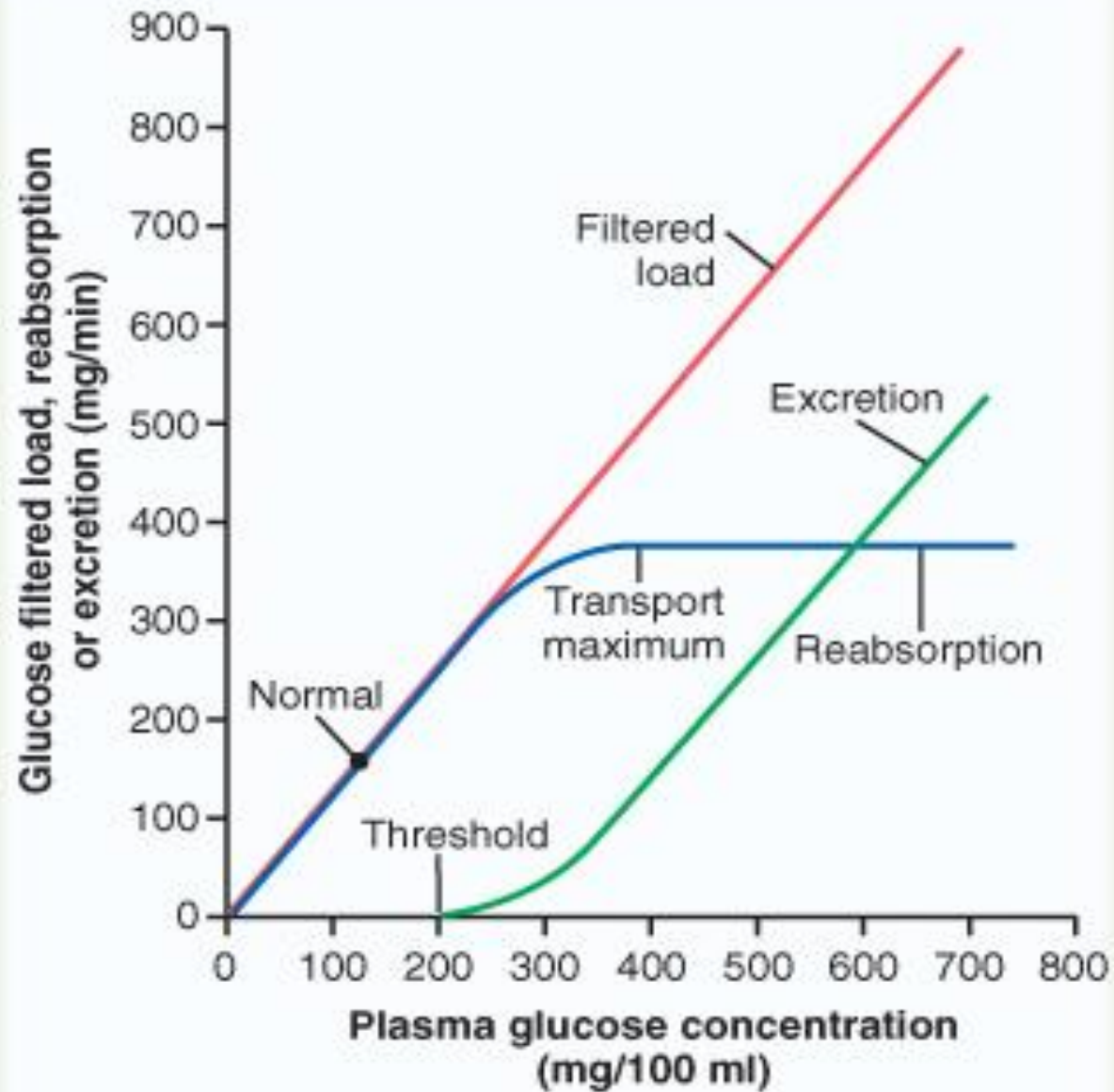
Tubular cells

Tubular lumen

Co-transport



Counter-transport



## Comparison of sodium and water reabsorption along the tubule

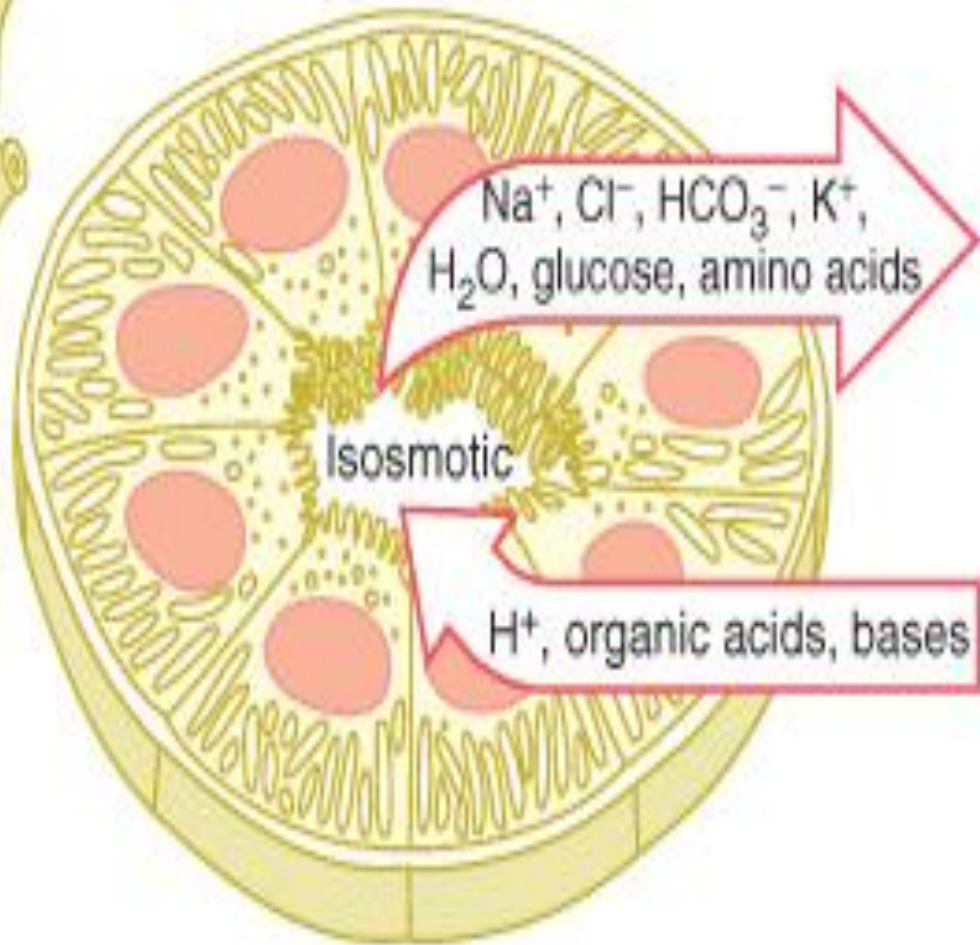
| <b>Tubular segment</b>                                       | <b>Percent of filtered load reabsorbed (%)</b> |  |
|--|--|--|
|  | <b>Sodium</b>                                  | <b>Water</b>   |
| Proximal tubule  | 65   | 65   |
| Descending thin limb of Henle's loop                         | 0  | 10   |
| Ascending thin limb and thick ascending limb of Henle's loop | 25   | 0  |
| Distal convoluted tubule                                     | 5  | 0  |
| Collecting-duct system                                       | 4-5  | 5 ( <i>during water-loading</i> )<br>>24 ( <i>during dehydration</i> ) |



65%



Proximal tubule



$\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{K}^+$ ,  
 $\text{H}_2\text{O}$ , glucose, amino acids

Isosmotic

$\text{H}^+$ , organic acids, bases

Interstitial fluid

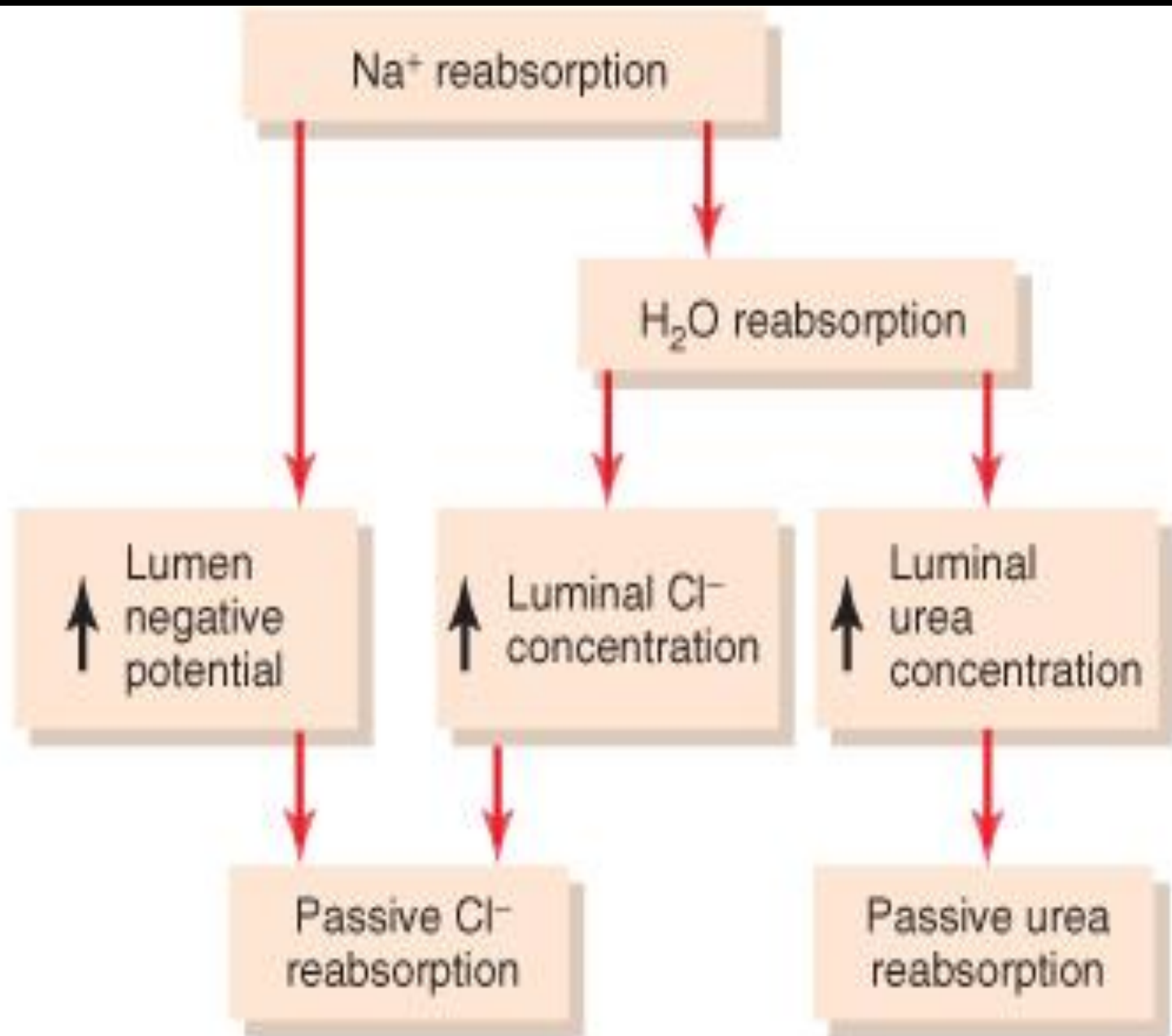
Tubular cells

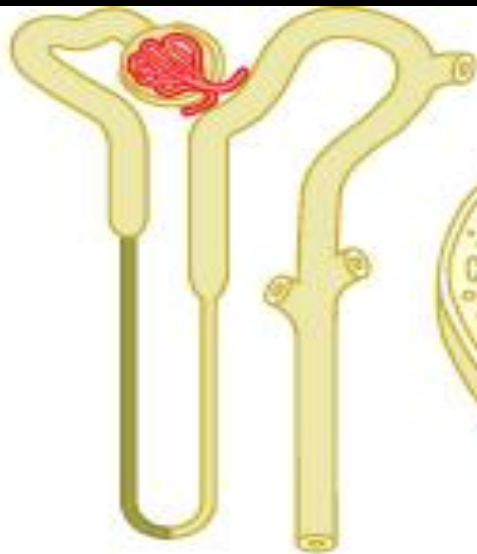
Tubular lumen

Co-transport

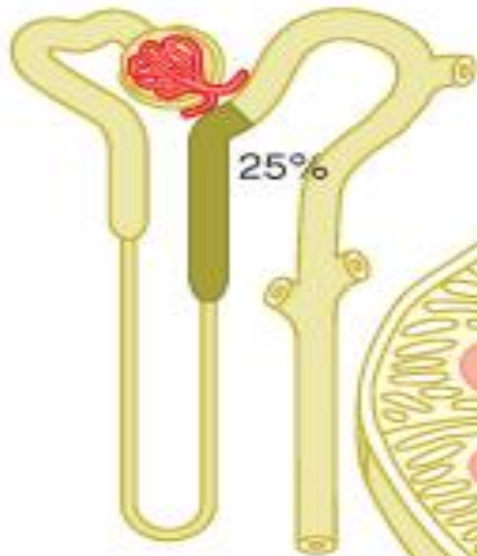
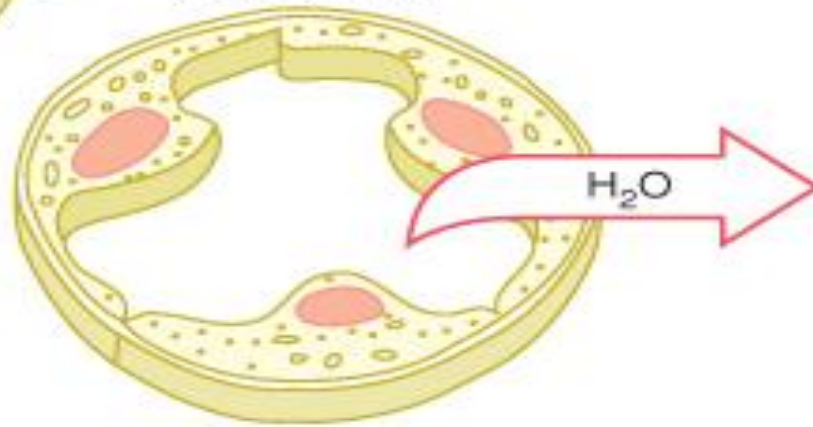


Counter-transport

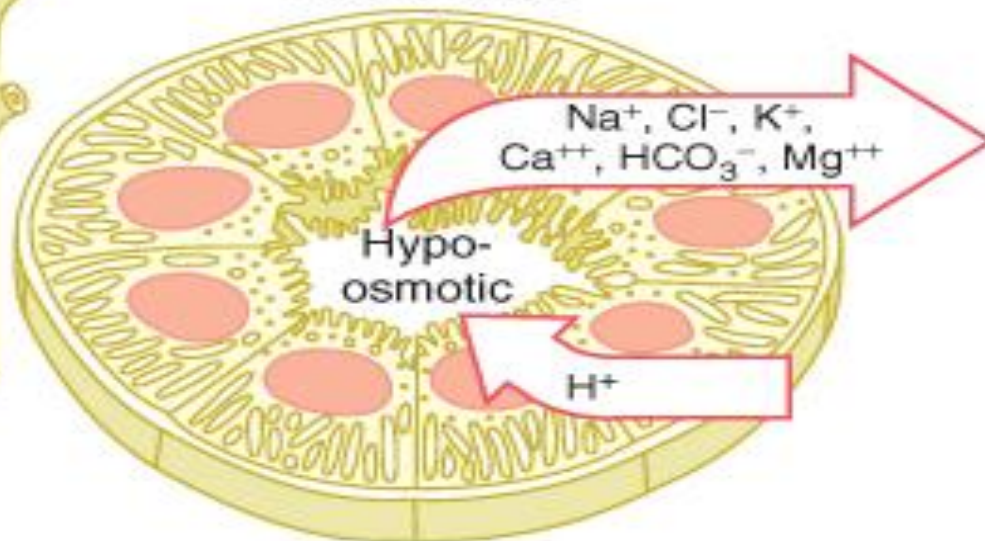


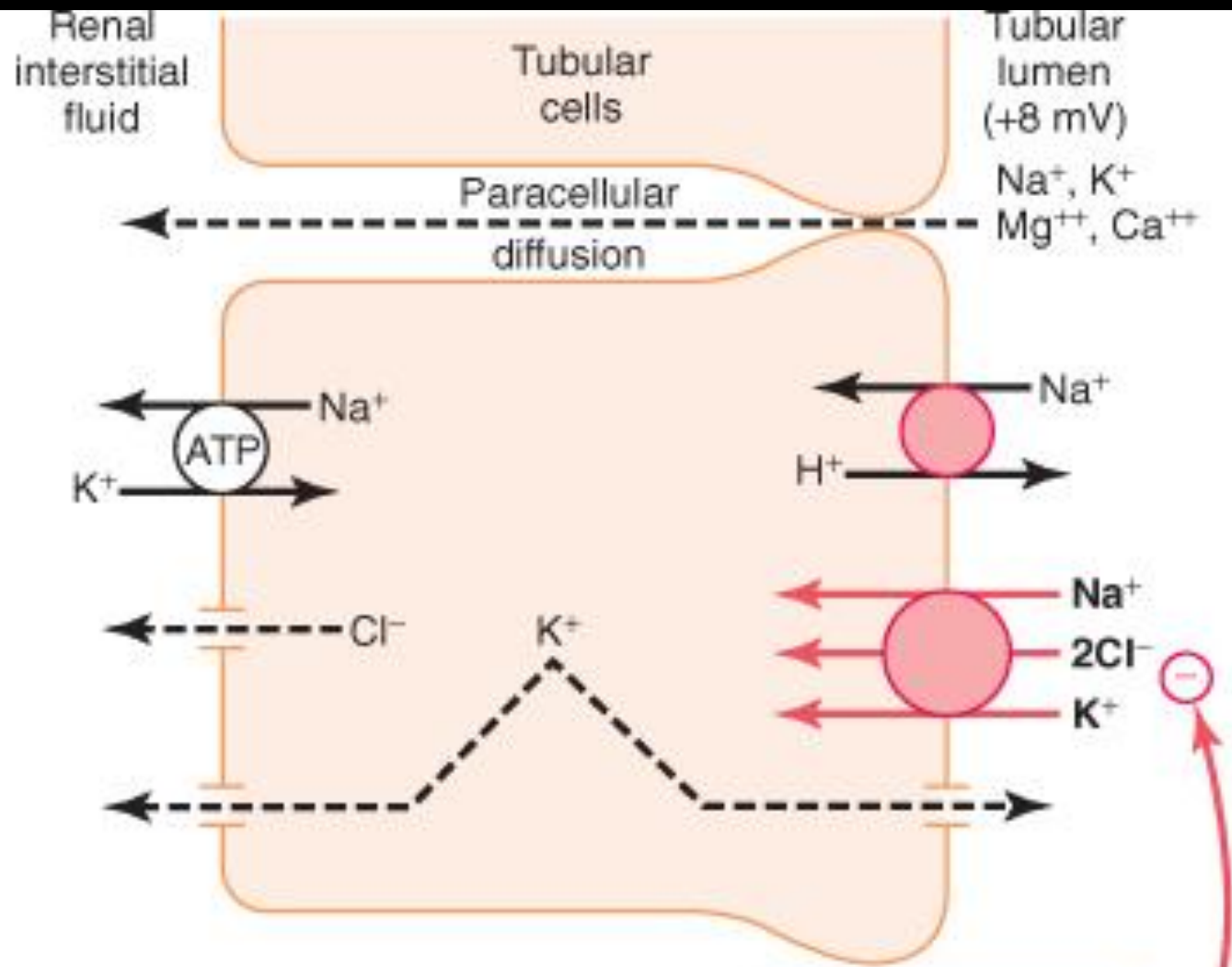


Thin descending loop of Henle



Thick ascending loop of Henle

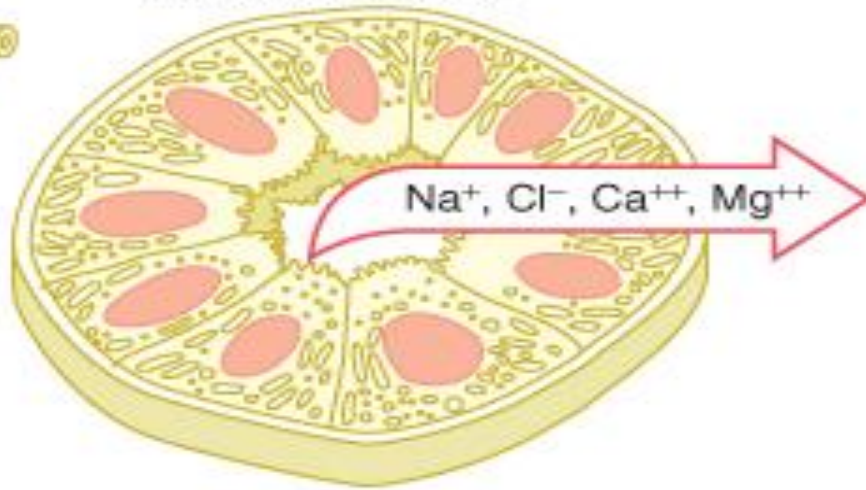
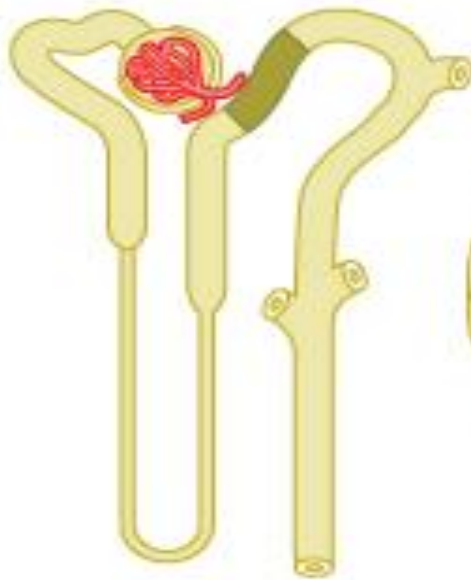




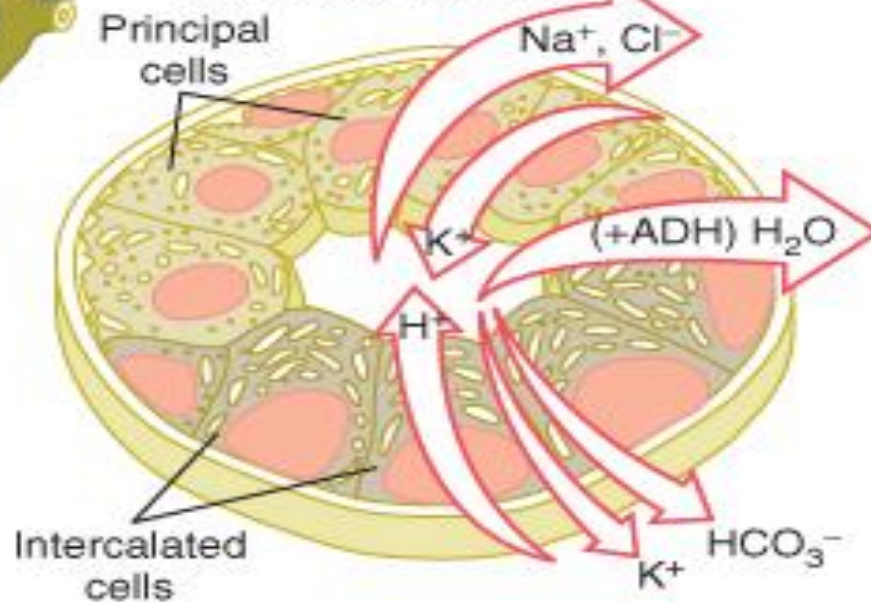
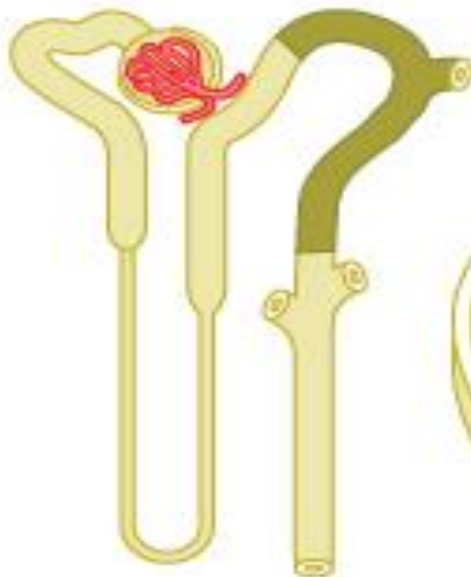
**Loop diuretics**

- Furosemide
- Ethacrynic acid
- Bumetanide

Early distal tubule



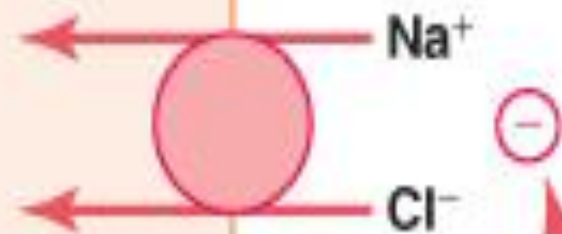
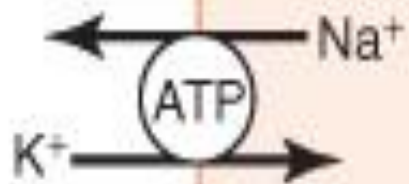
Late distal tubule and collecting tubule



Renal interstitial fluid

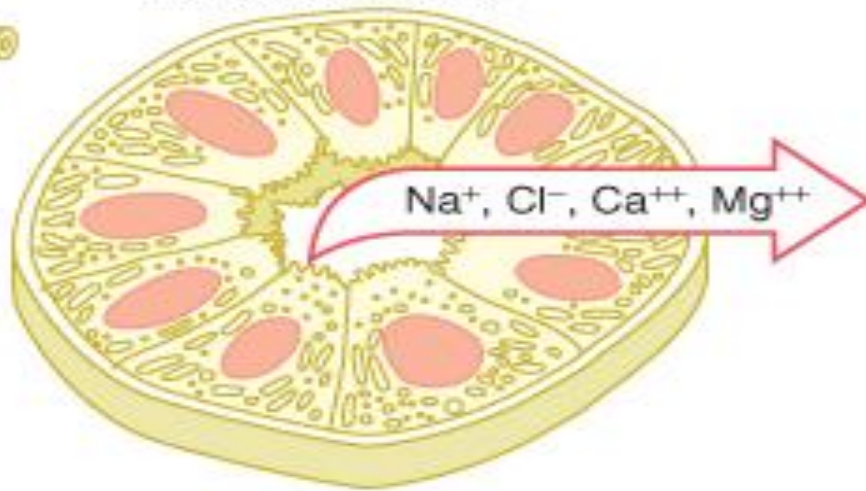
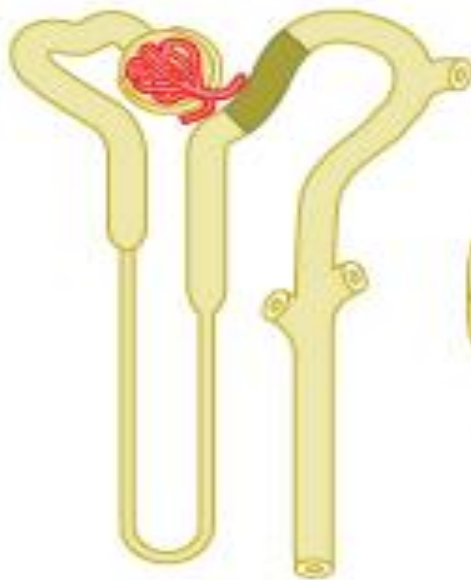
Tubular cells

Tubular lumen (-10mV)

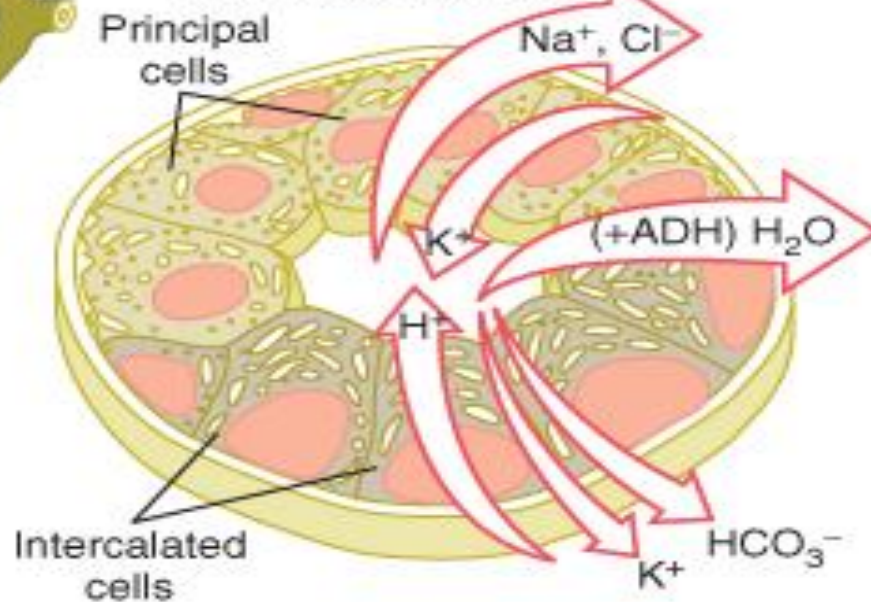
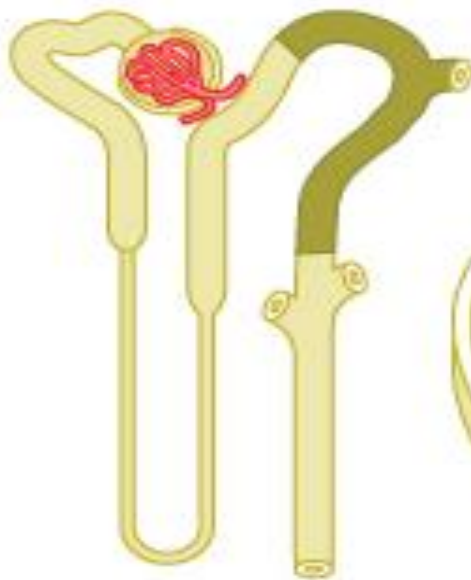


Thiazide diuretics:

Early distal tubule



Late distal tubule and collecting tubule





Renal interstitial fluid      Tubular cells      Tubular lumen (-50 mV)

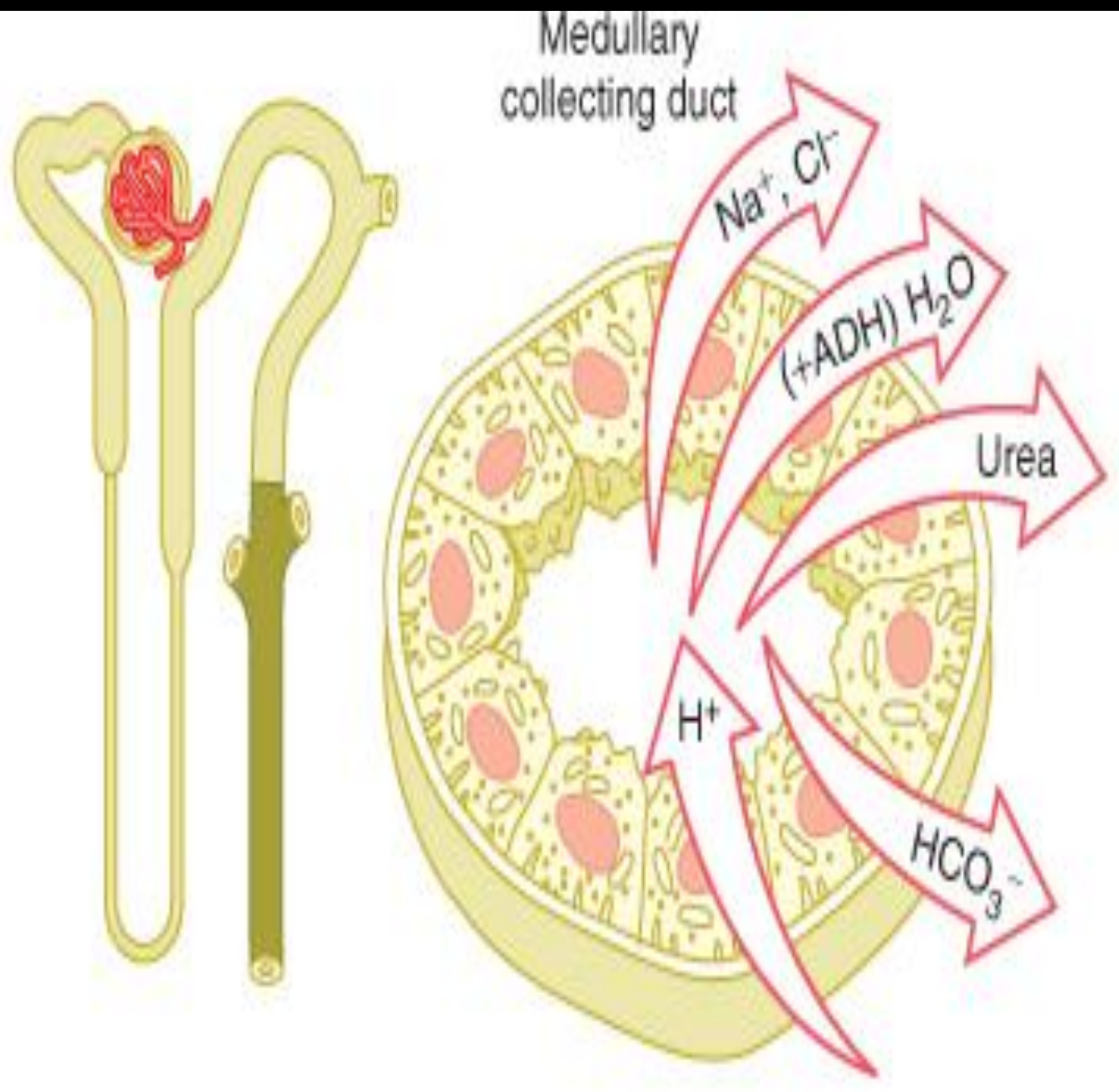


**Aldosterone antagonists**

- Spironolactone
- Eplerenone

**Na<sup>+</sup> channel blockers**

- Amiloride
- Triamterene



Medullary  
collecting duct

$\text{Na}^+$ ,  $\text{Cl}^-$

(+ADH)  $\text{H}_2\text{O}$

Urea

$\text{H}^+$

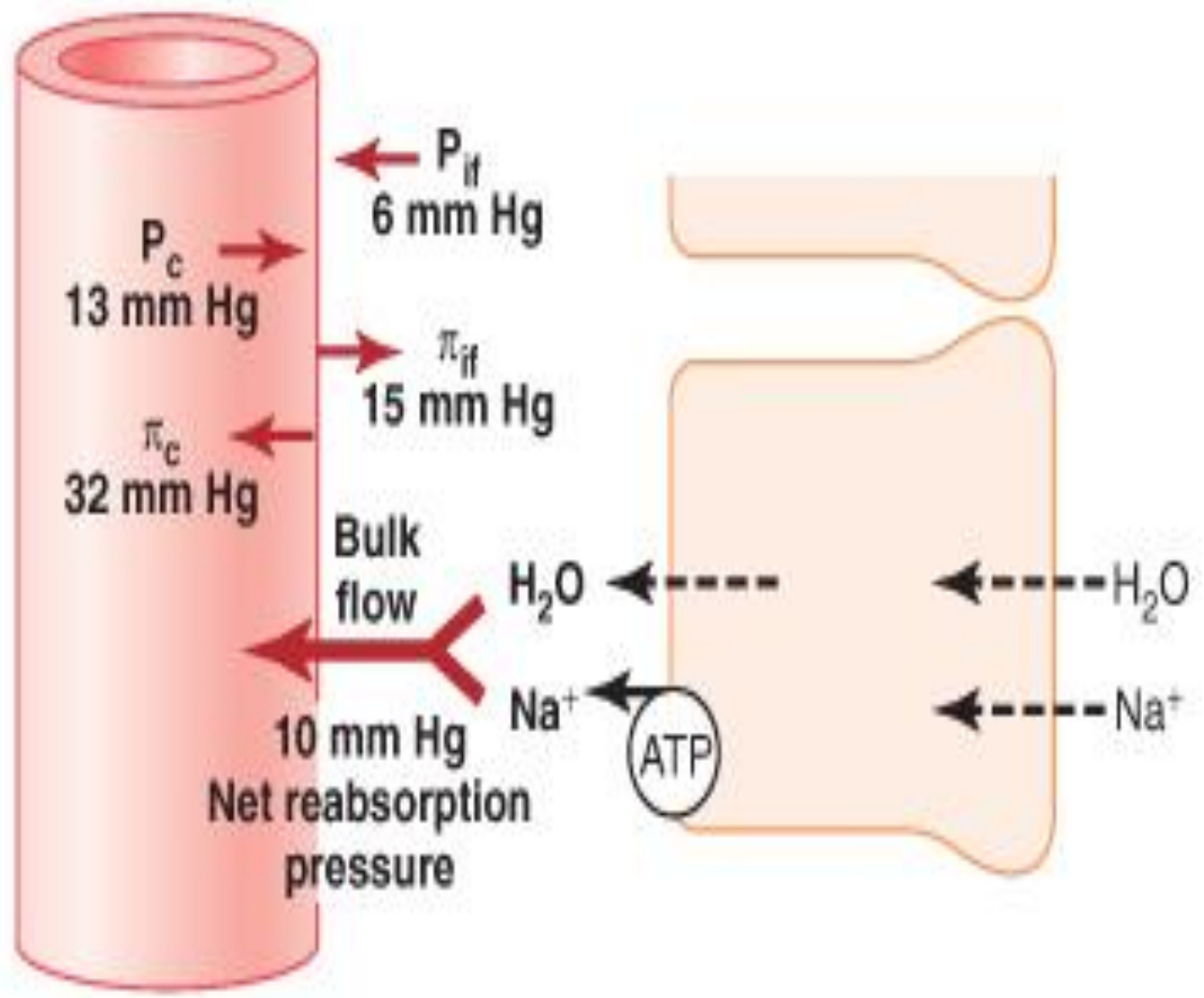
$\text{HCO}_3^-$

Peritubular capillary

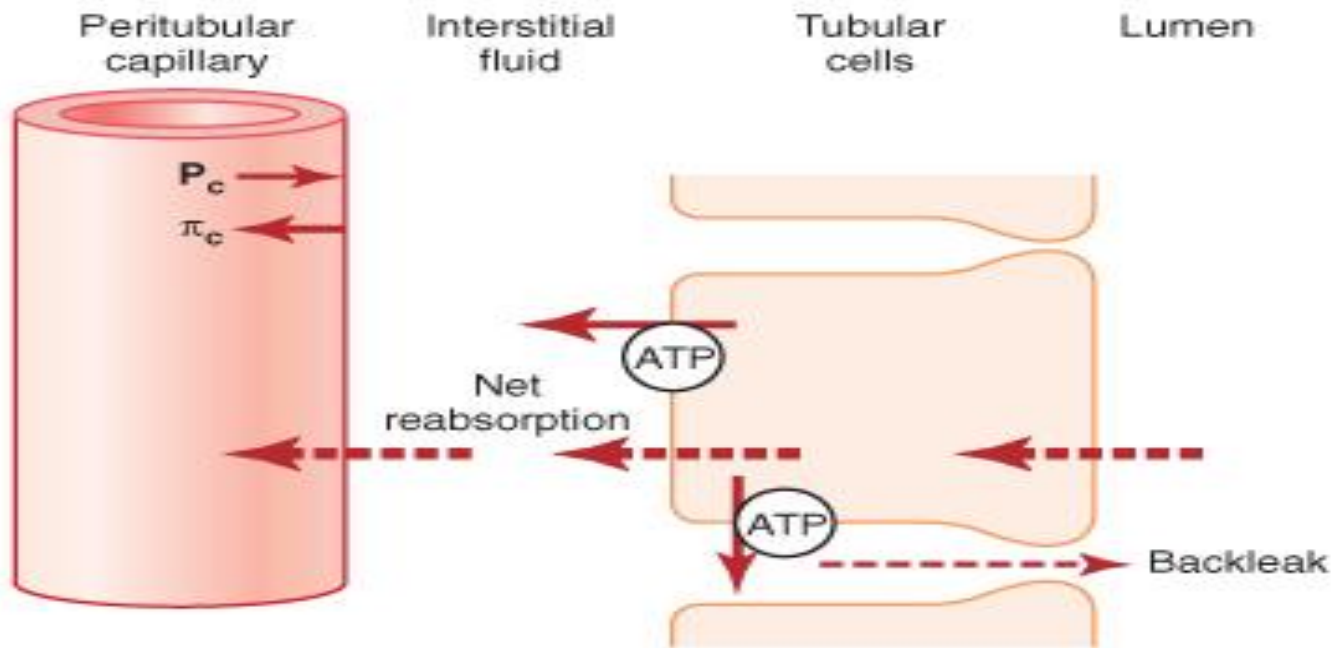
Interstitial fluid

Tubular cells

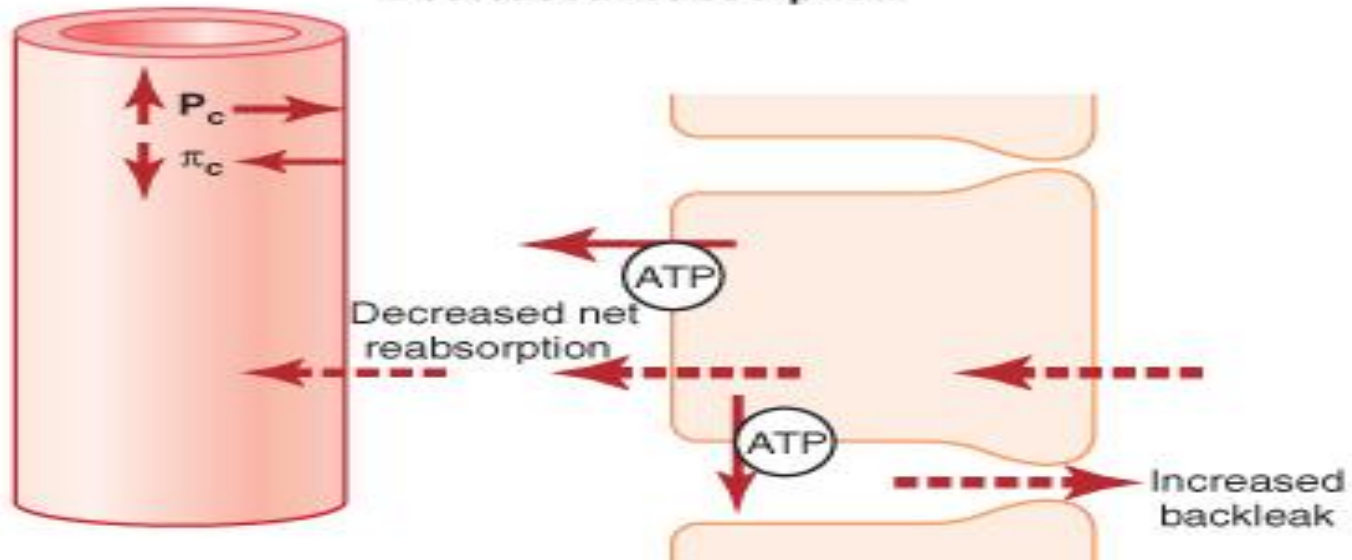
Tubular lumen

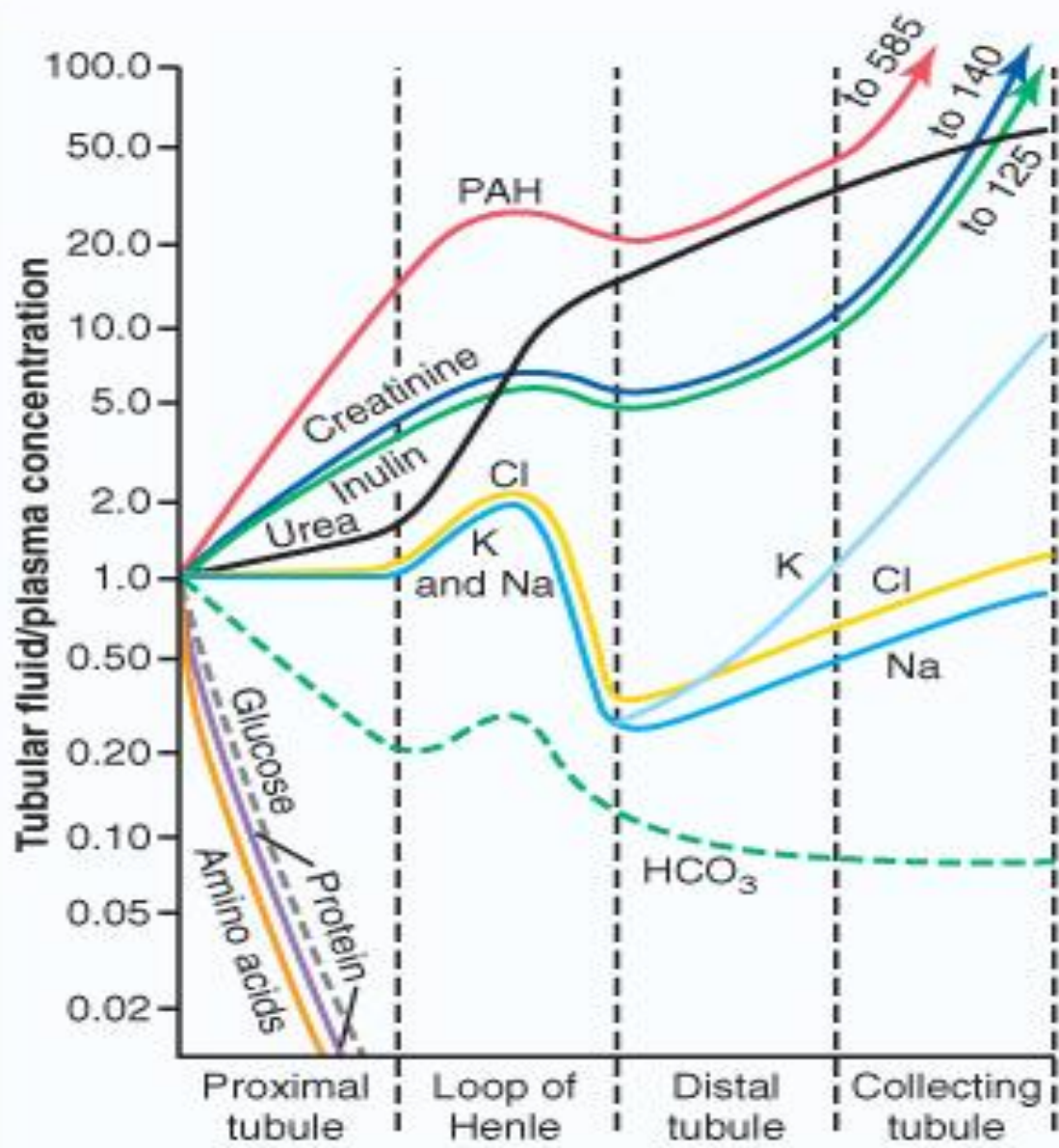


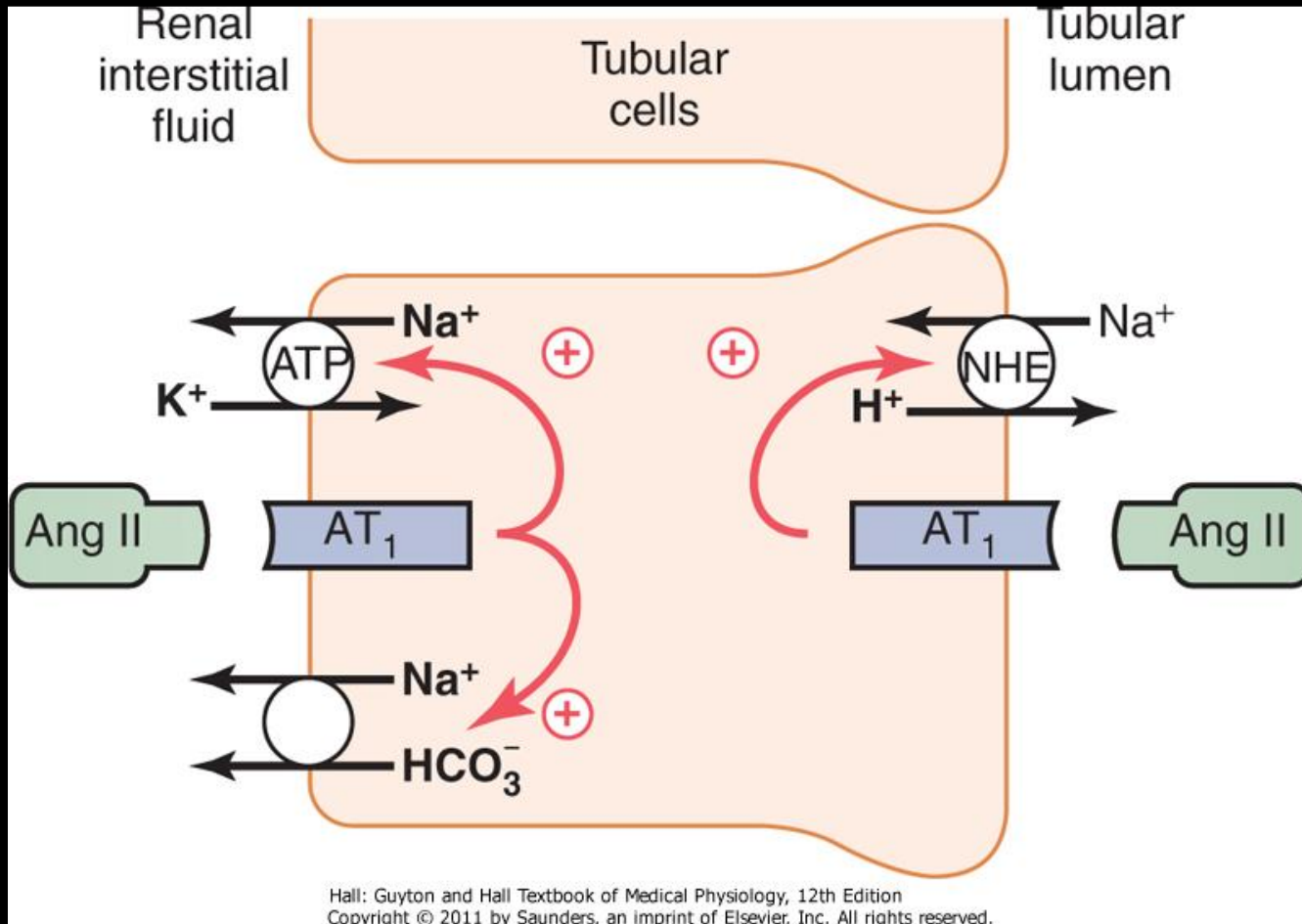
### Normal



### Decreased reabsorption







# Renal Regulation of Potassium Balance

$$E_{\text{ion}} = \frac{2.3 RT}{zF} \log_{10} \frac{[C_1]}{[C_2]}$$

$$E_{\text{ion}} = \frac{60 \text{ mV}}{1} \log_{10} \frac{100}{10}$$

$$= 60 \text{ mV} \times \log_{10} 10$$

$$= 60 \text{ mV} \times 1$$

$$= 60 \text{ mV (or -60 mV, cell interior negative)}$$

$E_{\text{ion}}$  = the electrical potential (mV)

R = natural gas constant

T = the absolute temperature ( $^{\circ}\text{K}$ )

z = the valence of the ion

F = the Faraday constant (96 500 colombs/mol)

$C_{1 \text{ (in)}}$  = the concentration of the ion inside the cell (mmol/L)

$C_{2 \text{ (out)}}$  = the concentration of the ion outside the cell (mmol/L)

2.3 RT/F = 60 mV at 37 $^{\circ}\text{C}$

$$E_{\text{ion}} = \frac{60 \text{ mV}}{1} \log_{10} \frac{100}{4}$$

$$= 60 \text{ mV} \times \log_{10} 25$$

$$= 60 \text{ mV} \times 1.40$$

$$= 84 \text{ mV (or -84 mV, cell interior negative)}$$

$$E_{\text{ion}} = \frac{60 \text{ mV}}{1} \log_{10} \frac{100}{1}$$

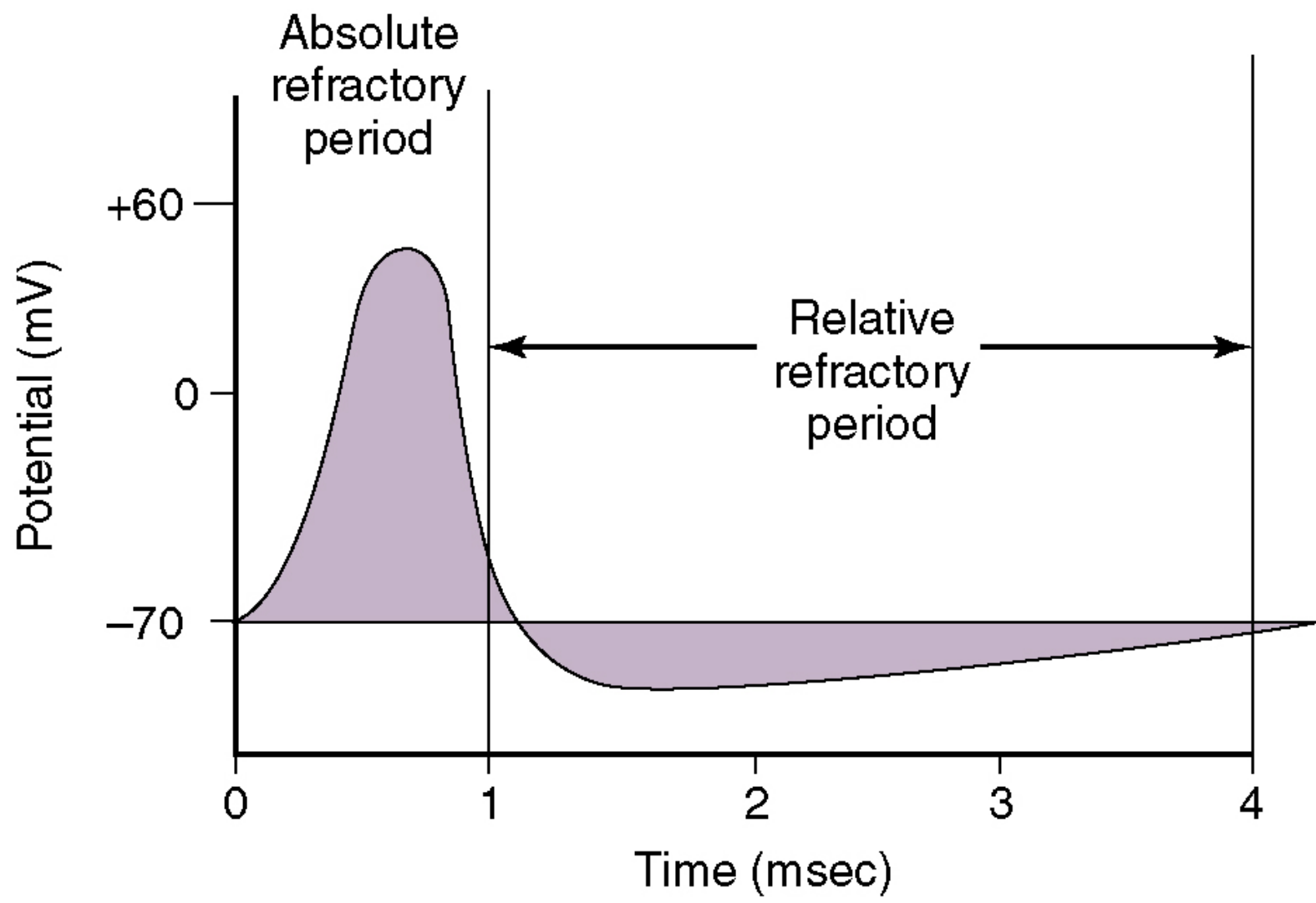
$$= 60 \text{ mV} \times \log_{10} 100$$

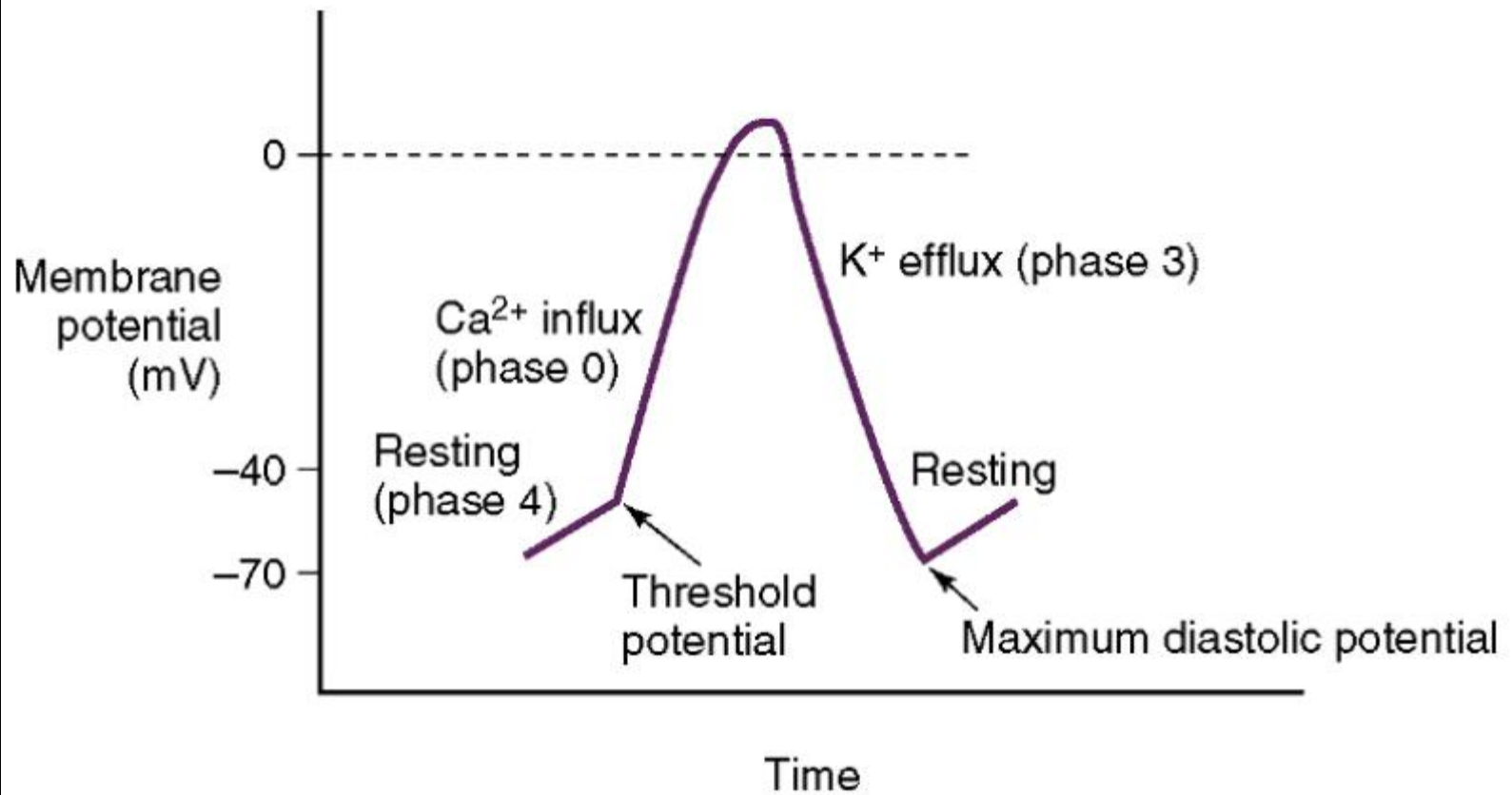
$$= 60 \text{ mV} \times 2$$

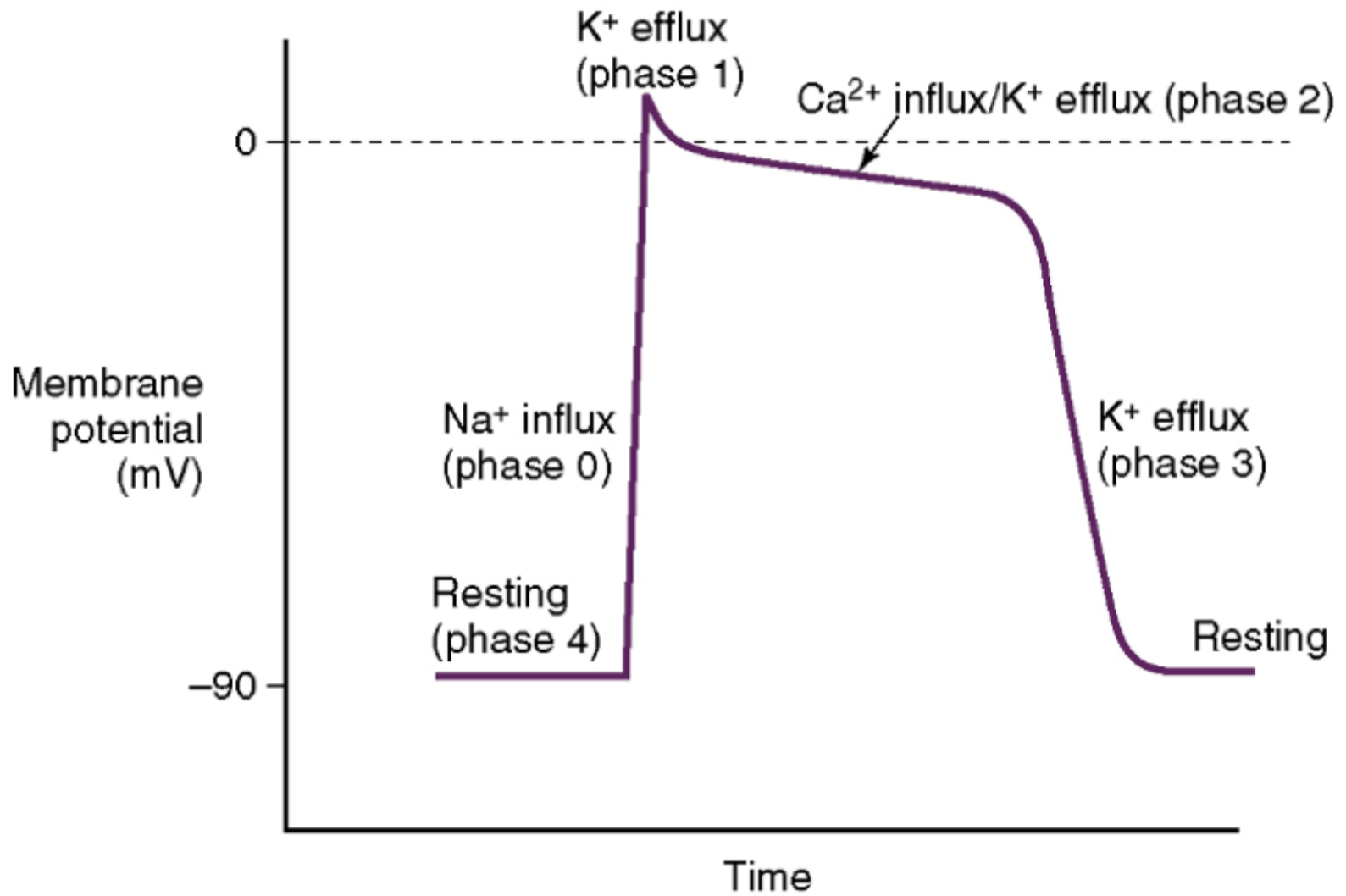
$$= 120 \text{ mV (or -120 mV, cell interior negative)}$$

Decreased serum  $\text{K}^+$  concentration „hyperpolarize“ the resting membrane potential and therefore „firing“ action potentials becomes more difficult



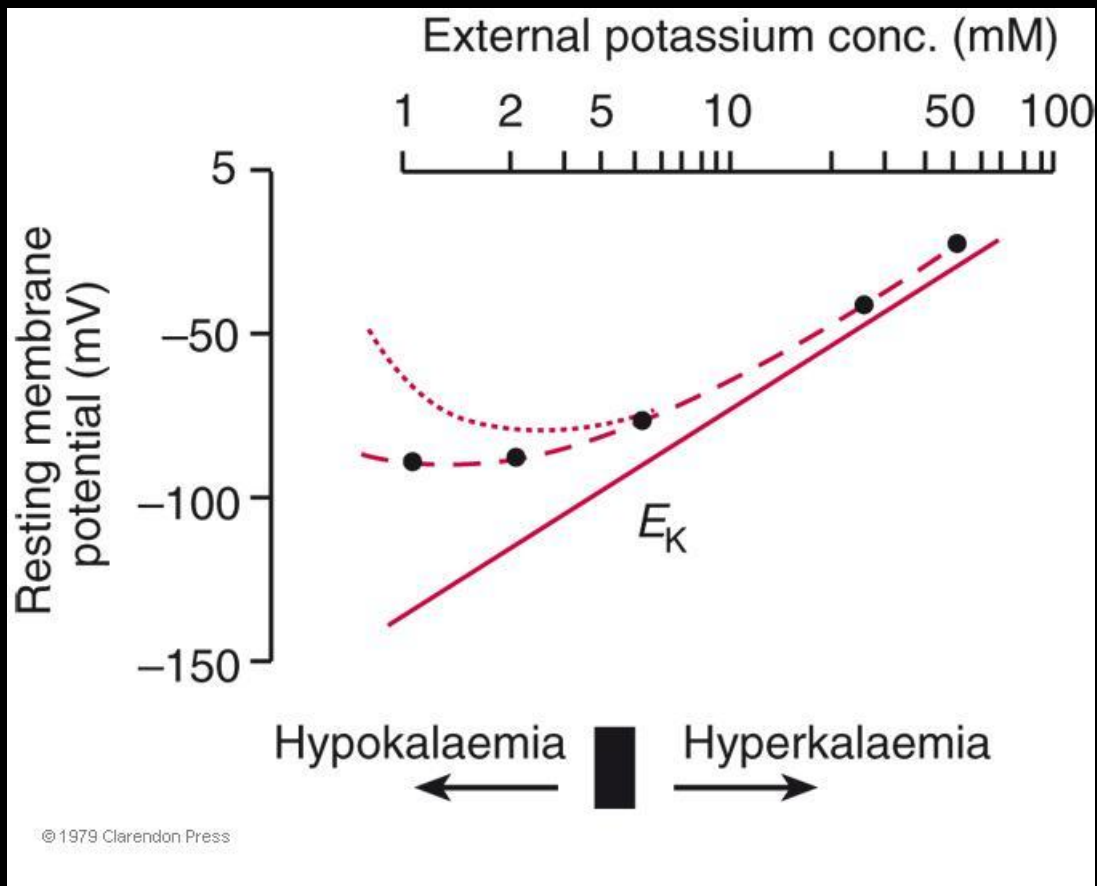






# Hyperkalemia

Reduces the Nerns  $K^+$  equilibrium potential and therefore the resting membrane potential



$$E_K = - \frac{2.3 RT}{zF} \log_{10} \frac{[C_1]}{[C_2]}$$

2.3 ET/F (60 mV at 37°C)

$$E_K = - \frac{60}{1} \log_{10} \frac{[100]}{[4]}$$

$$= 60 \times \log_{10} 25$$

$$= 60 \times 1.4$$

$$= 84 \text{ mV (or -84 mV, interior cell is negative)}$$

$$E_K = - \frac{60}{1} \log_{10} \frac{[100]}{[1]}$$

$$= 60 \times \log_{10} 100$$

$$= 60 \times 2$$

$$= 120 \text{ mV (or -120 mV)}$$

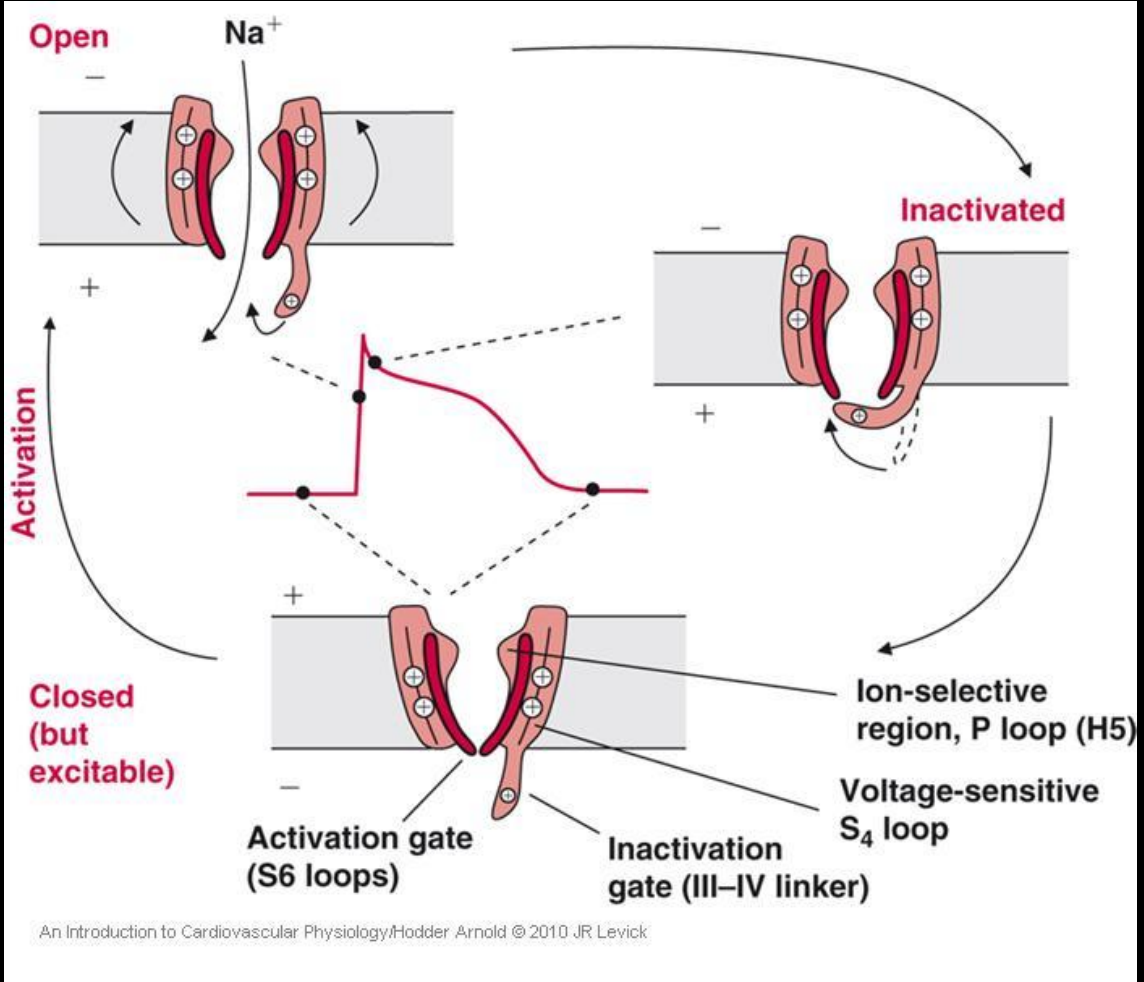
$$E_K = - \frac{60}{1} \log_{10} \frac{[100]}{[10]}$$

$$= 60 \times \log_{10} 10$$

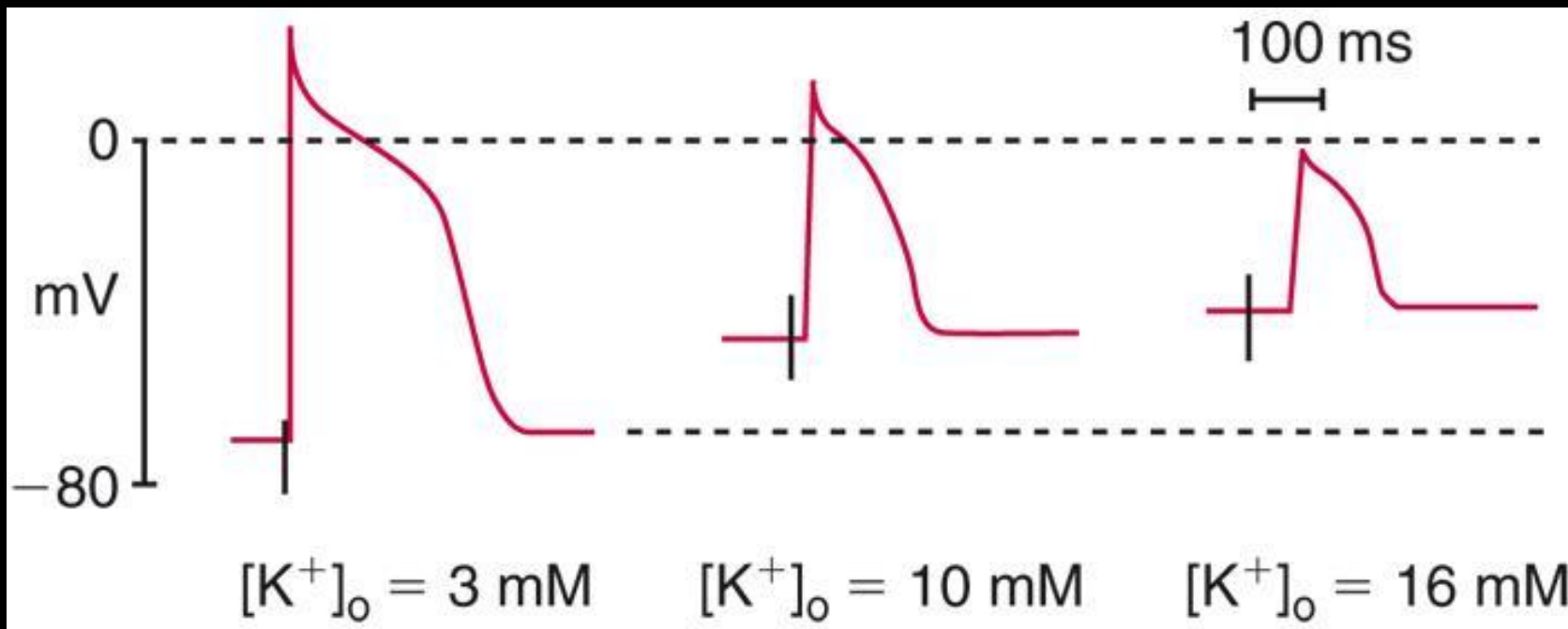
$$= 60 \times 1$$

$$= 60 \text{ mV (or -60 mV)}$$

Reduced resting membrane potential diminishes the action potential, because the low resting potential prevents many Na<sup>+</sup> channels from resetting from the inactivated state to the closed-but-activatable state

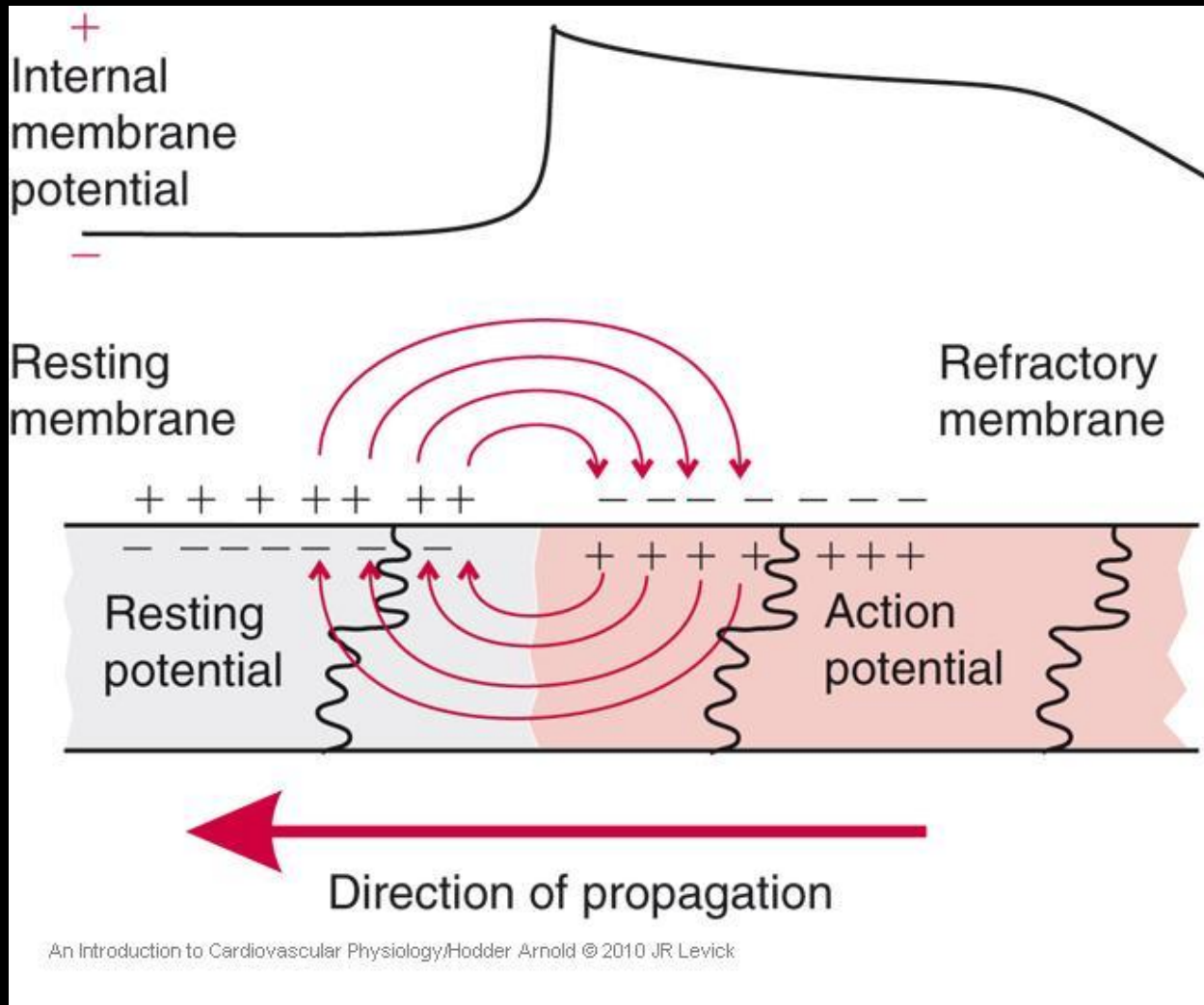


As a result the action potential begins to lose its sharp phase 0, and is eventually reduced to a sluggish rise of small amplitude dependent on  $I_{ca-L}$



© 1973 Davis

Small, slow-rising action potentials generate less propagating current, electrical transmission is slower and less secure. This can lead to heart block or a pathological ventricular tachycardia/fibrillation.



The raised extracellular  $K^+$  also stimulates the  $3Na^+-2K^+$  pump, enhances the activity of  $K^+$  channels  $K_{ir}$  and  $K_v$ , causing early repolarization.

Wide QRS is likely due to slow electrical propagation in the ventricle

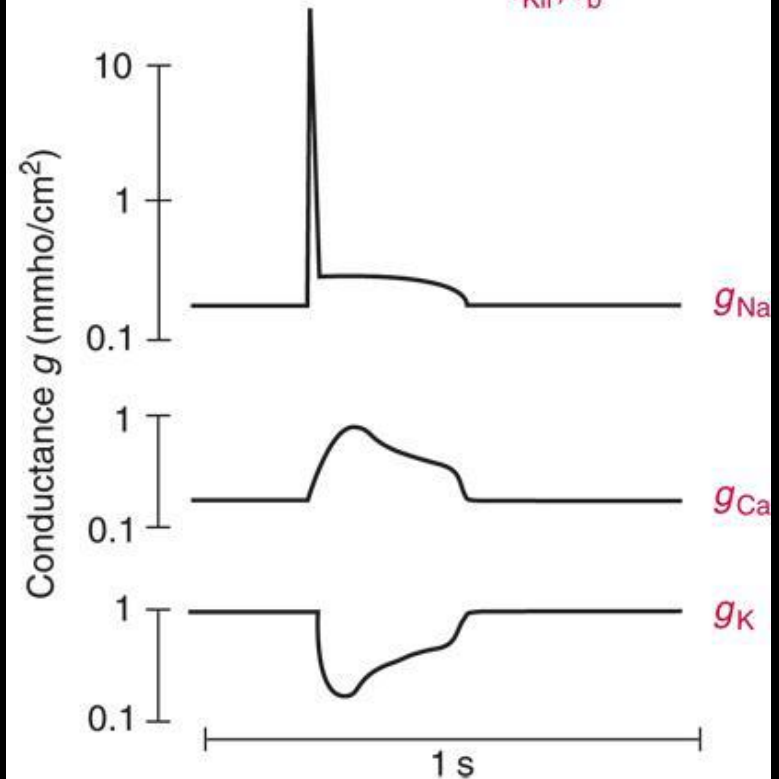
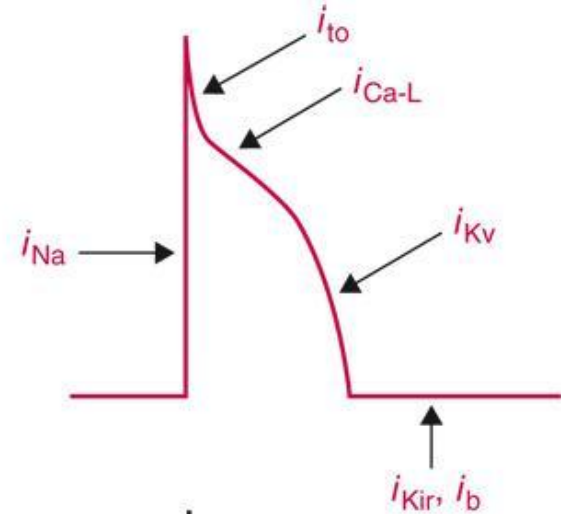
Tall, peaked T wave is likely due to enhanced repolarization  $K^+$  current (similar changes occur in ischemic myocardium)

## Hypokalemia

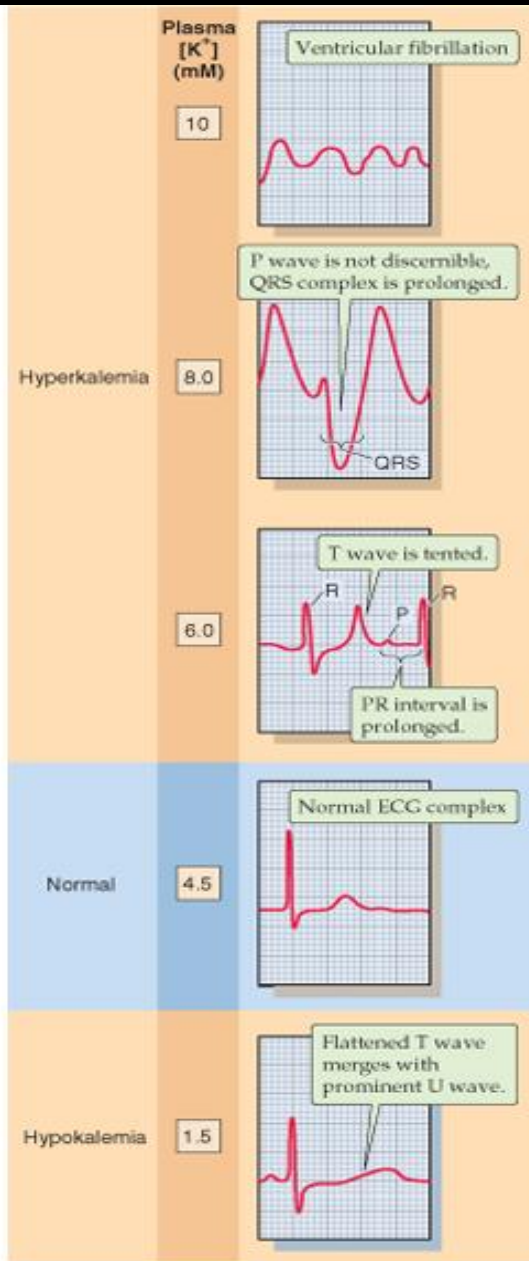
The low extracellular  $K^+$  also reduces the activity of the  $3Na^+-2K^+$  pump, and the activity of  $K^+$  channels  $K_{ir}$  and  $K_v$ , causing prolonged repolarization.

This is particularly true in  $K_v$  rich subepicardial myocytes.

Prolongation of the subepicardial action potentials leads to flattened or even inverted T waves, which are called a U wave.







Boron & Boulpaep: Medical Physiology, 2nd Edition.  
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**K<sup>+</sup> intake**  
**100 mEq/day**



Extracellular  
fluid K<sup>+</sup>

4.2 mEq/L  
x 14 L

**59 m Eq**

Intracellular  
fluid K<sup>+</sup>

140 mEq/L  
x 28 L

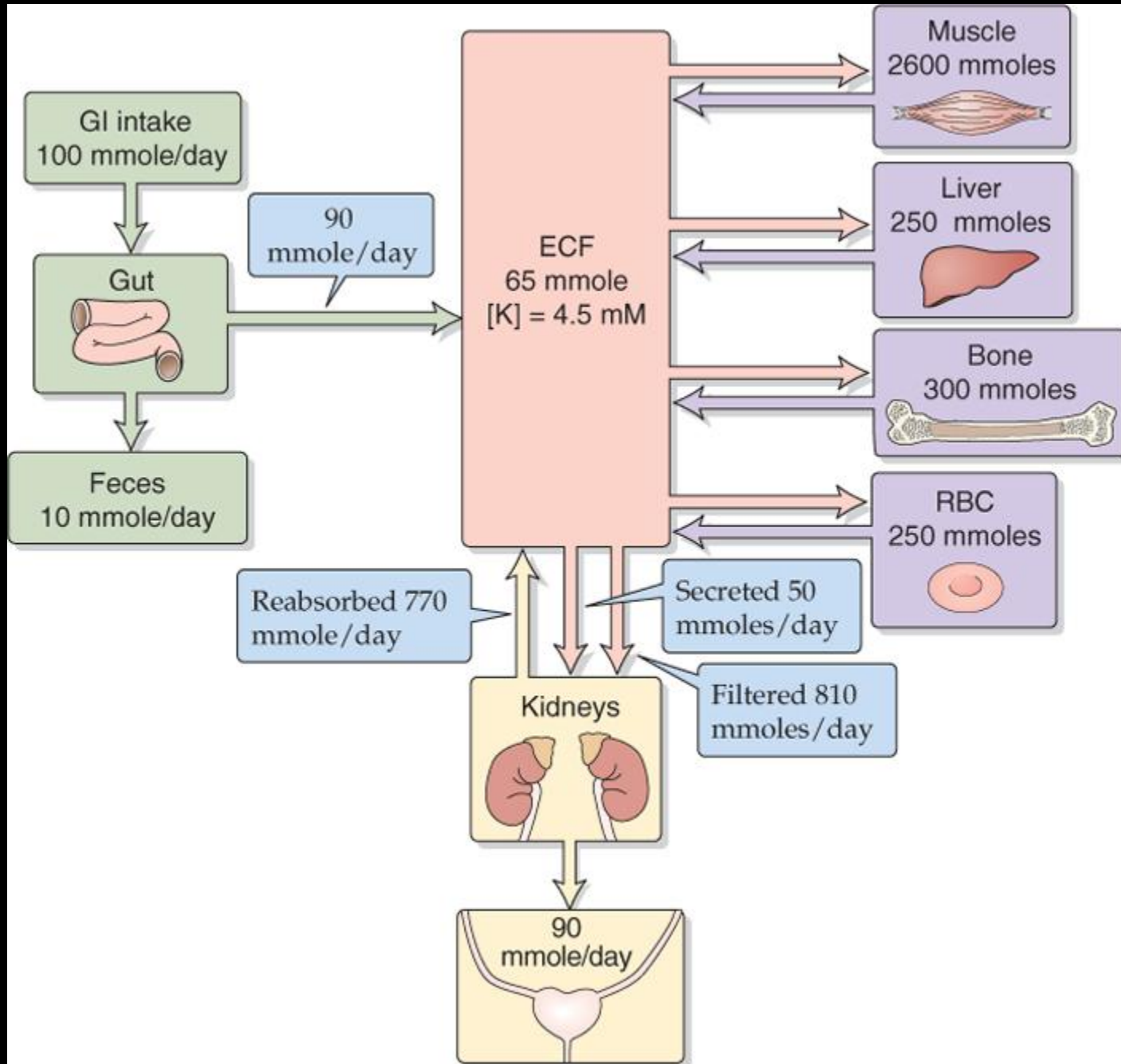
**3920 mEq**

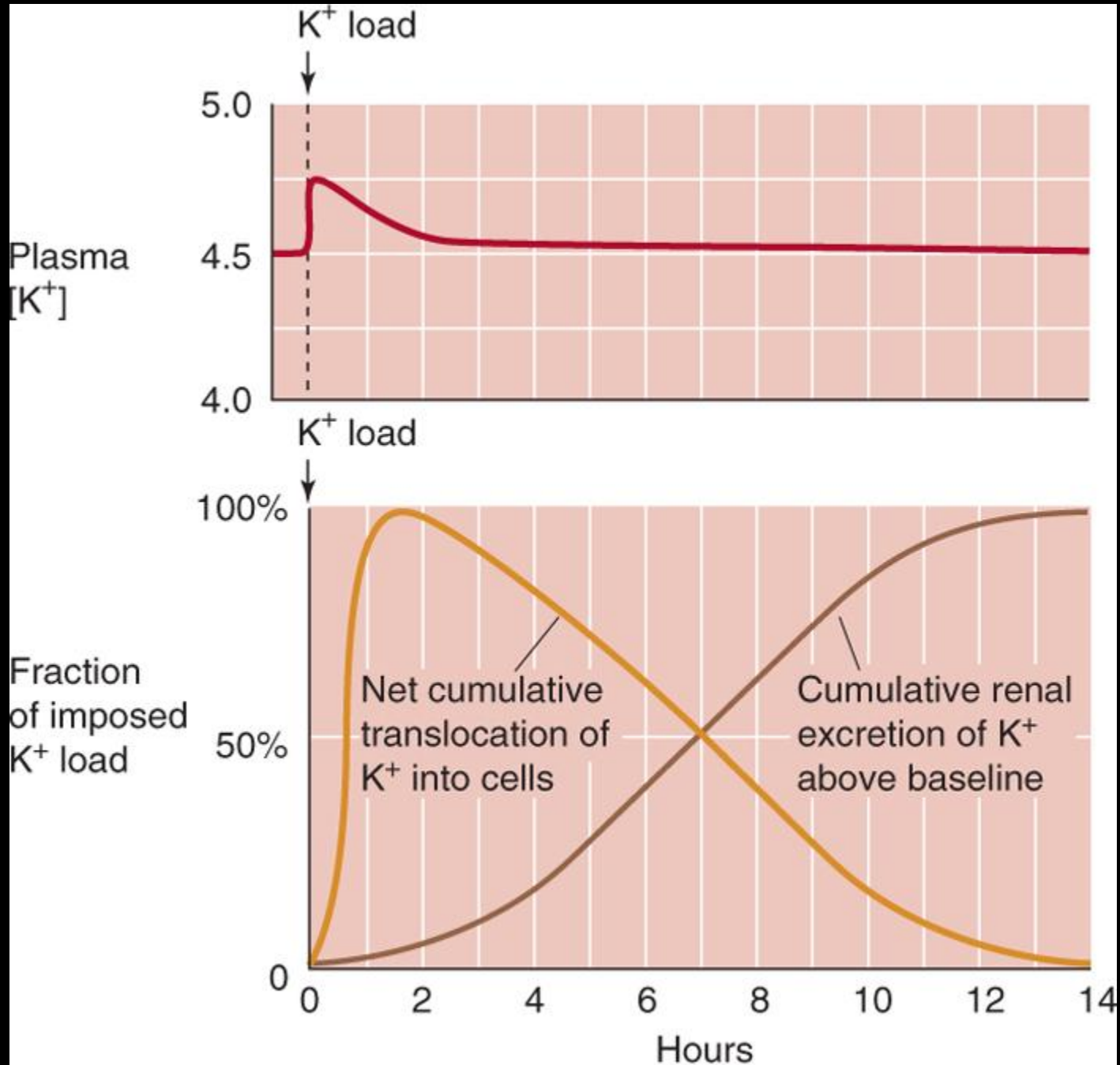
**K<sup>+</sup> output**  
Urine 92 mEq/day  
Feces 8 mEq/day  

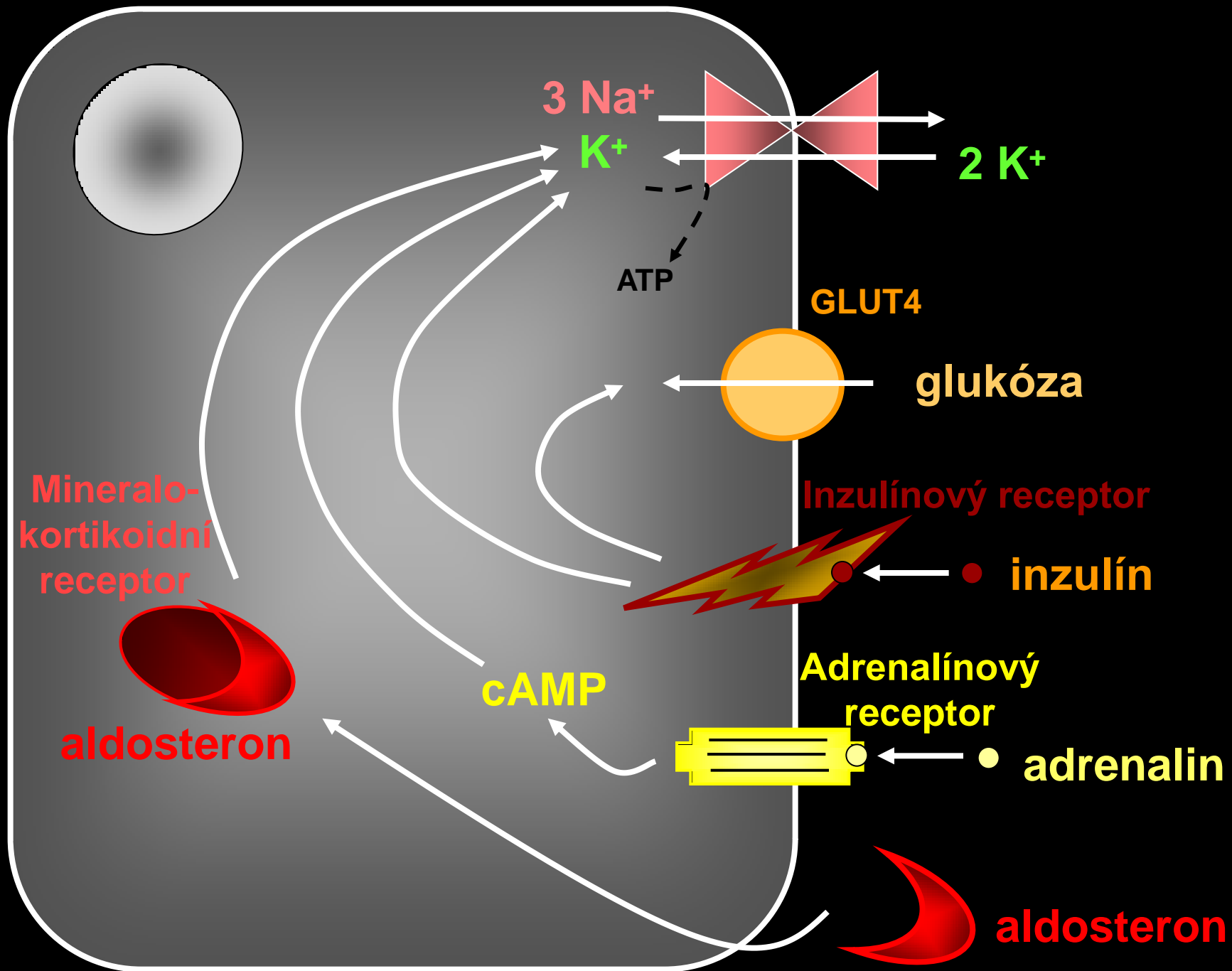
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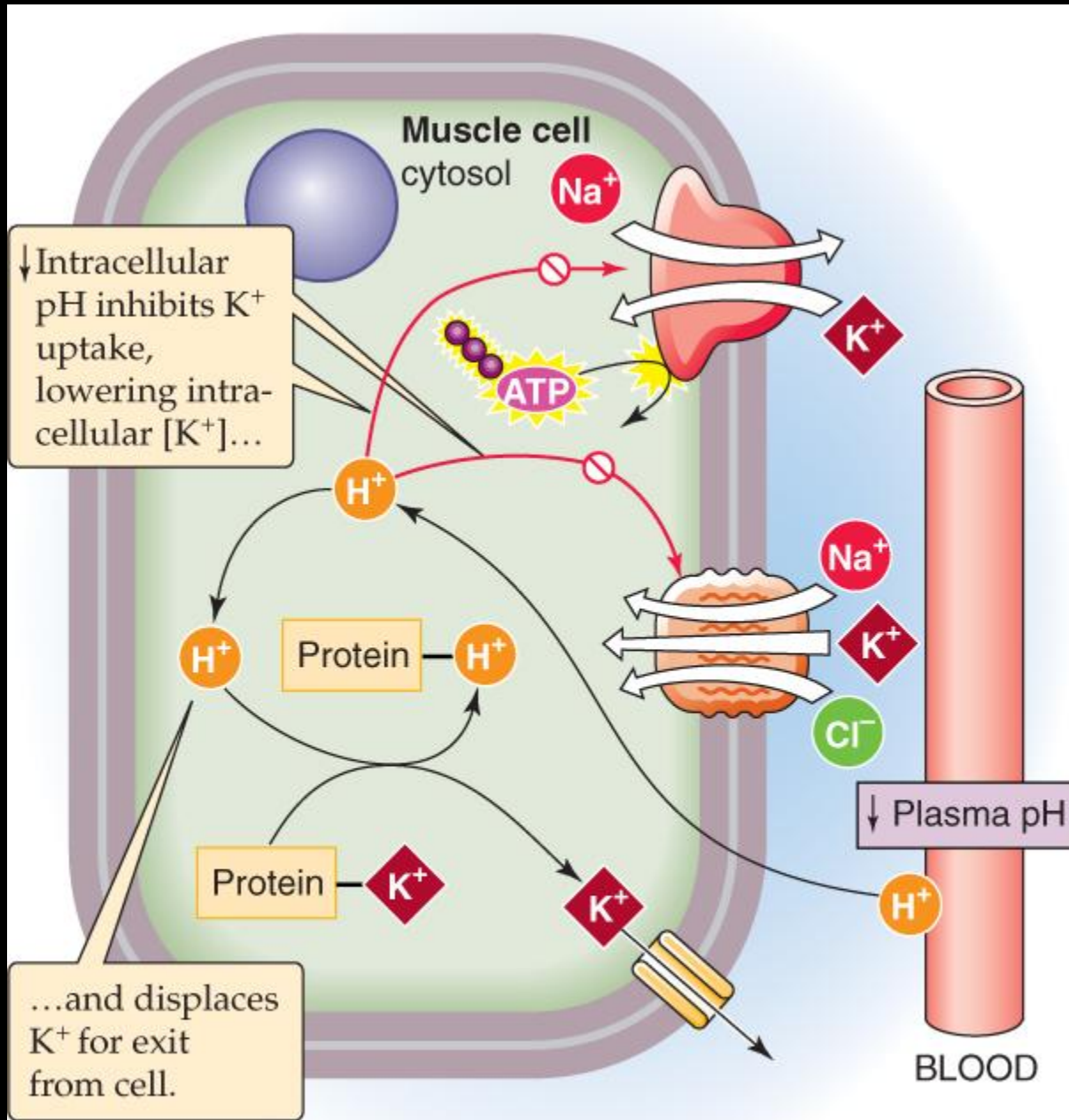
**100 mEq/day**





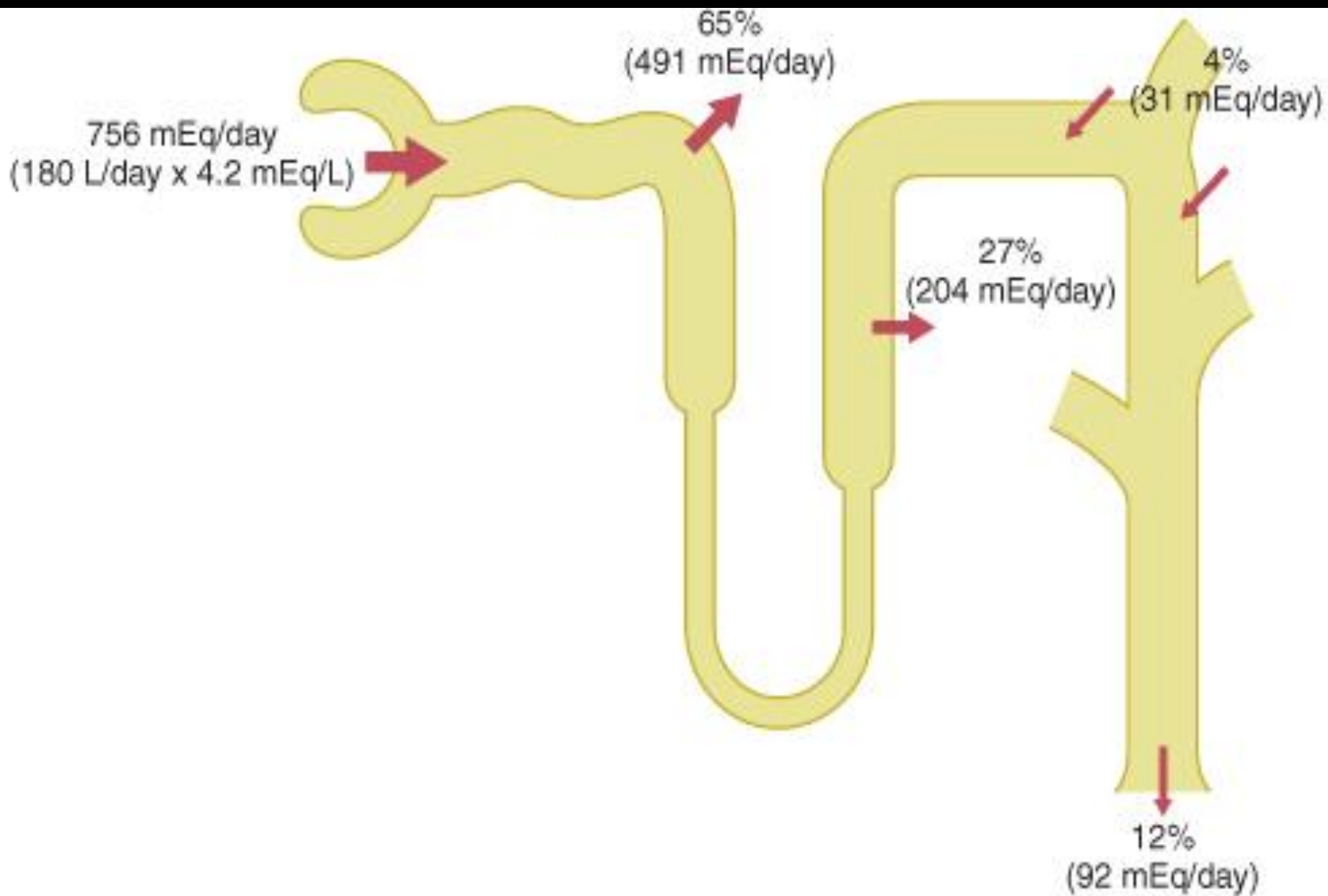






## Summary of tubular potassium transport

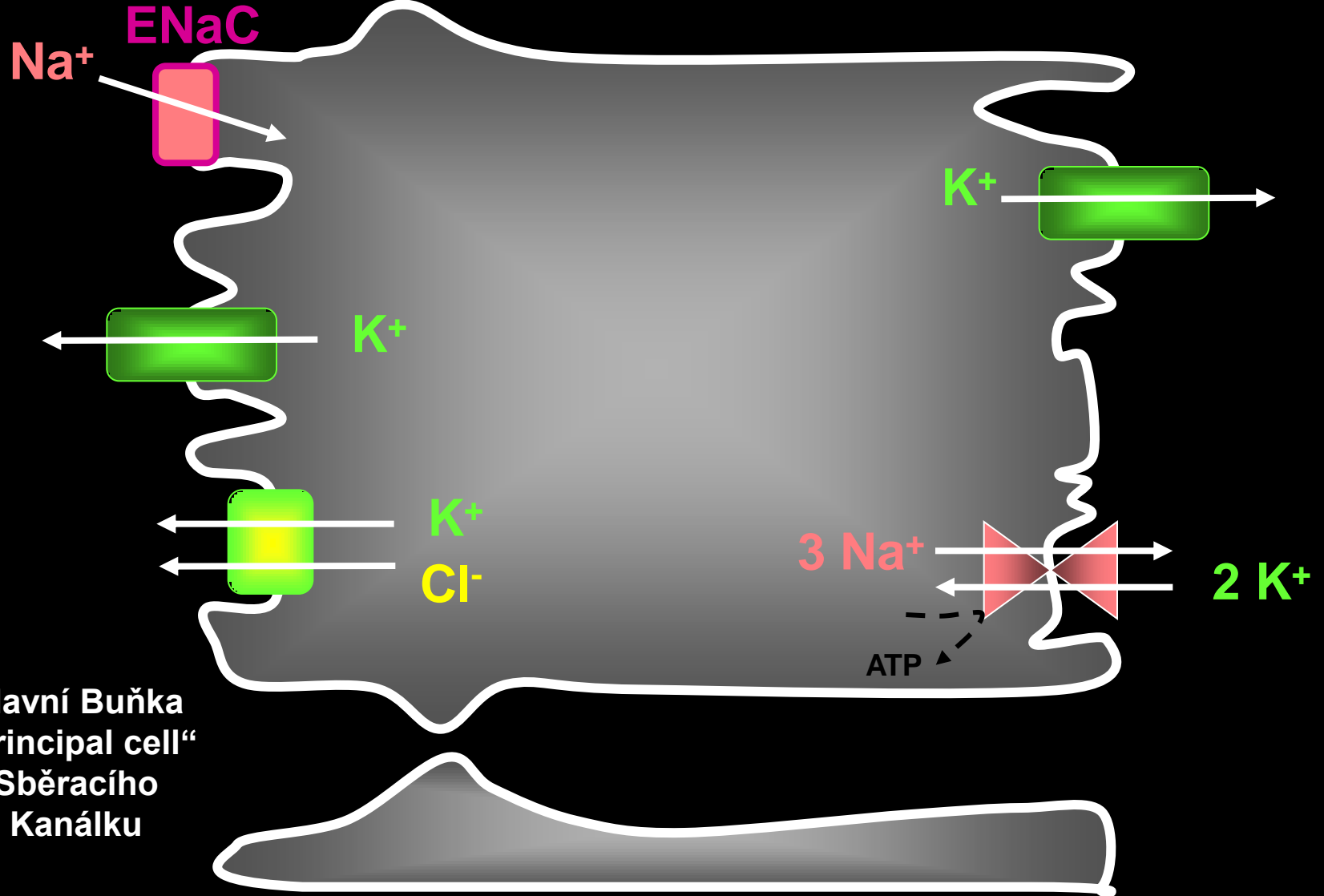
| <b>Tubular segment</b>                                  | <b>Normal- or high-potassium diet</b>       | <b>Low-potassium diet</b> |
|---|---|---------------------------|
| Proximal tubule   | Reabsorption (60-80 %)                      | Reabsorption (55 %)       |
| Thick ascending limb                                    | Reabsorption (5-25 %)                       | Reabsorption (30 %)       |
| Distal convoluted tubule                                | <b>Secretion</b>                            | Reabsorption              |
| Cortical collecting duct<br>(Principals cells)          | <b>Substantial secretion<br/>(15-180 %)</b> | 0                         |
| Cortical collecting duct<br>(Intecalated cells, type A) | Reabsorption (10 %)                         | Reabsorption (10 %)       |
| Medullary collecting duct                               | Reabsorption (5 %)                          | Reabsorption (5 %)        |





Lumen

Intersticiální Prostor

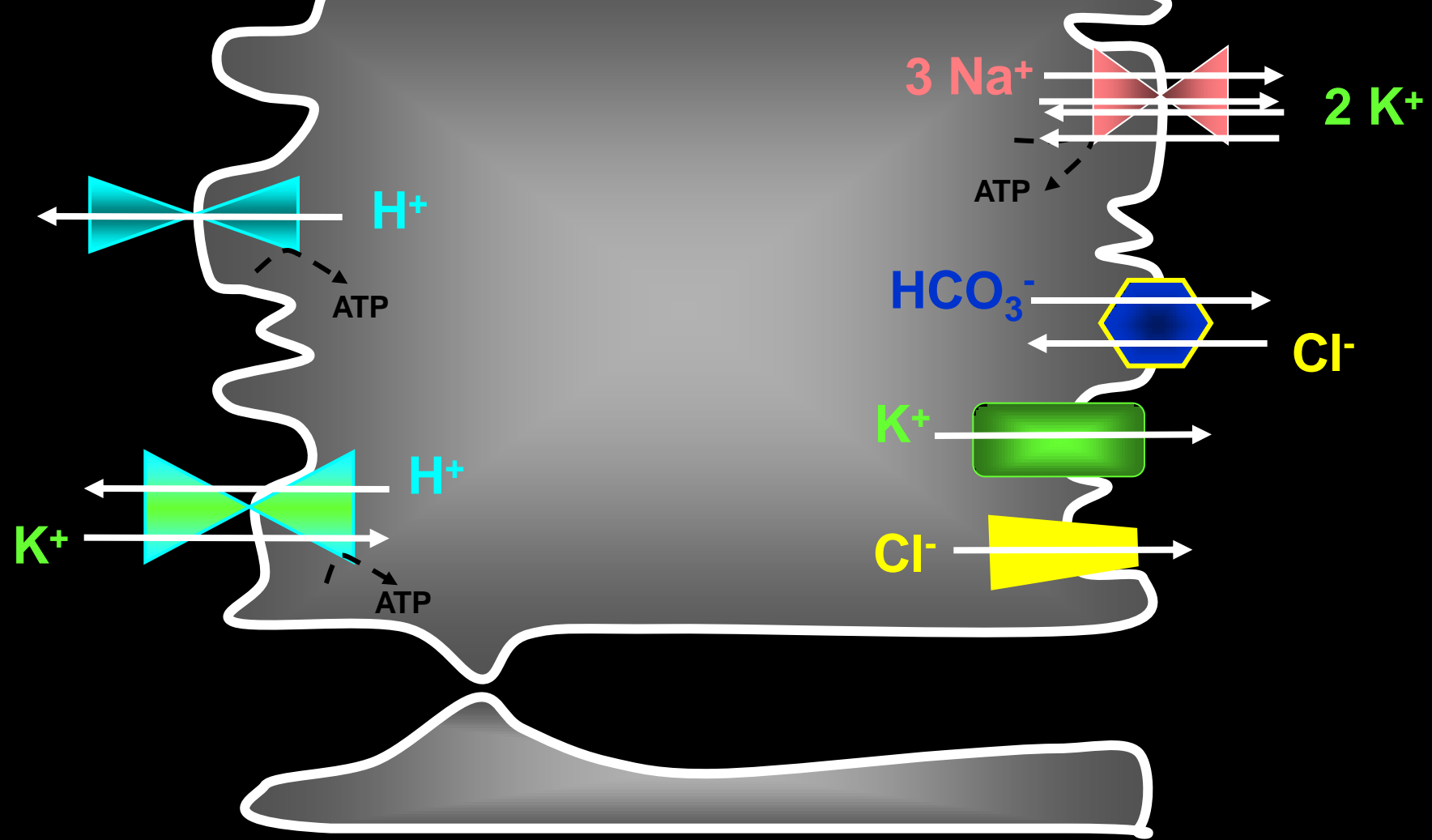


Hlavní Buňka  
„principal cell“  
Sběracího  
Kanálku

Lumen

Vmezeřená buňka  
„intercalated cell“  
Sběracího kanálku

Intersticiální Prostor



## **Homeostatic Control of Potassium Secretion by the Cortical Collecting Duct (3 key factors)**

- 1. Plasma concentration of potassium**
- 2. Plasma levels of aldosterone**
- 3. Delivery of sodium to the distal nephron**

### **Ad.1:**

The principal cells contains an isoform of Na-K-ATPase that is especially sensitive to increases in the concentrations in peritubular capillaries. It also reduces back leakage Potassium ions from inside the cells through the basolateral membrane.

### **Ad.2:**

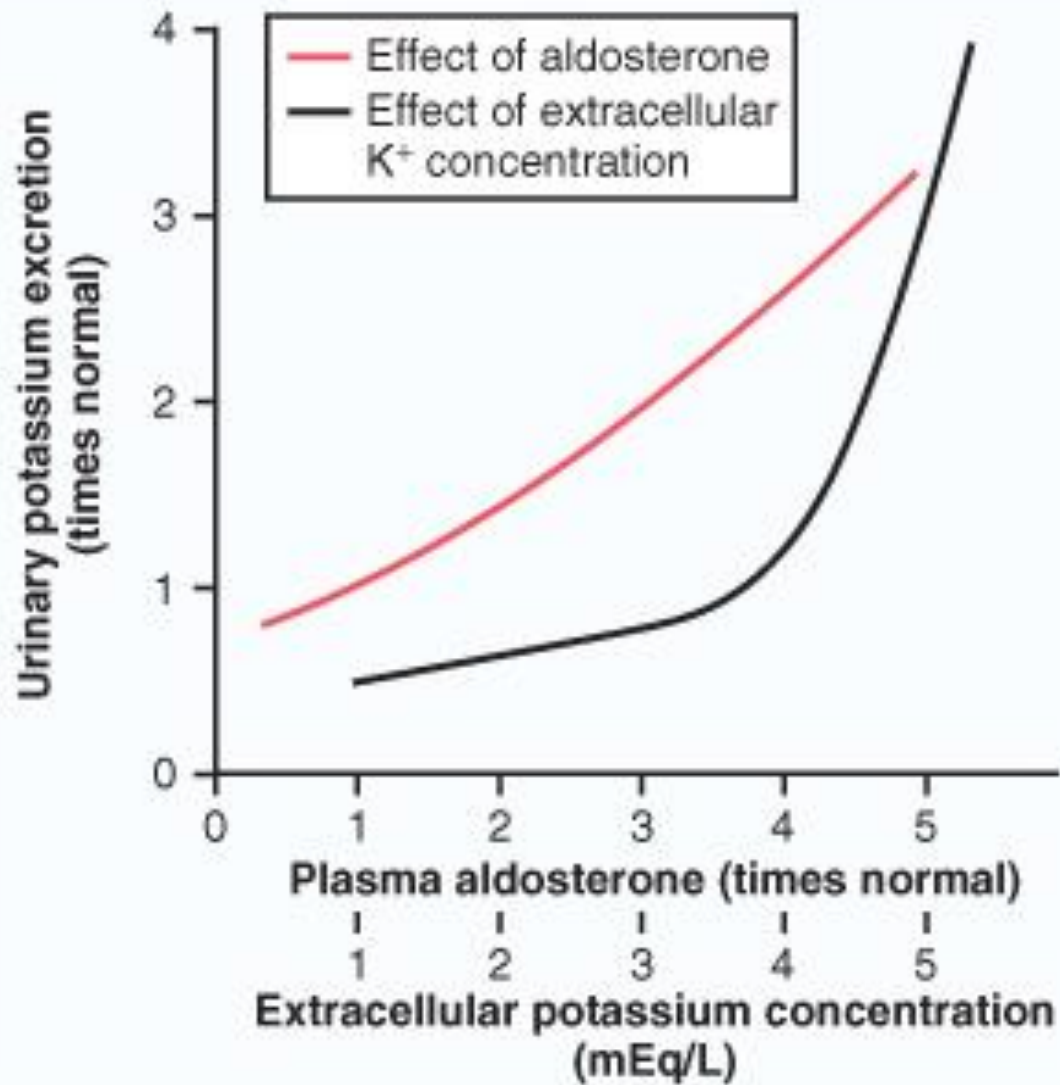
The luminal membrane pathway that allows potassium to exit the cell must be open and this is the function of aldosterone. It also stimulates Na-K-ATPase.

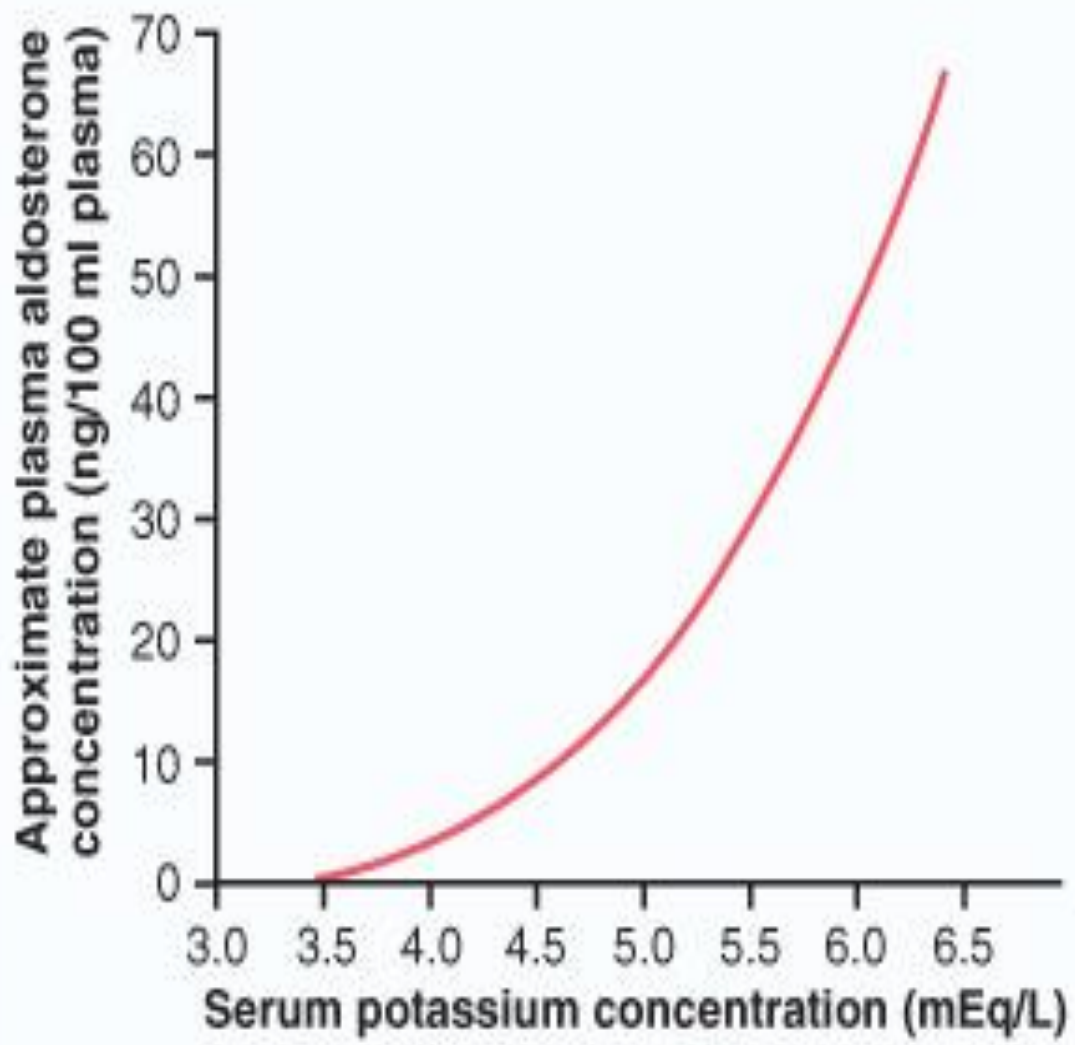
### **Ad.3:**

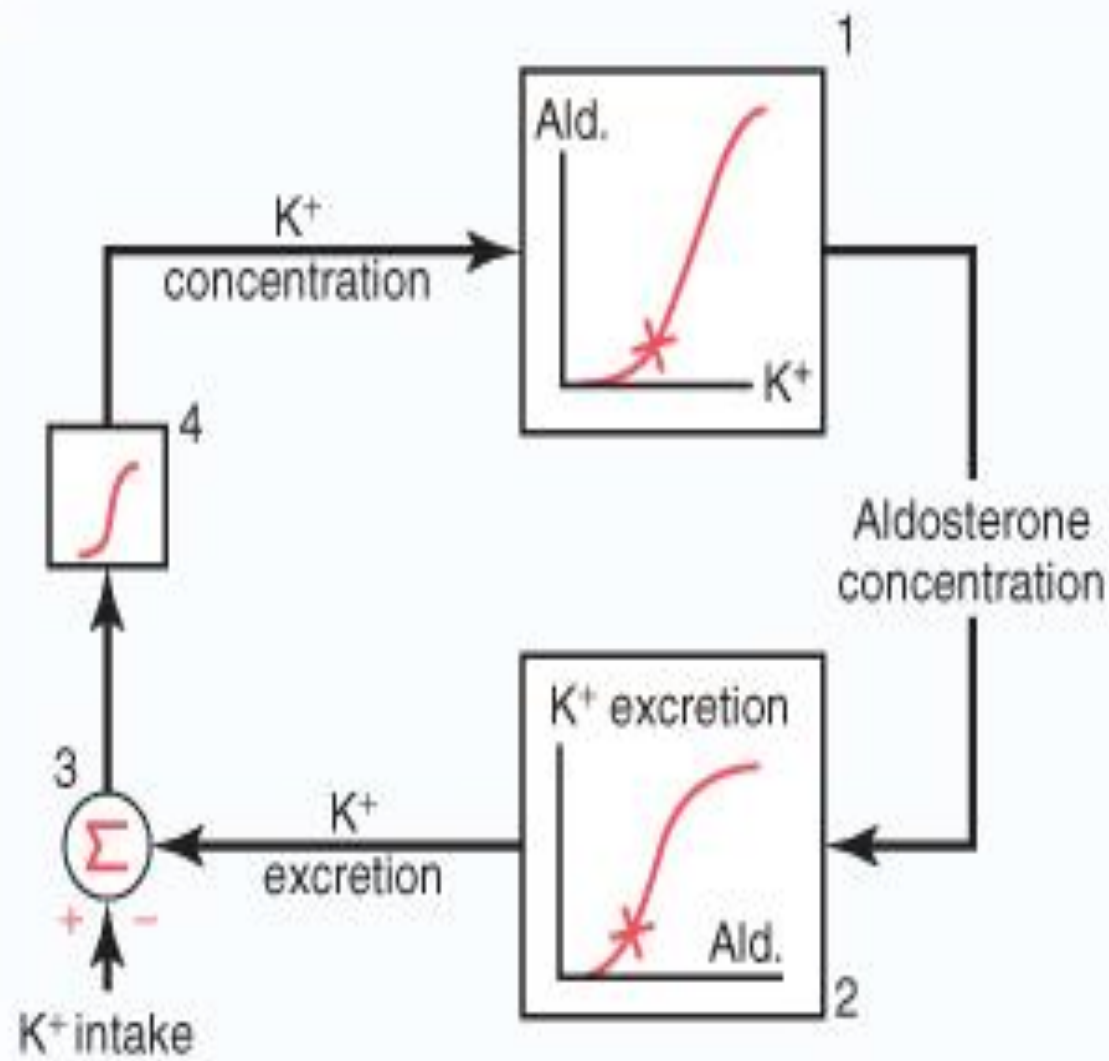
With an increased delivery of sodium to the cortical collecting duct, more sodium enters principal cells, and more potassium is secreted.

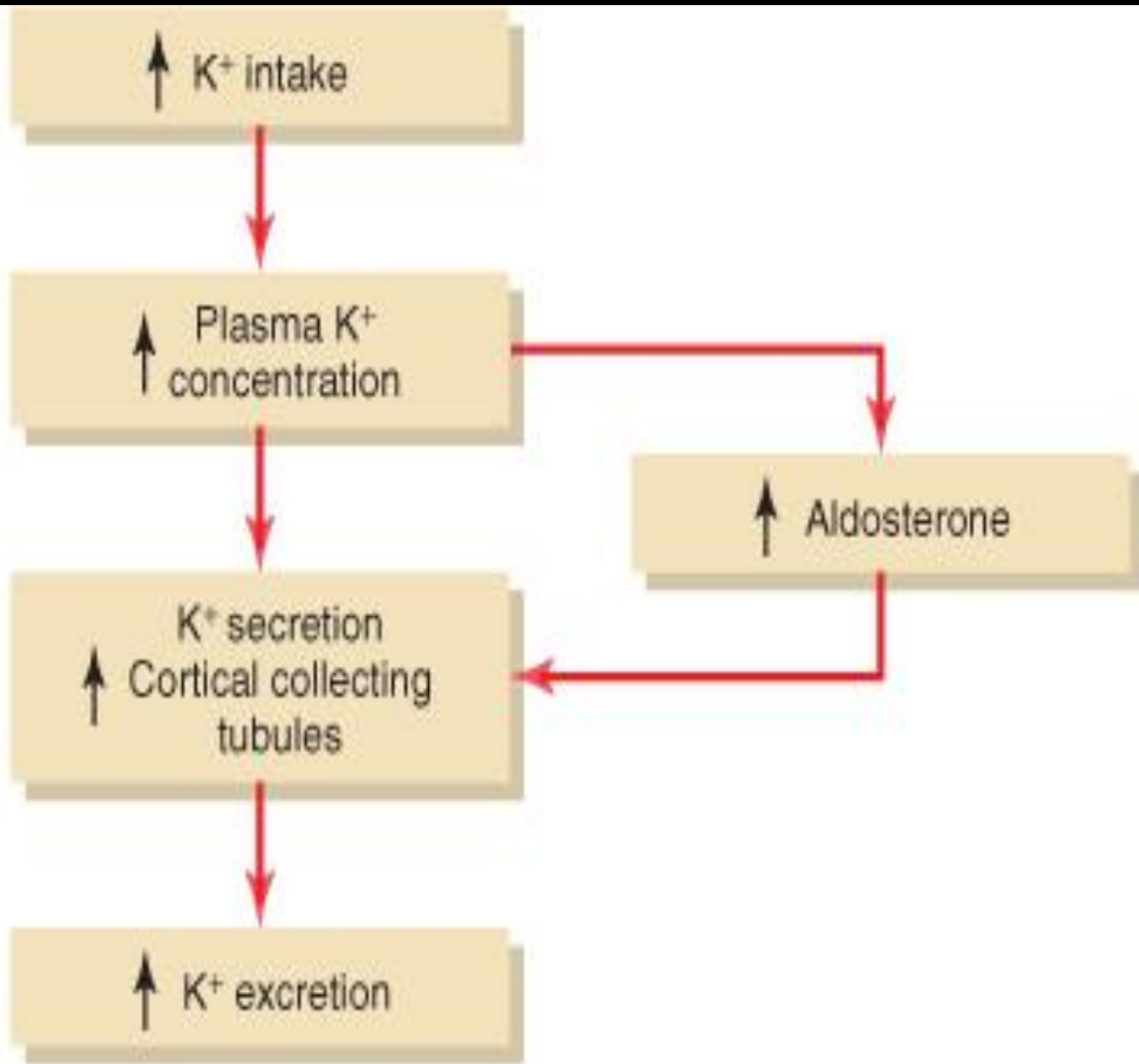
## **4. Acute acidosis decreases potassium secretion**

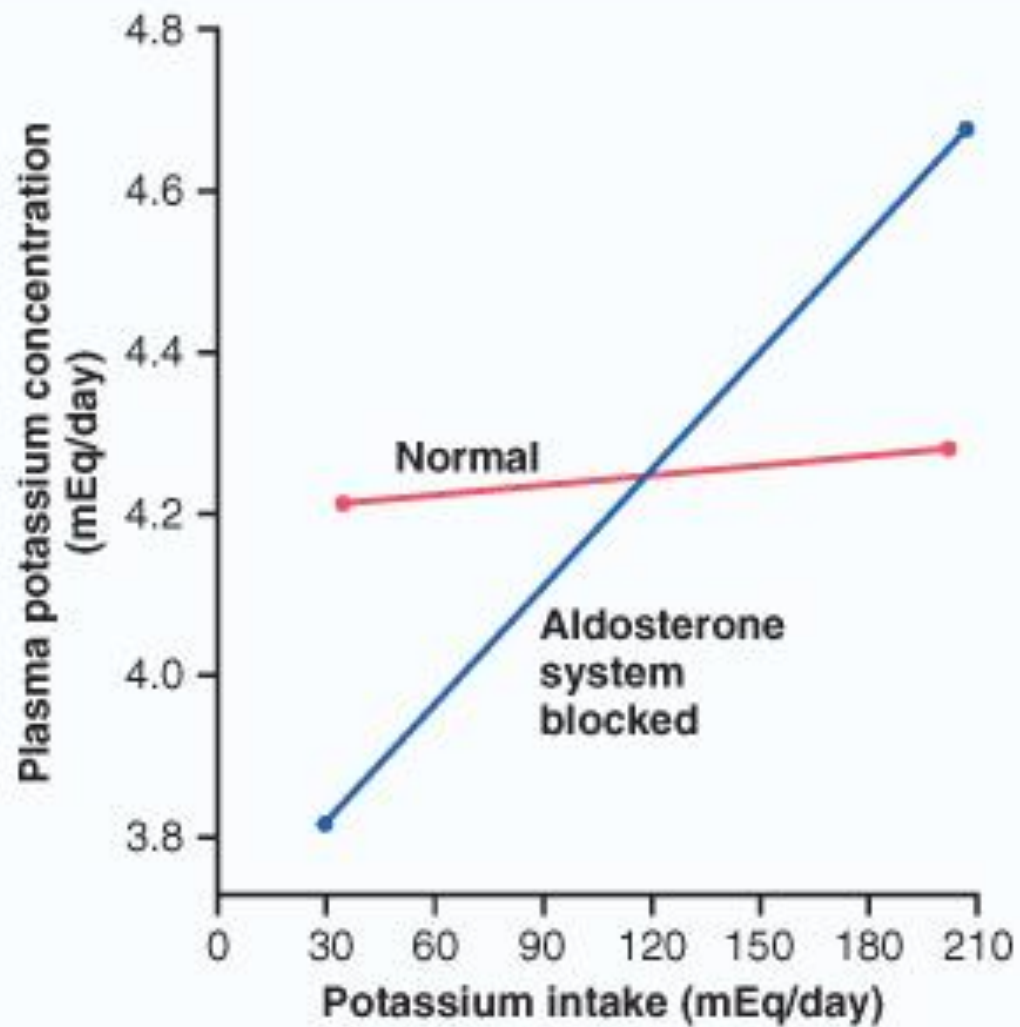
The primary mechanism is that increased hydrogen ion concentration reduces the activity of Na-K-ATPase pump. This in turn decreases intracellular potassium concentration and subsequent passive diffusion of potassium across the luminal membrane into the tubule.



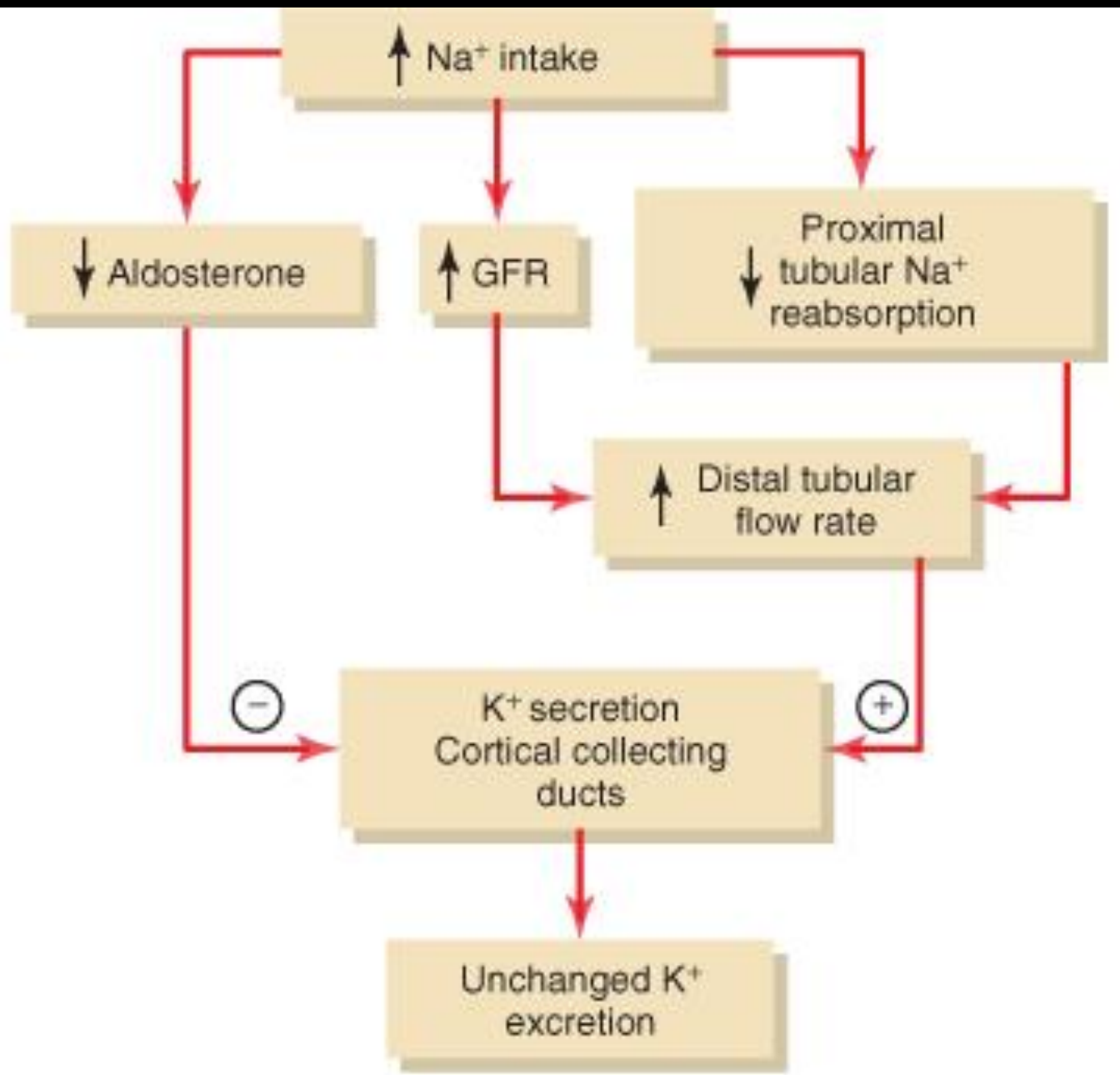


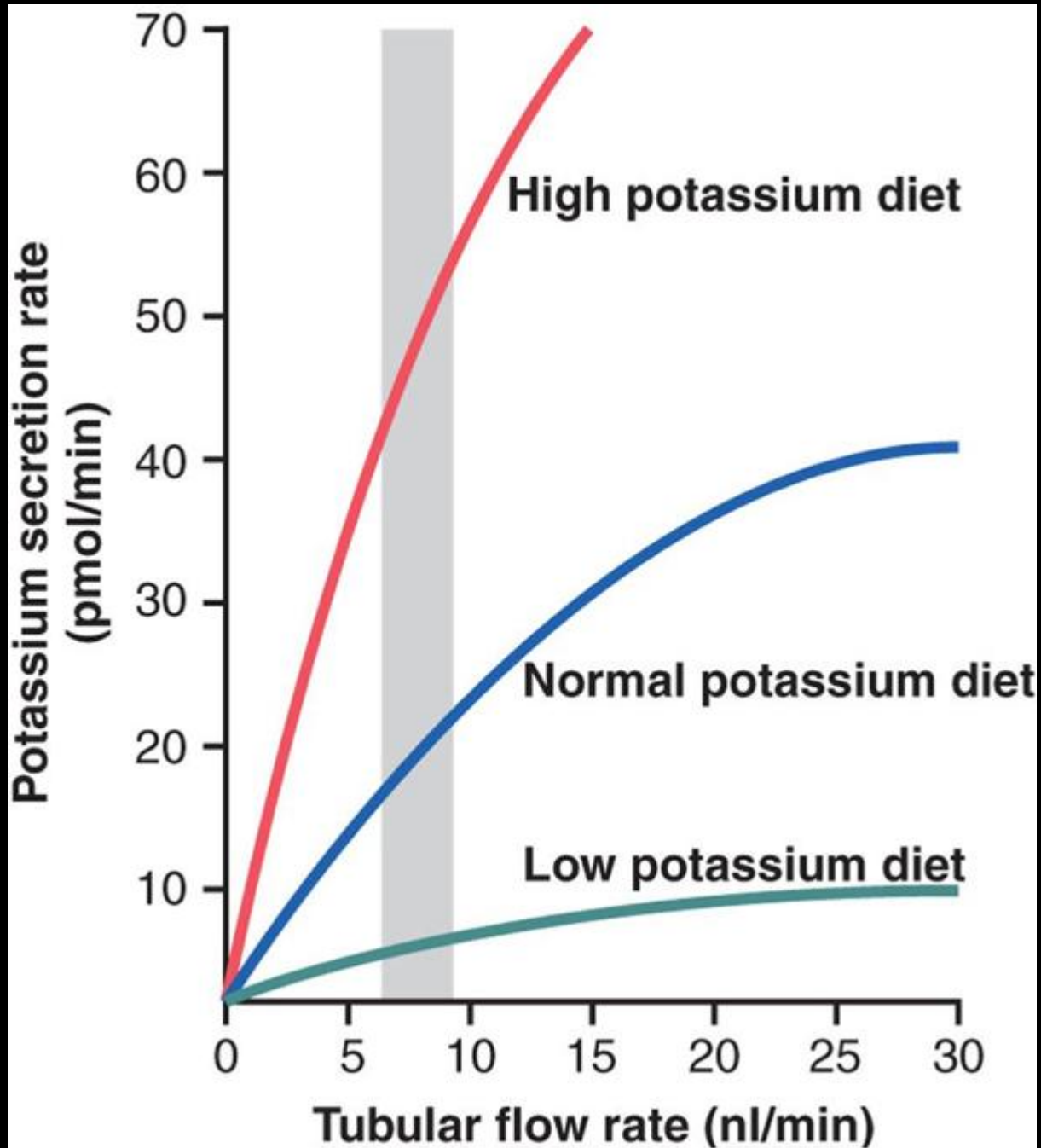










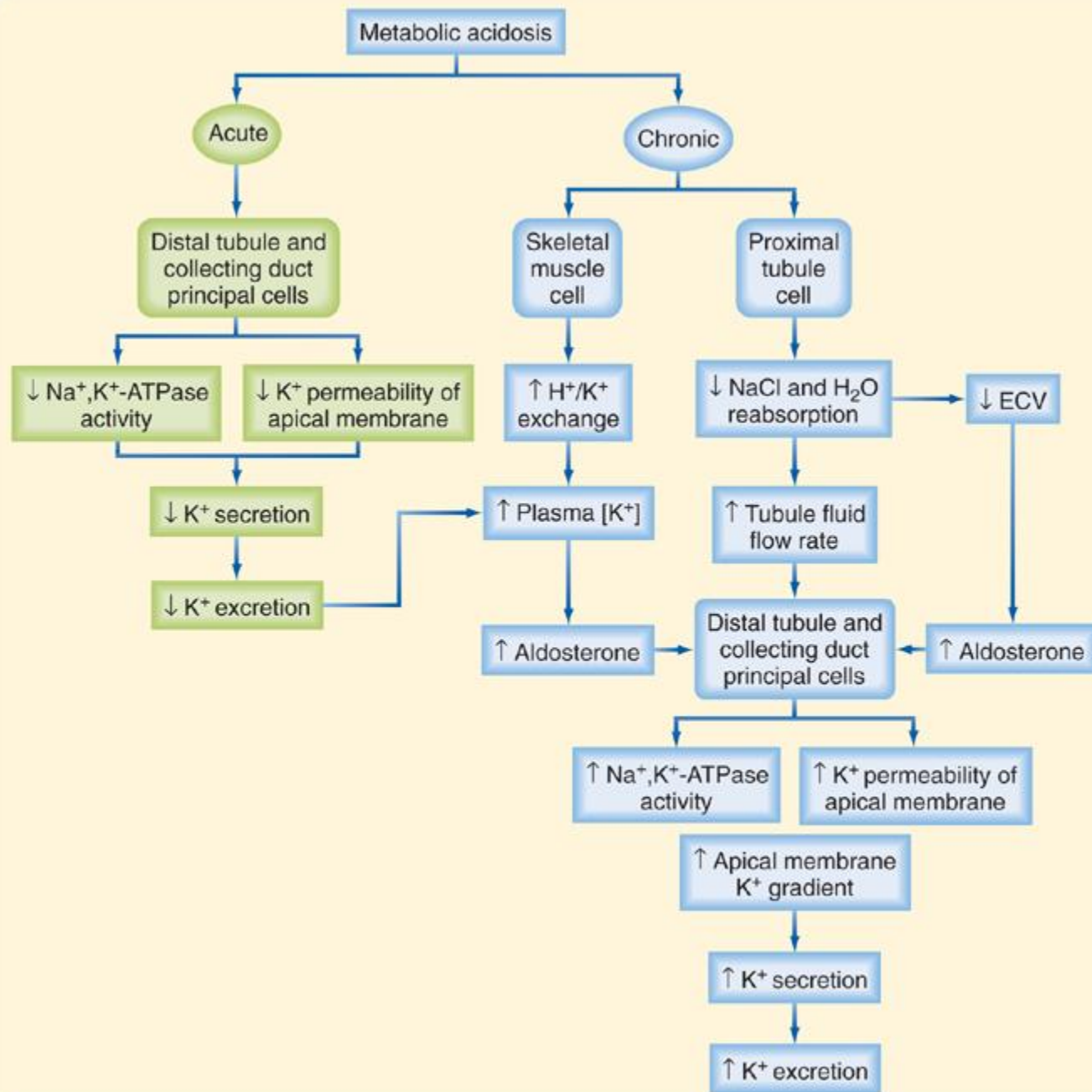


#### **4. Acute acidosis decreases potassium secretion**

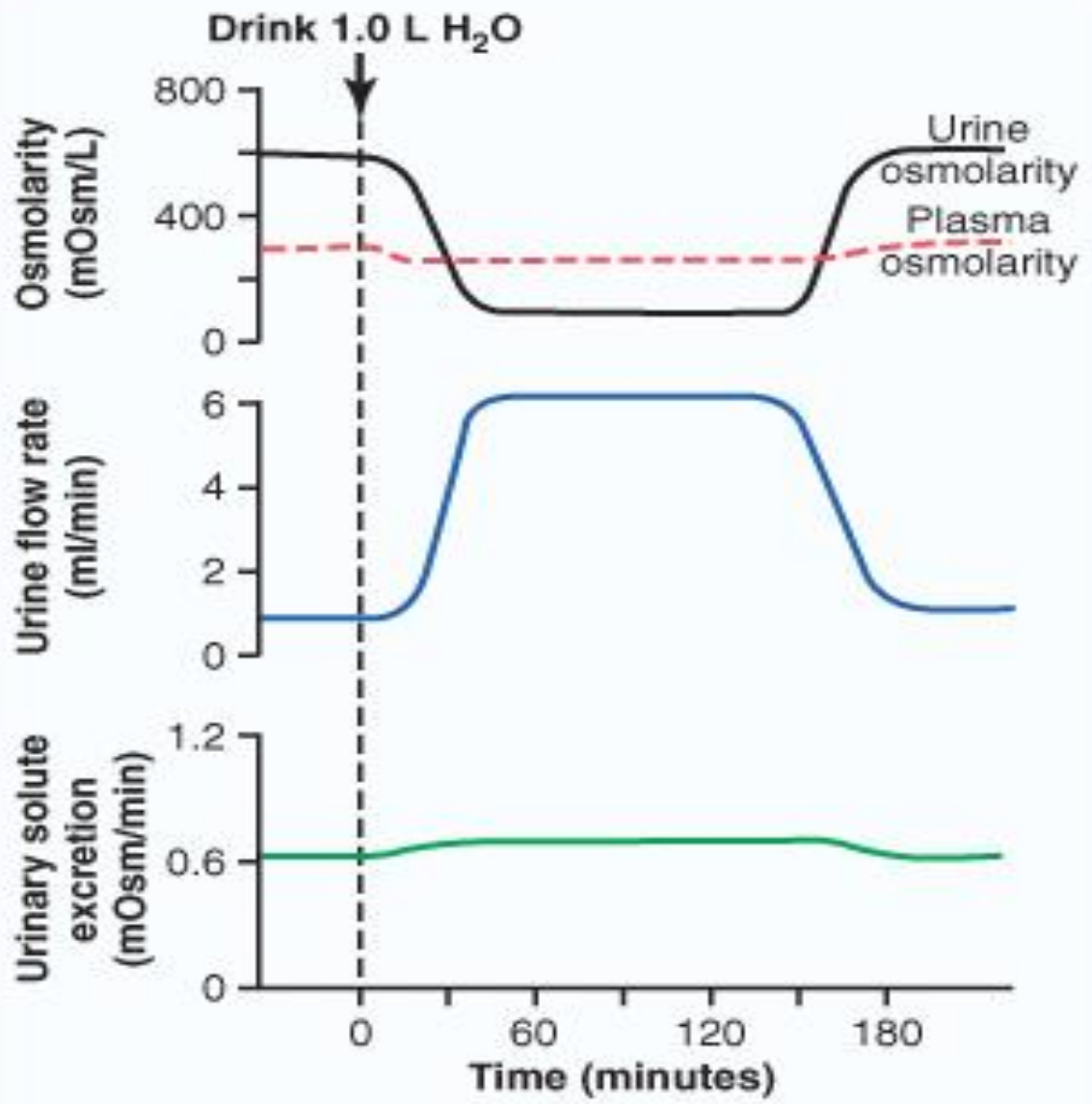
The primary mechanism is that increased hydrogen ion concentration reduces the activity of Na-K-ATPase pump. This in turn decreases intracellular potassium concentration and subsequent passive diffusion of potassium across the luminal membrane into the tubule.

#### **5. Chronic acidosis increases renal potassium excretion**

Underlying mechanism is that chronic acidosis inhibits sodium (and water) reabsorption in the proximal tubule, which increases distal volume delivery, thereby stimulating the secretion of potassium.



# Regulation of Extracellular Fluid Osmolarity and Sodium Concentration



## Obligatory urine volume

$$\frac{600 \text{ mOsm/day}}{1200 \text{ mOsm/L}} = 0.5 \text{ L/day}$$

## Proč nepít mořskou vodu?

1 L mořské vody = 1 200 mOsm = příjem 1 200 mOsm/L

Organismus se musí denně zbavit minimálně 600 mOsm denně

To znamená, že musíme vyloučit 1800 mOsm, což i při tvorbě maximálně koncentrované moči (1200 mOsm/l) musíme vyloučit 1.5 L.

Z toho vyplývá, že máme minimální ztrátu 500 ml.



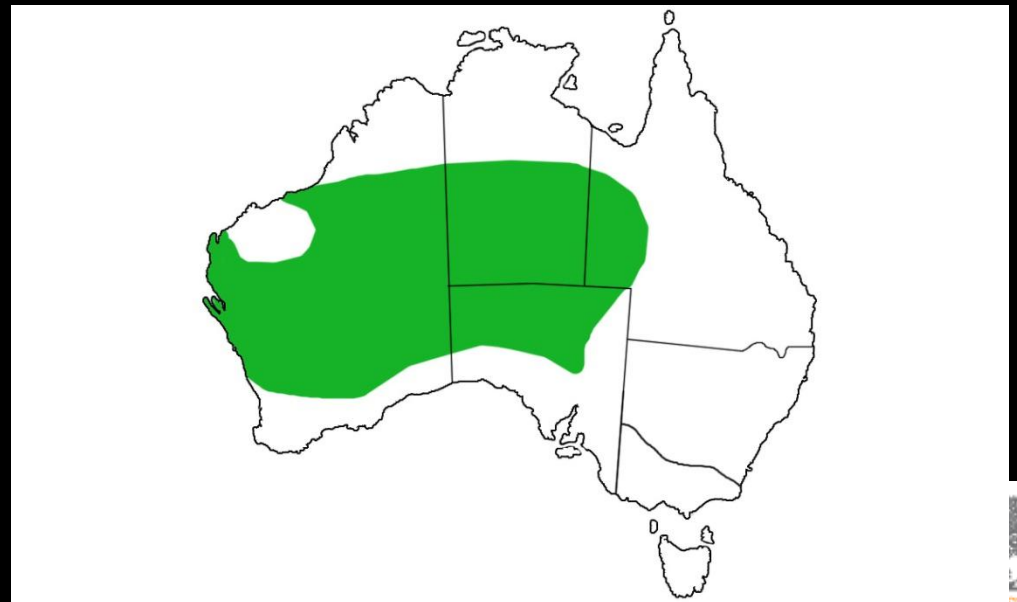


Australian hopping mouse

*Notomys alexis*

Klokanomyš spinifexová

Can concentrate urine to 10 000 mOsm/L



## Requirement for Excreting a Concentrated Urine

1. High level of ADH (antidiuretic hormone)
2. High osmolarity of the renal medullary interstitial fluid

← Permeability →

Active NaCl Transport

H<sub>2</sub>O

NaCl

Urea

Proximal Tubule

++

++

+

+

Thin descending limb

0

++

+

+

Thin ascending limb

0

0

+

+

Thick ascending limb

++

0

0

0

Distal tubule

+

+ADH

0

0

Cortical collecting tubule

+

+ADH

0

0

Inner medullary collecting duct

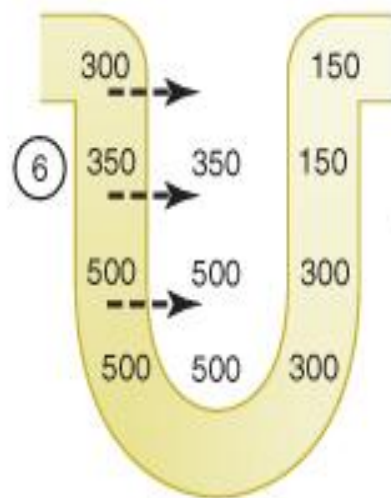
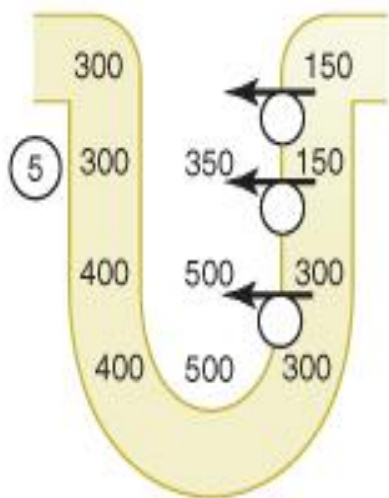
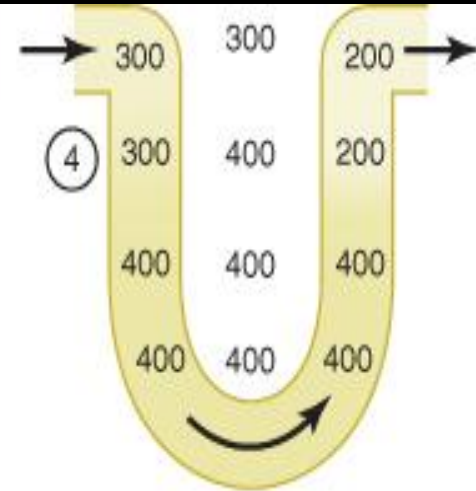
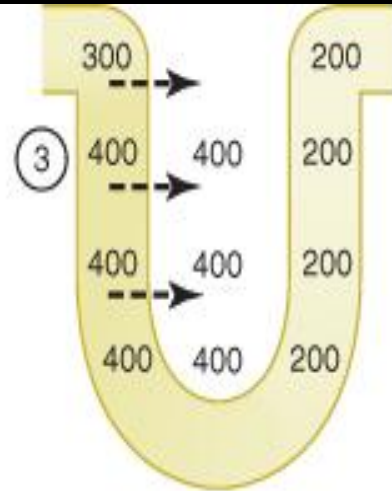
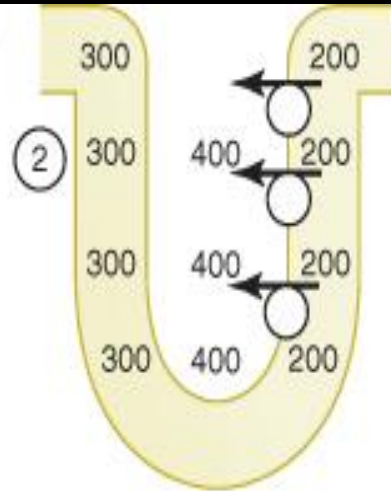
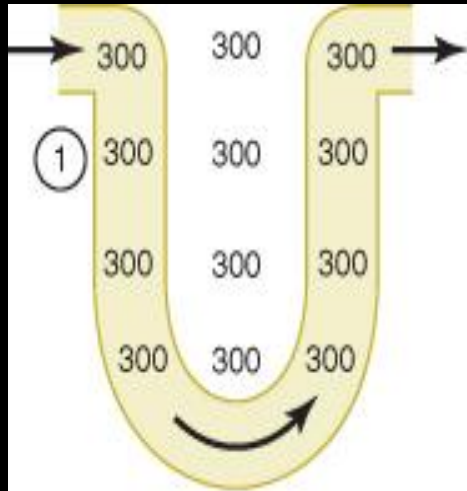
+

+ADH

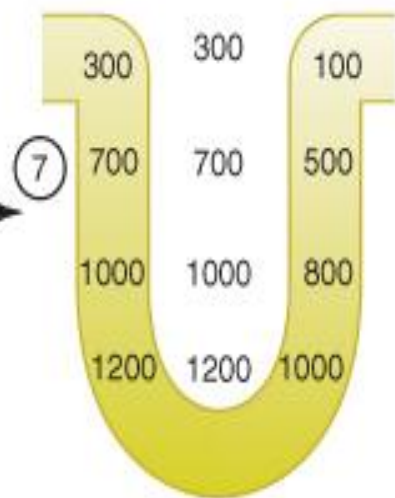
0

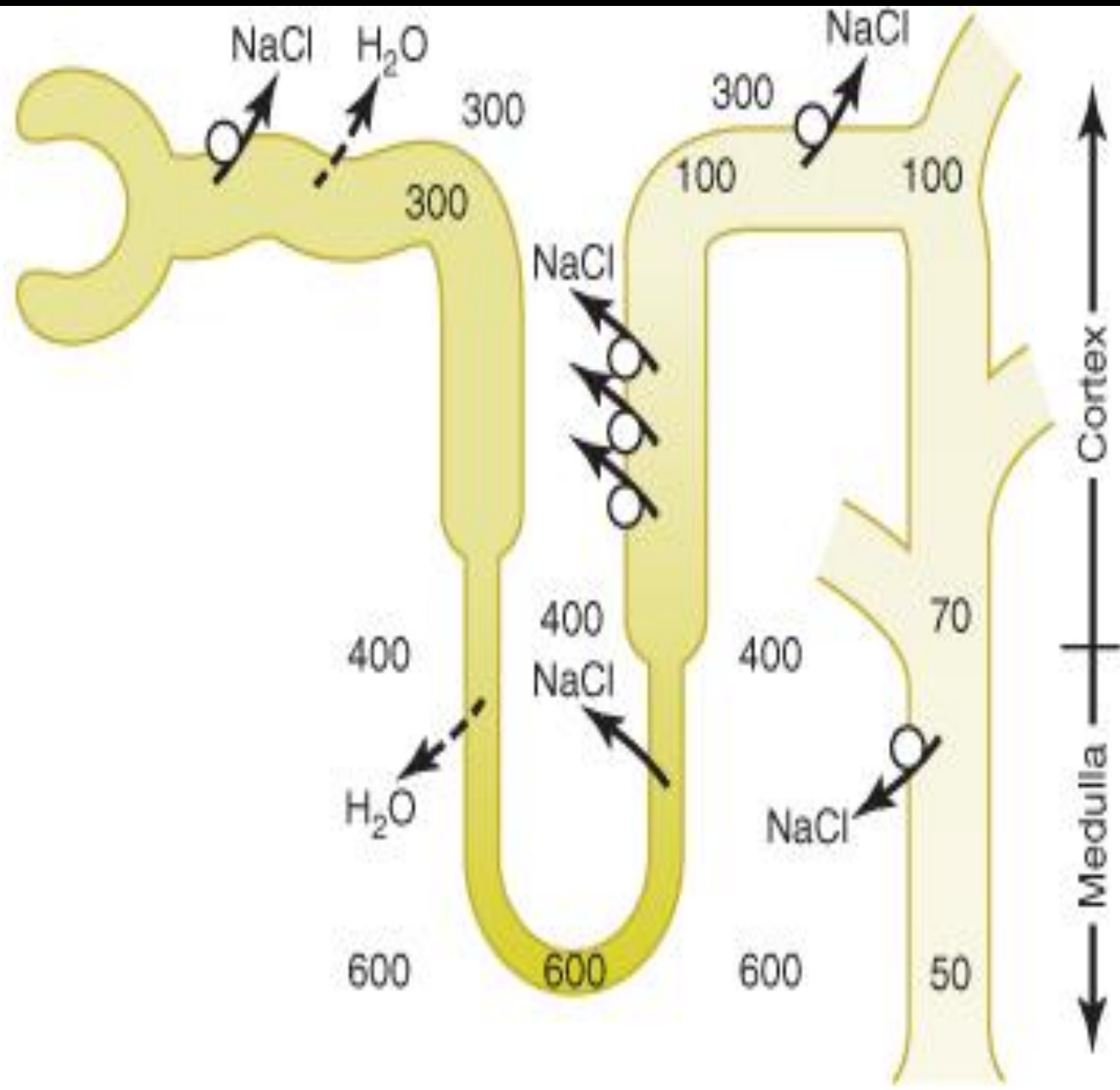
++ADH

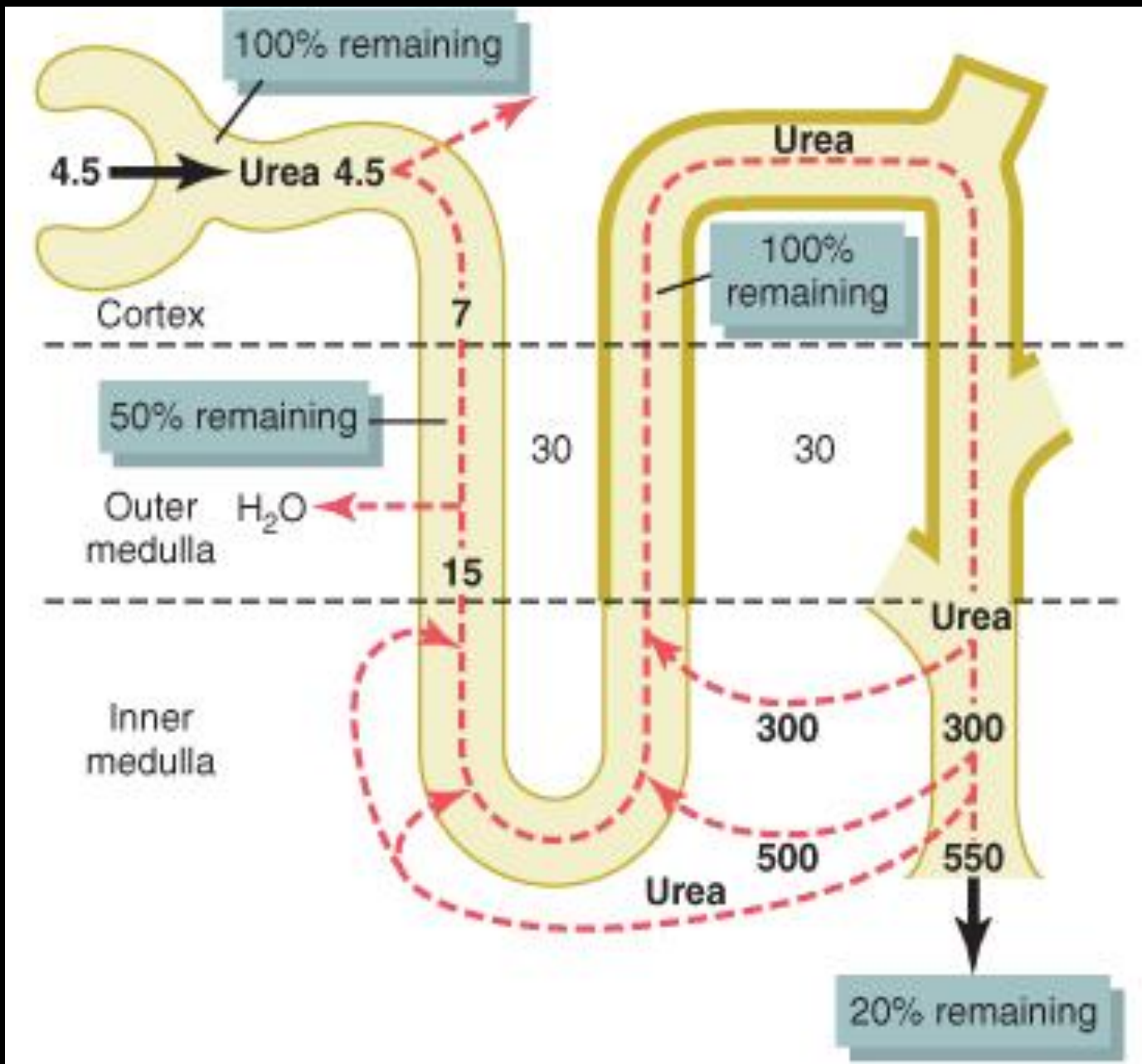


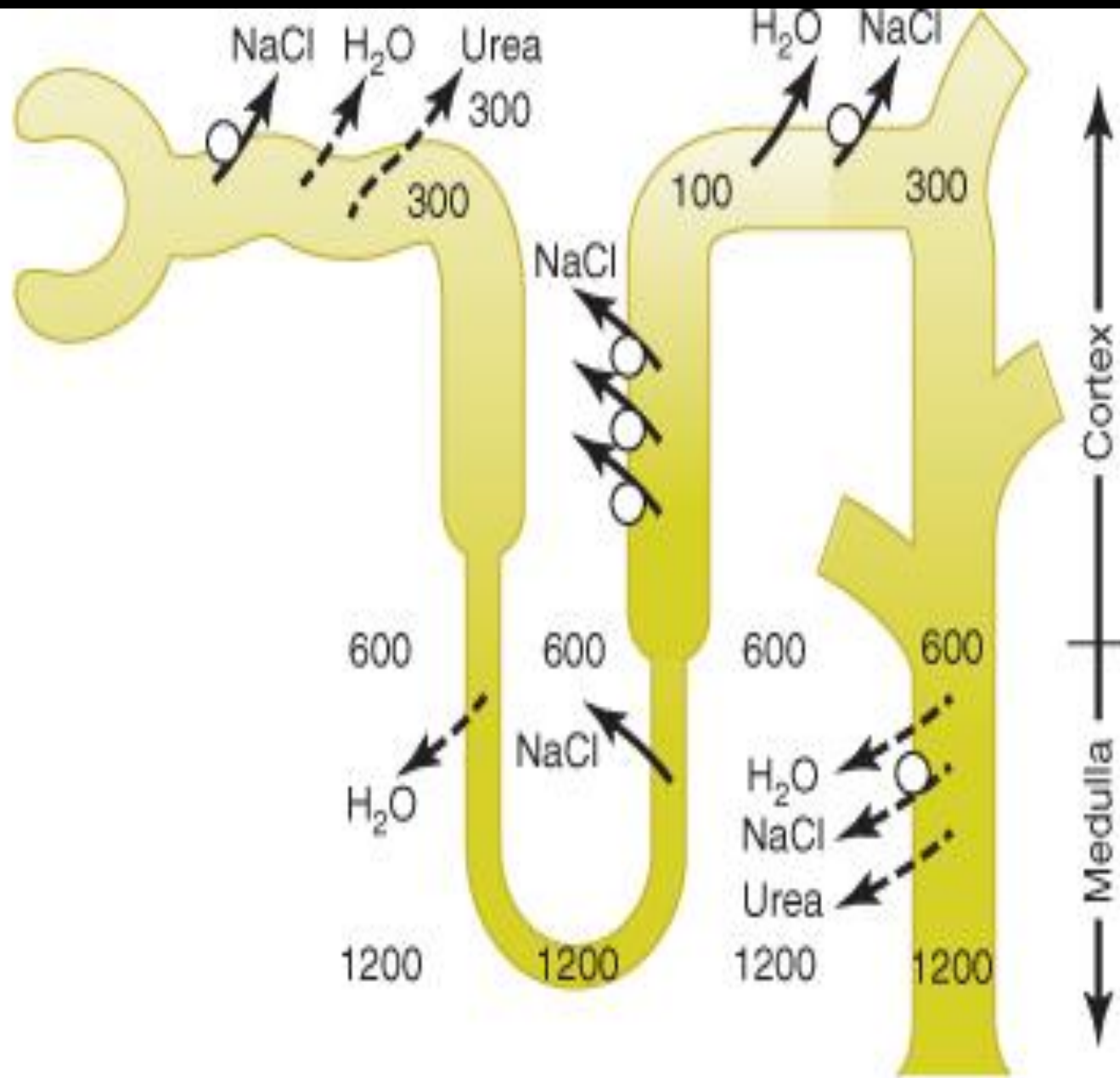


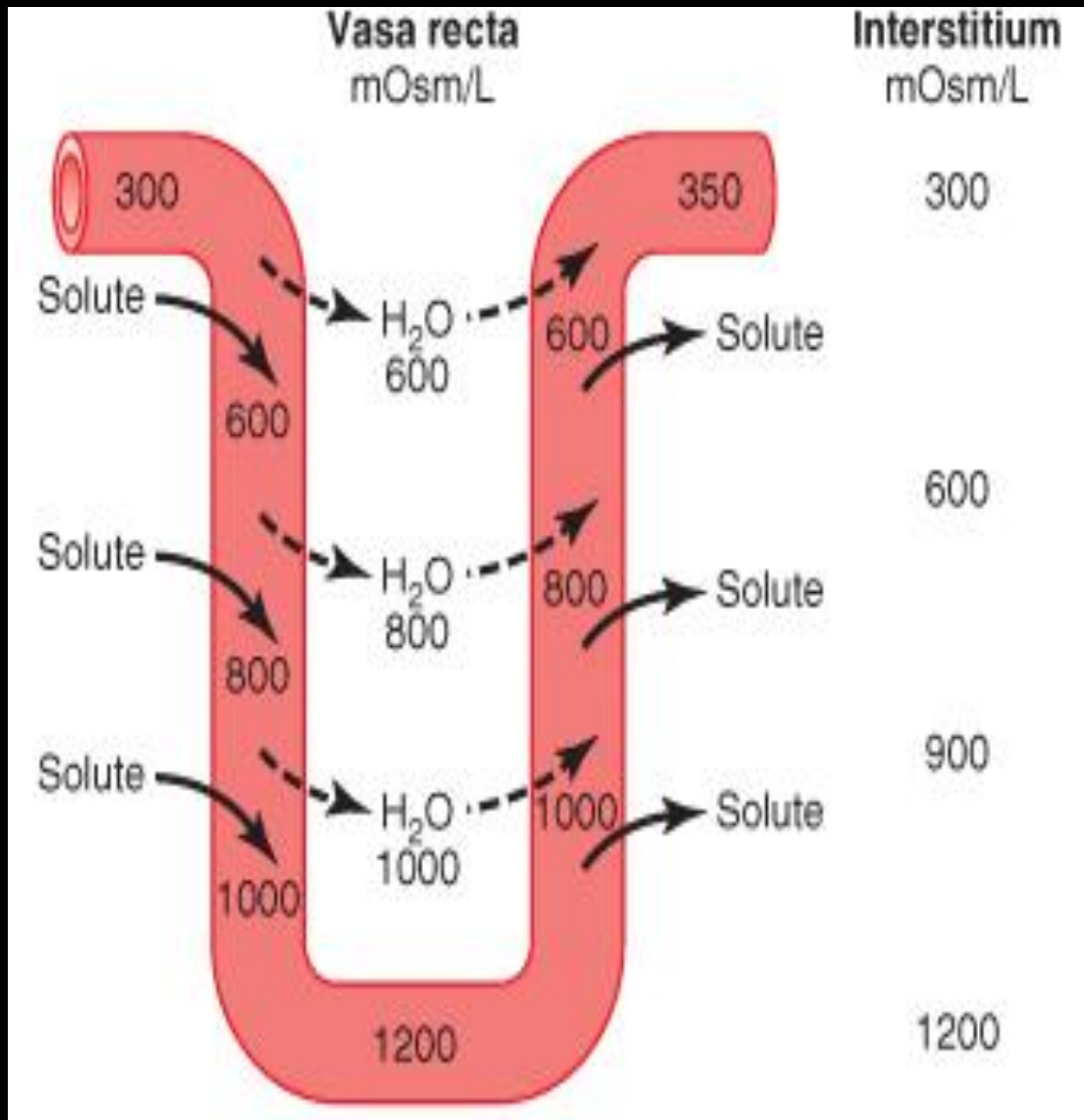
Repeat Steps 4-6





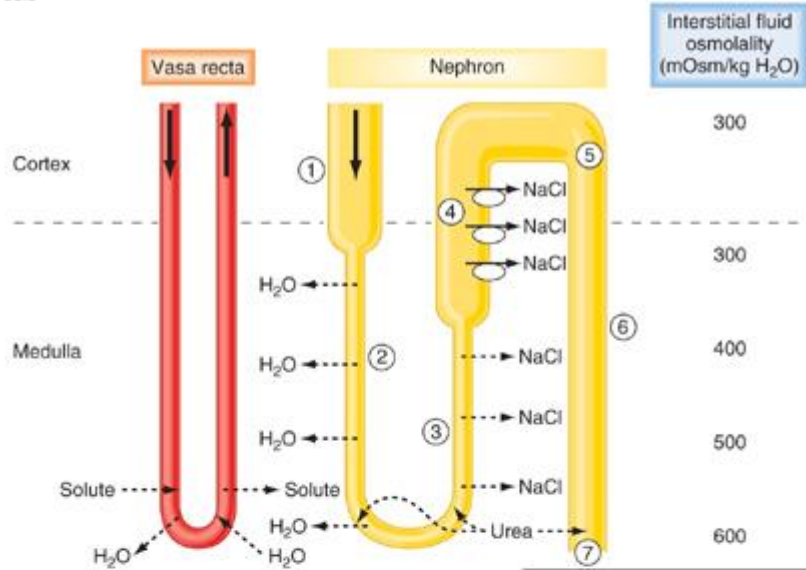






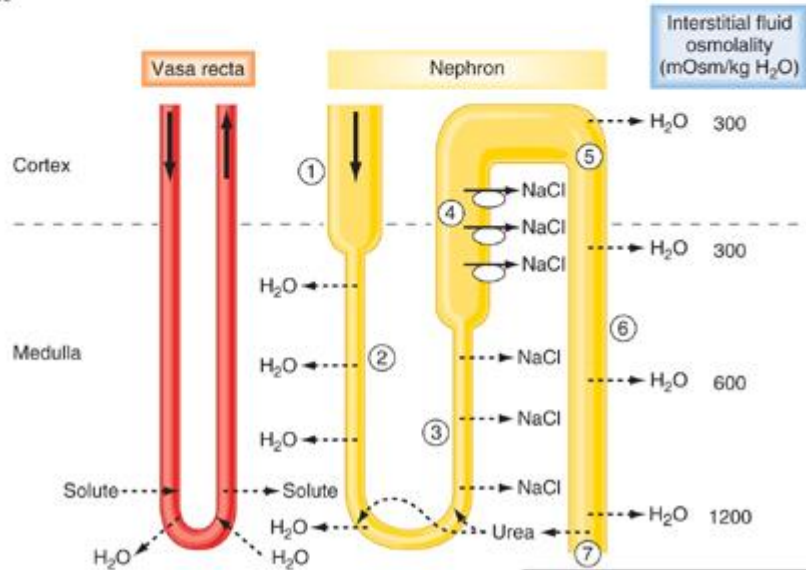


Water diuresis

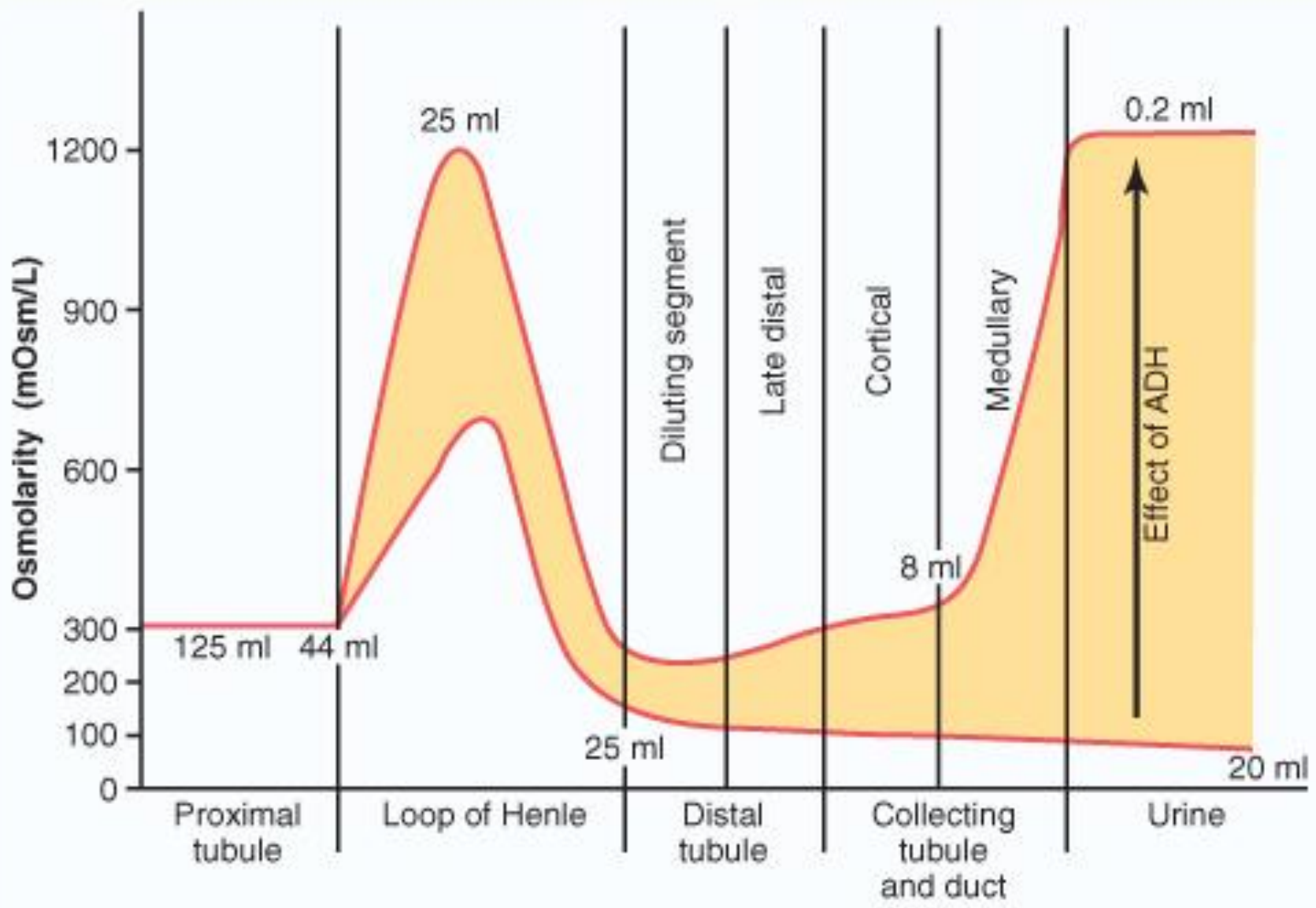


A

Antidiuresis



B



$$V = C_{\text{osm}} + C_{\text{H}_2\text{O}}$$

**V = urine flow**

**C<sub>osm</sub> = osmolal clearance**

**C<sub>H<sub>2</sub>O</sub> = free water clearance**

**Quantifying renal urine concentration and dilution:  
„Free water“ and osmolar clearance**

Osmolar clearance ( $C_{\text{osm}}$ ): *this is the volume of plasma cleared of solutes each minute.*

$P_{\text{osm}}$  = plasma osmolarity, 300 mOsm/L

$U_{\text{osm}}$  = urine osmolarity, 600 mOsm/L

$V$  = urine flow, 1 ml/min (0.001 L/min)

$$C_{\text{osm}} = \frac{U_{\text{osm}} \times V}{P_{\text{osm}}} = \frac{600 \times 0.001}{300} = \frac{0.6 \text{ mOsm/min}}{300 \text{ mOsm/L}} = 0.002 \text{ L/min (2 ml/min)}$$

*This means that 2 ml of plasma are being cleared of solute each minute*

Free-water clearance ( $C_{\text{H}_2\text{O}}$ ): is calculated as the difference between urine flow and  $C_{\text{osm}}$

$$C_{\text{H}_2\text{O}} = V - C_{\text{osm}} = V - \frac{U_{\text{osm}} \times V}{P_{\text{osm}}}$$

$$C_{\text{H}_2\text{O}} = 1 \text{ ml/min} - 2 \text{ ml/min} = -1 \text{ ml/min}$$

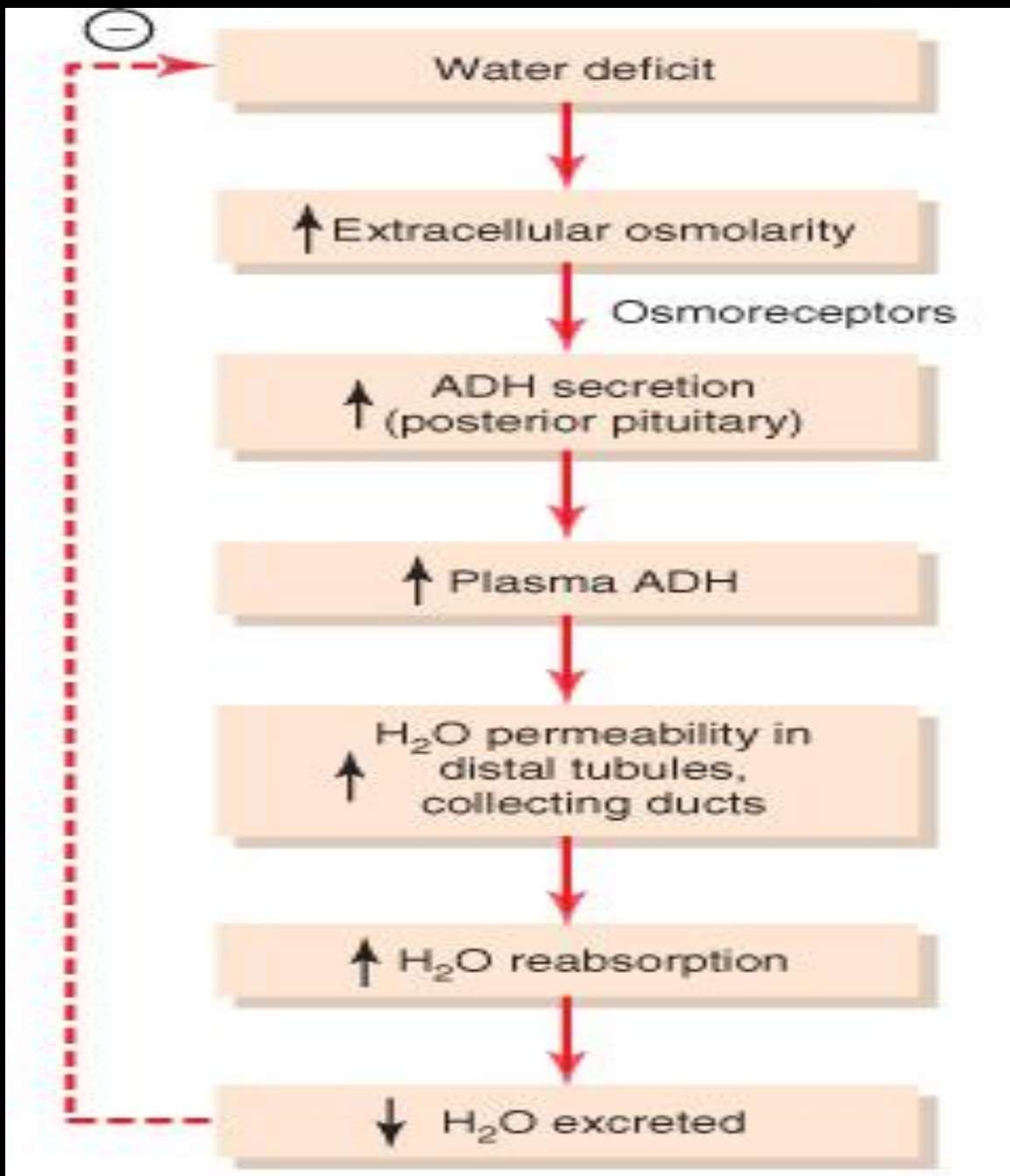
*When  $C_{\text{H}_2\text{O}}$  is positive, excess water is being excreted by the kidneys, when  $C_{\text{H}_2\text{O}}$  is negative excess solutes, are being removed from the plasma by the kidneys and water is being conserved.*

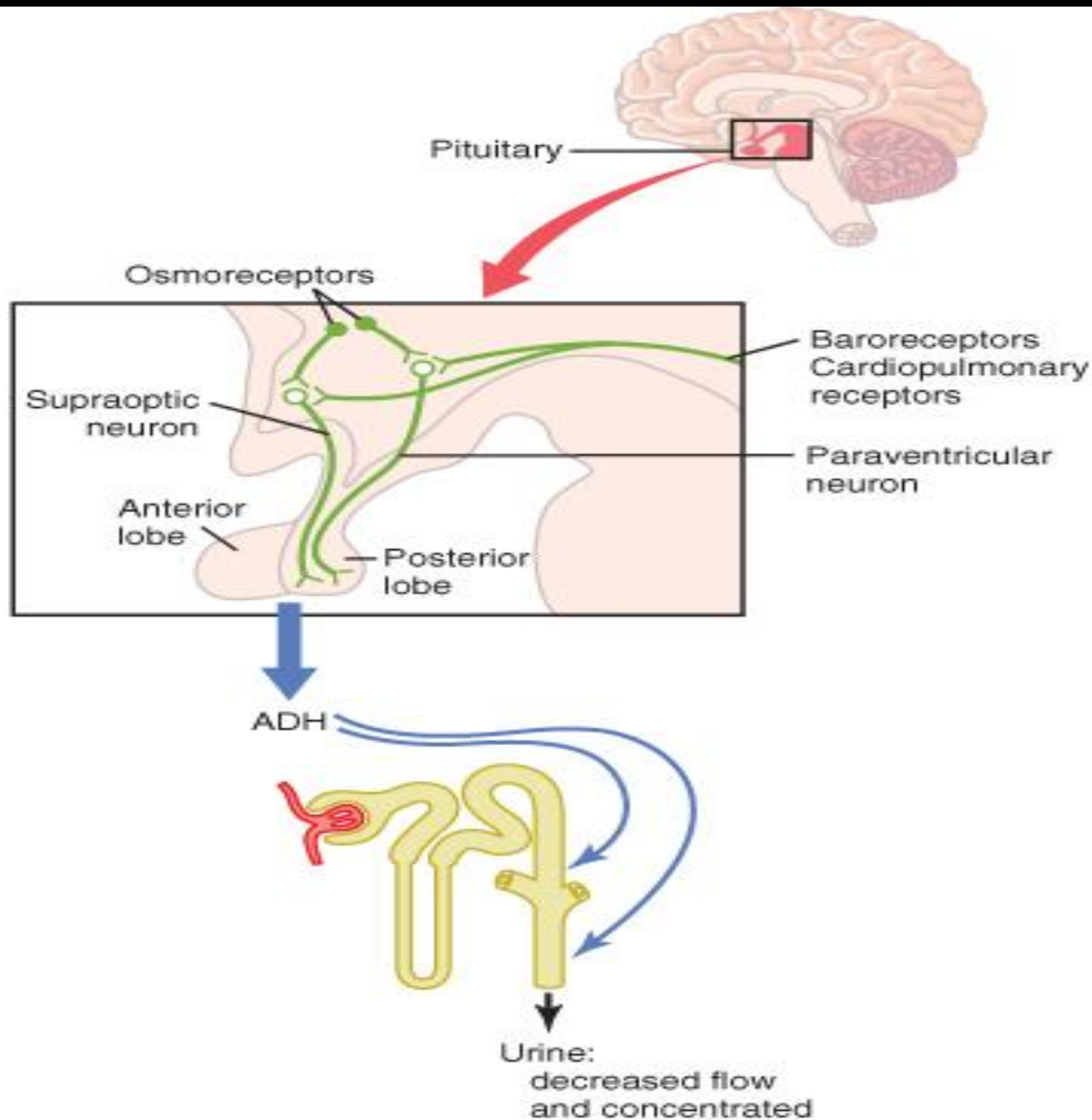
***Thus, whenever urine osmolarity is greater than plasma osmolarity, free-water clearance is negative, indicating water conservation***

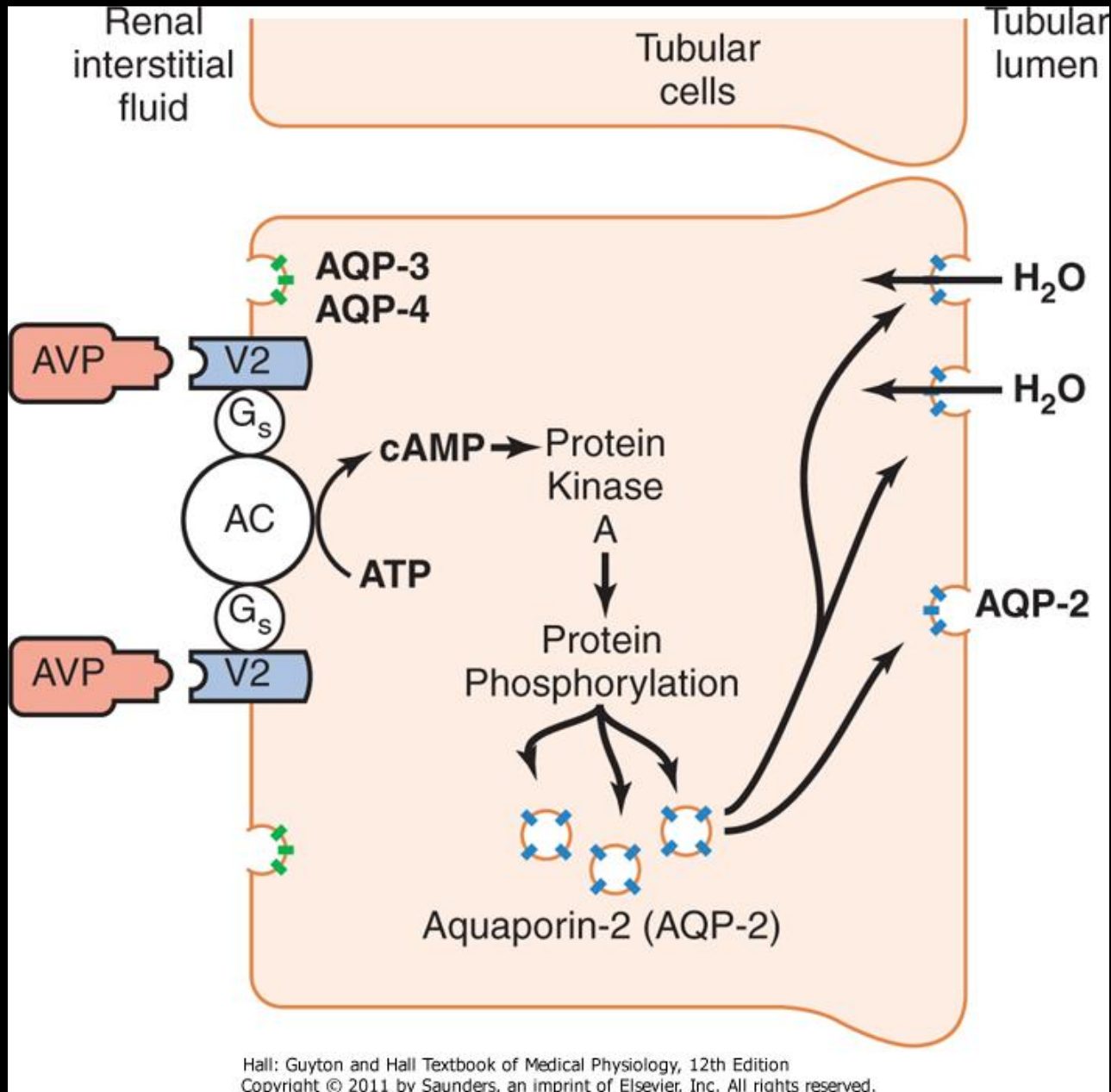
## **Estimating plasma osmolarity from plasma sodium concentration**

$$\mathbf{P_{osm} = 2.1 \times \text{Plasma sodium concentration}}$$

**Sodium ions and associated anions (bicarbonate and chloride) represents 94 % of the ECFV solutes. Glucose and urea contribute about 3 – 5 %.**

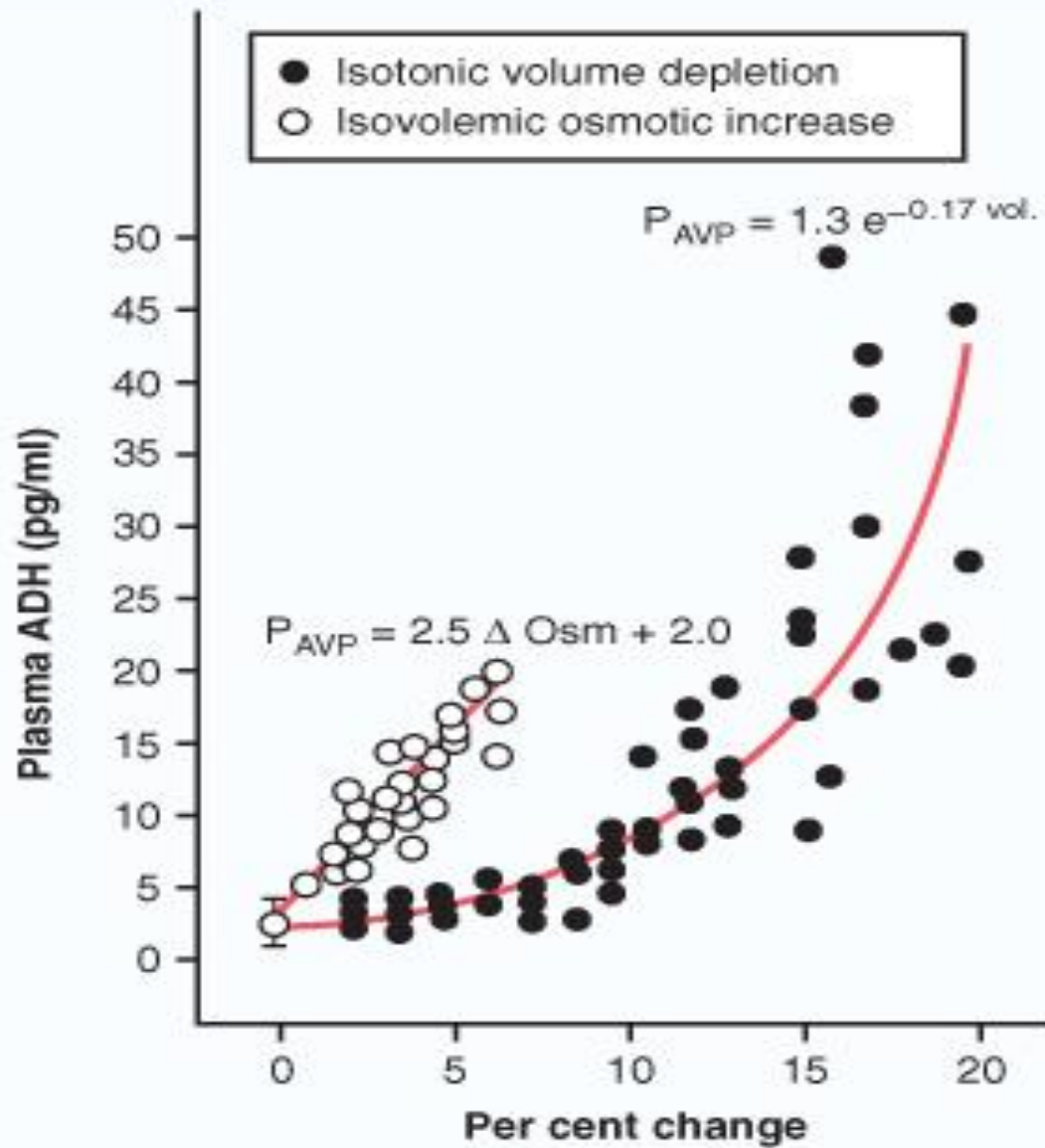


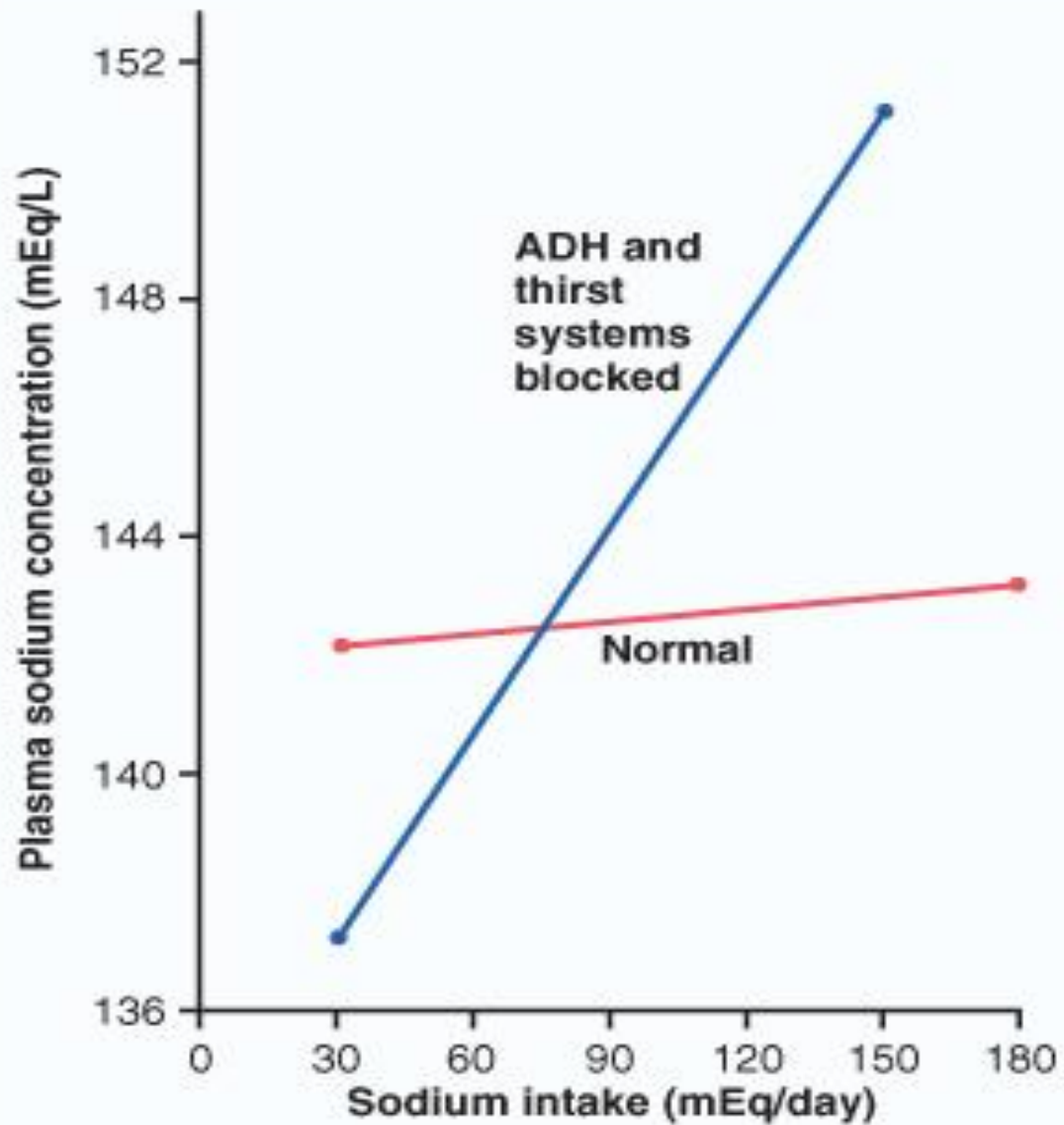


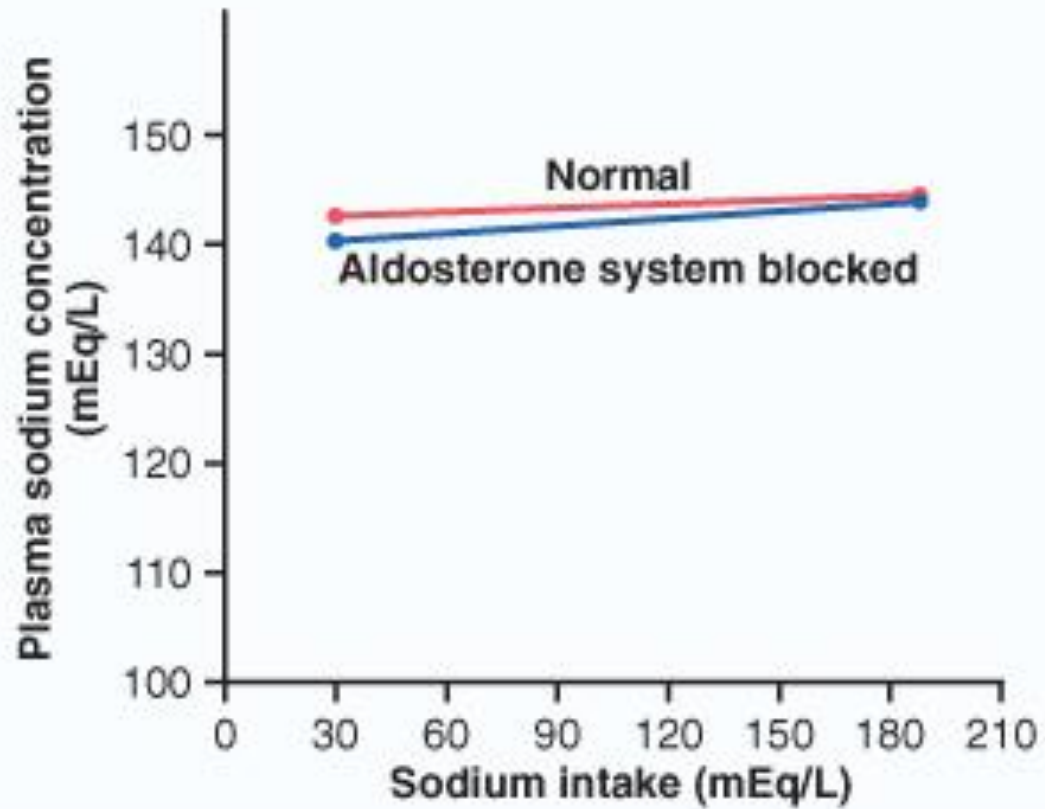


Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition  
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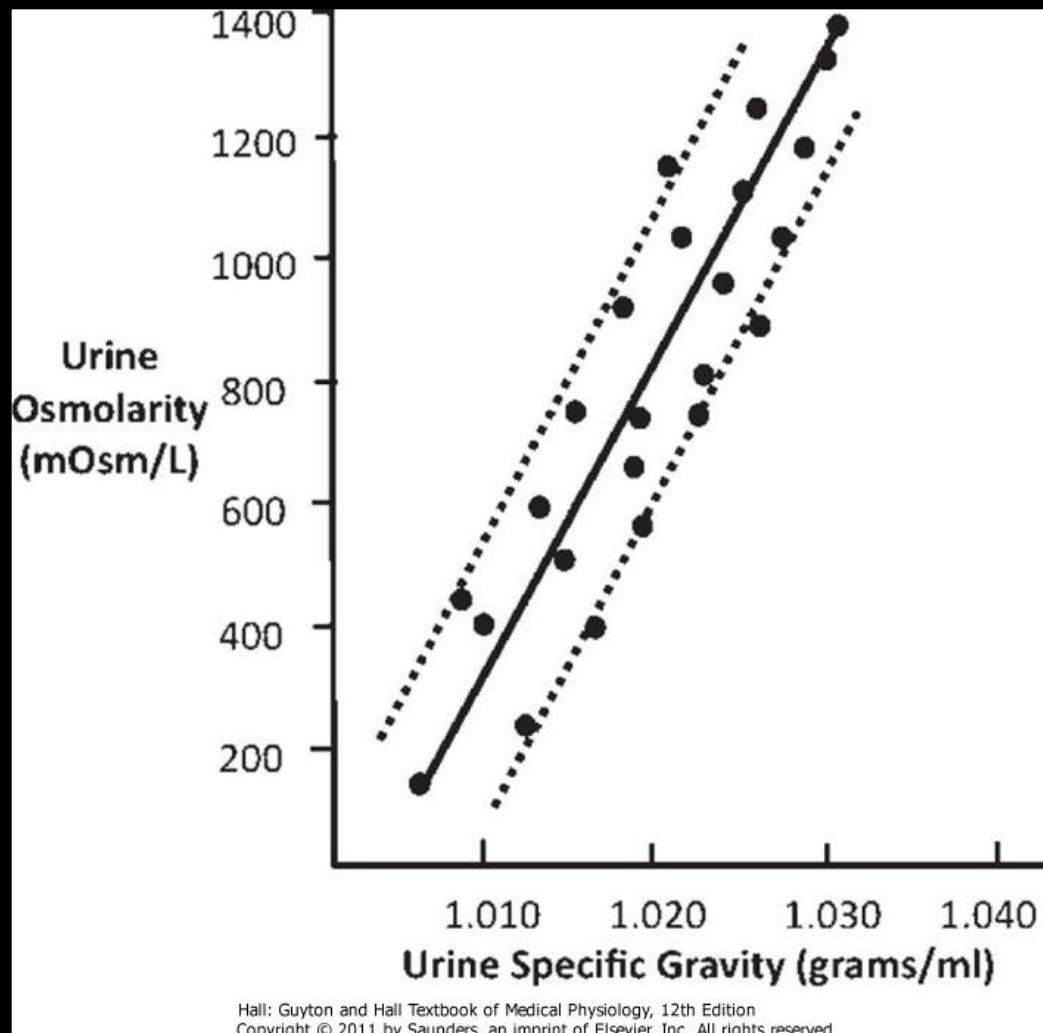








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Urine specific gravity is a measure of the weight of solutes in a given volume of urine. Therefore, it is determined by the **number** and **size** of the solute molecules. In contrast, osmolarity is determined only by the **number** of solute in a given volume. Therefore, when there are significant amounts of large molecules in the urine (such as glucose), urine specific gravity may falsely suggest a very concentrated urine, despite a normal osmolarity.

**Almond CSD et al. Hyponatremia among runners in the Boston marathon.  
*N Engl J Med* 325: 1550-1556, 2005.**

**Valtin H. „Drink at least eight glasses of water a day.“ Really? Is there scientific  
Evidence for „8 x 8“?  
*Am J Physiol* 283: R993-R1004, 2002.**

# Renal Control of Acid-Base Balance

# Acids and Bases – their definitions and meanings

Molecules containing hydrogen atoms that can release hydrogen ions in solutions are referred to as **acids**. (HCl – H<sup>+</sup> Cl<sup>-</sup>) (H<sub>2</sub>CO<sub>3</sub> → H<sup>+</sup> HCO<sub>3</sub><sup>-</sup>)

A **base** is an ion or a molecule that can accept a hydrogen ion. (HPO<sub>4</sub><sup>2-</sup> is base because it can accept hydrogen ion to form H<sub>2</sub>PO<sub>4</sub><sup>-</sup>)

The proteins in the body also as bases because some of the amino acids that make up proteins have negative charges that readily accept hydrogen ions.

**Alkalosis** refers to excess removal of hydrogen ions from the body fluids.

**Acidosis** refers to the excess addition of hydrogen ions in the body fluids.

A **strong acid** is one that rapidly dissociates and releases large amounts of H<sup>+</sup> in solution (HCl)

A **weak acid** have less tendency to dissociate its ions and, therefore release H<sup>+</sup> (H<sub>2</sub>CO<sub>3</sub>)

# Control of Acid-Base Balance

1. There must be a balance between the production of  $H^+$  and the net removal of  $H^+$  from the body.
2. Precise  $H^+$  regulation is essential because the activities of almost all enzyme systems in the body are influenced by  $H^+$  concentration.
3.  $Na^+ = 142 \text{ mmol/L}$ ,  $H^+ = 0.00004 \text{ mmol/L}$  (40 nmol/L)
4.  $pH = -\log [H^+] = -\log[0.00004] = 7.4$   
(The lower limit of pH at which a person can live more than a few hours is about 6.8 and the upper limit is about 8.0)
5. There are three primary systems that regulate the  $H^+$  concentration in body fluids to prevent acidosis:

**A/ Chemical acid-base buffer systems of the body fluids (seconds)**

**B/ Lungs (few minutes)**

**C/ Kidneys (hours to days)**



# Metabolic Sources of Acids and Bases

## A. Reactions producing CO<sub>2</sub> (Merely a Potential Acid)

1. Complete oxidation of neutral carbohydrates and fat  $\longrightarrow$  CO<sub>2</sub> + H<sub>2</sub>O
2. Oxidation of most neutral amino acids  $\longrightarrow$  Urea + CO<sub>2</sub> + H<sub>2</sub>O

## B. Reactions producing nonvolatile acids

1. Oxidation of sulfur-containing amino acids  $\longrightarrow$  Urea + CO<sub>2</sub> + H<sub>2</sub>O + H<sub>2</sub>SO<sub>4</sub>  $\longrightarrow$  2H<sup>+</sup> + SO<sub>4</sub><sup>2-</sup>  
(examples: methionine, cysteine)
2. Metabolism of phosphorous-containing compounds  $\longrightarrow$  H<sub>3</sub>PO<sub>4</sub>  $\longrightarrow$  H<sup>+</sup> + H<sub>2</sub>PO<sub>4</sub><sup>2-</sup>
3. Oxidation of cationic amino acids  $\longrightarrow$  Urea + CO<sub>2</sub> + H<sub>2</sub>O + H<sup>+</sup>  
(examples: lysine<sup>+</sup>, arginine<sup>+</sup>)
4. Production of nonmetabolizable organic acids  $\longrightarrow$  HA  $\longrightarrow$  H<sup>+</sup> + A<sup>-</sup>  
(examples: uric acid, oxalic acid)
5. Incomplete oxidation of carbohydrate and fat  $\longrightarrow$  HA  $\longrightarrow$  H<sup>+</sup> + A<sup>-</sup>  
(examples: lactic acid, ketoacidosis)

## C. Reactions producing nonvolatile bases

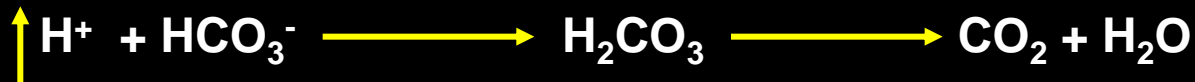
1. Oxidation of anionic amino acids  $\longrightarrow$  Urea + CO<sub>2</sub> + H<sub>2</sub>O + HCO<sub>3</sub><sup>-</sup>  
(examples: glutamate<sup>-</sup>, aspartate<sup>-</sup>)
2. Oxidation of organic anions  $\longrightarrow$  CO<sub>2</sub> + H<sub>2</sub>O + HCO<sub>3</sub><sup>-</sup>  
(examples: lactate<sup>-</sup>, acetate<sup>-</sup>)

# Buffering of Hydrogen Ions in the Body Fluids

Daily production of  $H^+$  = 80 mmol,  
Body fluid concentration = 0.00004 mmol/L

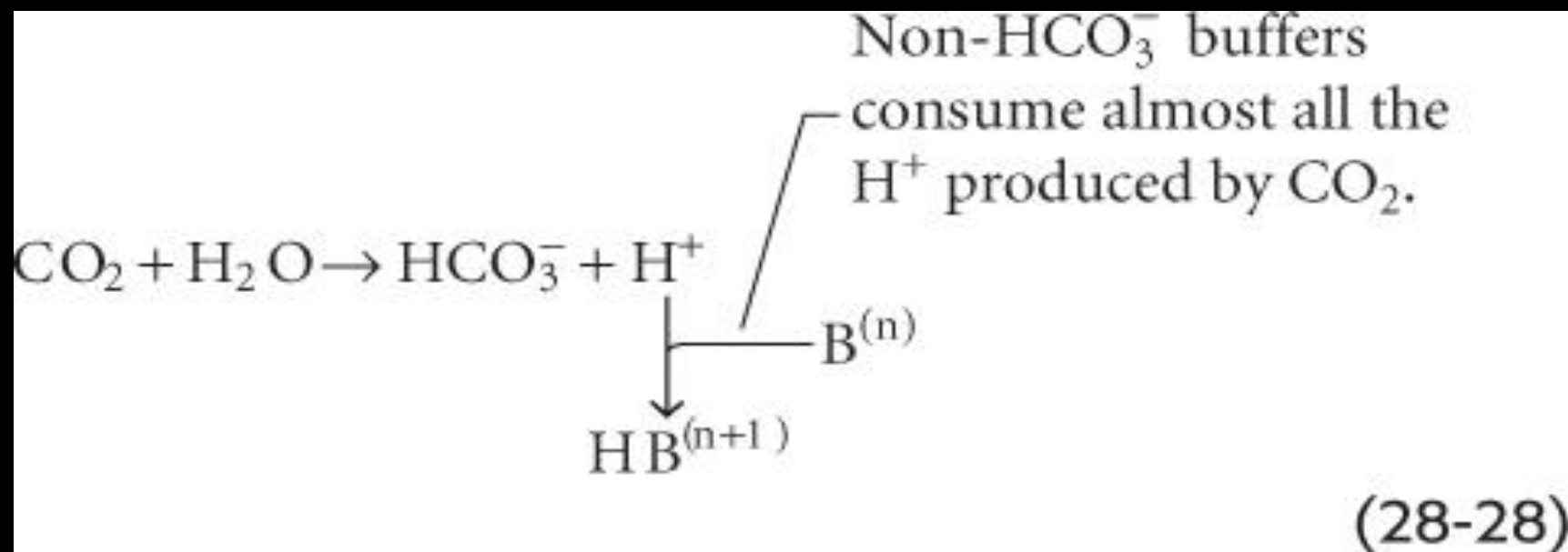


## Bicarbonate Buffer System



From these reactions, one can see that the hydrogen ions from the strong acid react with  $HCO_3^-$  to form the very weak acid ( $H_2CO_3$ ), which in turn forms  $CO_2$  and  $H_2O$ .  
The excess of  $CO_2$  stimulates respiration





## Henderson-Hasselbalch Equation:

$$\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{0.03 \times \text{pCO}_2}$$

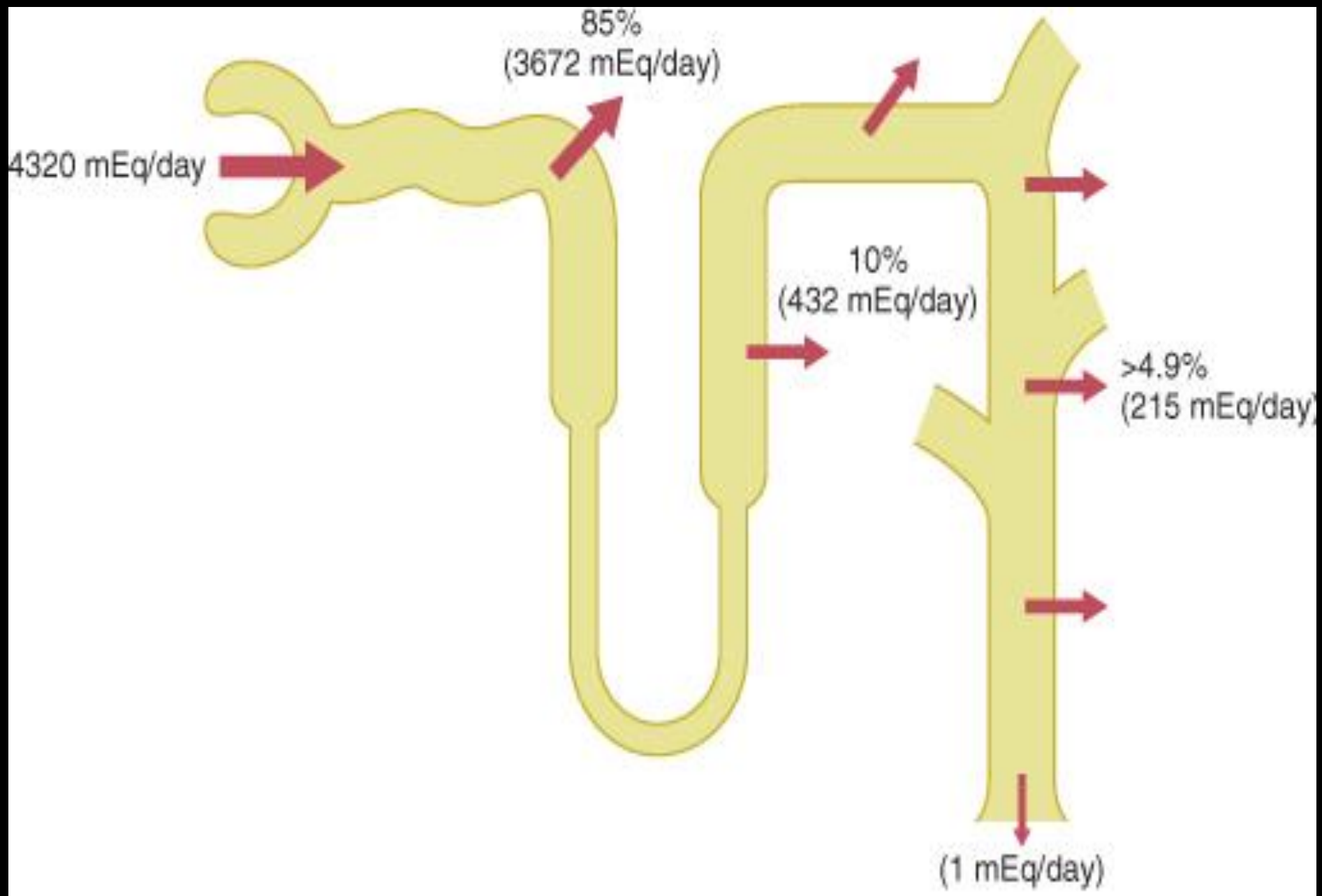
1. Increase in bicarbonate ion concentration causes the pH to rise.
  2. Increase in pCO<sub>2</sub> causes the pH to decrease.
- 
1. Bicarbonate concentration is regulated mainly by the kidneys.
  2. pCO<sub>2</sub> concentration is regulated by the rate of respiration.
- 
1. When disturbances of acid-base balance results from a primary changes in extracellular fluid **bicarbonate** concentrations are referred to as **metabolic** acid-base disorders.
  2. When disturbances of acid base balance results from a primary changes in **pCO<sub>2</sub>** are referred as **respiratory** acid-base disorders.

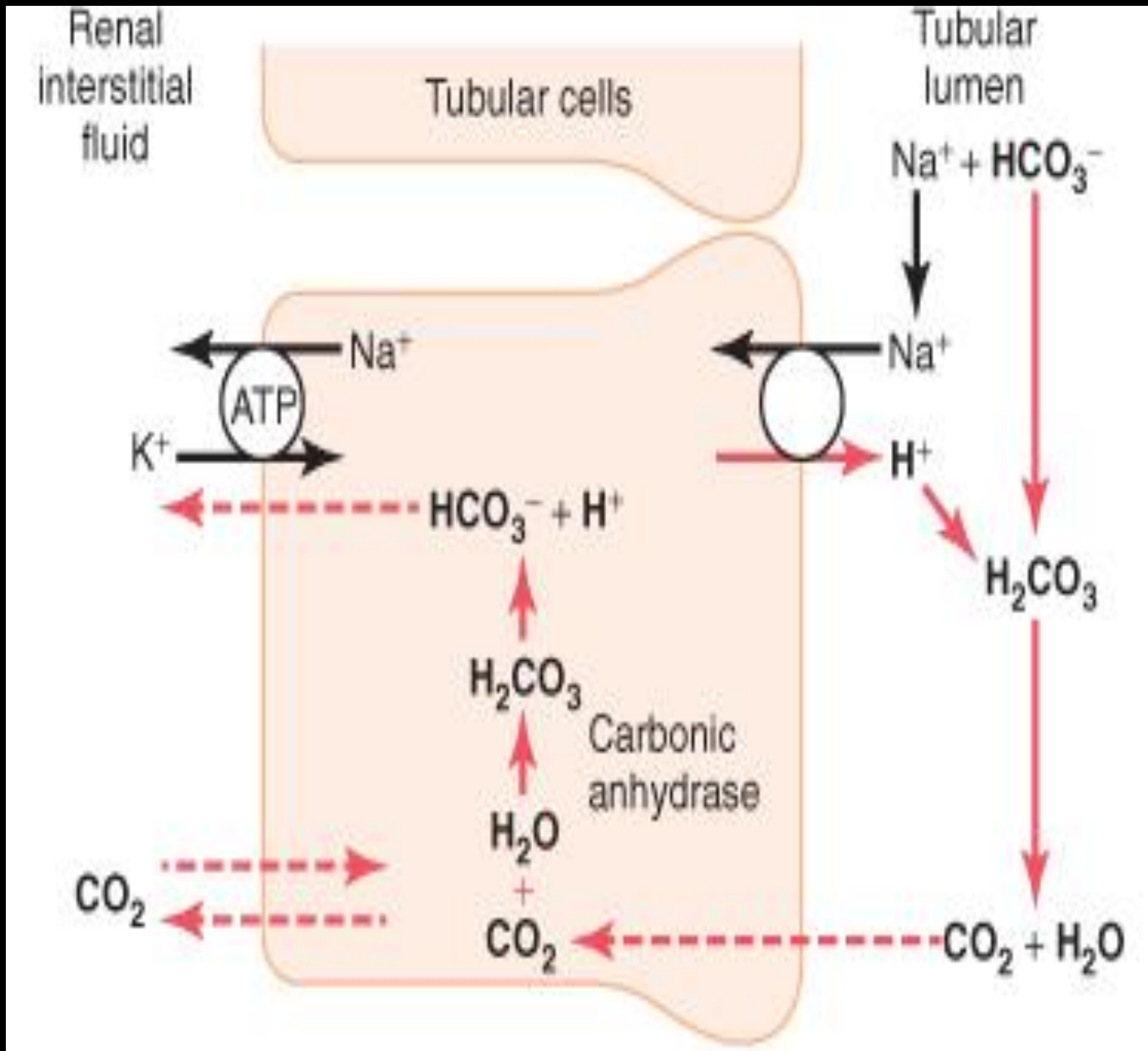
**The kidneys regulate extracellular fluid  $H^+$  concentrations through three fundamental mechanisms:**

- 1. Reabsorption of filtered  $HCO_3^-$**
- 2. Secretion of  $H^+$**
- 3. Production of new  $HCO_3^-$**

**Ad. 1.**

**$180 \text{ L/day} \times 24 \text{ mmol/L} = 4320 \text{ mmol of } HCO_3^-$**





Proximal tubule, thick ascending loop of Henle, early distal tubule



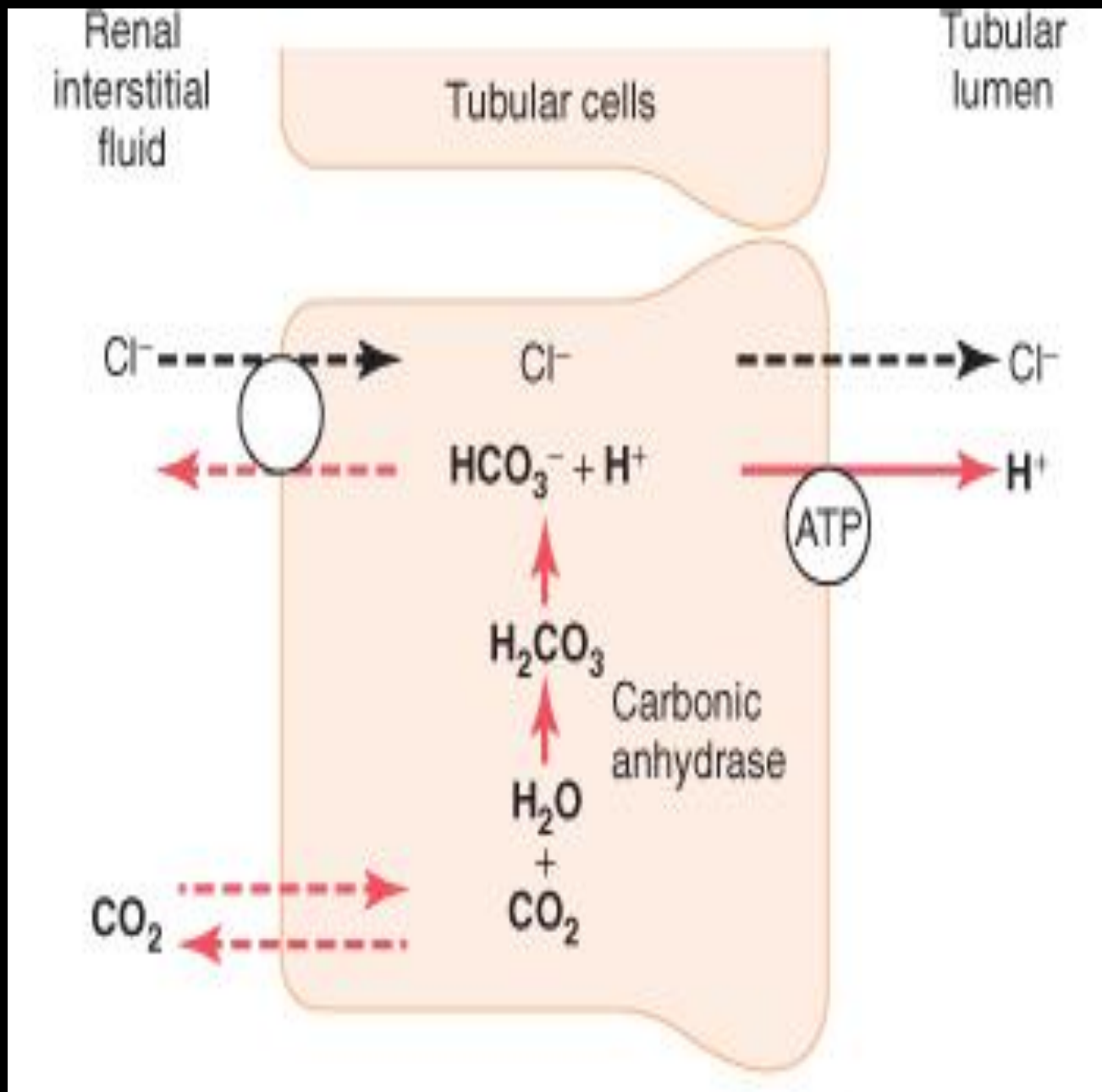
Thus, each time a hydrogen ion is formed in the tubular epithelial cells, a bicarbonate ion is also formed and released back into the blood. The net effect of these reactions is a „reabsorption“ of bicarbonate, although the bicarbonate ions that actually enter the extracellular fluid are not the same.

The transport of  $\text{HCO}_3^-$  accros the basolateral membrane is facilitated by:

1.  $\text{Na}^+\text{-HCO}_3^-$  co-transporter
2.  $\text{Cl}^-\text{-HCO}_3^-$  exchange

**Although the secretion of hydrogen ions in the late distal tubule and collecting duct accounts for only percent of the total hydrogen secreted, this mechanism is important in forming a maximally acidic urine.**

**In the proximal tubules, hydrogen ion concentration can increase only about threefold (compared to the filtered load), in the collecting tubule the hydrogen concentration can be increased as 900-fold.**

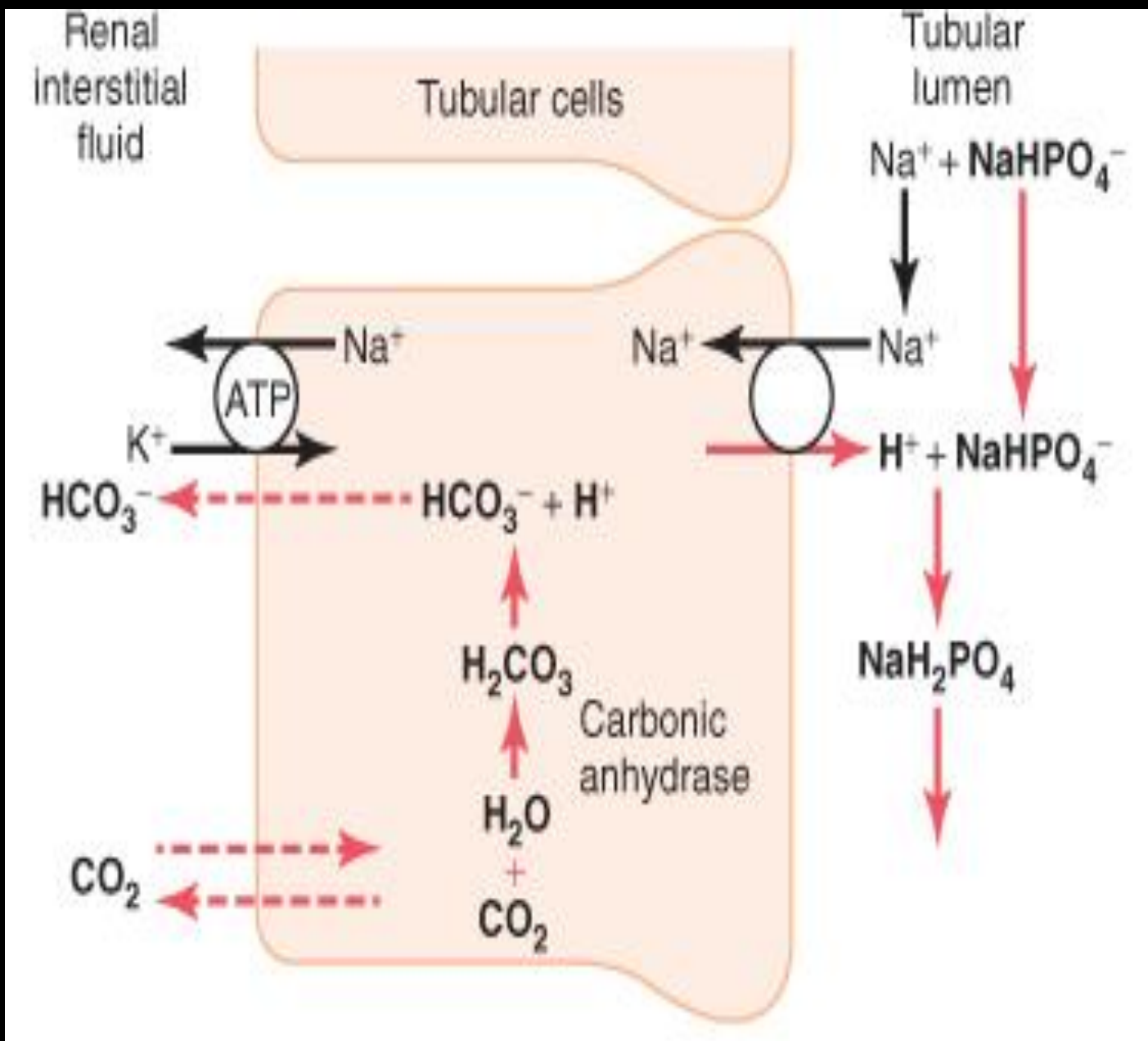


Late distal tubule and collecting tubules (intercalated cells)

## Phosphate and Ammonia Buffers

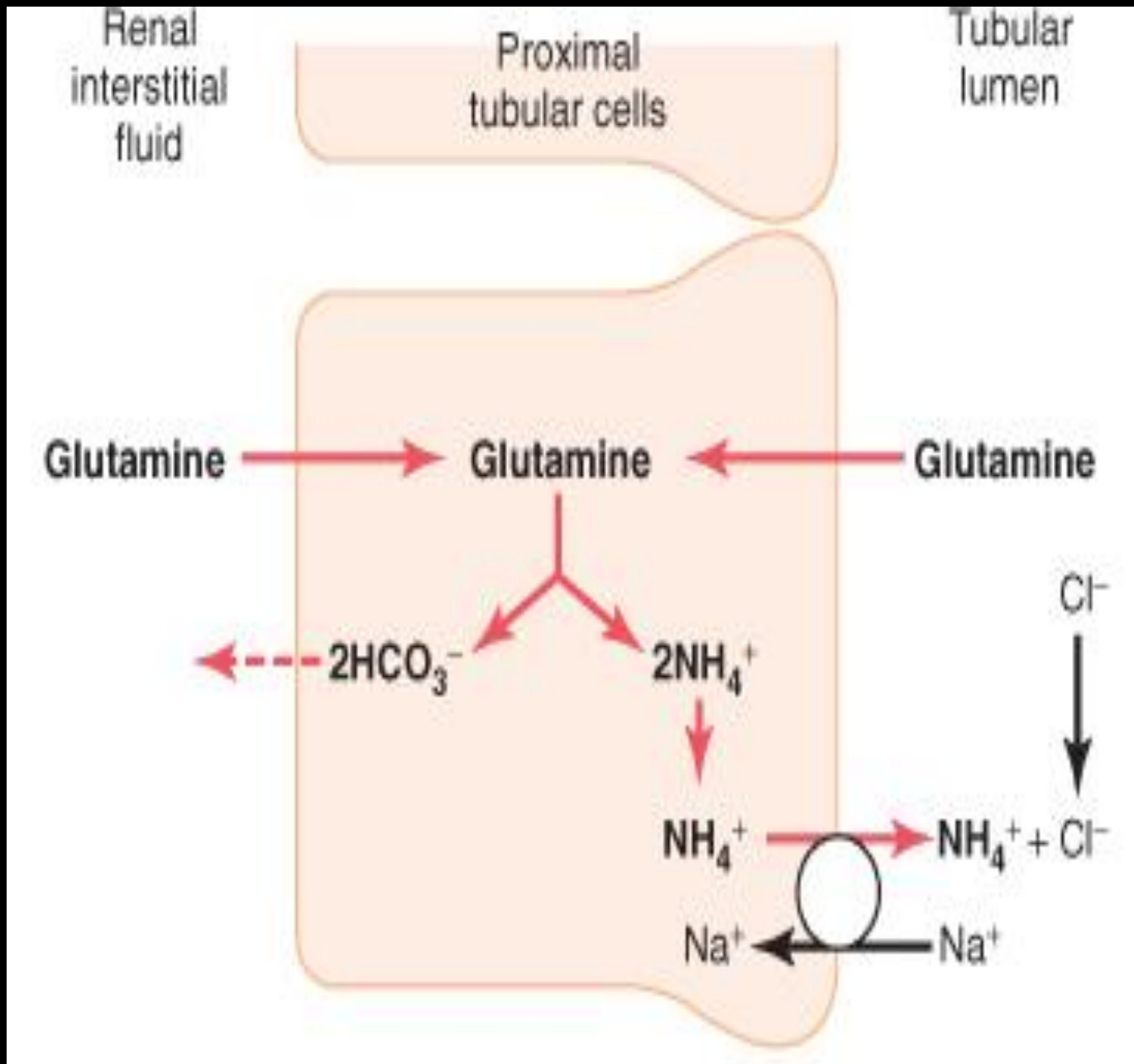
Minimal urine pH is 4.5, corresponding to an  $H^+$  concentration 0.03 mmol/L. In order, to excrete the 80 mmol of nonvolatile acid formed each day, about 2667 liters of urine would have to be excreted if the  $H^+$  remained free in solution.

500 mmol/day of  $H^+$  must be sometimes excreted.

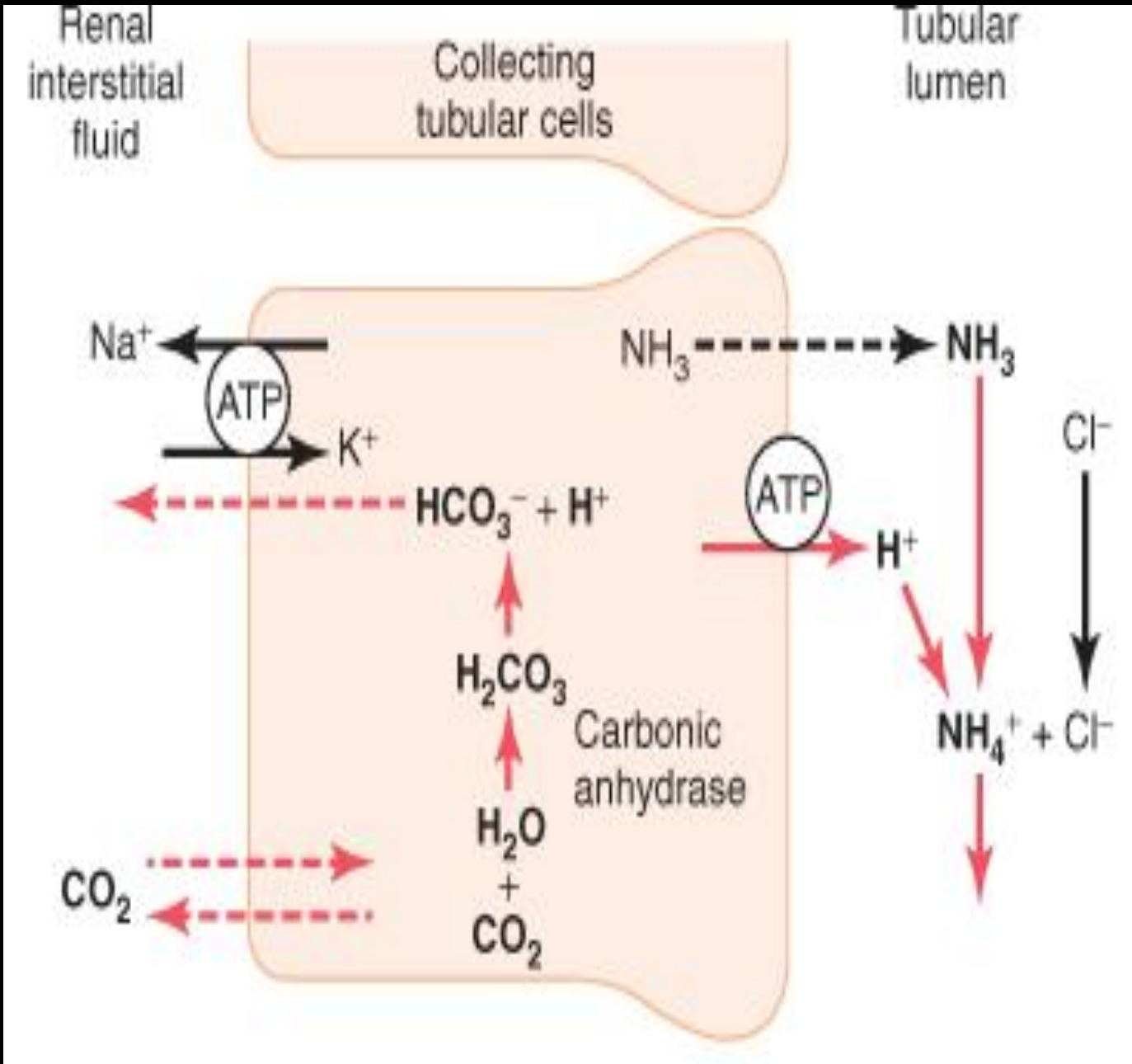


**Therefore, whenever an  $H^+$  secreted into the tubular lumen combines with a buffer other than,  $HCO_3^-$  the net effect is addition of a new  $HCO_3^-$  to the blood.**

**A second buffer system in the tubular fluid that is even more important quantitatively than the phosphate buffer system is composed of ammonia ( $NH_3$ ) and the ammonium ion ( $NH_4^+$ ).**

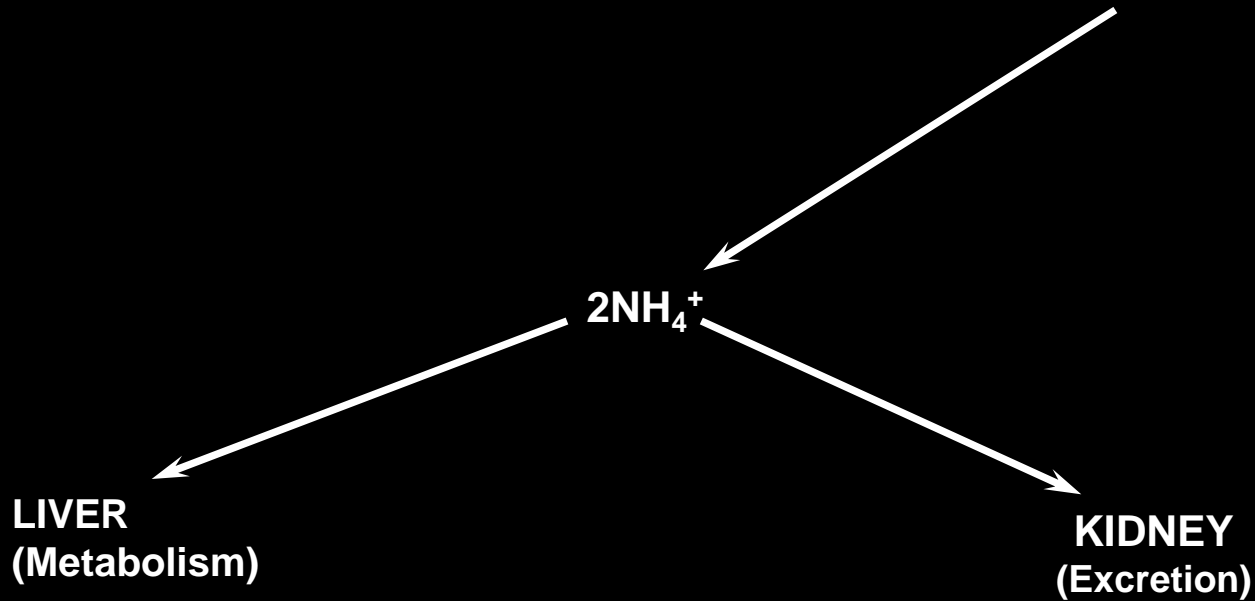


Proximal tubule, thick ascending limb of the loop of Henle, distal tubule



Collecting duct





Loss of  $2\text{HCO}_3^-$  by buffering of  $2\text{H}^+$

Save  $2\text{HCO}_3^-$  by excretion of  $2\text{NH}_4^+$

**Under conditions of chronic acidosis, the rate of  $\text{NH}_4^+$  excretion can increase to as much 500 mmol/day. Therefore, with chronic acidosis, the dominant mechanism by which acid is eliminated from the body is excretion of  $\text{NH}_4^+$ .**

## Quantifying Renal Acid-Base Excretion

**Net acid excretion =  $\text{NH}_4^+$  excretion + Urinary titratable acid – bicarbonate excretion**

Titratable acid represents the nonbicarbonate, non- $\text{NH}_4^+$  buffer excreted in the urine (phosphate and other organic buffers)

The most important stimuli for increasing  $\text{H}^+$  secretion by the tubules are:

1. An increase in  $\text{pCO}_2$  of extracellular fluid.
2. An in  $\text{H}^+$  concentration in extracellular fluid.

$$\mathbf{TK = SV \times PCR}$$

**TK = arteriální krevní tlak**

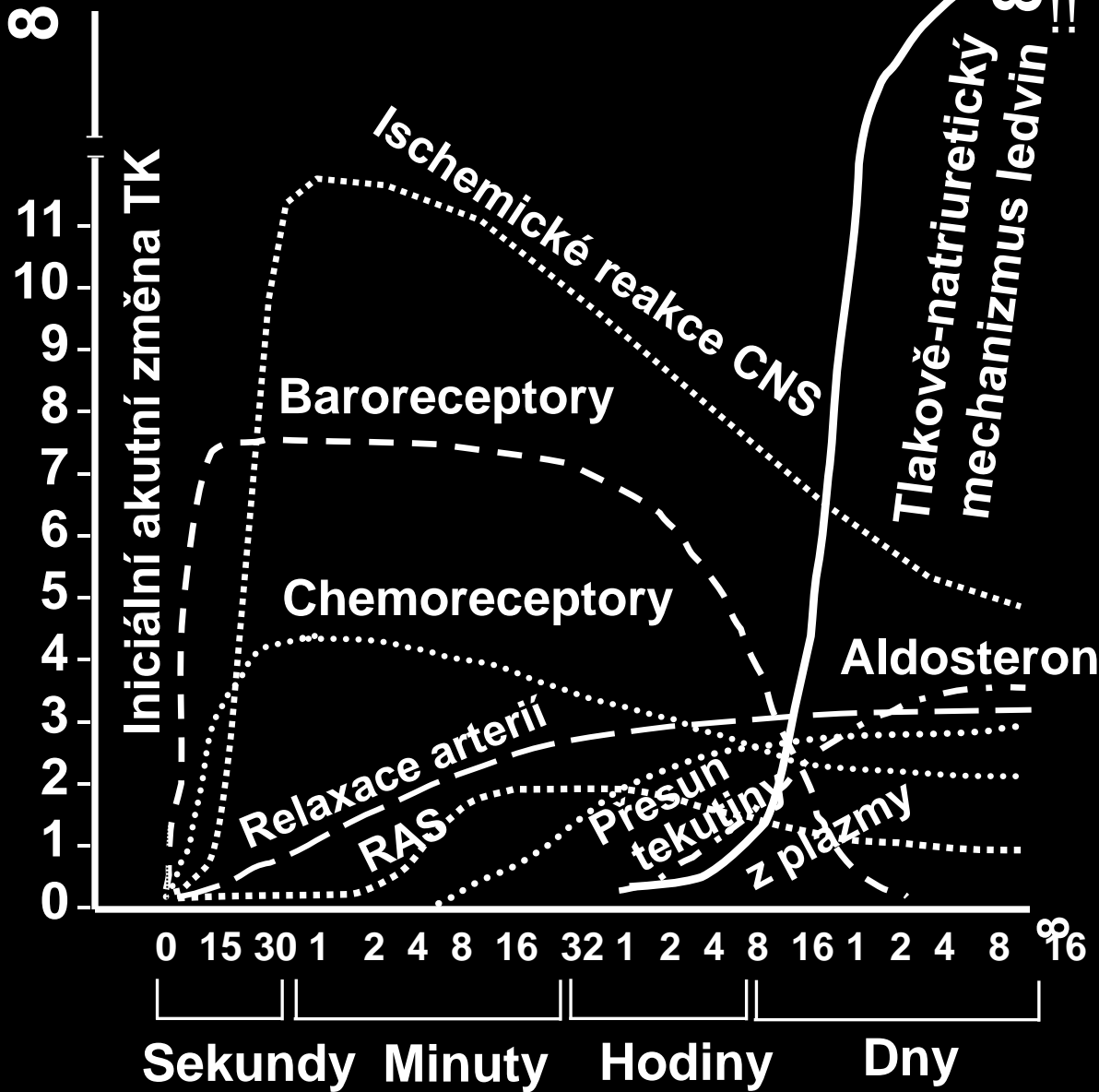
**SV = srdeční výdej**

**PCR = periferní cévní rezistence**

# Akutní mechanizmy regulace krevního tlaku

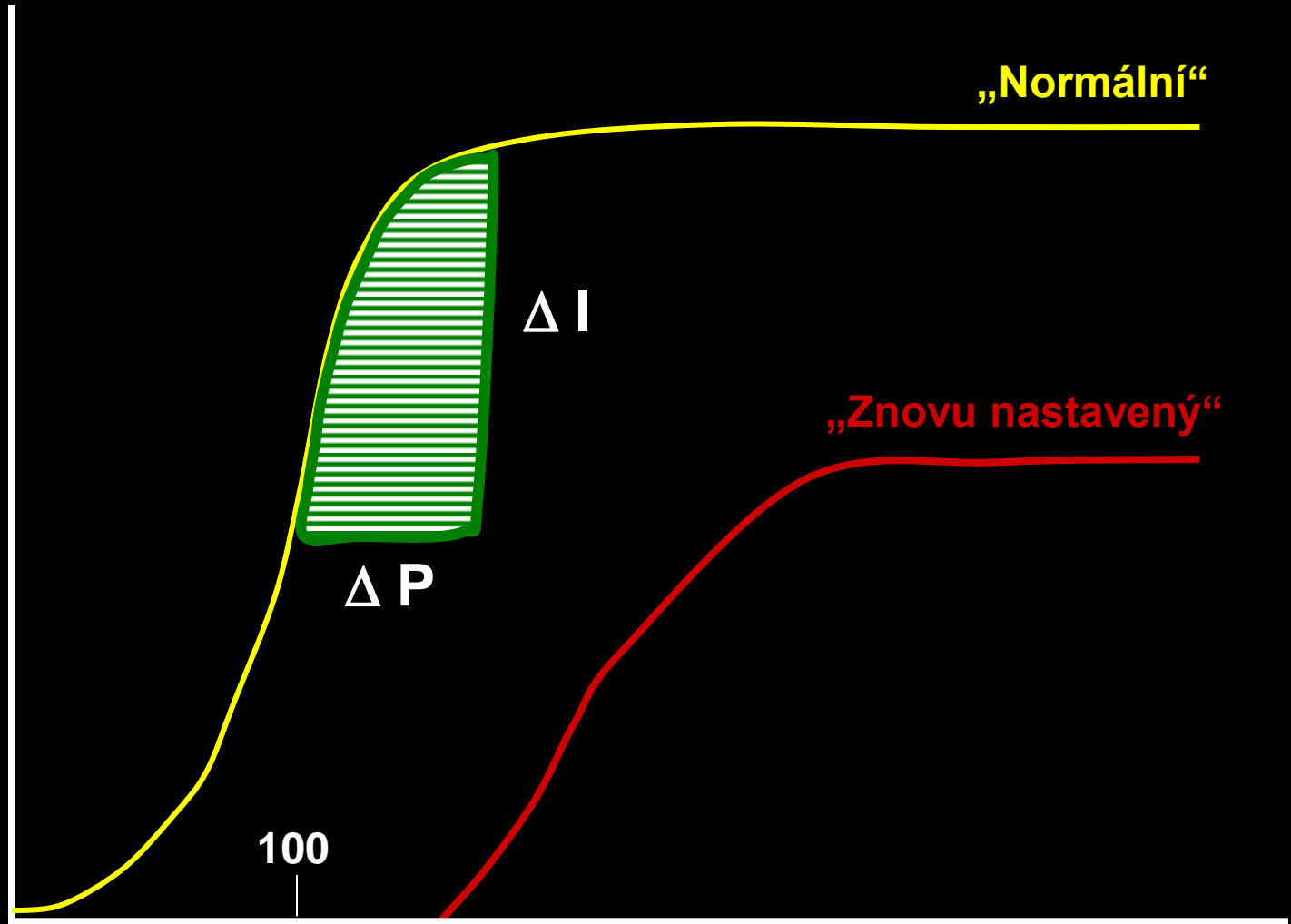
- 1. Arteriální baroreflex**
- 2. Arteriální chemoreceptory**
- 3. Bainbridgeův reflex**
- 4. Ischemické receptory CNS**

Síla zpětnovazebního mechanismu

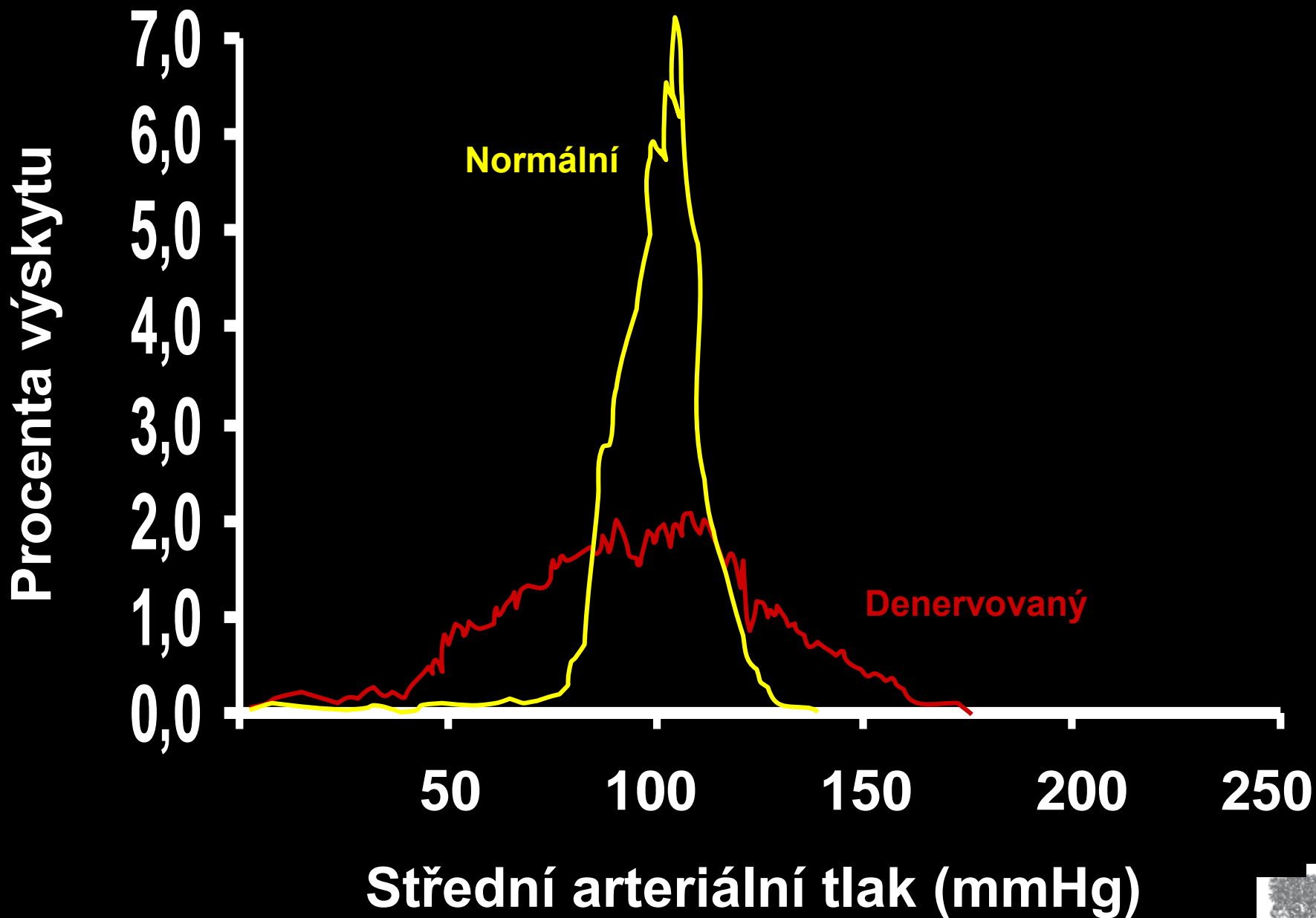


Čas po náhlé změně TK

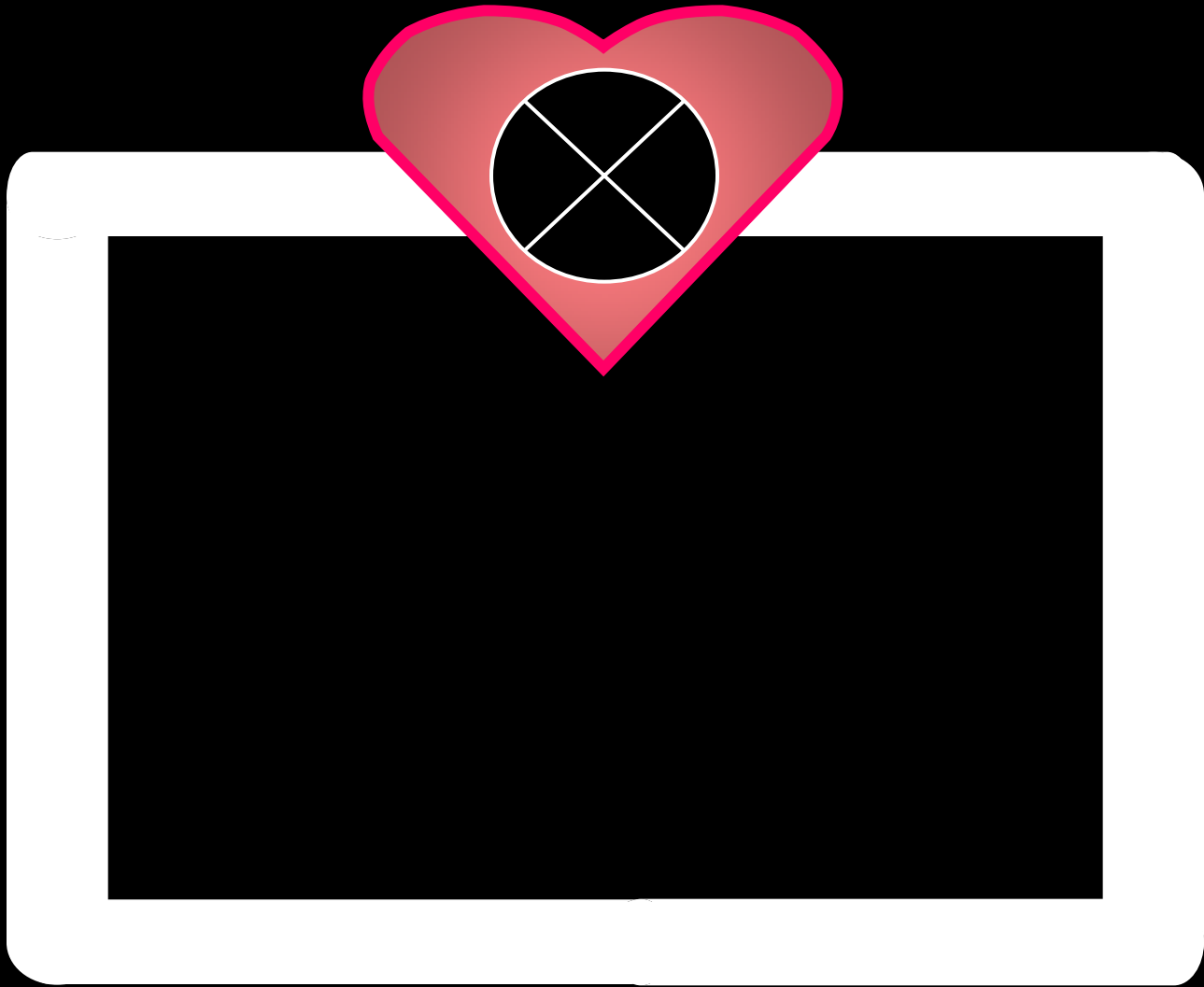
Počet impulzů (impulz/sek)

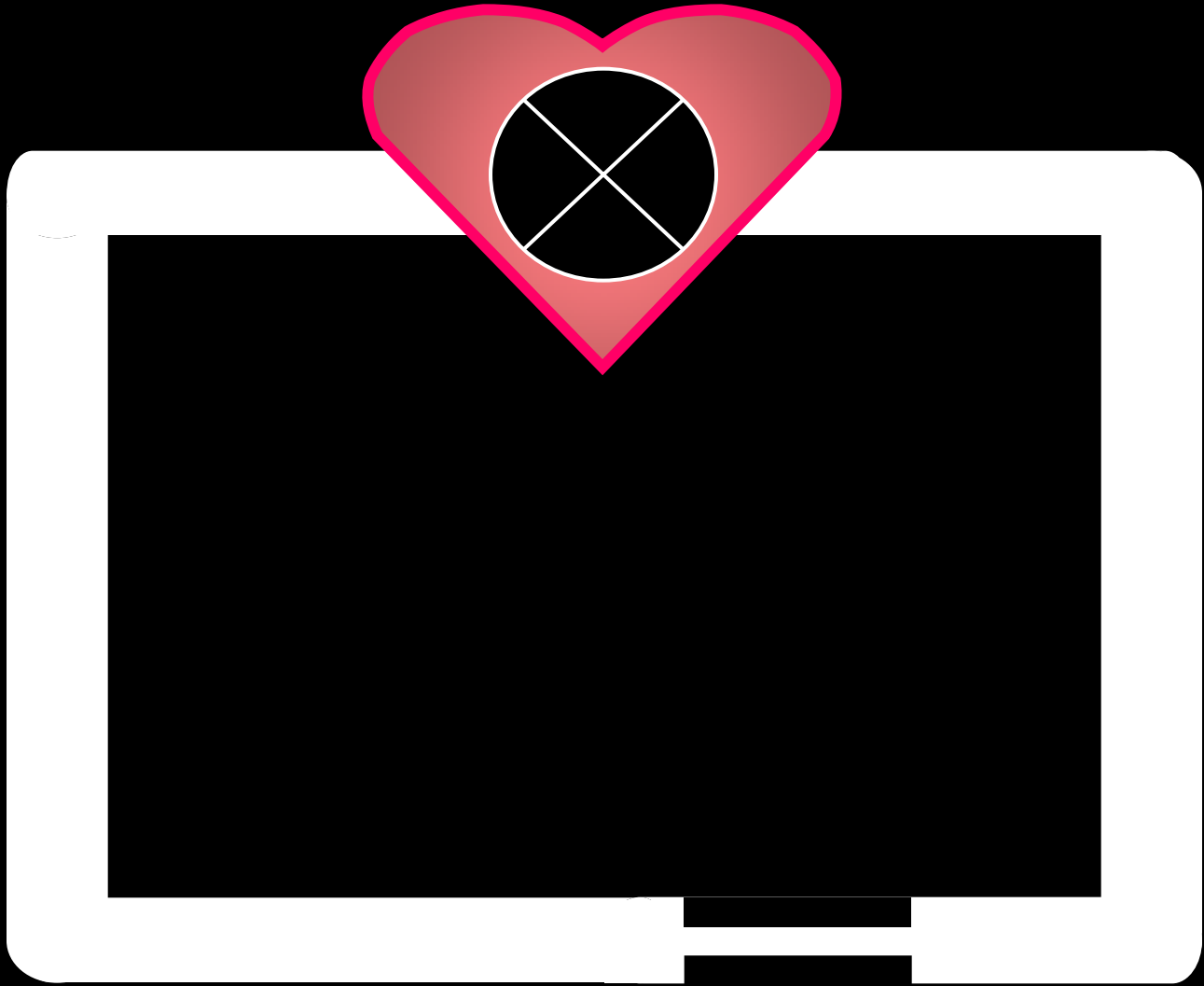


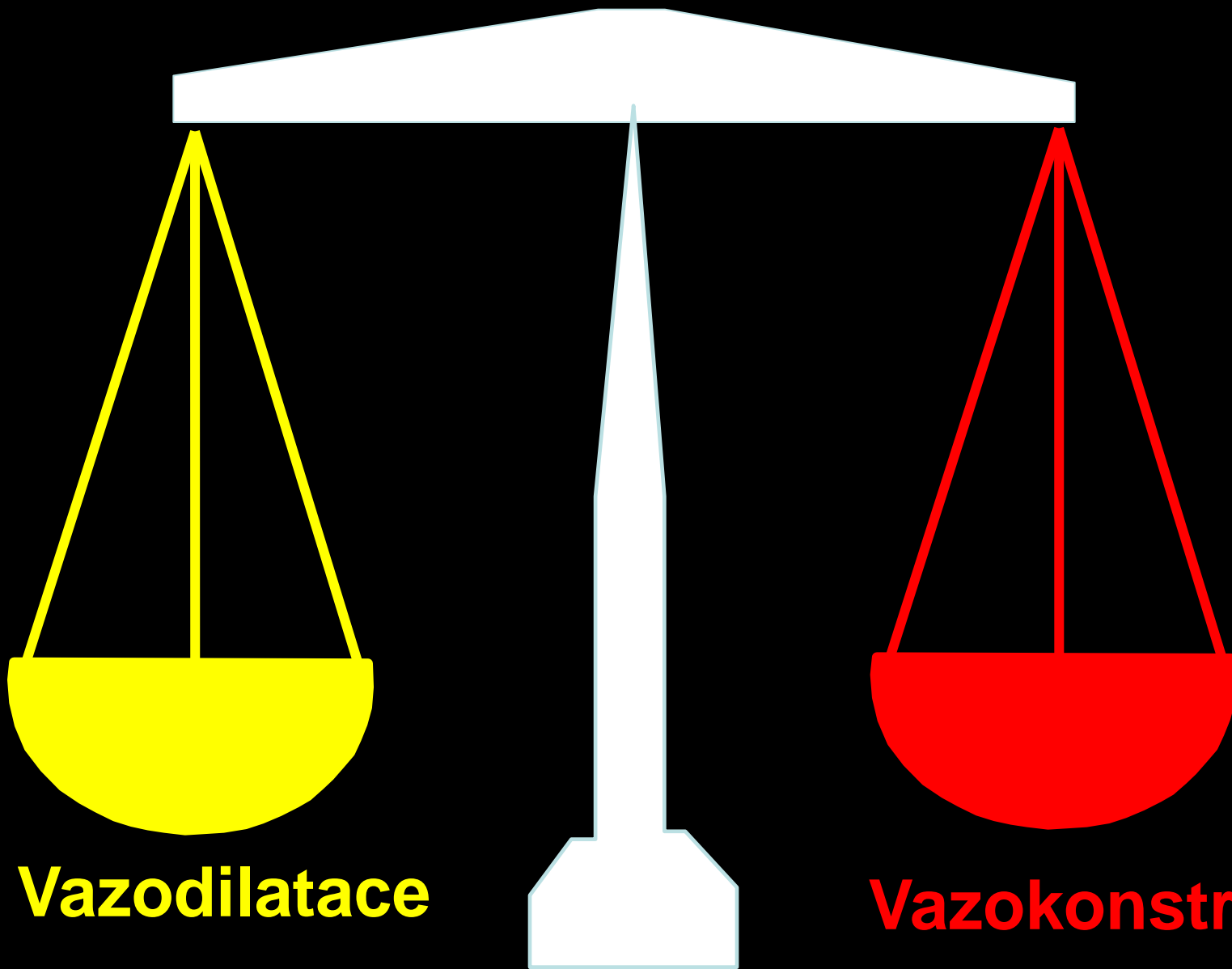
Arteriální tlak (mmHg)











**Vazodilatace**

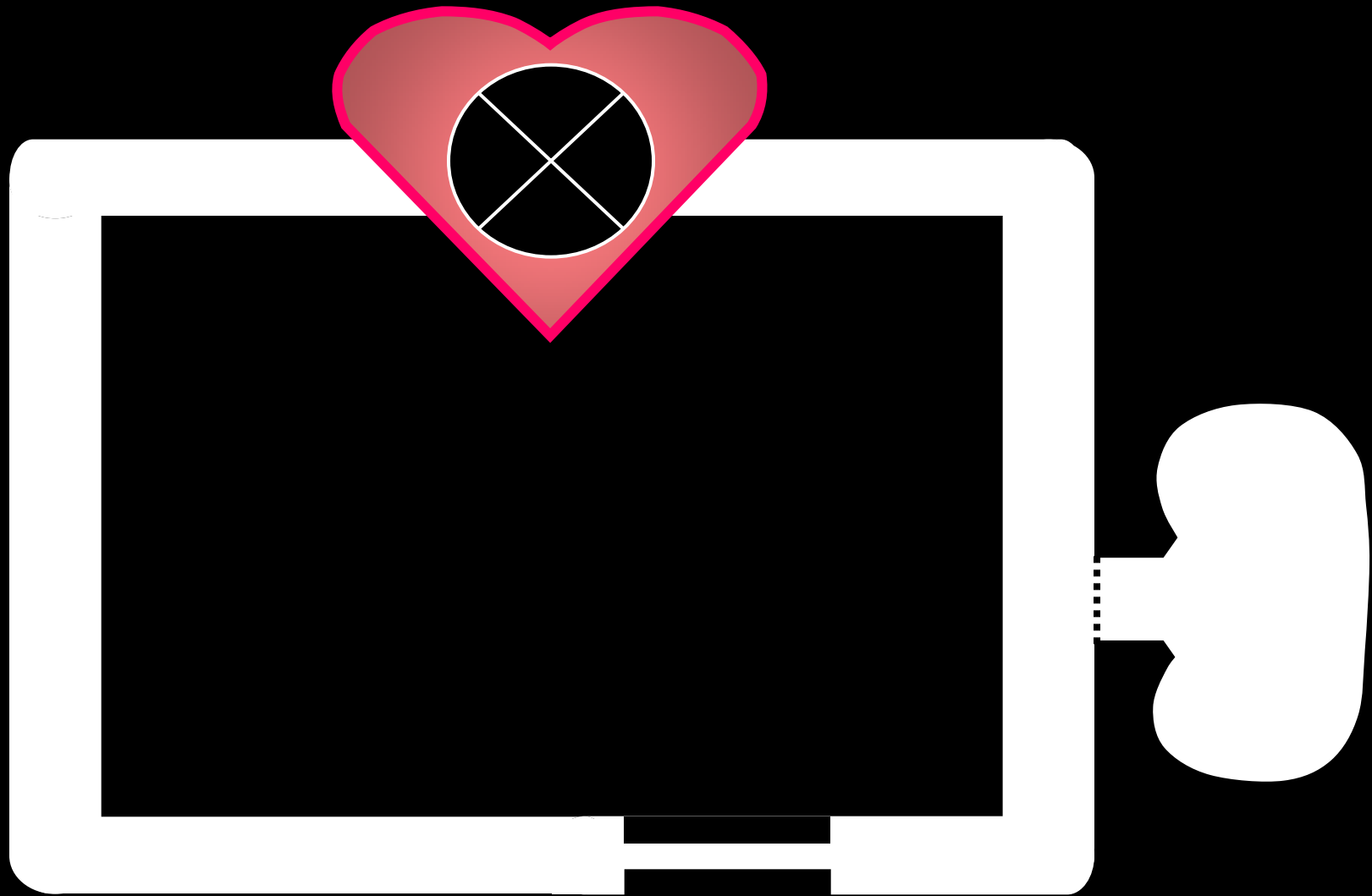
**Vazokonstrikce**

**“The first slide of the lecturer, who was an intrepid young cardiovascular physiologist, was Figure 1 from Guyton and Coleman’s epic paper. It was clear that the audience was already becoming nervous. There was some whispering, shuffling, and a sense of unease.**

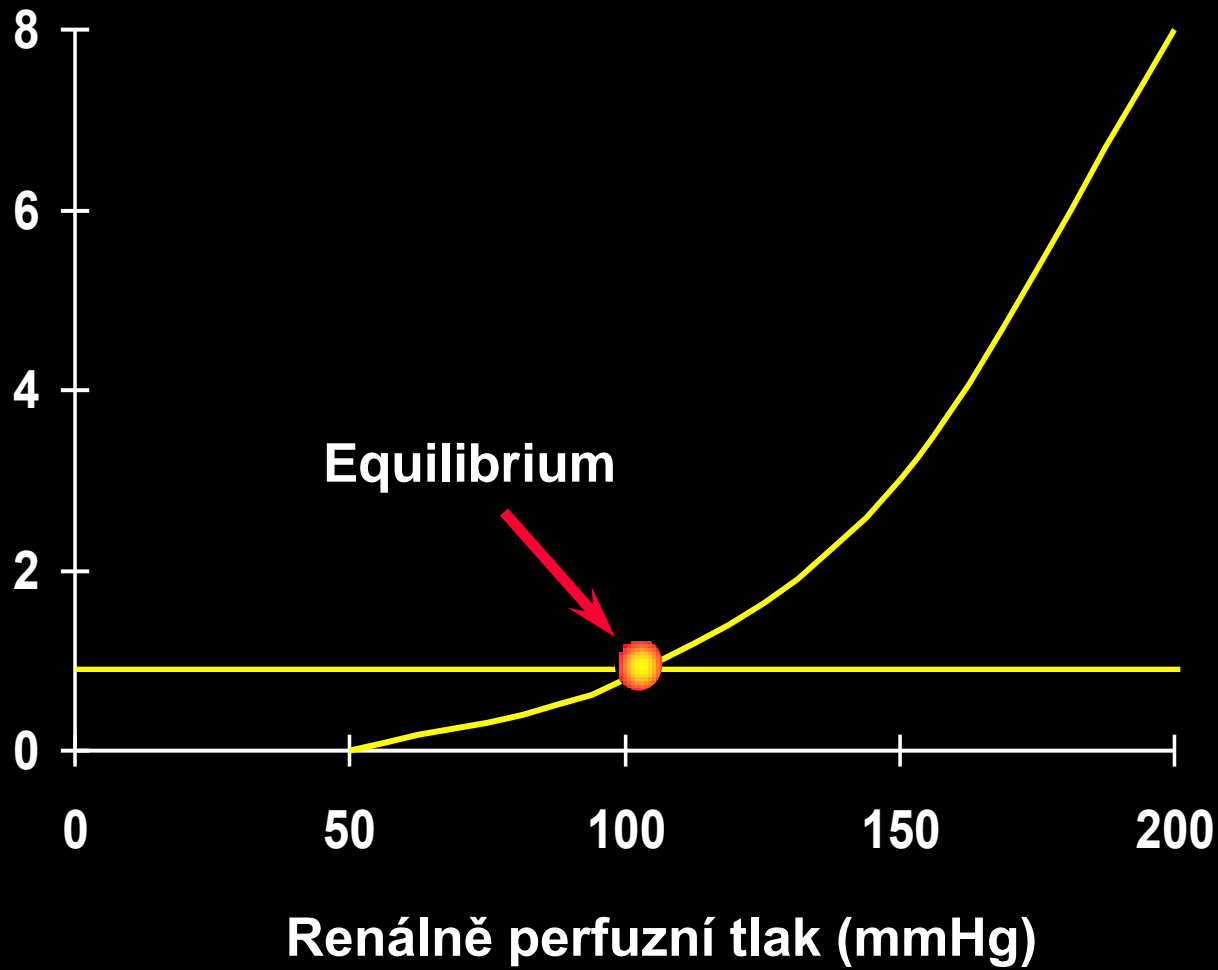
**The lecturer’s second slide was met with a more definite response. There was derision, laughter, and spontaneous comments from the audience.....  
I witnessed, for the only time in my academic life,  
a lecturer being chased from the podium by the audience”**

**Christopher S. Wilcox**

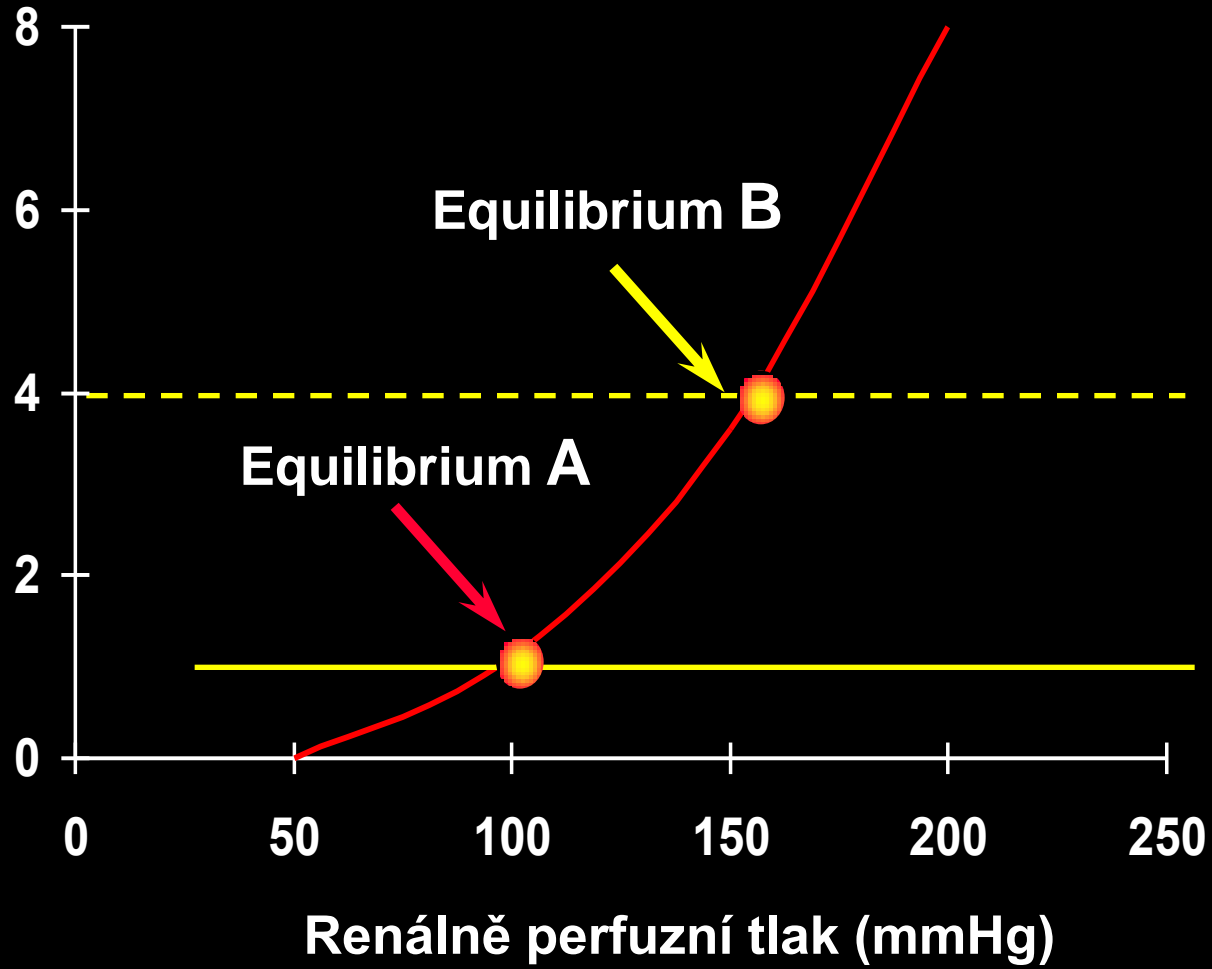




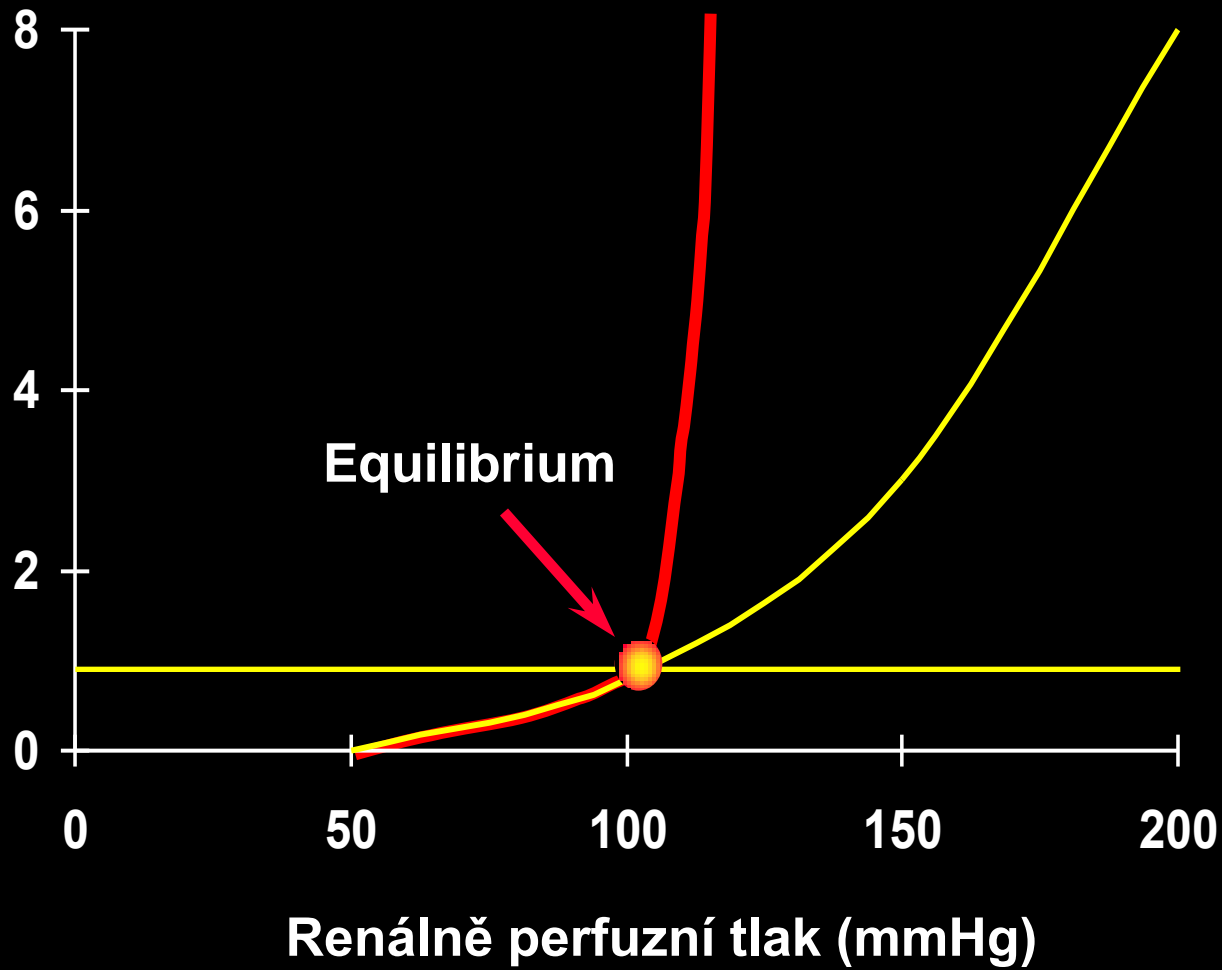
Příjem nebo vylučování sodíku  
(x normálu)



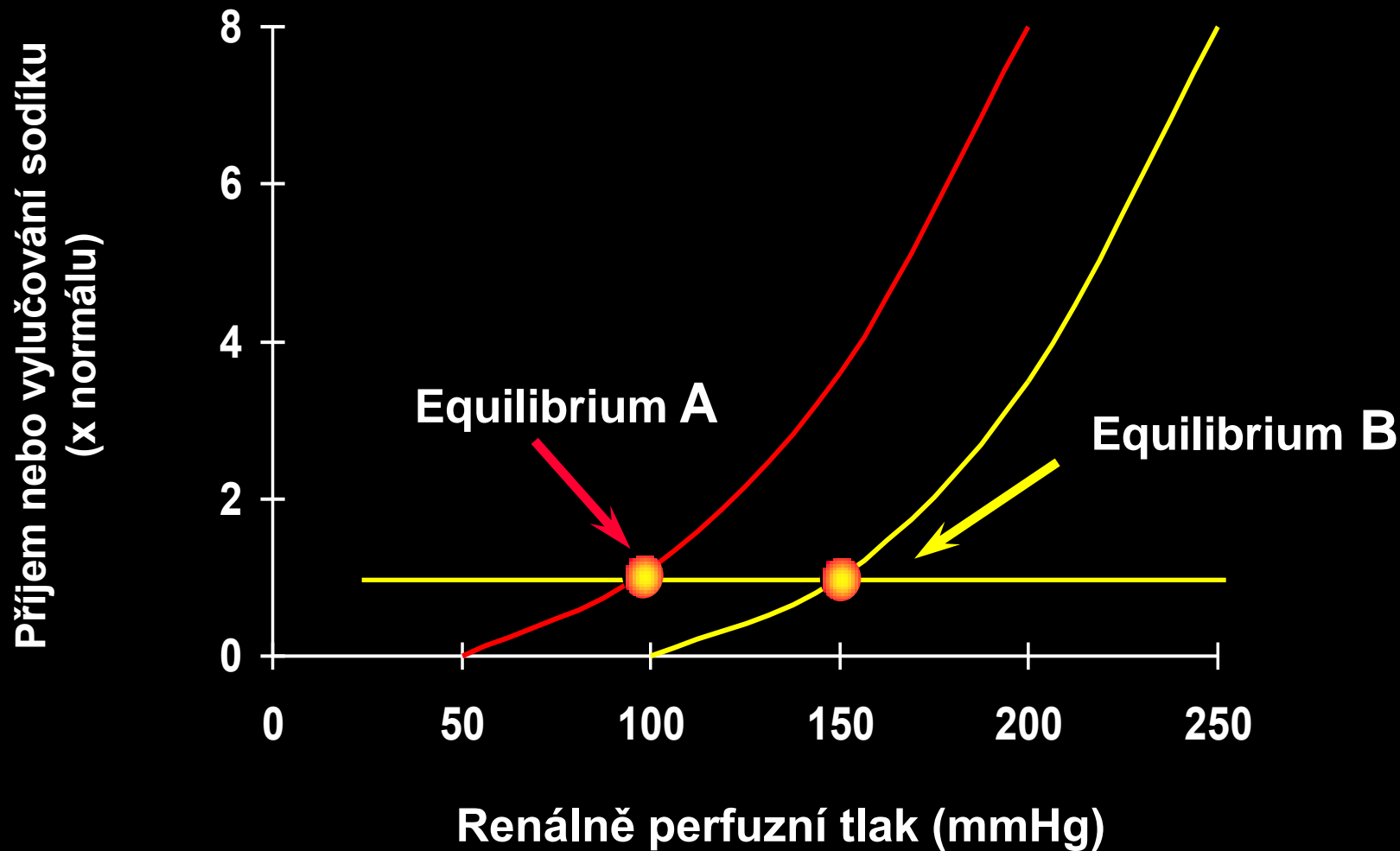
Příjem nebo vylučování sodíku  
(x normálu)



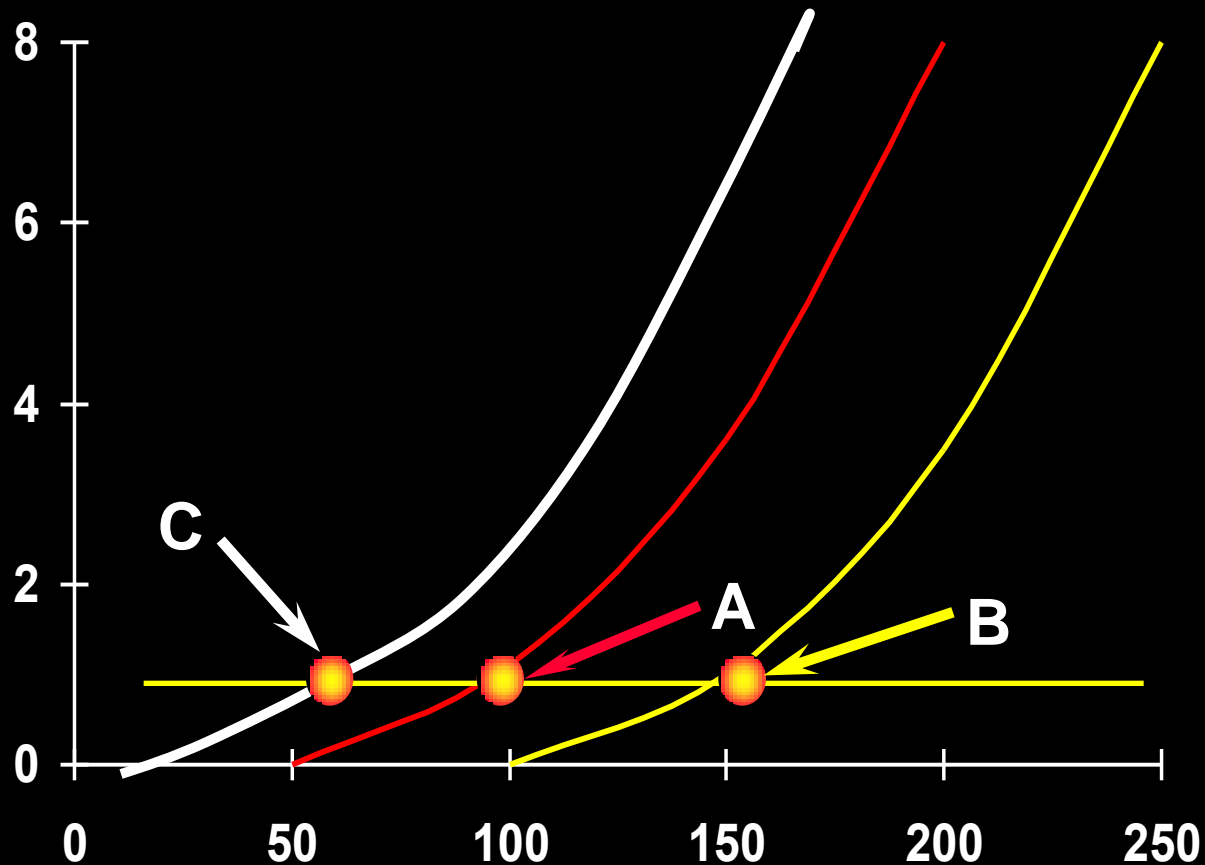
Příjem nebo vylučování sodíku  
(x normálu)



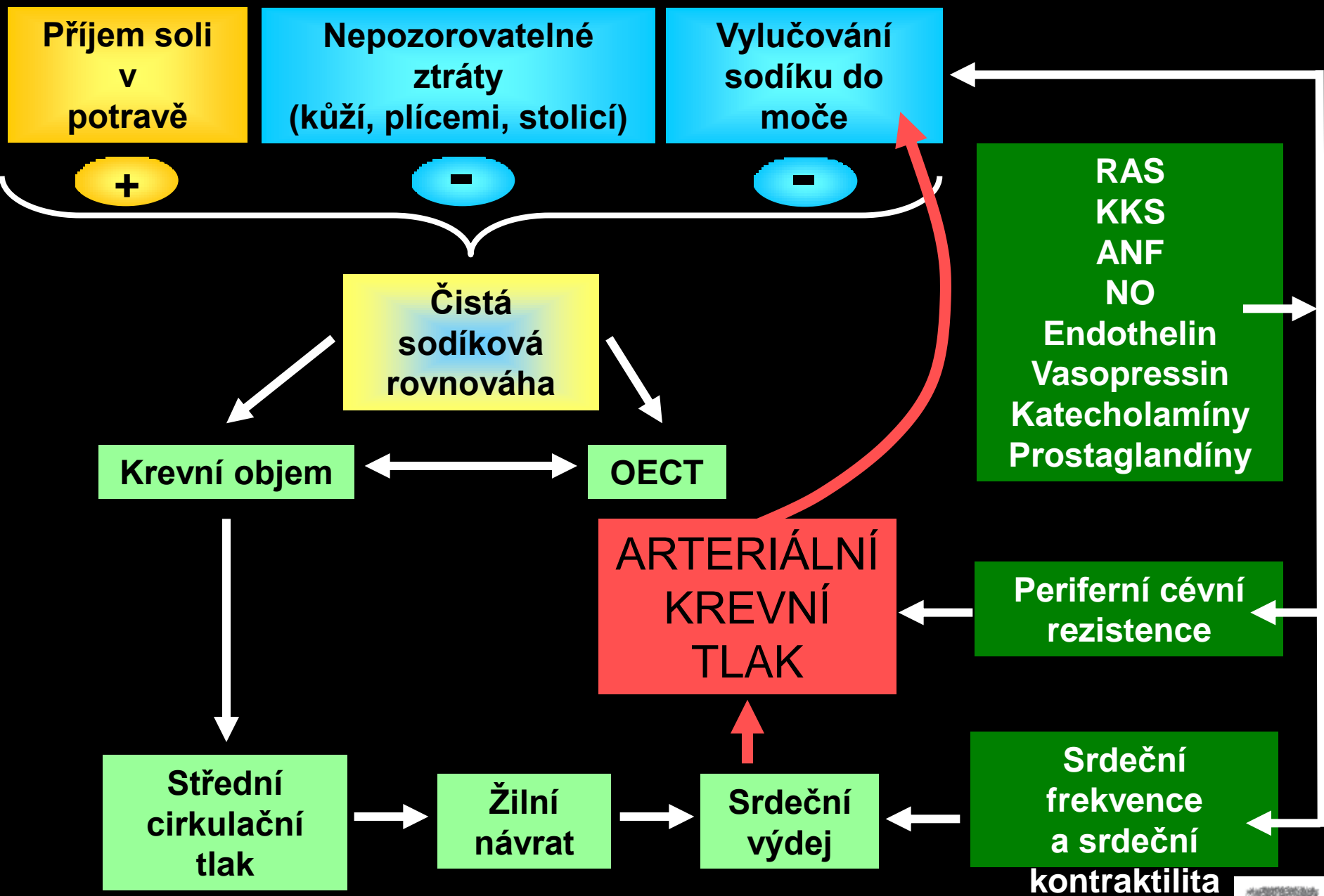




Příjem nebo vylučování sodíku  
(x normálu)



Renálně perfuzní tlak (mmHg)



Počáteční  
vzestup  
PCR

Počáteční  
vzestup  
OECT

Nervové nebo  
hormonální podněty

Vazokonstriční  
účinky

Retence  
sodíku a vody  
v ledvinách

Efektivní  
krevní  
objem

↑ OECT

↑ Srdeční  
výdej

Kapacita  
cévního  
řečiště

↑ Perfúze  
tkání

Vzestup PCR

Autoregulační  
úprava  
rezistence

↑ ARTERIÁLNÍ KREVNÍ TLAK



# Formy Hypertenze

**A. Esenciální (Primární) Hypertenze**

**B. Sekundární Hypertenze**

**1. Renovaskulární Hypertenze**

**2. Renální (parenchymatózní) Hypertenze**

**3. Endokrinně Podmíněné Formy Hypertenze**

a/ Primární hyperaldosteronismus

b/ Pseudohyperaldosterinismus - Liddleuv syndrom

c/ Pseudohyperaldosterinismus - způsobený defektem 11- $\beta$ HSD

d/ Hyperaldosterinismus ovlivnitelný glukokortikoidy

e/ Cushingův syndrom

f/ Feochromocytom

# Primární hyperaldosteronismus

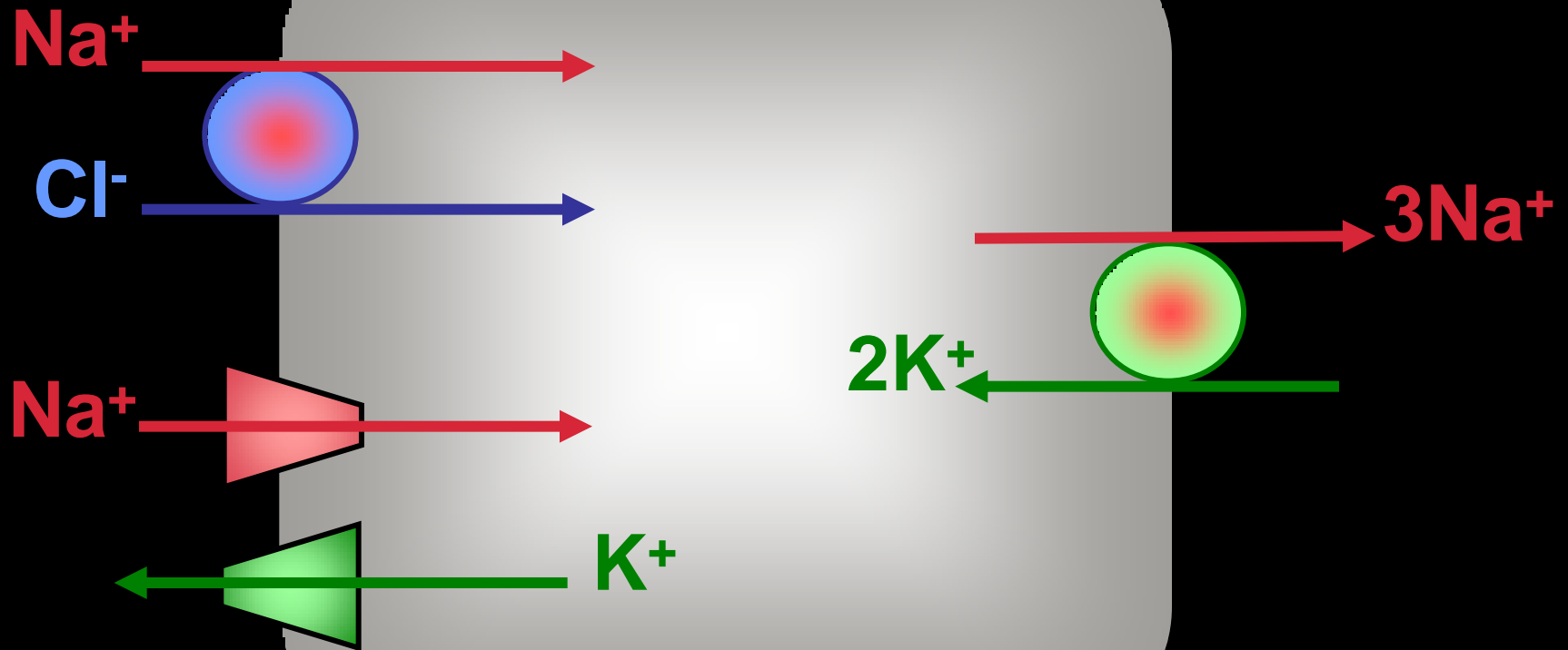
**Nadbytek mineralokortikoidů produkovaných adenomem (tzv. Connův syndrom) způsobí:**

- 1. Zvýšenou aktivitu  $\text{Na}^+\text{-K}^+$  pumpy v bazolaterální membrá**
- 2. Zvýšenou aktivitu epiteliálních kanálů pro  $\text{Na}^+$  (ENaC) v luminální membráně.**

# Primární hyperaldosteronismus

lumen

intersticiium



# Liddleuv syndrom - pseudohyperaldosteronis

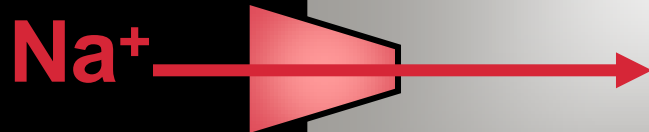
**Tento syndrom je způsoben mutací jedné ze tří podjednotek ENaC kanálu, což způsobuje, že tento kanál zůstává konstitutivně**



# Liddleův syndrom - pseudohyperaldosterinismus

lumen

intersticium



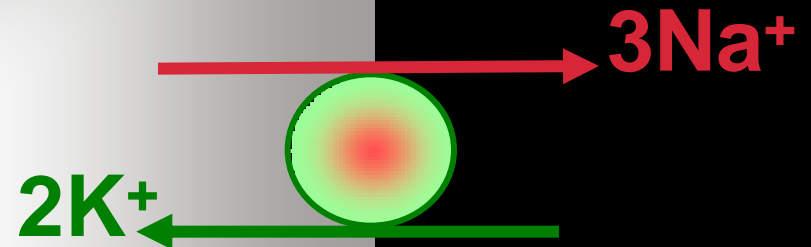
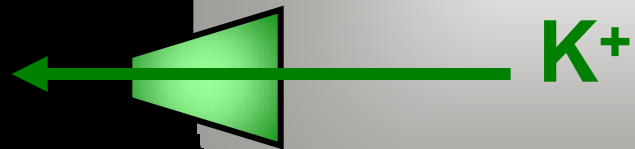
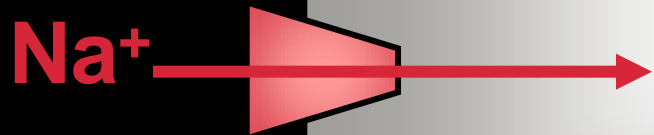
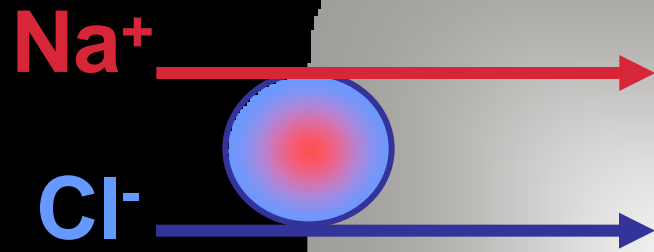
# Pseudohyperaldosteronismus

způsobený defektem 11-beta-hydroxysteroiddehydrogenázy

**Mineralokortikoidní receptor je nitrobuněčný cytoplazmatický protein, který může vázat jak aldosteron, tak i glukokortikoidní hormon kortizol. Buňky (distálního tubulu) mají na svém povrchu enzym 11- $\beta$ -HSD, která mění kortizol na kortizon, což sekundárně způsobí, že v okolí těchto buněk je lokálně dostupný pouze aldosteron.**

**lumen**

**intersticiium**



# Pseudohyperaldosteronismus

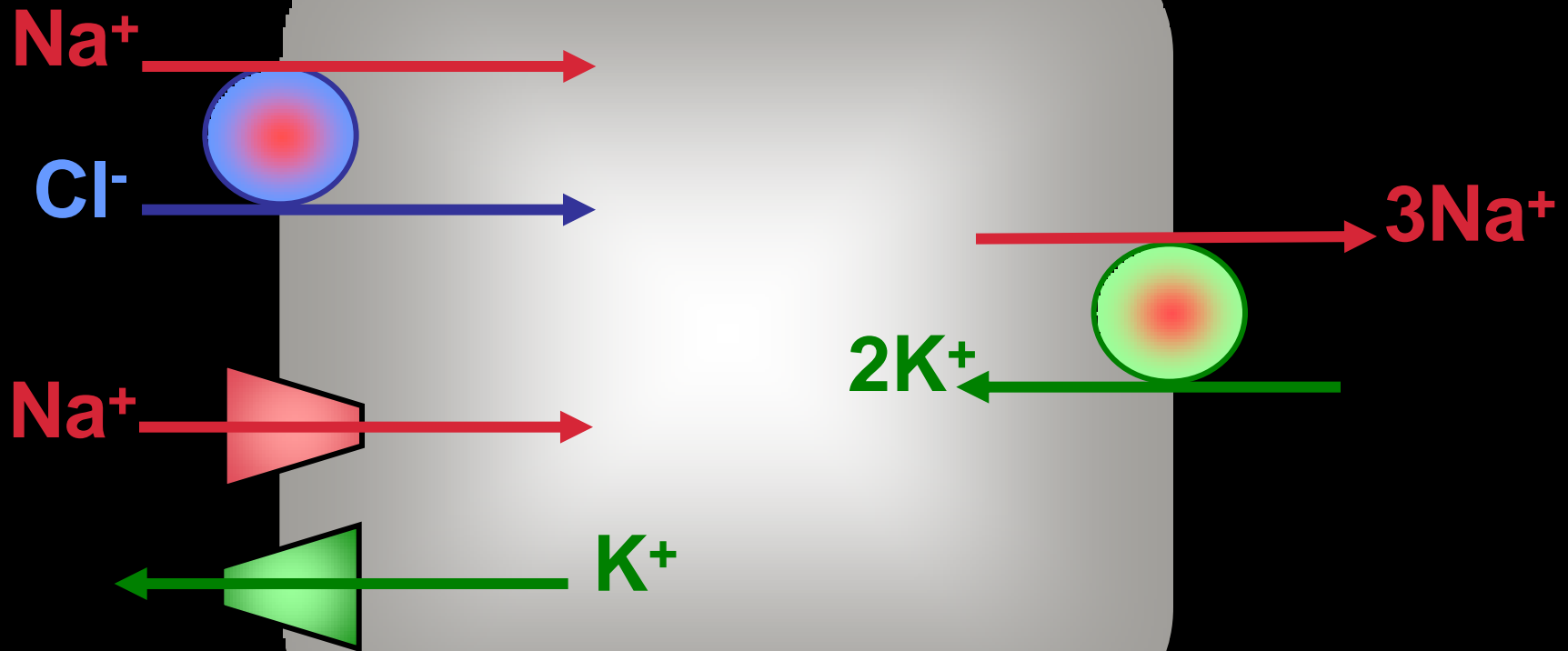
příznivě ovlivnitelný glukokortikoidy

**Dochází k nadprodukci aldosteronu a gen aldosteronsyntáza je napojen na regulační gen 11-betahydroxylázy, což dostává syntézu pod kontrolu ACTH.**

# Hyperaldosterinismus – ovlivněný glukokortikoidy

lumen

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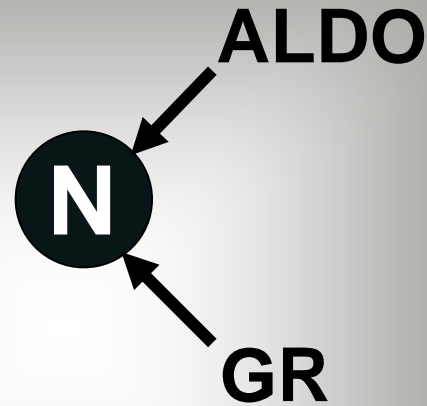
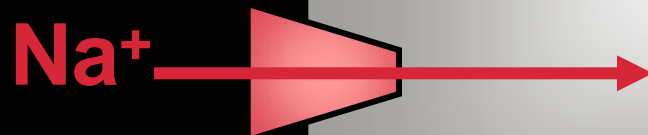
# Cushingův syndrom

případě nadměrného (farmakologického) podávání glukokortikoidů  
tak i funkční 11- $\beta$ -HSD není schopna „odbourat“ všechny kortizol  
a dochází k aktivaci mineralokortikoidních receptorů

# Cushingův syndrom

lumen

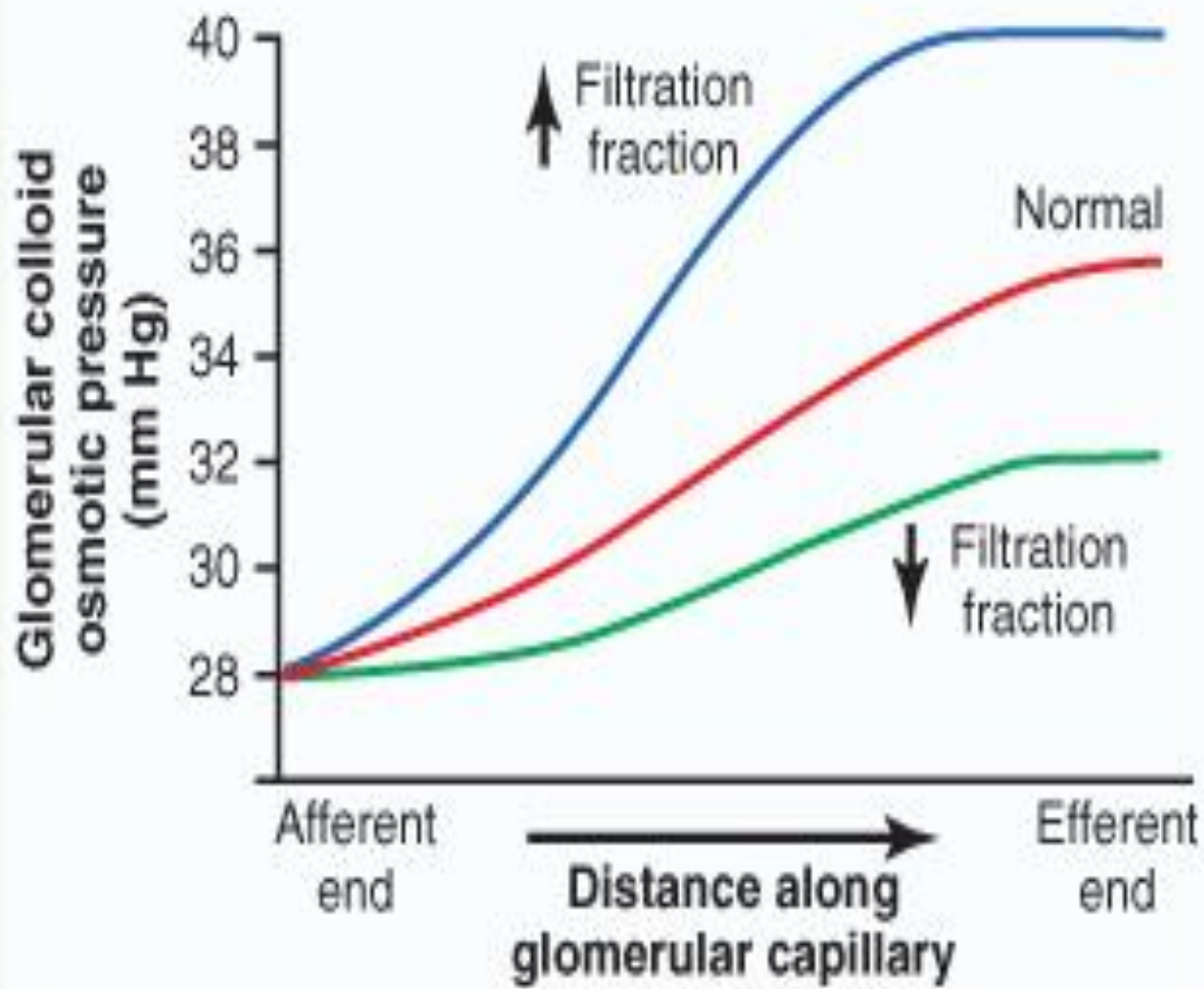
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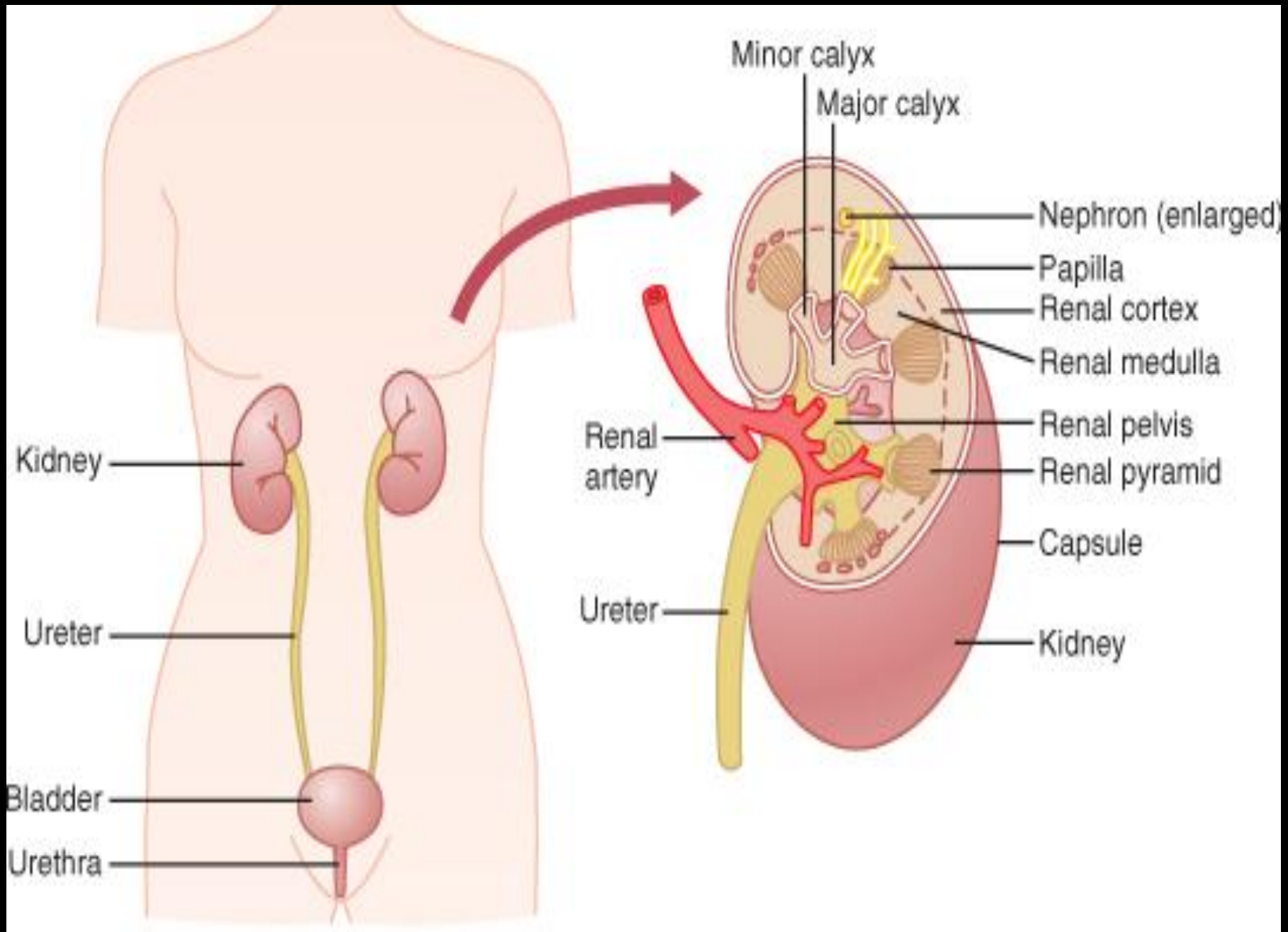


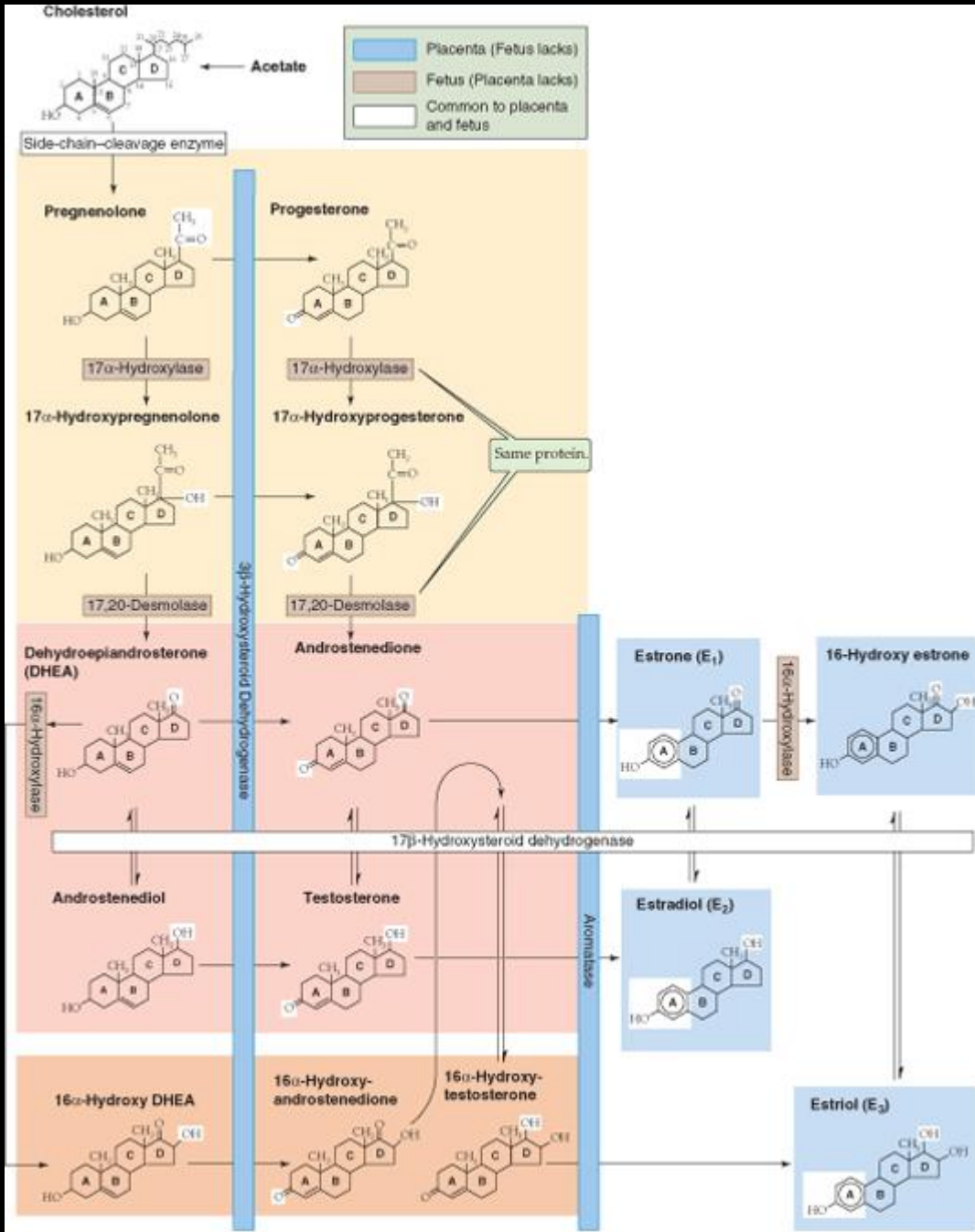
# Feochromocytom

**Nádor dřeně nadledvin produkuje enormní množství katecholaminů**

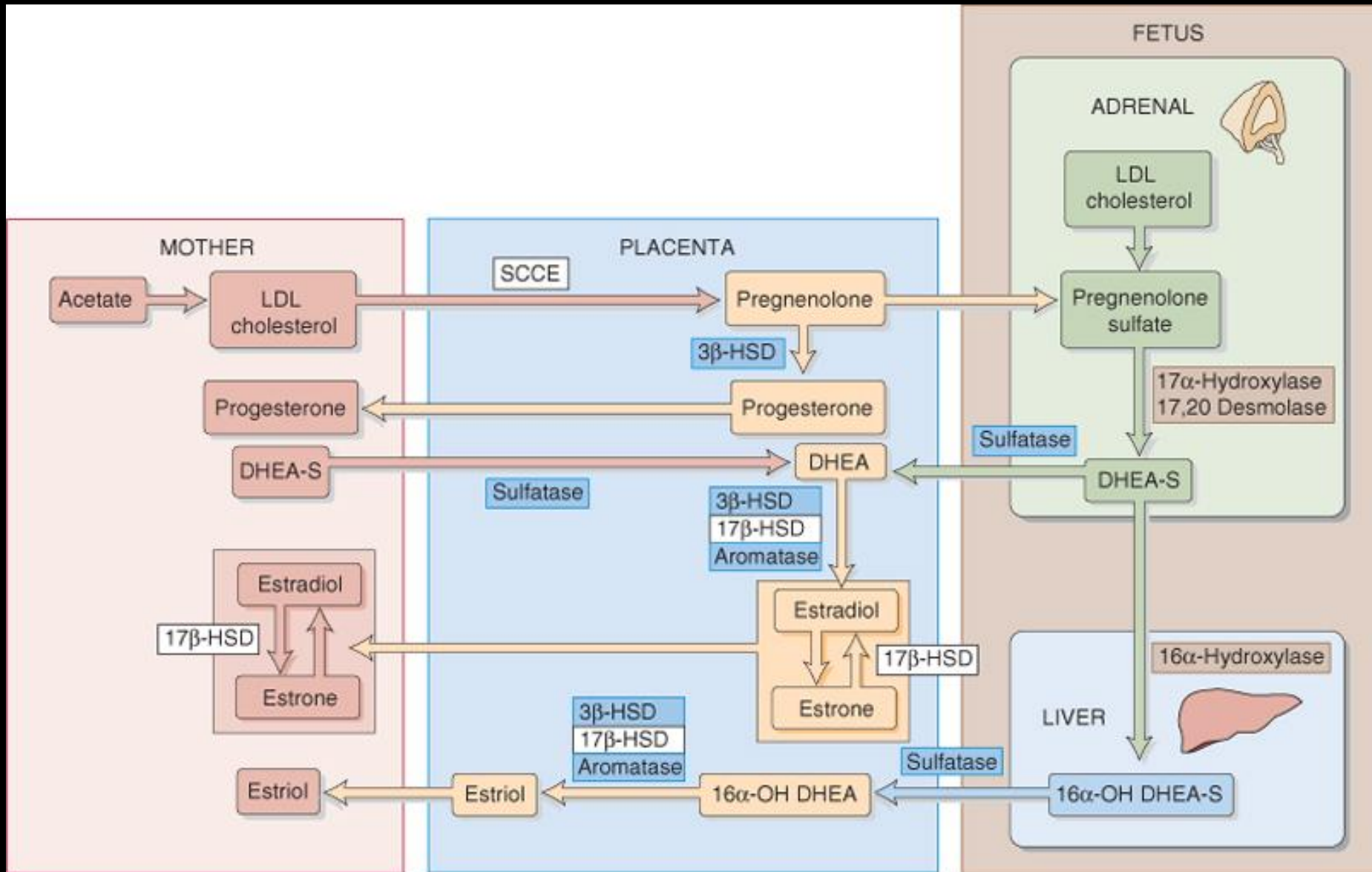




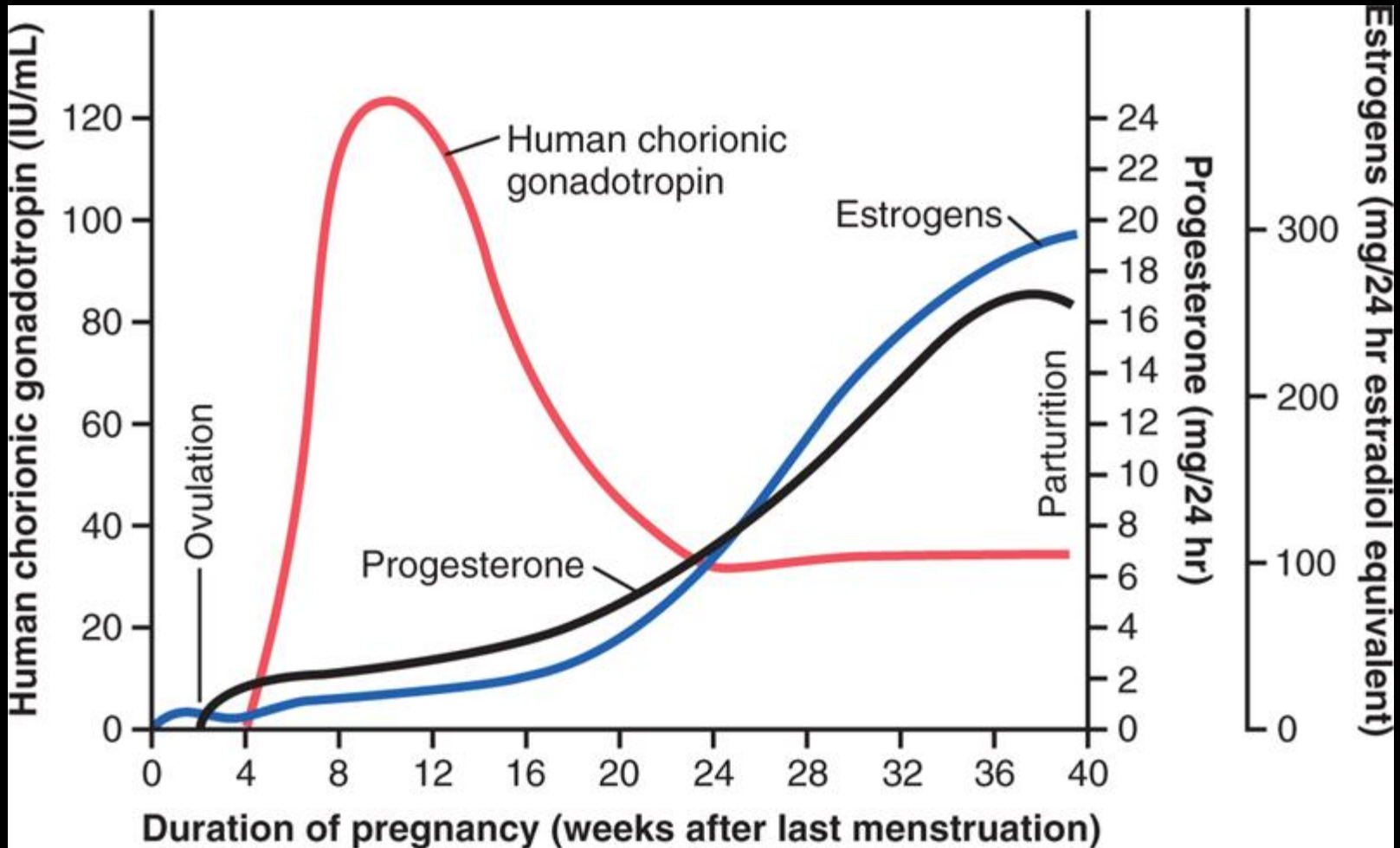




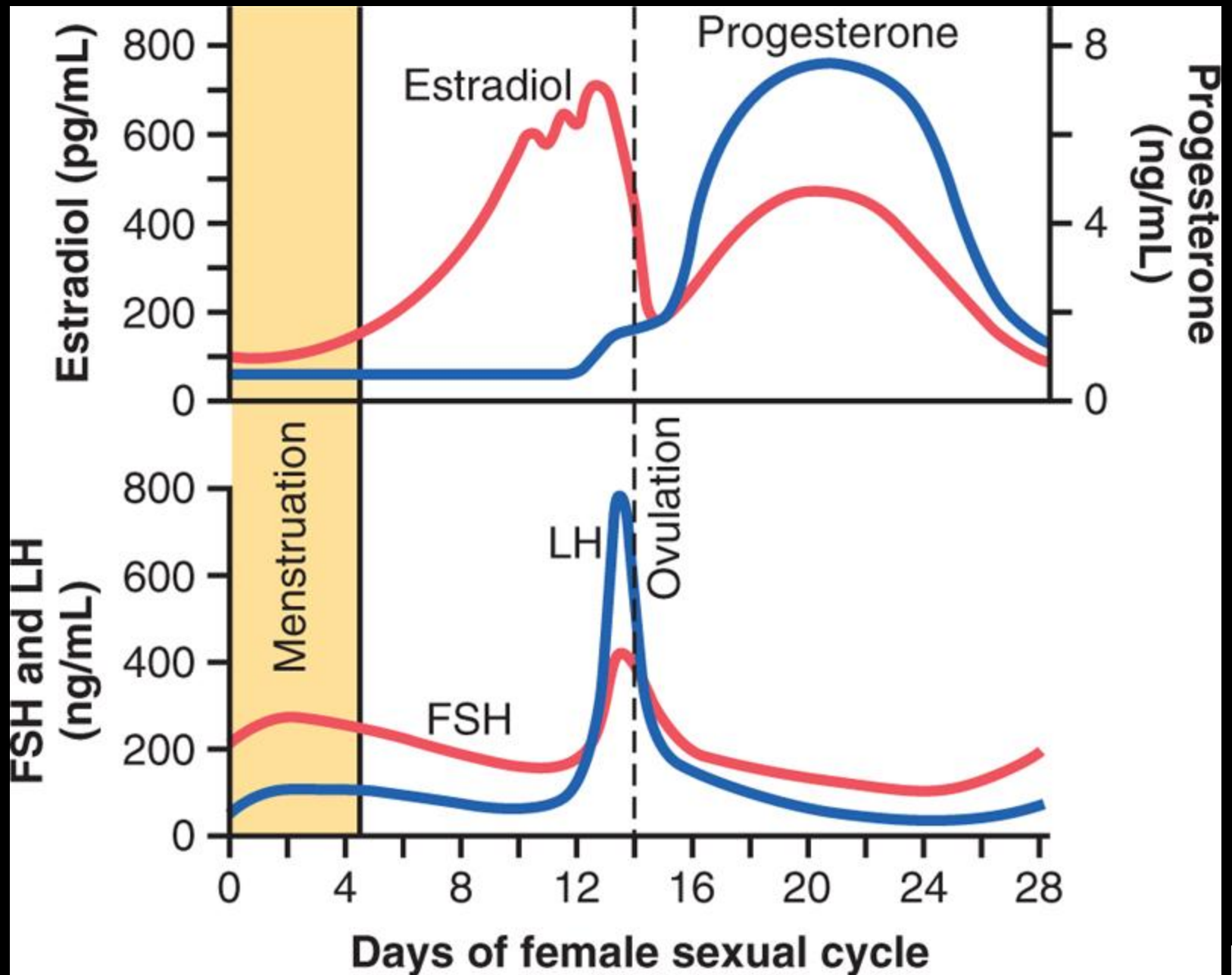
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# Koncentrační mechanismus ledvin

Organismus se musí denně zbavit minimálně 600 mOsm denně

$$C_{\text{osm}} = \frac{U_{\text{osm}} \times V}{P_{\text{osm}}}$$

$$C_{\text{osm}} = \frac{600 \text{ mOsm}}{300 \text{ mOsm/L}} = 2 \text{ L/24 hodin}$$

$$C_{\text{osm}} = \frac{600 \text{ mOsm}}{1200 \text{ mOsm/L}} = 0.5 \text{ L/24 hodin}$$

Množství vody bez solutů, která musí být přidána (nebo odebrána) od výše uvedeného objemu moči, tak aby byl vytvořen konečný objem moči  
Za účelem zachování vyrovnané vodní (a osmotické) bilance nazýváme  
**„Clearance volné vody“** ( $C_{\text{vody}}$ ), což ve své podstatě není clearance,  
ale rozdíl mezi diurézou a osmotickou clearance.

Množství denní moči je určeno následující rovnicí:

$$V = C_{\text{osm}} + C_{\text{vody}}$$

$$C_{\text{vody}} = V - C_{\text{osm}}$$

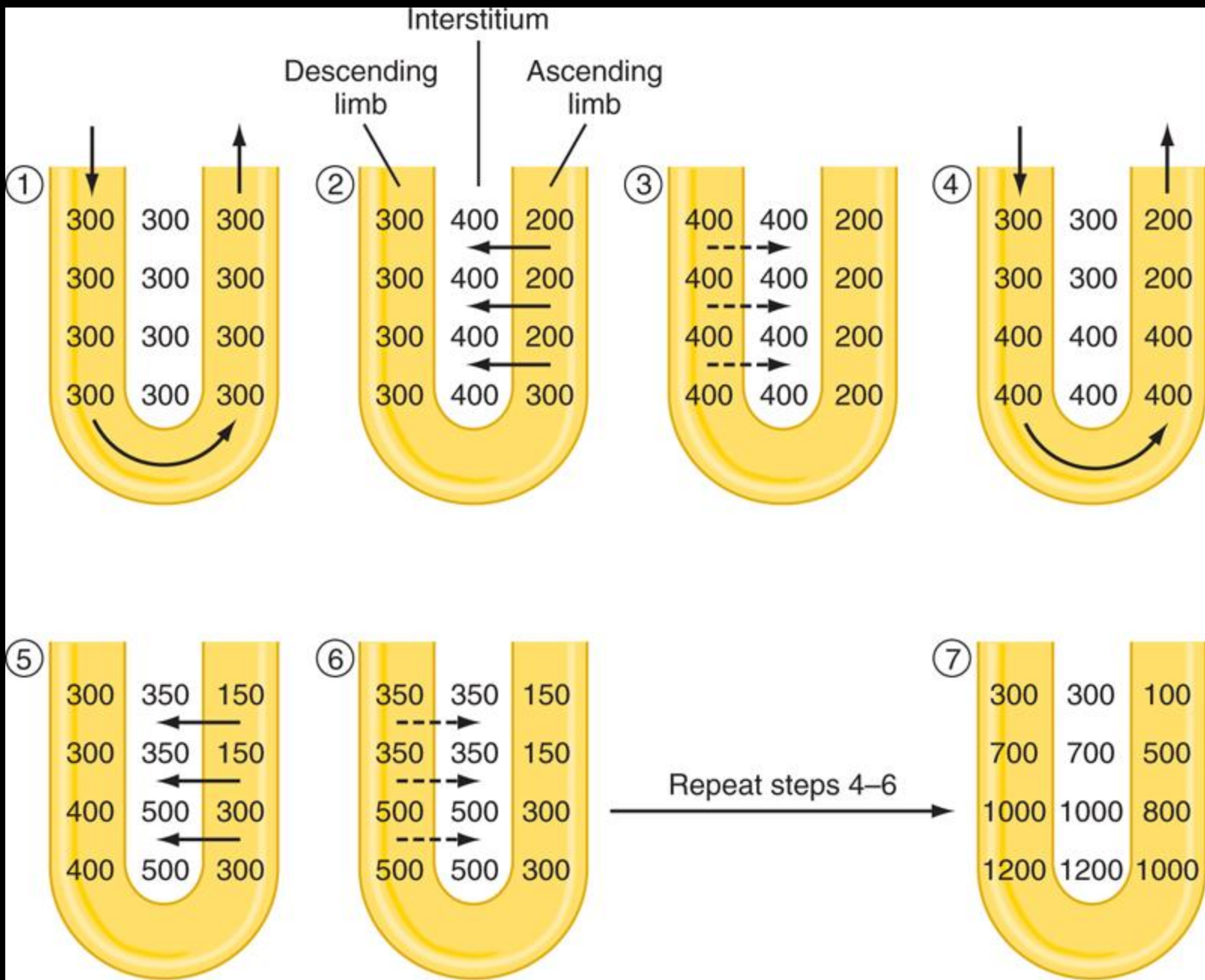
Takže při tvorbě maximálně zředěné moči (30 mOsm) je  $C_{\text{vody}}$ :

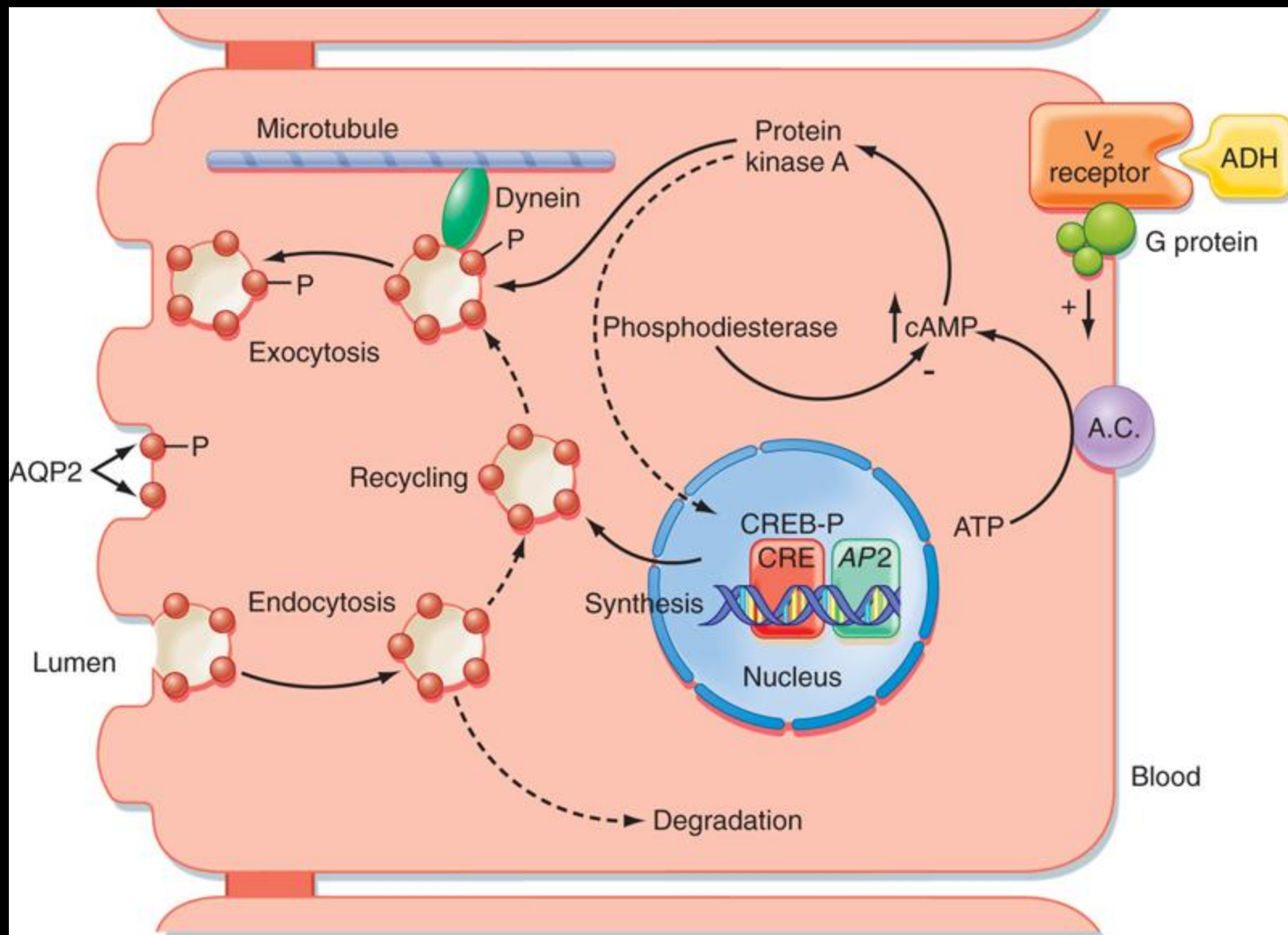
$$C_{\text{vody}} = 20 \text{ L/den} - 2 \text{ L/den} = 18 \text{ L/den}$$

Naopak při tvorbě maximálně koncentrované moči (1200 mOsm) je  $C_{\text{vody}}$ :

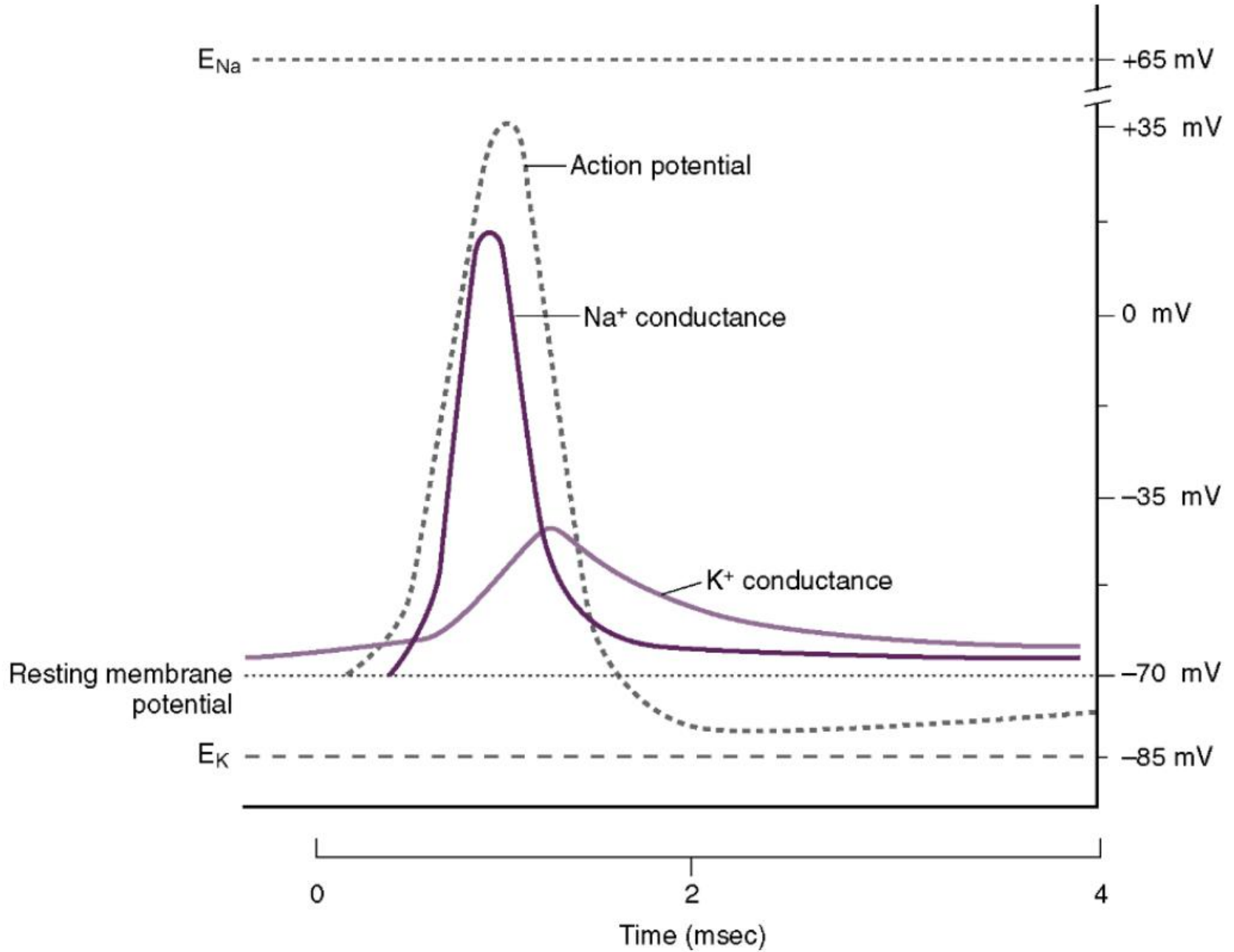
$$C_{\text{vody}} = 0,5 \text{ L/den} - 2 \text{ L/den} = -1,5 \text{ L/den}$$

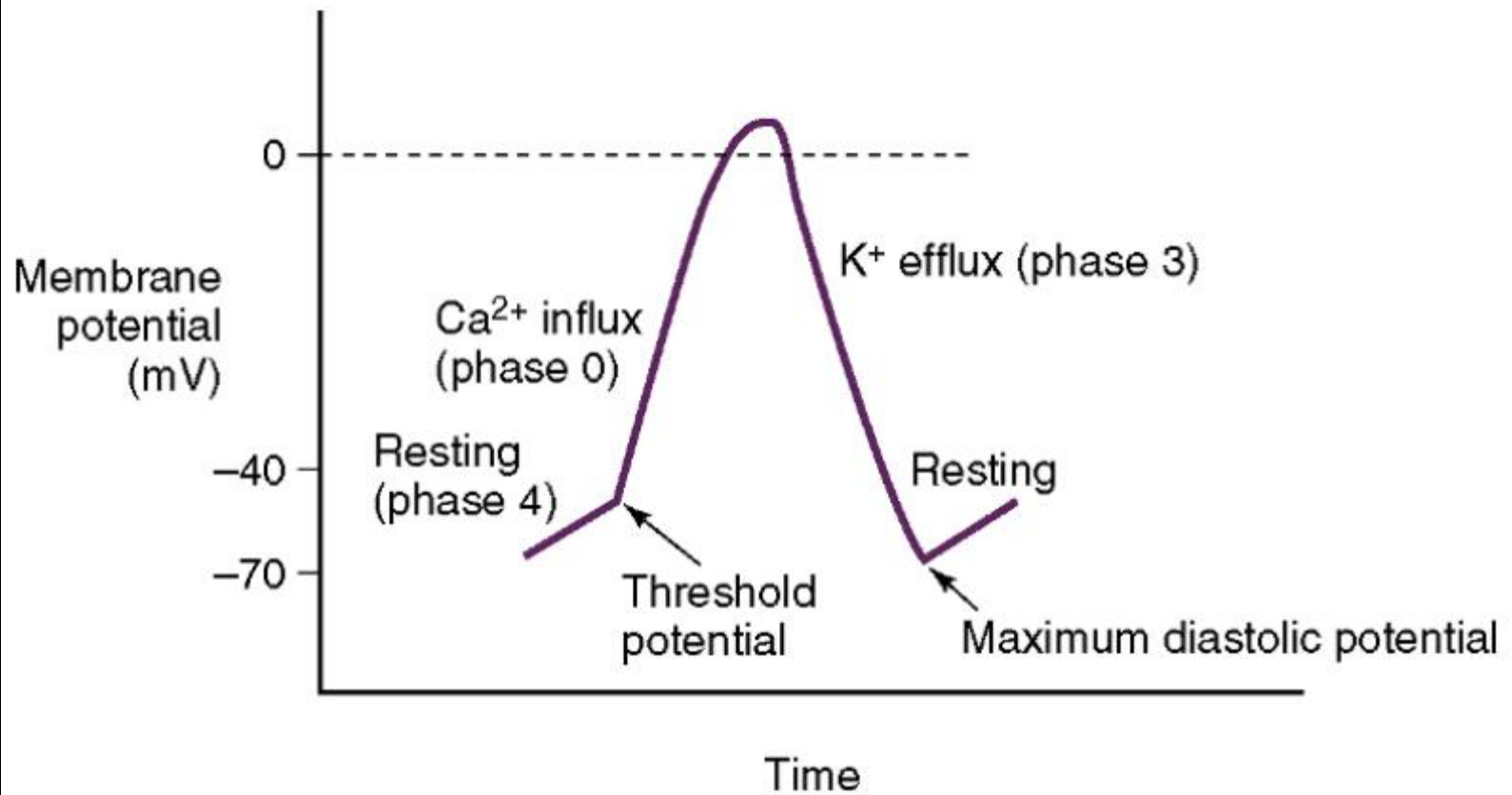


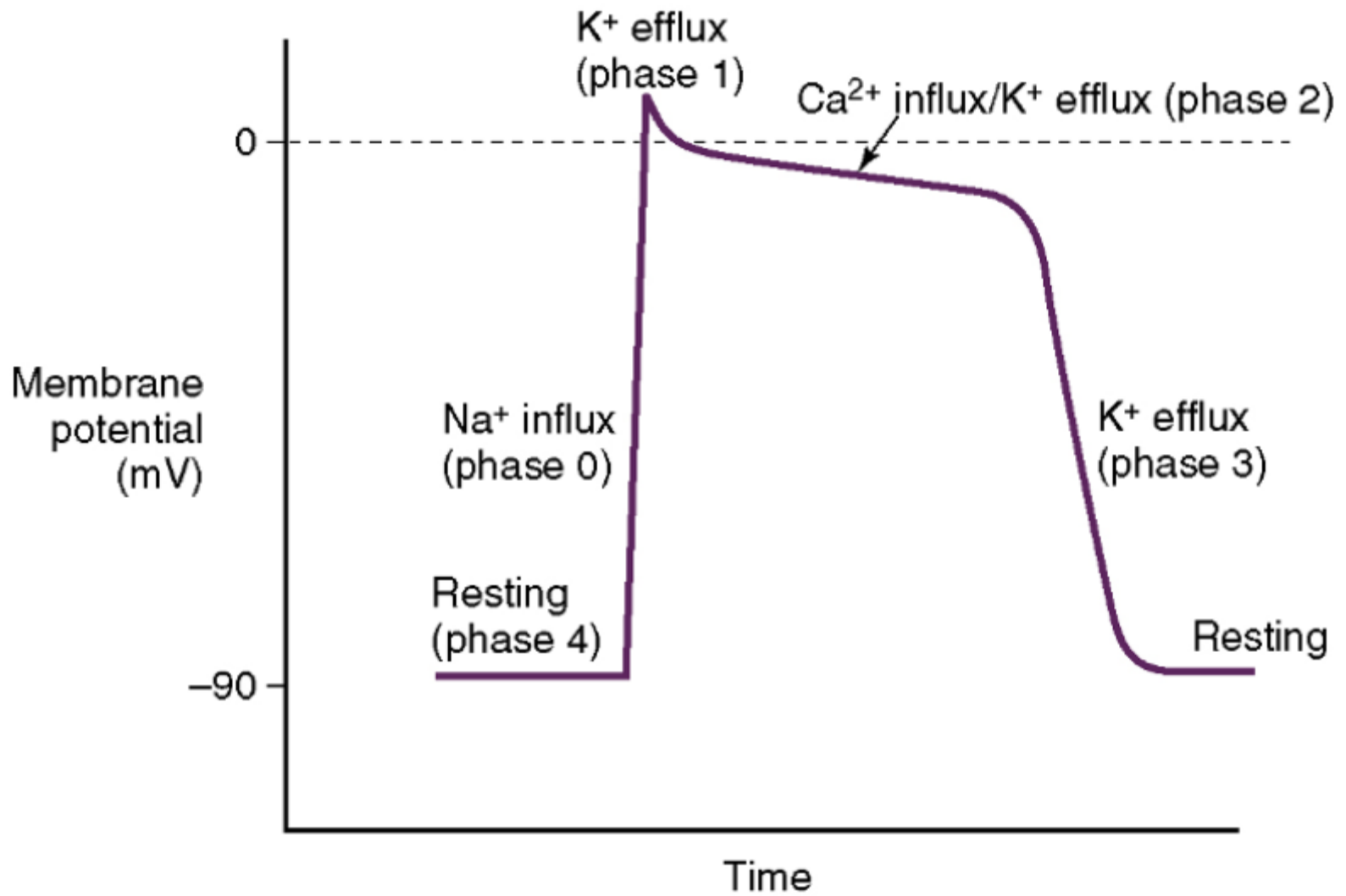


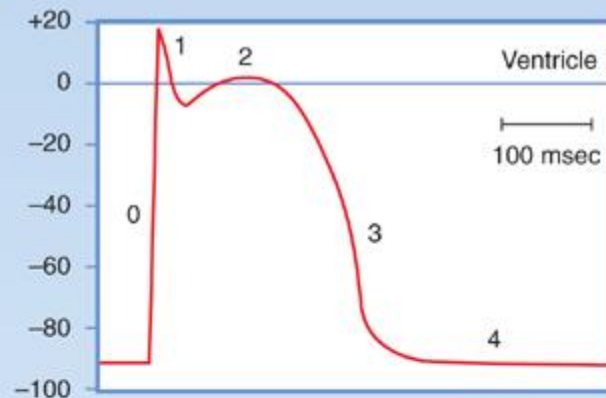


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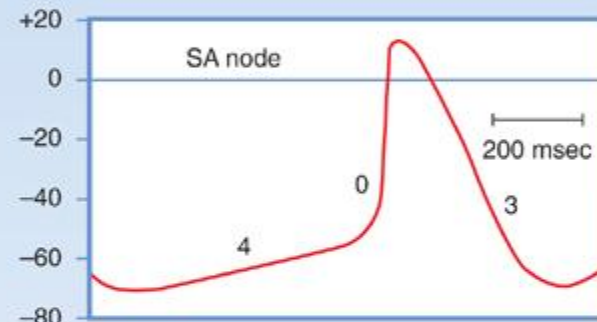




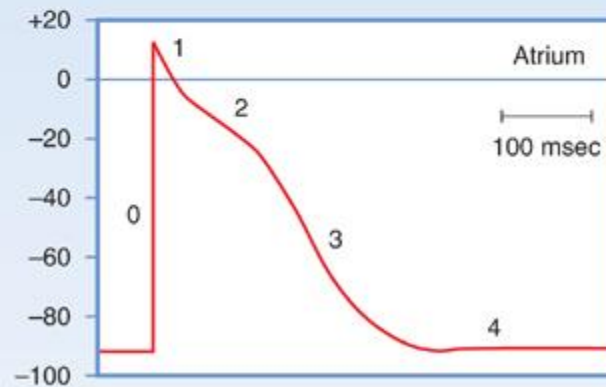




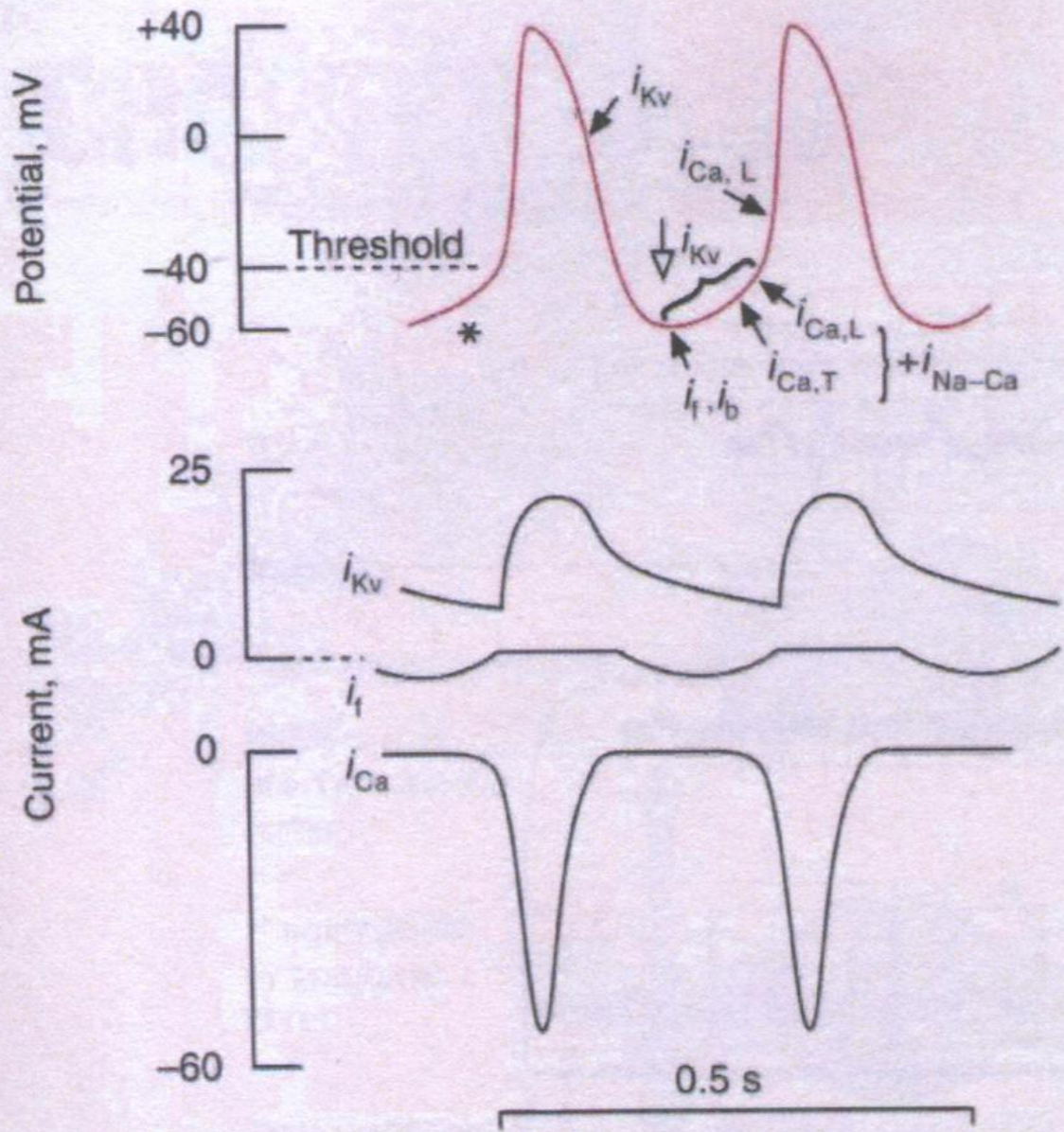
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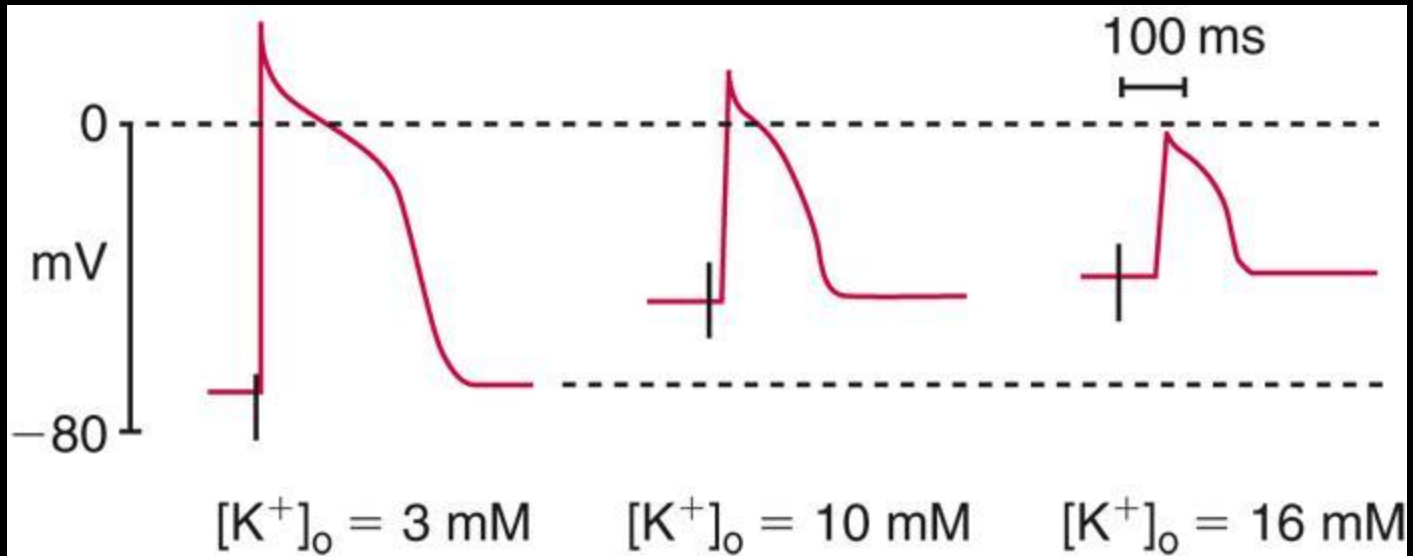


B



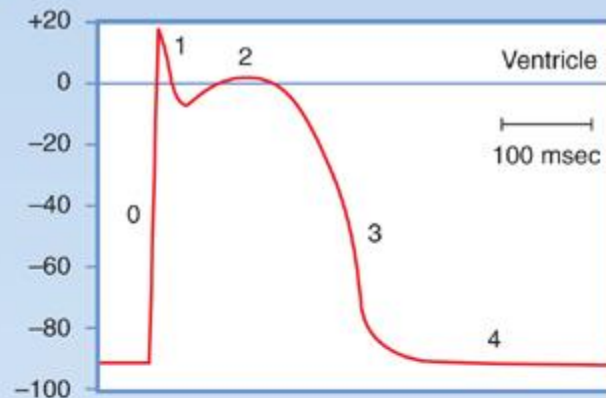
C



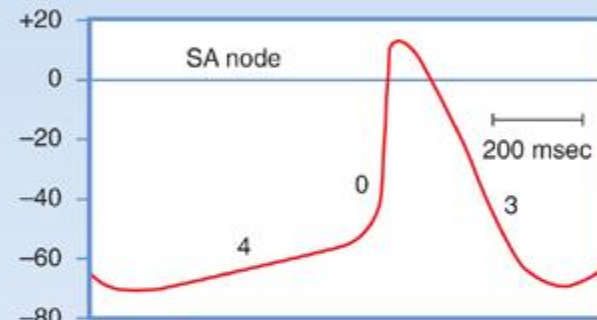


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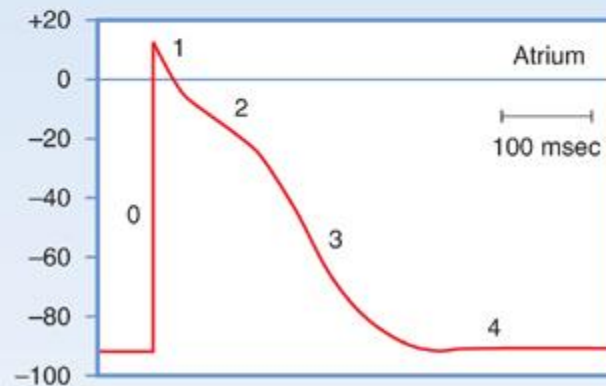




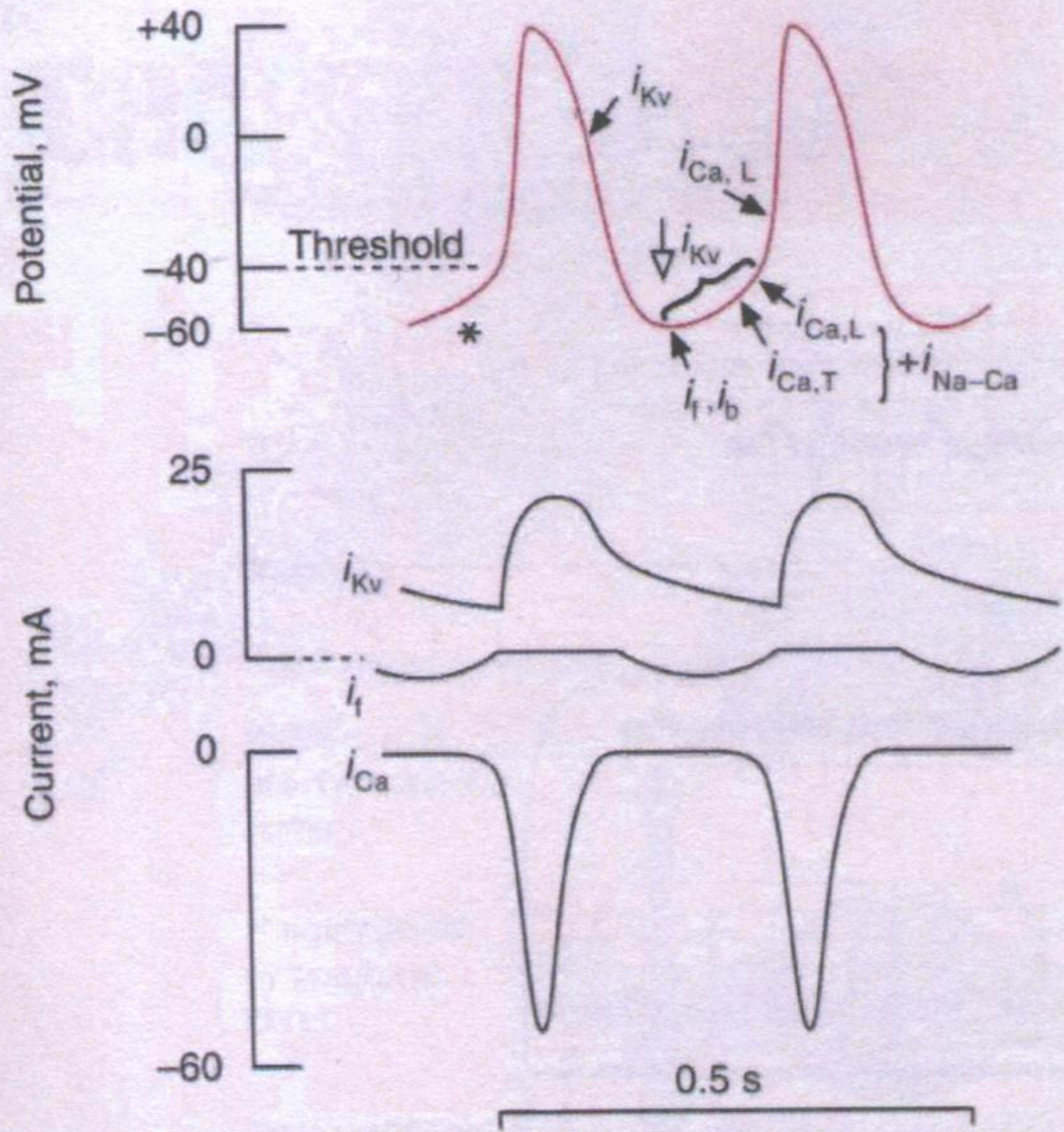
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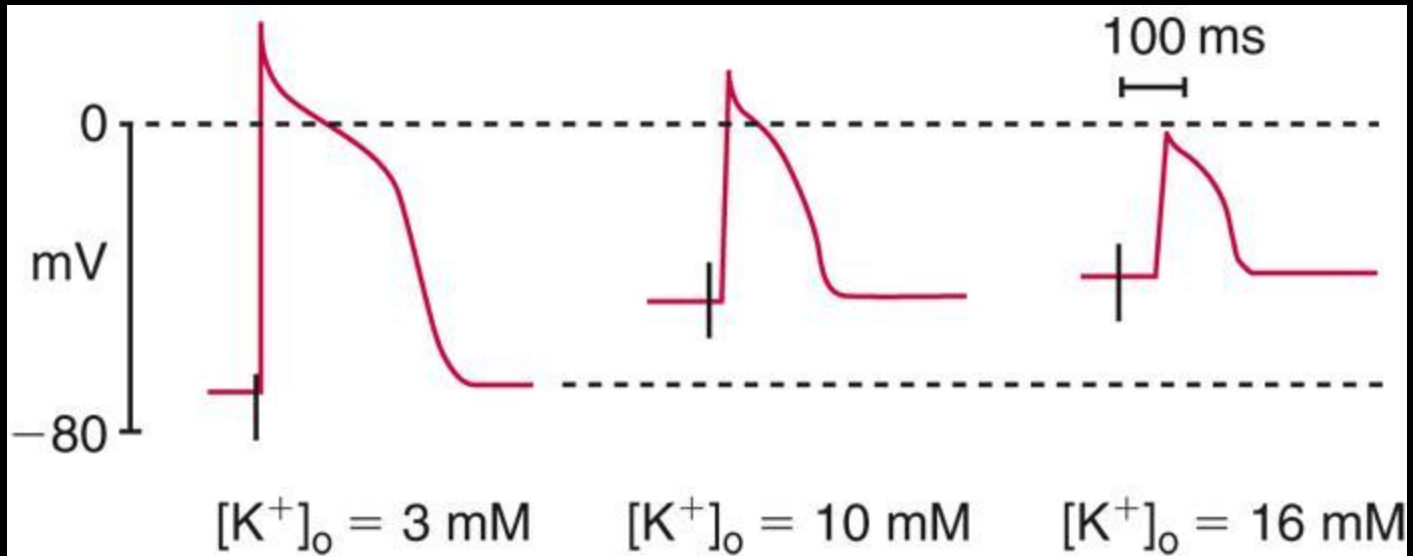


B



C





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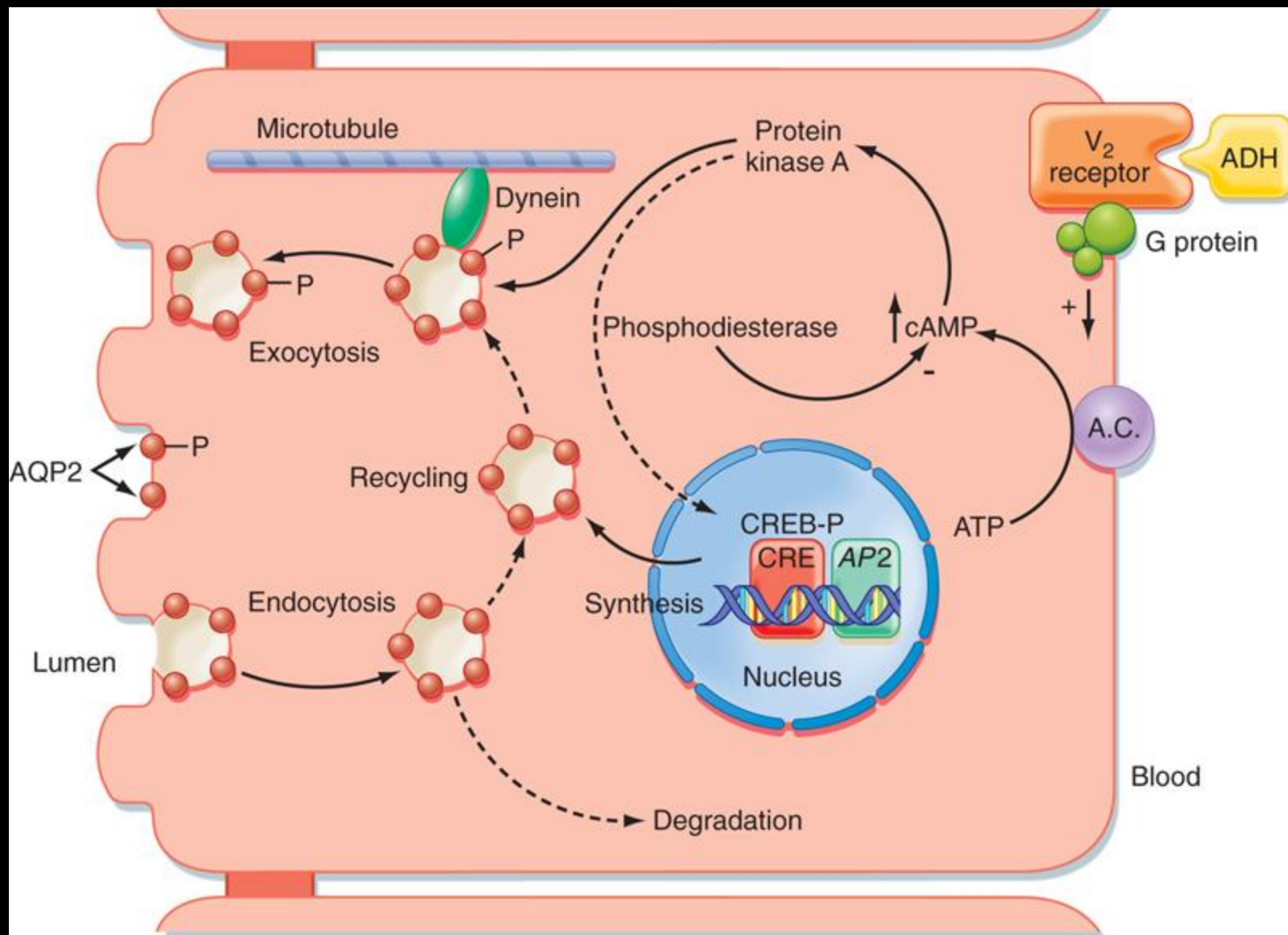






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