Renal physiology

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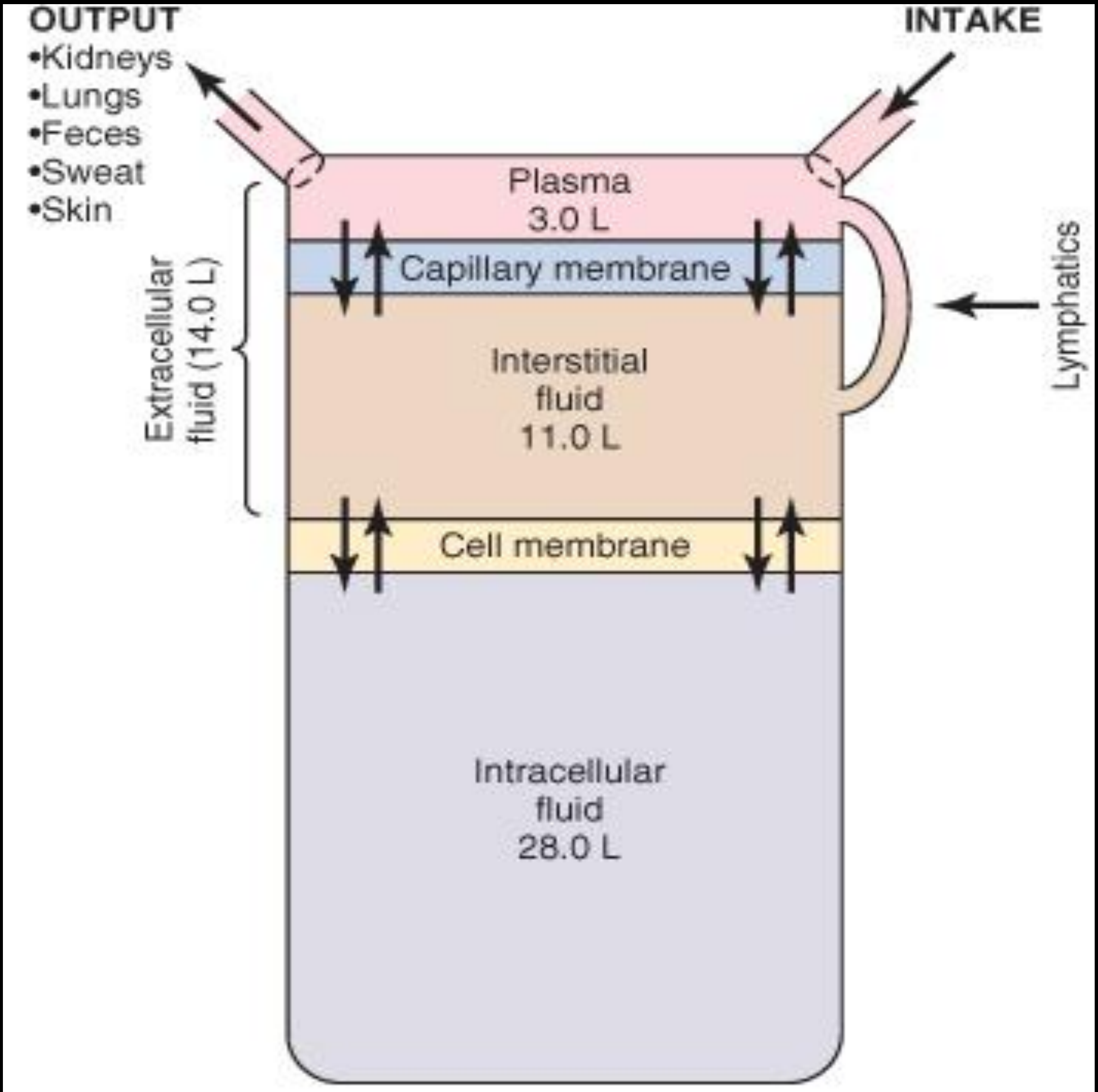
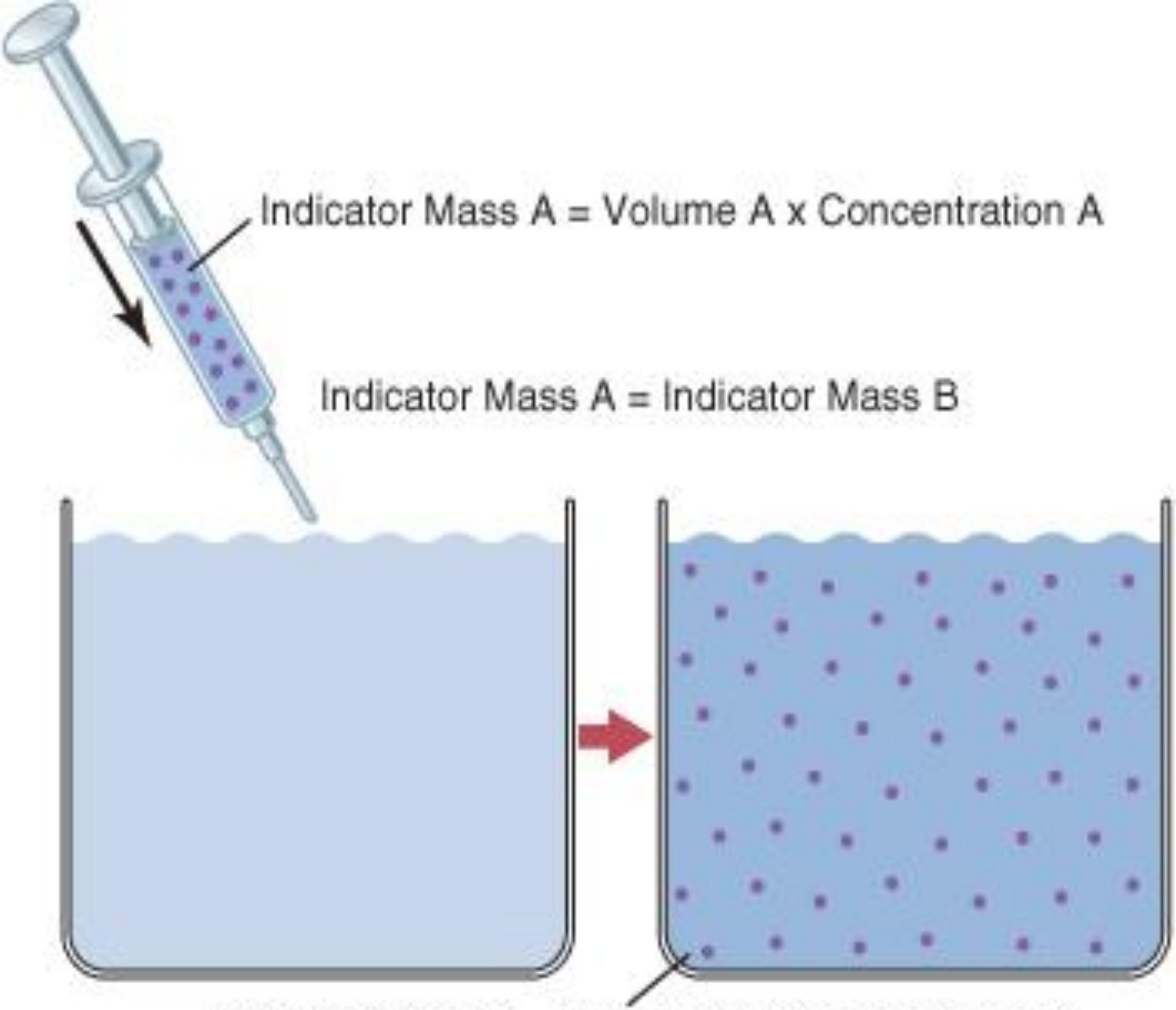

OUTPUT
•Kidneys
•Lungs
•Feces
•Sweat
•Skin
INTAKE
Plasma
3.0 L
Capillary membrane
Interstitial
fluid
11.0 L
Lymphatics
Extracellular
fluid (14.0 L)
Cell membrane
Intracellular
fluid
28.0 L

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	

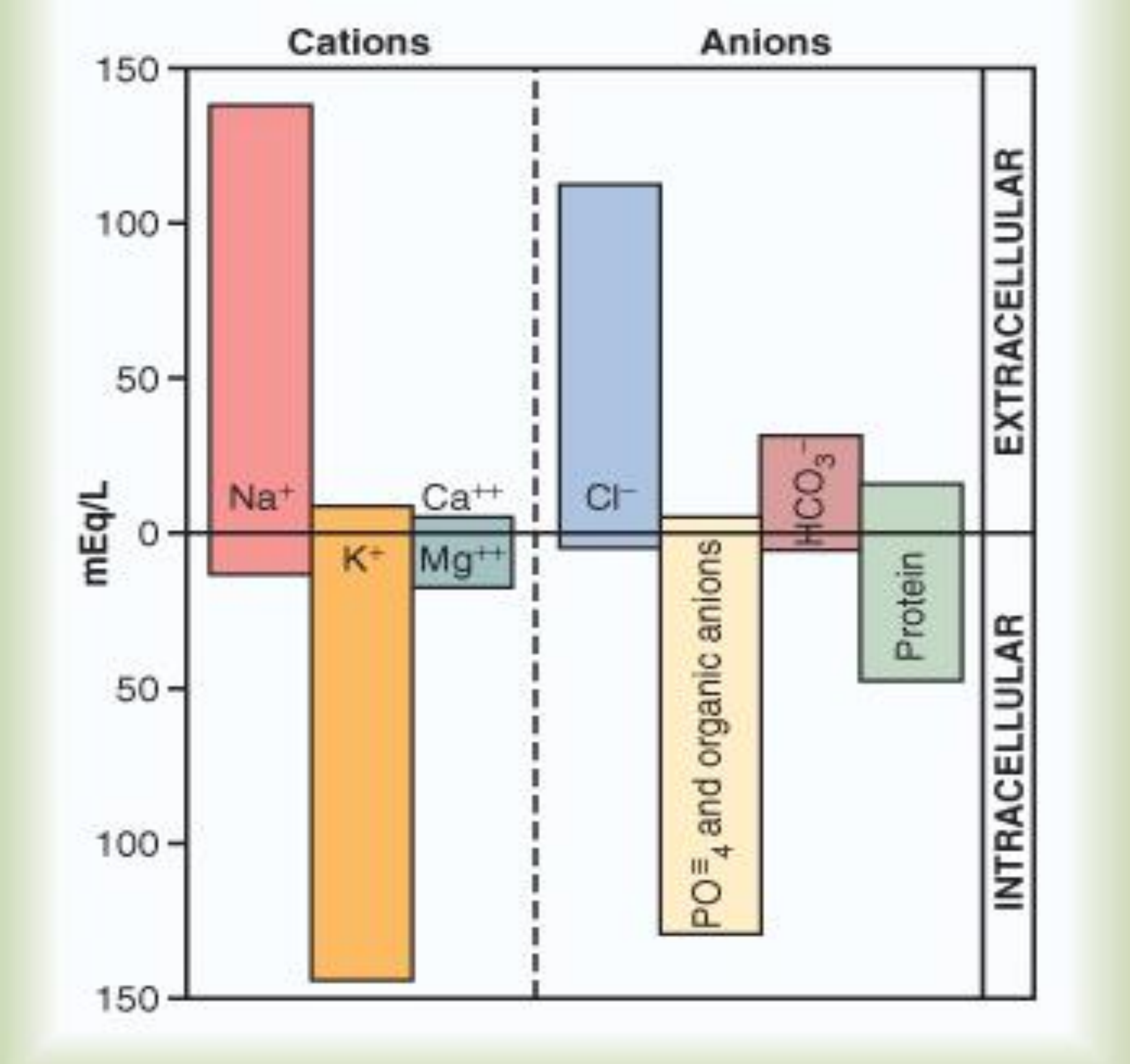


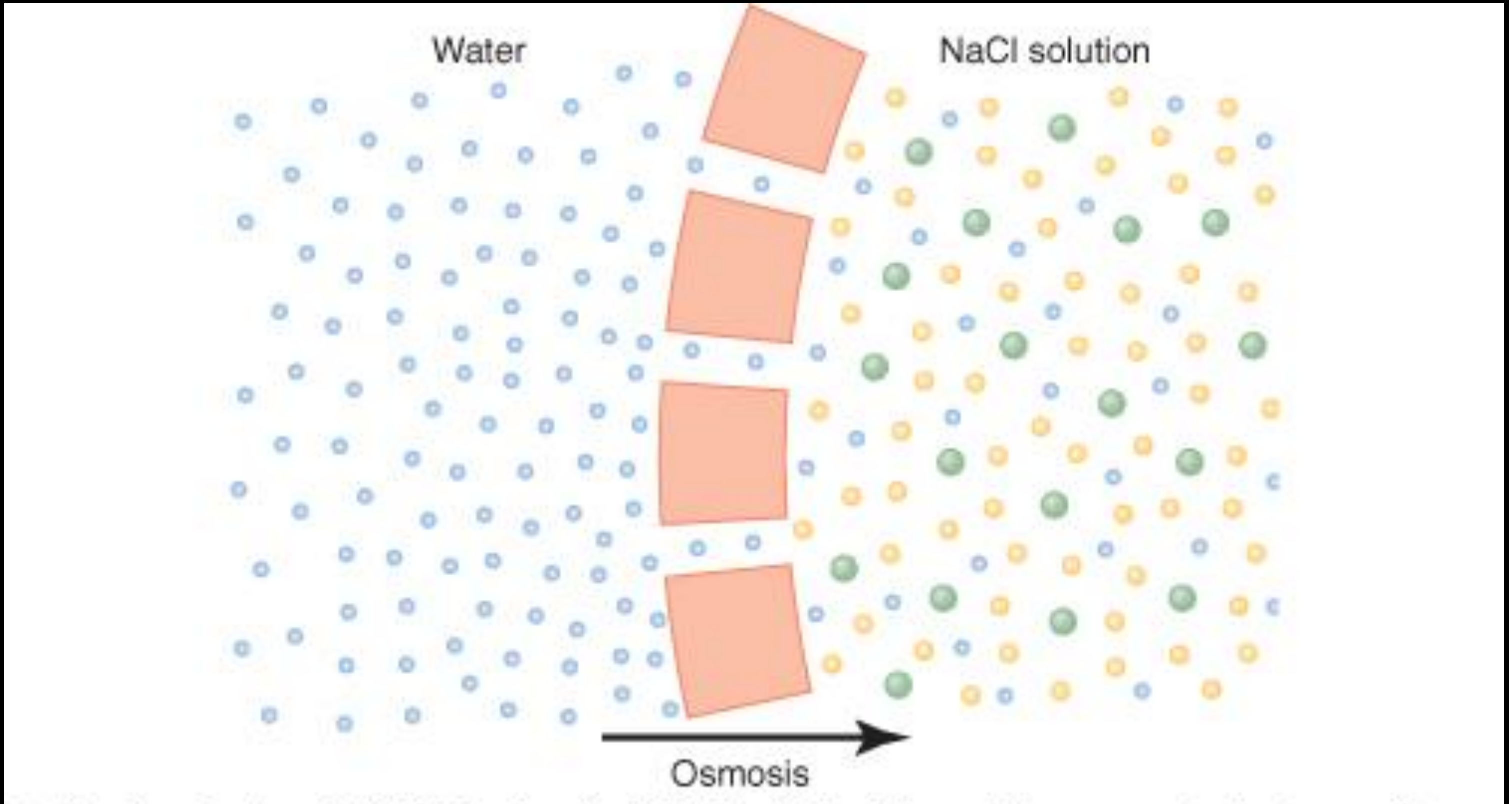
Indicator Mass A = Volume A x Concentration A

Indicator Mass A = Indicator Mass B

Indicator Mass B = Volume B x Concentration B

Volume B = Indicator Mass B / Concentration B


Cations
Anions
150
100
50
0
50
100
150
mEq/L
Na+
K+
Ca++
Mg++
Cl−
PO≡4 and organic anions
HCO3−
Protein
EXTRACELLULAR
INTRACELLULAR



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

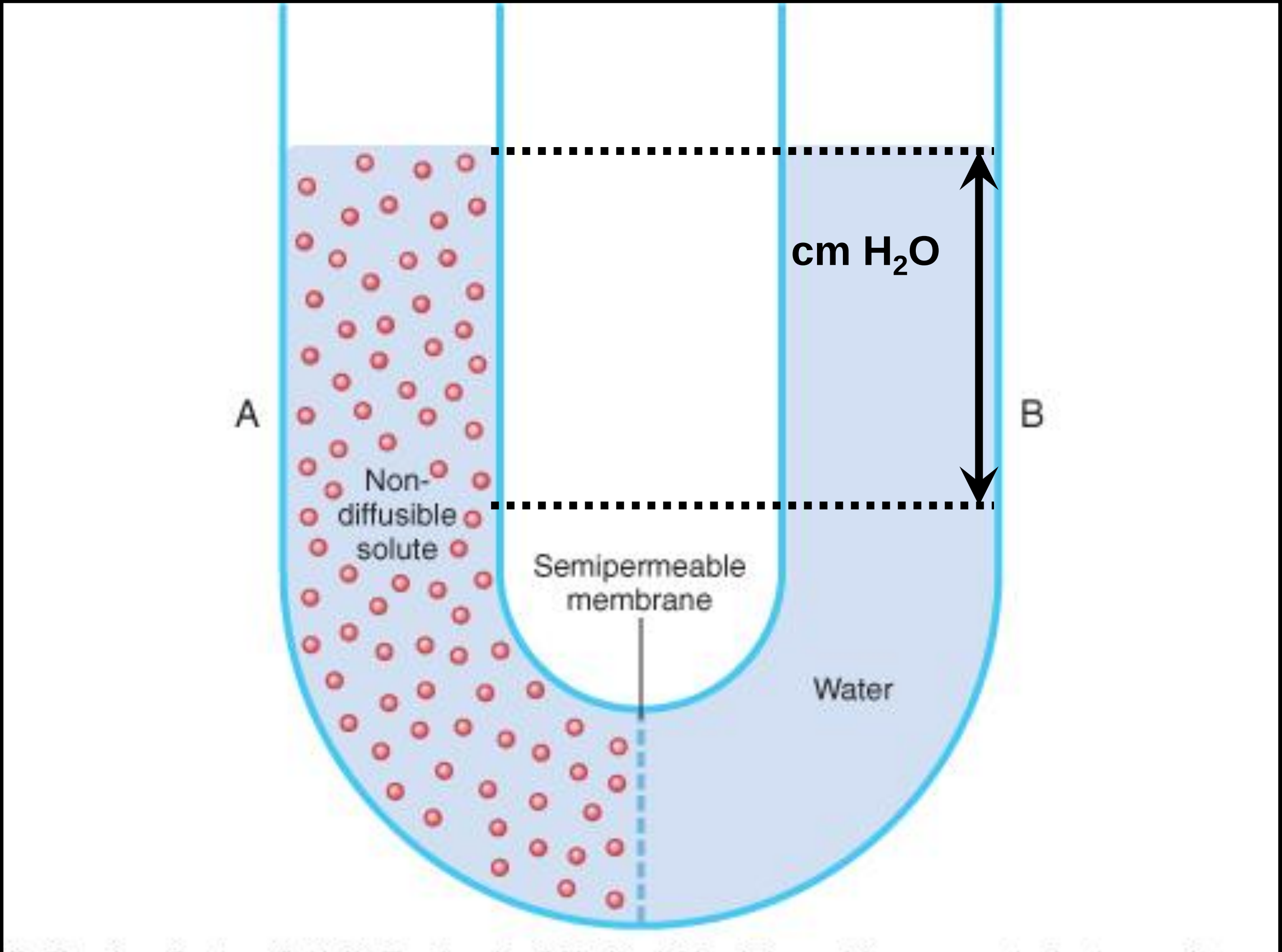
Osmotic pressure is determined by the *number* of particles per volume of fluid, not by the *mass* of the particles.
each particle in a solution, regardless of its mass, exerts, on average the same amount of pressure against the membrane.

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

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 that to the molar concentration.

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



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

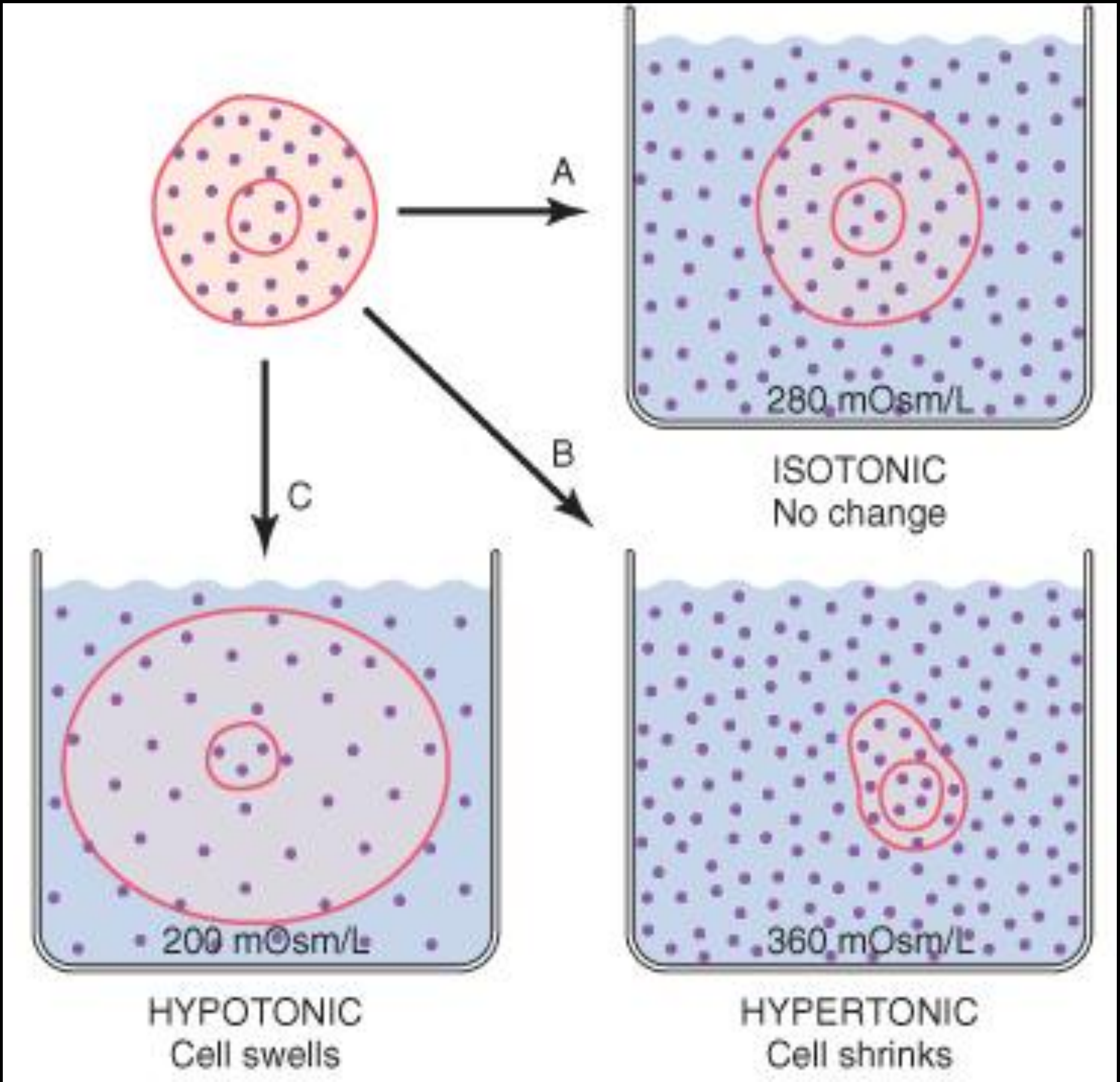
Corrected osmolar activity (*osmotic coefficient*) = 0.93
The reason for this correction is that cations and anions exert interionic attraction, which
Can cause a slight decrease in the osmotic „activity“ of the dissolved substance

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 x 0.154 = 0.308 osm/L = 308 mOsm/L
308 mOsm/L x 0.93 (osmotic coefficient) = 286 mOsm/L is the actual osmolarity of 0.9 % NaCl

	Plasma (mOsm/L H_2O)	Interstitial	Intracellular
Na^+	142	139	14
K^+	4.2	4	140
Mg^{2+}	1.3	1.2	0
Cl^-	108	108	4
HCO_3^-	24	28.3	10
HPO_4^{2-}, $H_2PO_4^-$	2	2	11
SO_4^{2-}	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
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity	282.0	281.0	281.0


A
280 mOsm/L
ISOTONIC
No change
B
C
200 mOsm/L
HYPOTONIC
Cell swells
360 mOsm/L
HYPERTONIC
Cell shrinks

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 mOsml/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 (liters)	Concentration (mOsm/l)	Total (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 0.516).

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

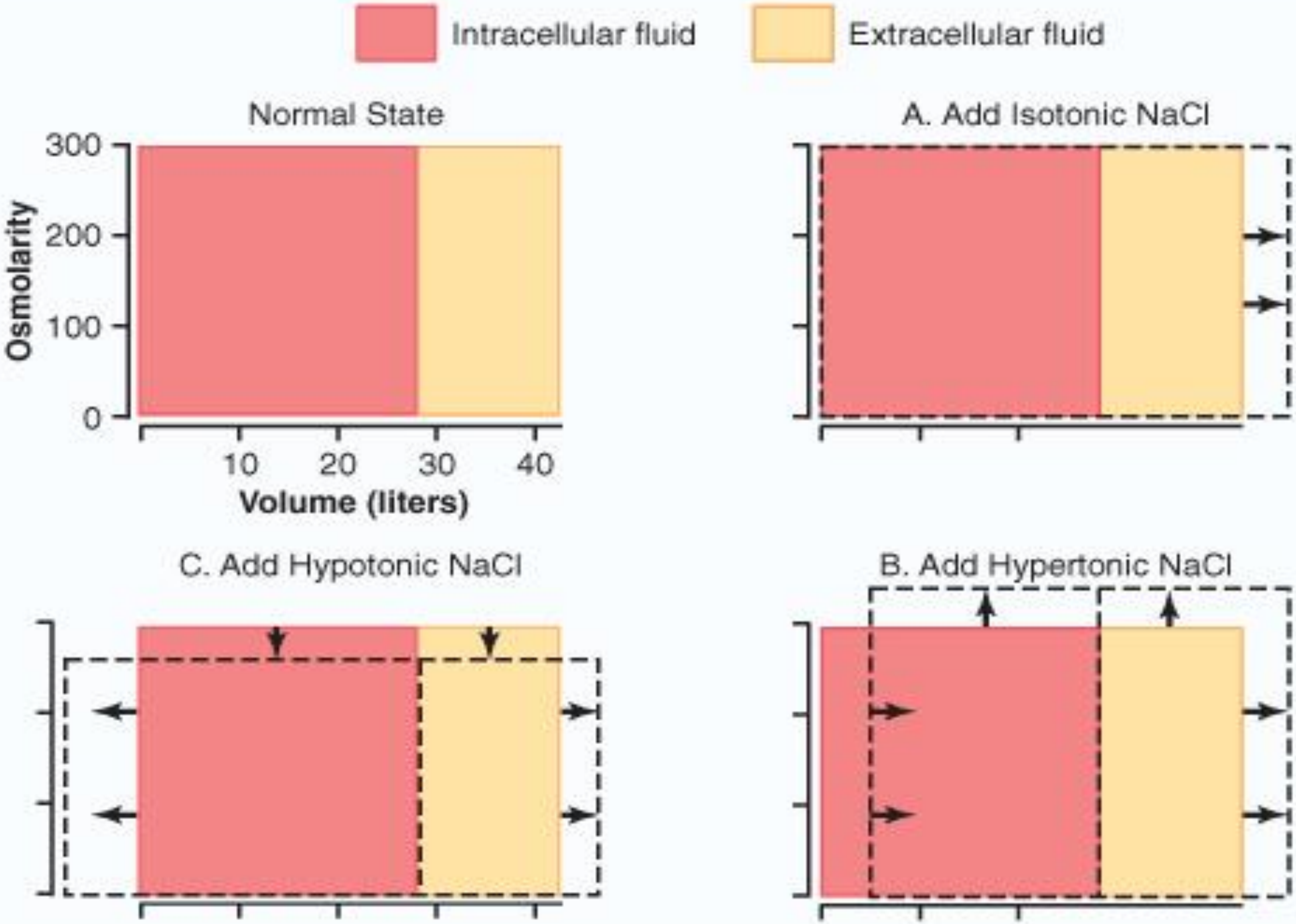
	Volume (liters)	Concentration (mOsm/l)	Total (mOsm)
Extracellular fluid	16	373	5972
	14 + 2	5972 : 16	3920 + 2052
Intracellular fluid	28	280	7 840
Total body fluid	44	no equilibrium	13 812

Final osmolarity after reaching equilibrium must be: 13 812 : 44 = 313.9 mOsm/L

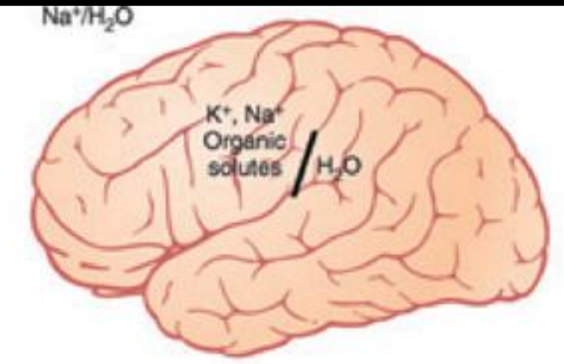
Effect of Adding 2 Liters of 3.0 % NaCl after Osmotic Equilibrium

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

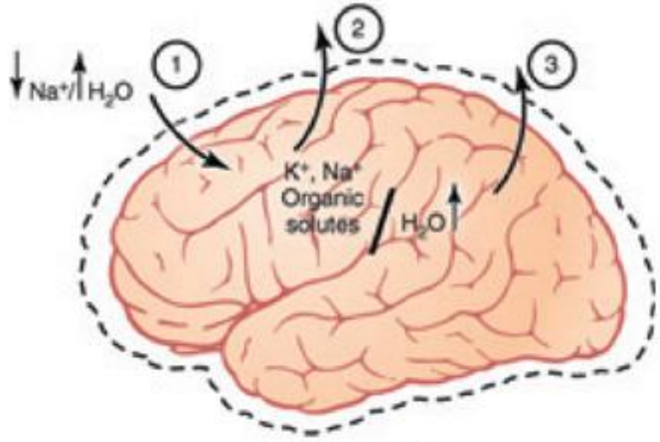
One can see that adding 2 liters of hypertonic NaCl solution causes more tha 5-liters increase in extracellular fluid volume (19.02 – 14 = 5.02), while decreasing intracellular fluid volume by 3 liters (24.98 – 28 = -3.02).


Intracellular fluid
Extracellular fluid
Normal State
Osmolarity
300
200
100
0
10
20
30
40
Volume (liters)
A. Add Isotonic NaCl
C. Add Hypotonic NaCl
B. Add Hypertonic NaCl

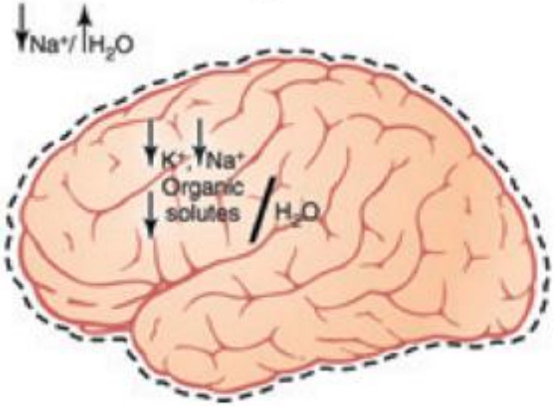
	Abnormality	Cause	Plasma Na^+ Concentration	ECFV	ICFV
	Hyponatremia Dehydration	Adrenal insuffficiency overuse of diuretics vomiting and diarrhea	↓	↓	↑
C	Hyponatremia Overhydratation	Excess ADH (SIADH)	↓	↑	↑
	Hypernatremia Dehydration	Diabetes insipidus excessive sweating (without water intake)	↑	↓	↓
	Hypernatremia Overhydration	Cushing´s disease primary aldosteronism	↑	↑	↓



Normonatremia

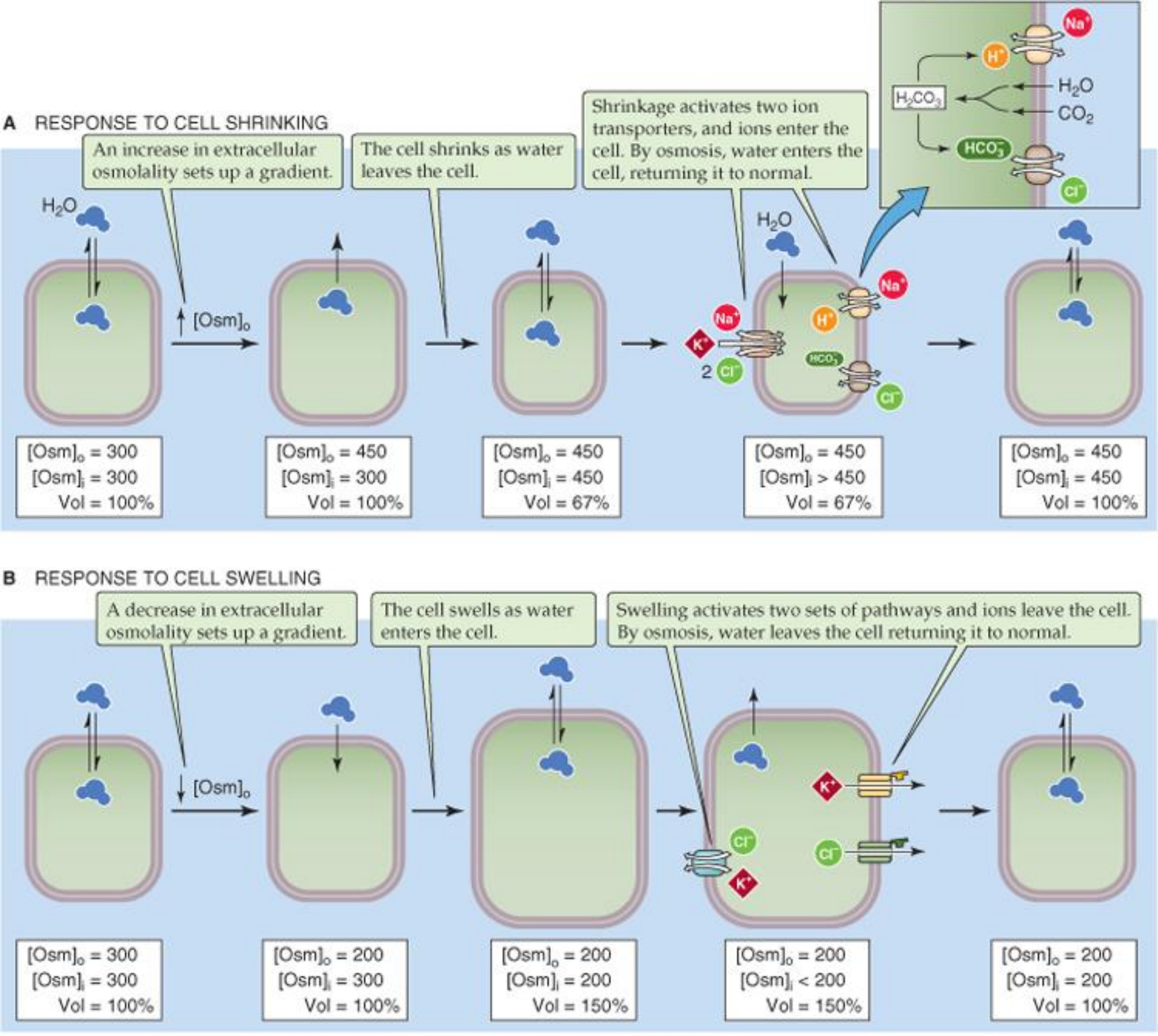


Acute hyponatremia



Chronic hyponatremia

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



A RESPONSE TO CELL SHRINKING

An increase in extracellular osmolality sets up a gradient.

The cell shrinks as water leaves the cell.

Shrinkage activates two ion transporters, and ions enter the cell. By osmosis, water enters the cell, returning it to normal.

$[Osm]_o = 300$
$[Osm]_i = 300$
Vol = 100%

$[Osm]_o = 450$
$[Osm]_i = 300$
Vol = 100%

$[Osm]_o = 450$
$[Osm]_i = 450$
Vol = 67%

$[Osm]_o = 450$
$[Osm]_i > 450$
Vol = 67%

$[Osm]_o = 450$
$[Osm]_i = 450$
Vol = 100%

B RESPONSE TO CELL SWELLING

A decrease in extracellular osmolality sets up a gradient.

The cell swells as water enters the cell.

Swelling activates two sets of pathways and ions leave the cell. By osmosis, water leaves the cell returning it to normal.

$[Osm]_o = 300$
$[Osm]_i = 300$
Vol = 100%

$[Osm]_o = 200$
$[Osm]_i = 300$
Vol = 100%

$[Osm]_o = 200$
$[Osm]_i = 200$
Vol = 150%

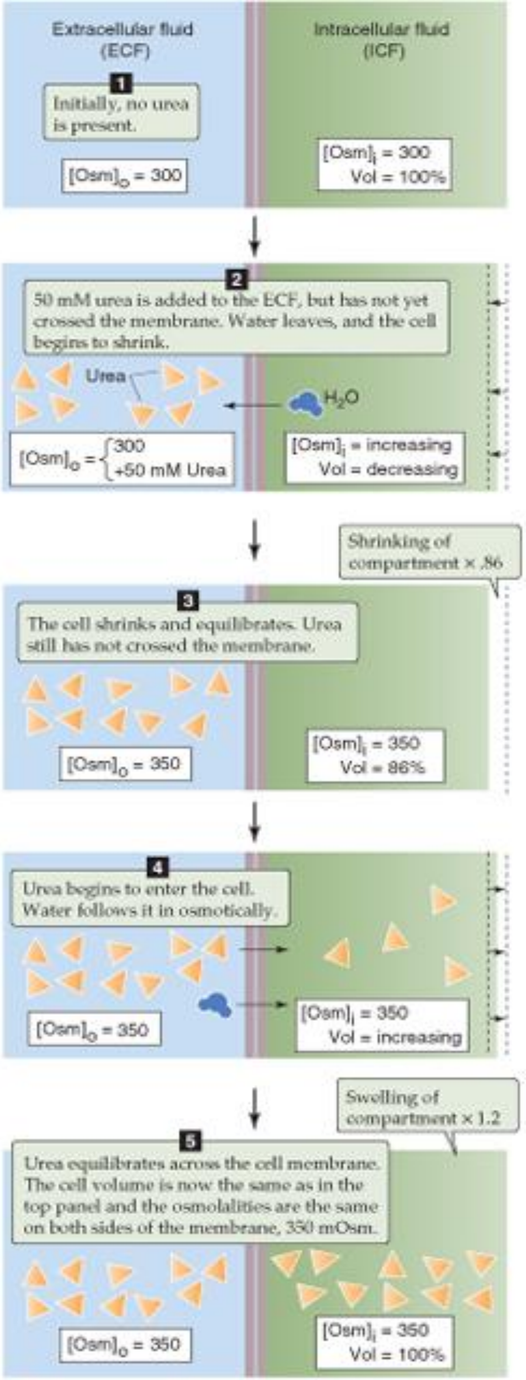
$[Osm]_o = 200$
$[Osm]_i < 200$
Vol = 150%

$[Osm]_o = 200$
$[Osm]_i = 200$
Vol = 100%

Boron & Boulpaep: Medical Physiology, 2nd Edition.

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

Regulatory volume decrease



1 Initially, no urea is present.

2 50 mM urea is added to the ECF, but has not yet crossed the membrane. Water leaves, and the cell begins to shrink.

Shrinking of compartment × .86

3 The cell shrinks and equilibrates. Urea still has not crossed the membrane.

4 Urea begins to enter the cell. Water follows it in osmotically.

Swelling of compartment × 1.2

5 Urea equilibrates across the cell membrane. The cell volume is now the same as in the top panel and the osmolalities are the same on both sides of the membrane, 350 mOsm.

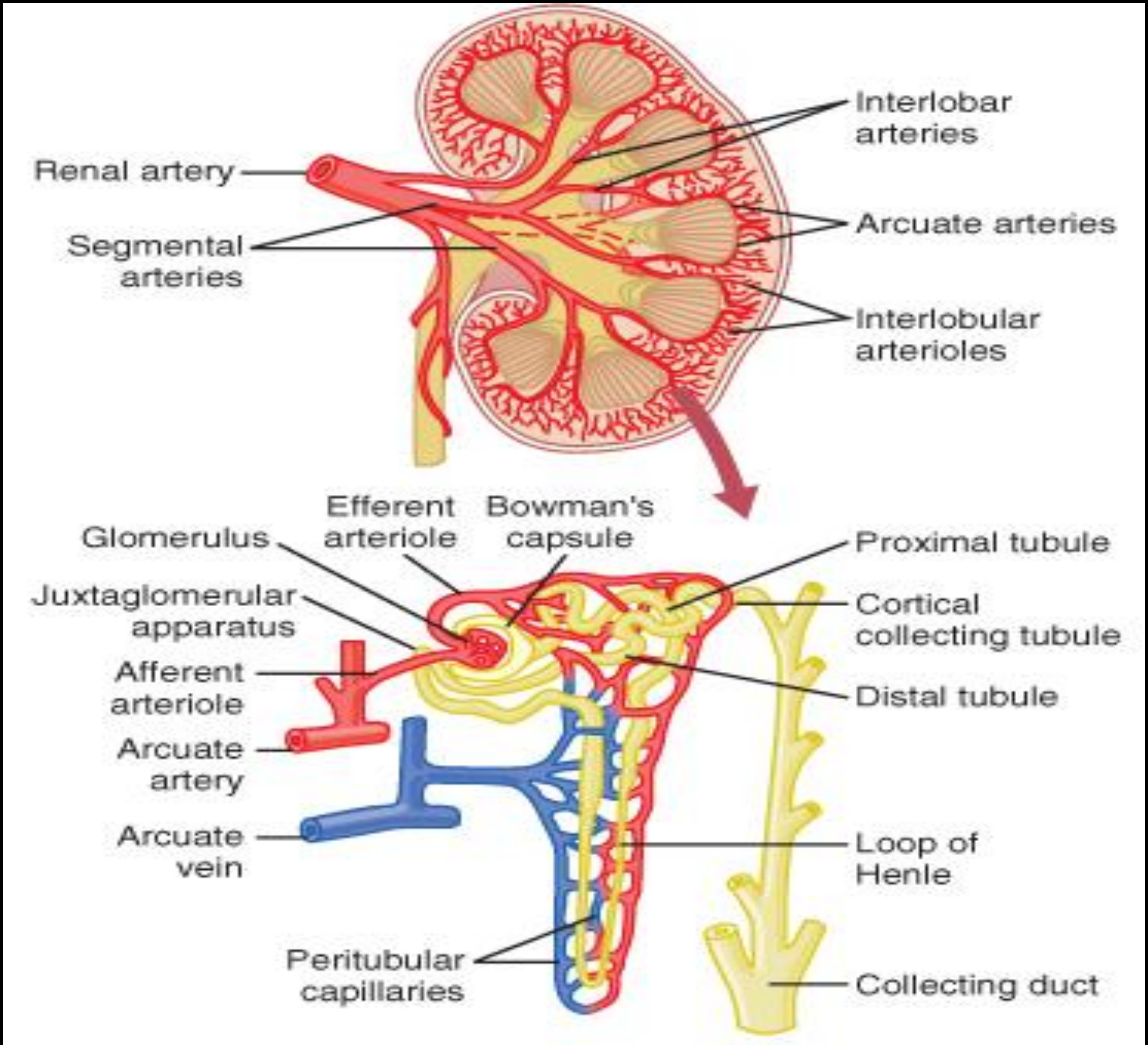
$$\text{Total osmolality (mOsm)} \cong 2\cdot[\text{Na}^+] + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

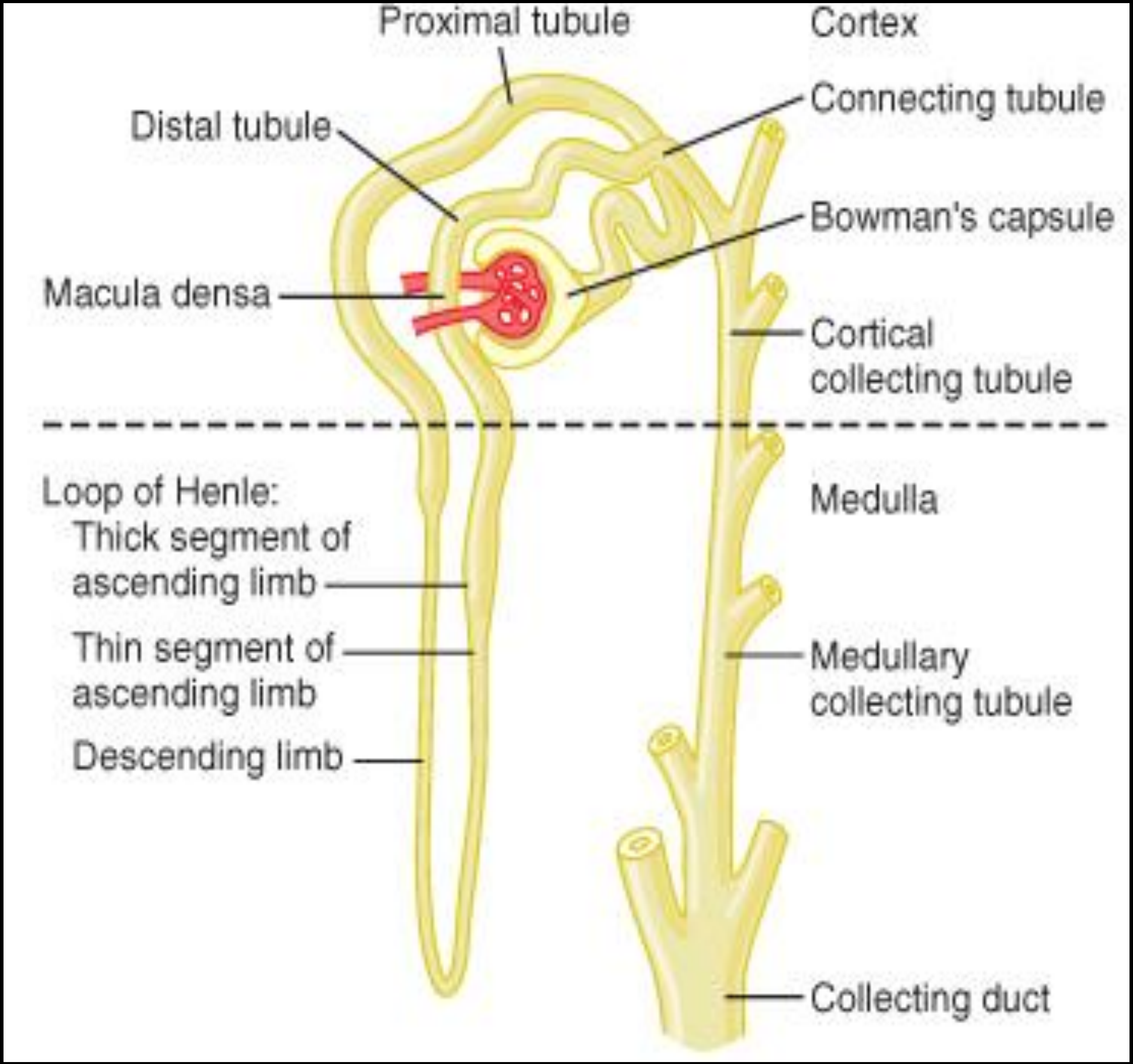
$$\text{Tonicity or effective osmolality (mOsm)} \cong 2\cdot[\text{Na}^+] + \frac{\text{Glucose (mg/dL)}}{18} \qquad (5\text{-}32)$$

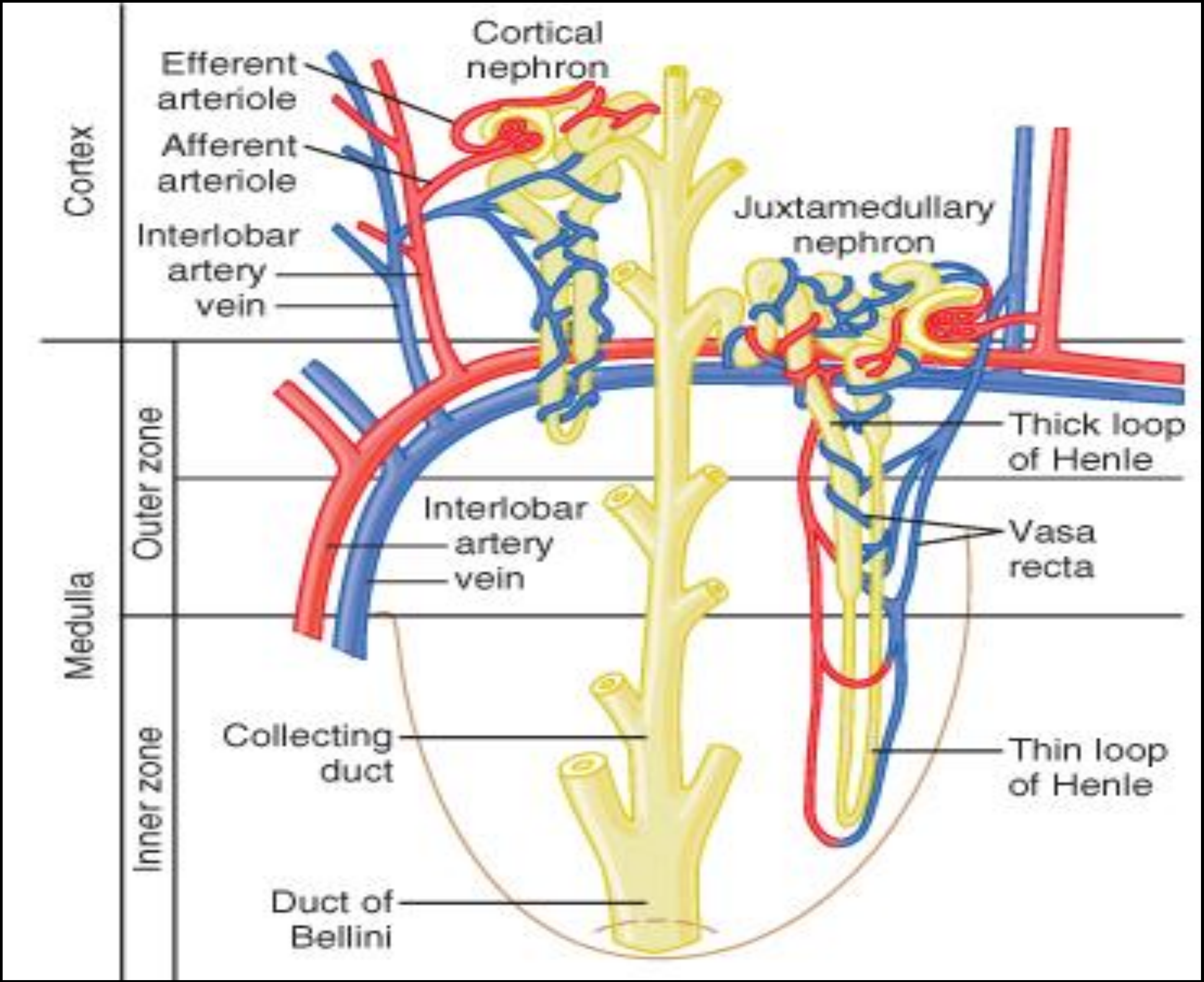
Boron & Boulpaep: Medical Physiology, 2nd Edition.

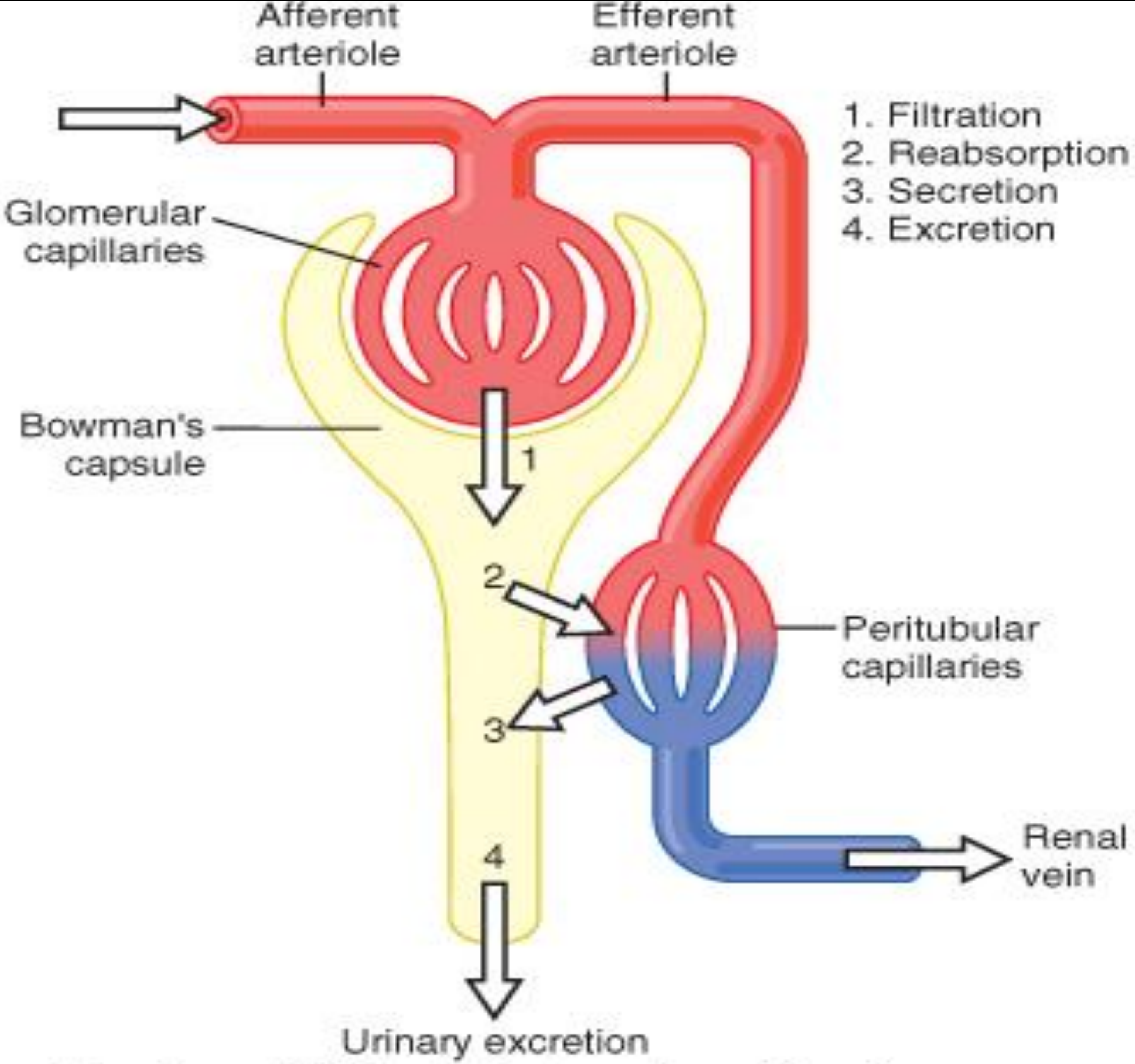
Kidneys serve following functions:

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

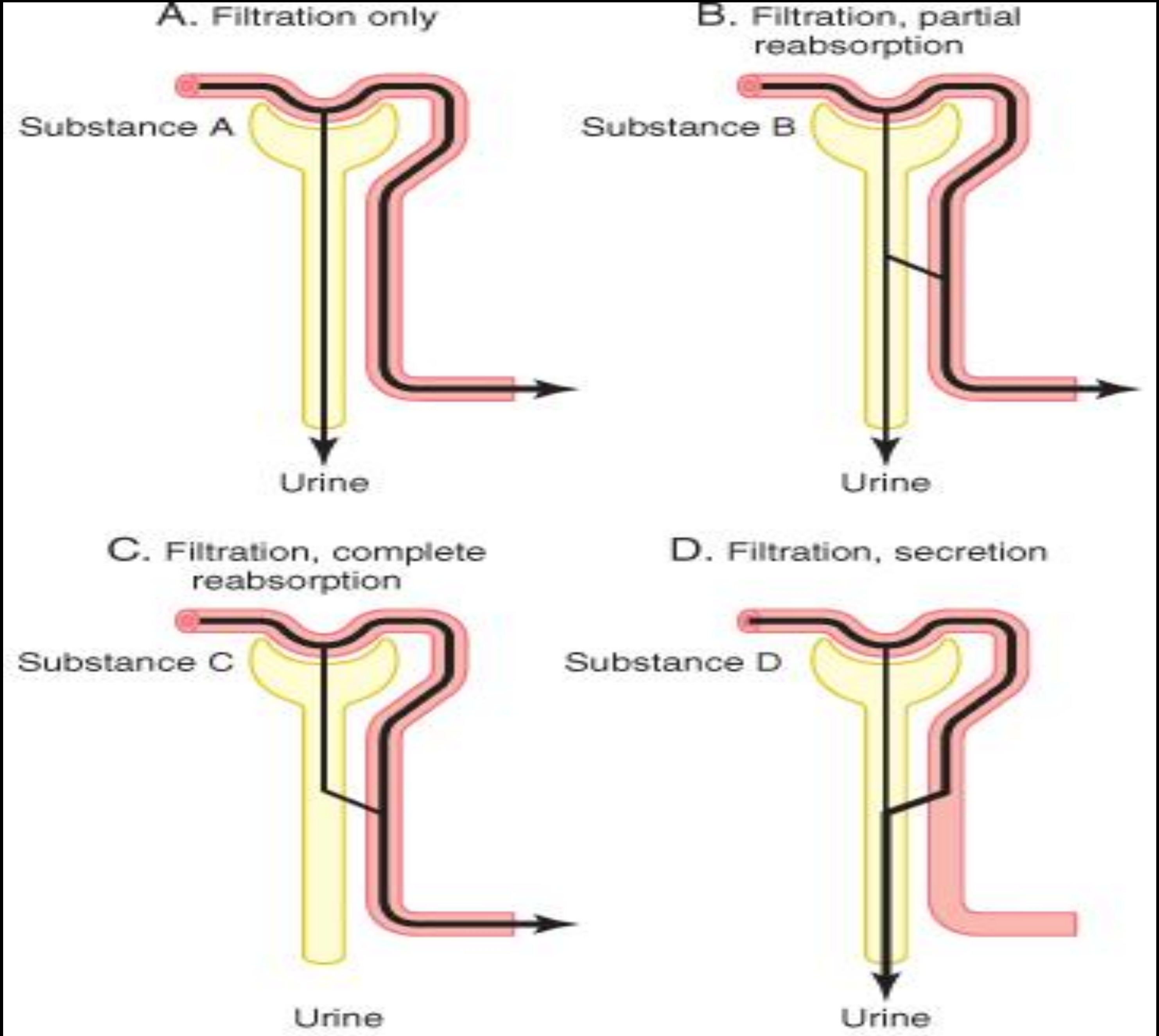

Interlobar arteries
Renal artery
Arcuate arteries
Segmental arteries
Interlobular arterioles
Efferent arteriole
Bowman's capsule
Glomerulus
Proximal tubule
Juxtaglomerular apparatus
Cortical collecting tubule
Afferent arteriole
Distal tubule
Arcuate artery
Arcuate vein
Loop of Henle
Peritubular capillaries
Collecting duct


Proximal tubule
Cortex
Connecting tubule
Distal tubule
Bowman's capsule
Macula densa
Cortical collecting tubule
Loop of Henle:
Medulla
Thick segment of ascending limb
Thin segment of ascending limb
Medullary collecting tubule
Descending limb
Collecting duct


Cortical nephron
Efferent arteriole
Afferent arteriole
Cortex
Interlobar
artery
vein
Juxtamedullary nephron
Thick loop of Henle
Outer zone
Interlobar
artery
vein
Vasa recta
Medulla
Collecting duct
Thin loop of Henle
Inner zone
Duct of Bellini



Excretion = Filtration – Reabsorption + Secretion

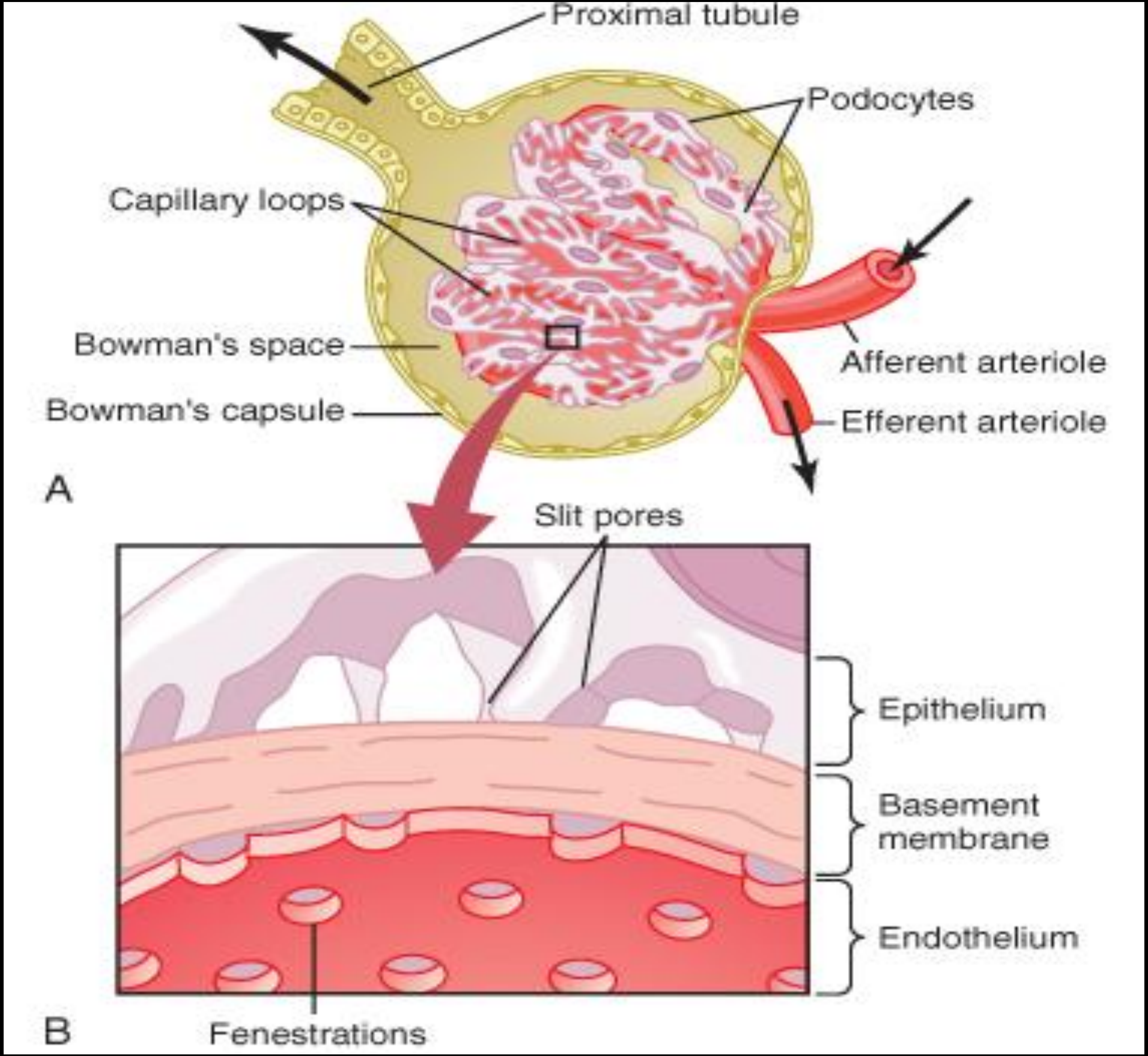


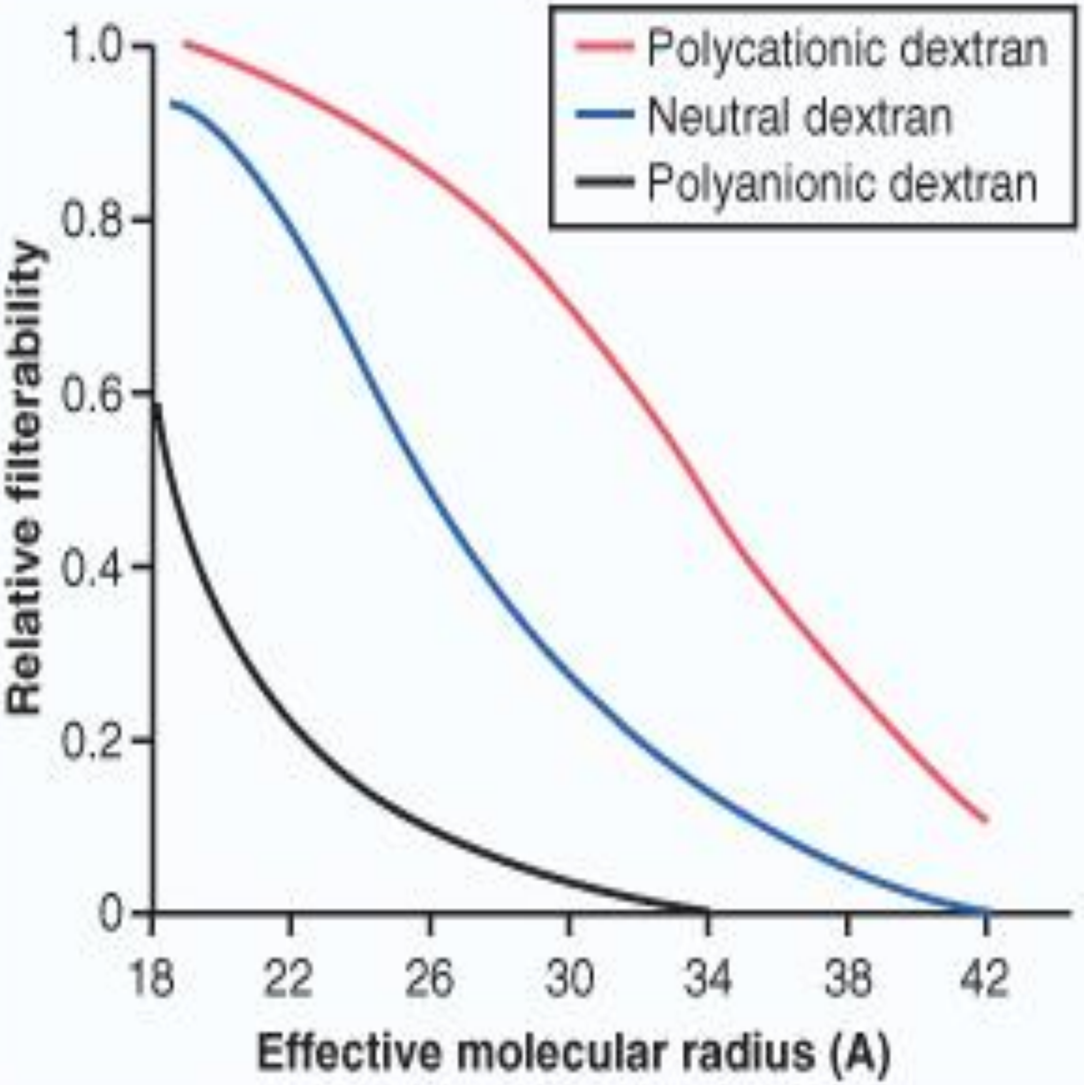
A. Filtration only

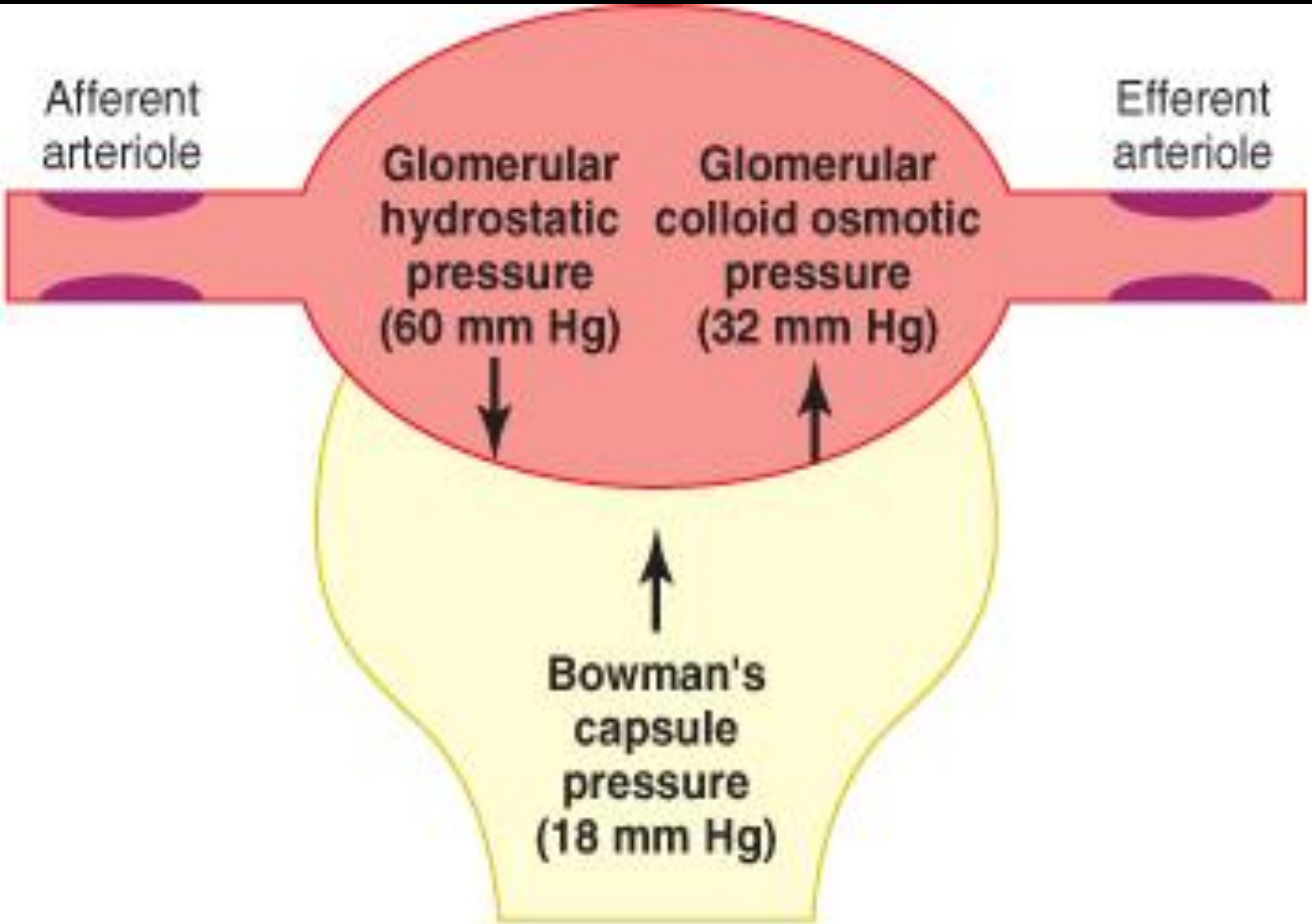
B. Filtration, partial reabsorption

C. Filtration, complete reabsorption

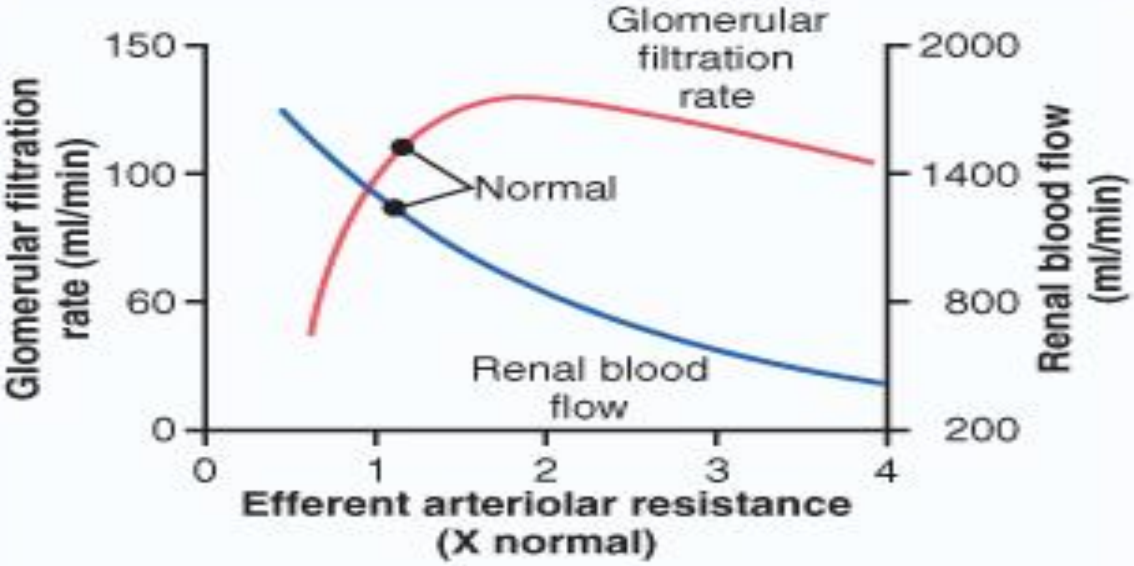
D. Filtration, secretion

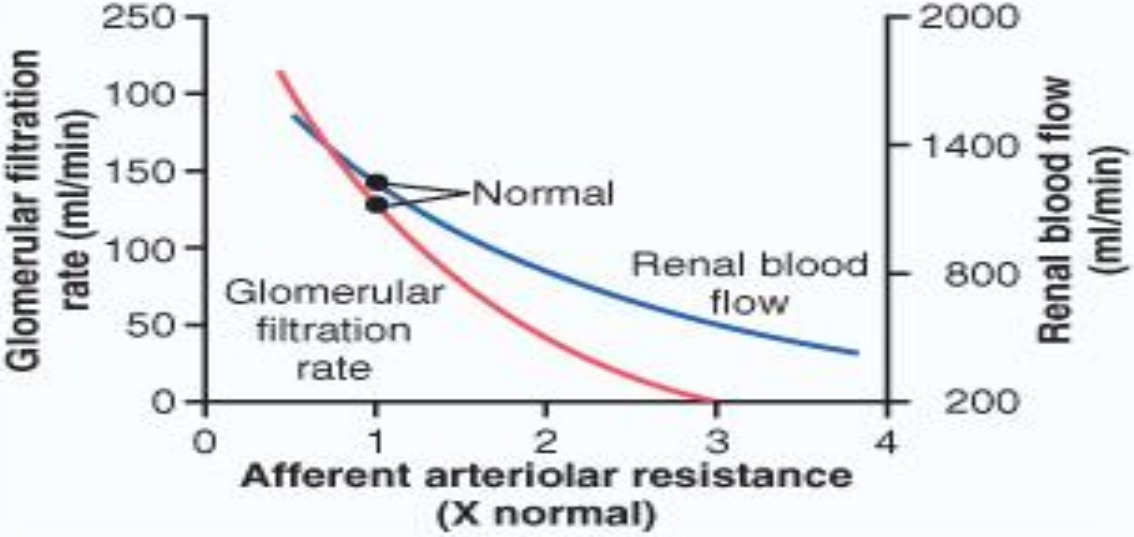

Proximal tubule
Podocytes
Capillary loops
Bowman's space
Bowman's capsule
Afferent arteriole
Efferent arteriole
A
Slit pores
Epithelium
Basement membrane
Endothelium
B
Fenestrations


Polycationic dextran
Neutral dextran
Polyanionic dextran
Relative filterability
1.0
0.8
0.6
0.4
0.2
0
18
22
26
30
34
38
42
Effective molecular radius (A)

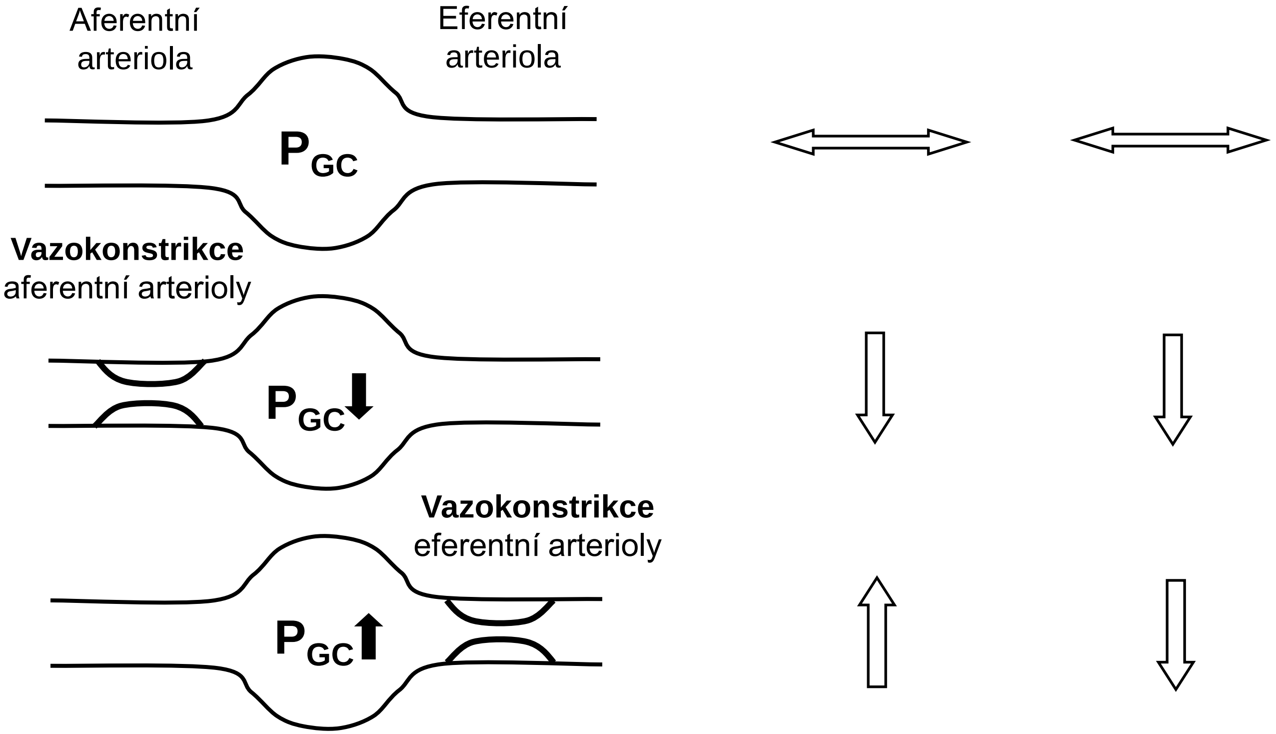


Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) – Bowman's capsule pressure (18 mm Hg) – Glomerular oncotic pressure (32 mm Hg)

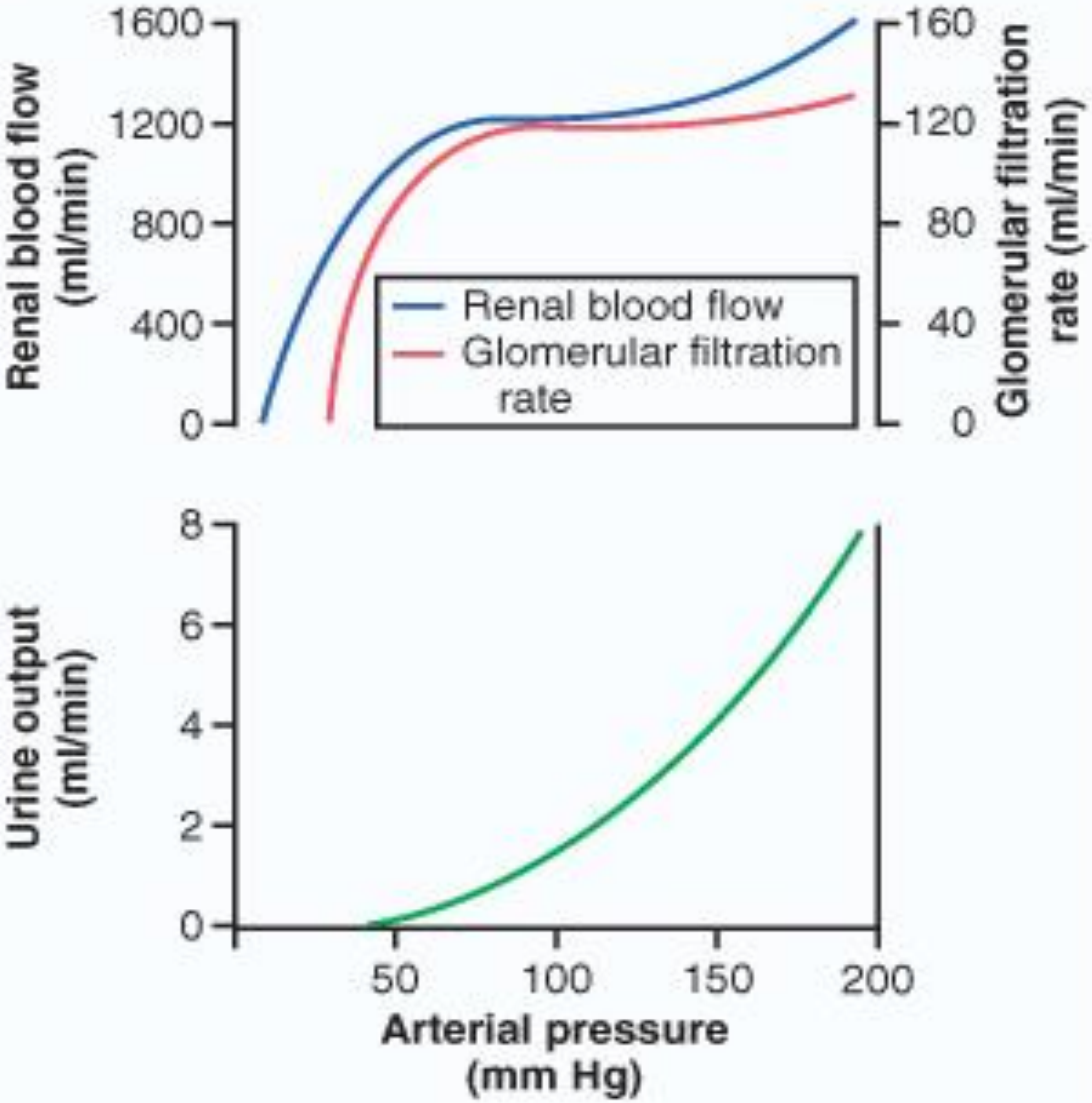

Glomerular filtration rate
Glomerular filtration rate (ml/min)
150
100
60
0
Normal
Renal blood flow
Renal blood flow (ml/min)
2000
1400
800
200
0
1
2
3
4
Efferent arteriolar resistance (X normal)


Glomerular filtration rate (ml/min)
250
100
150
100
50
0
Normal
Renal blood flow
Glomerular filtration rate
Renal blood flow (ml/min)
2000
1400
800
200
0
1
2
3
4
Afferent arteriolar resistance (X normal)

GLOMERULÁRNÍ KAPILÁRY

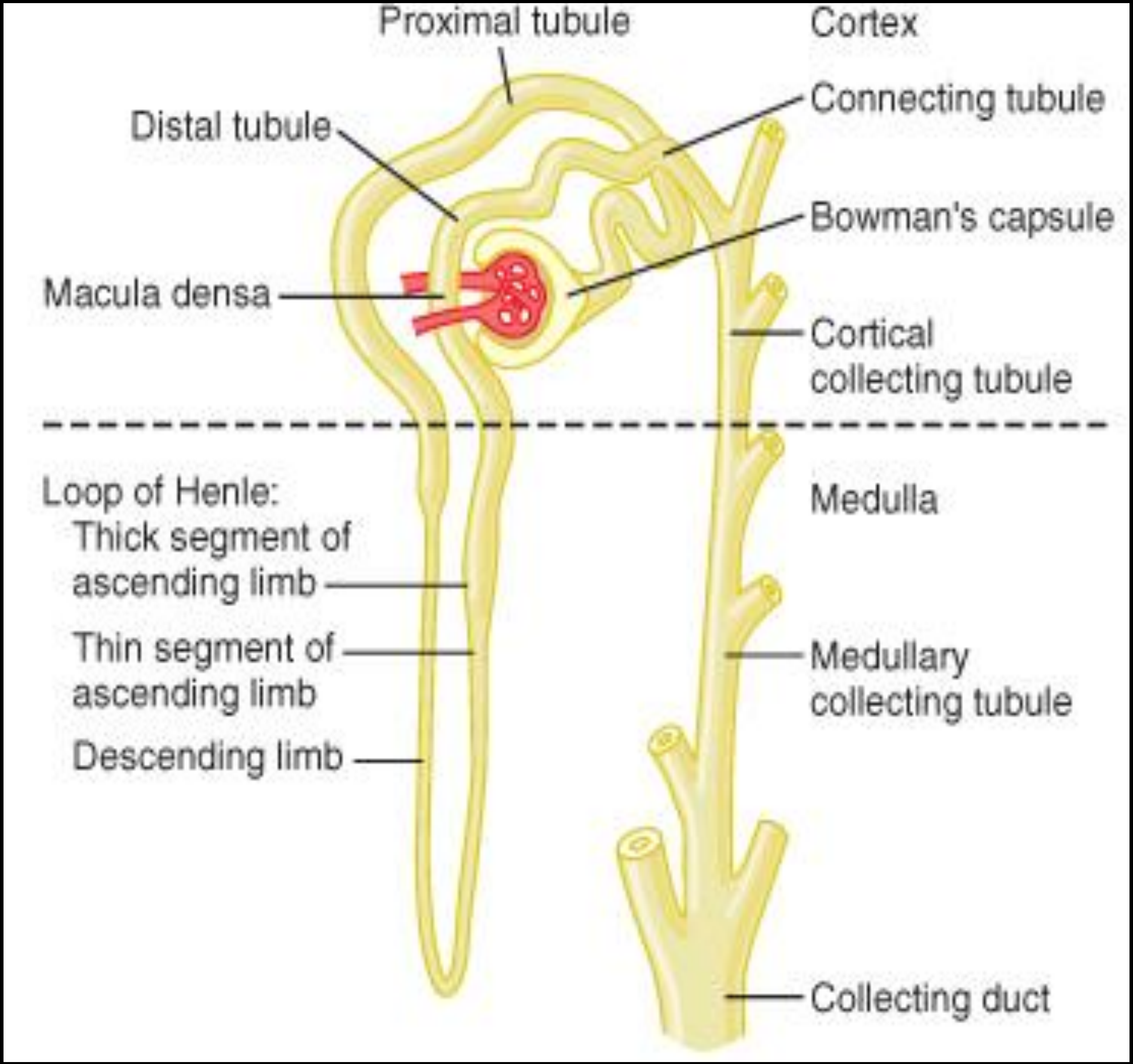


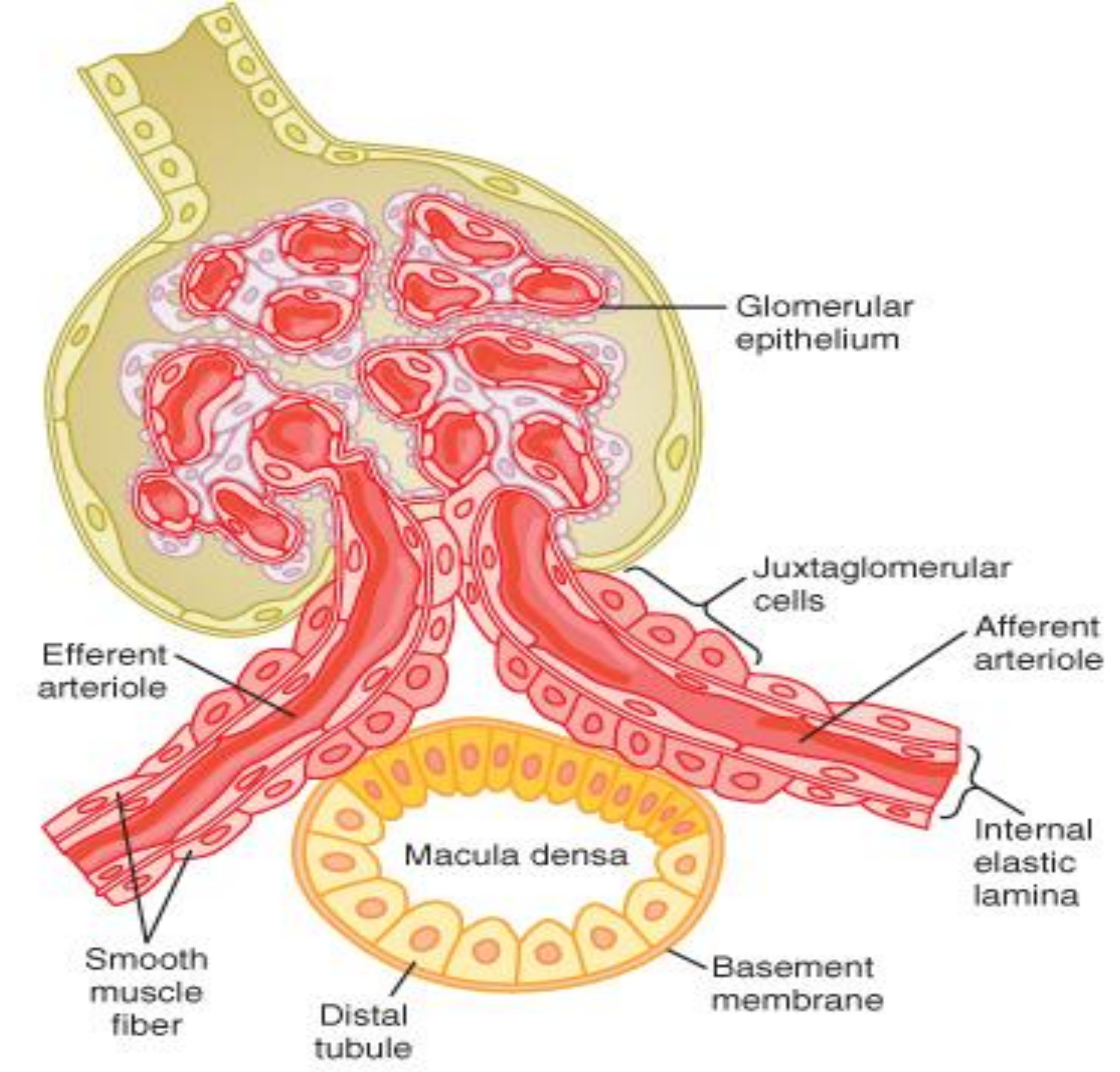
	GLOMERULÁRNÍ FILTRACE	**PRŮTOK KRVE LEDVINAMI**
P_{GC}	⇔	⇔
Vazokonstrikce aferentní arterioly P_{GC} ↓	⇩	⇩
Vazokonstrikce eferentní arterioly P_{GC} ↑	⇧	⇩

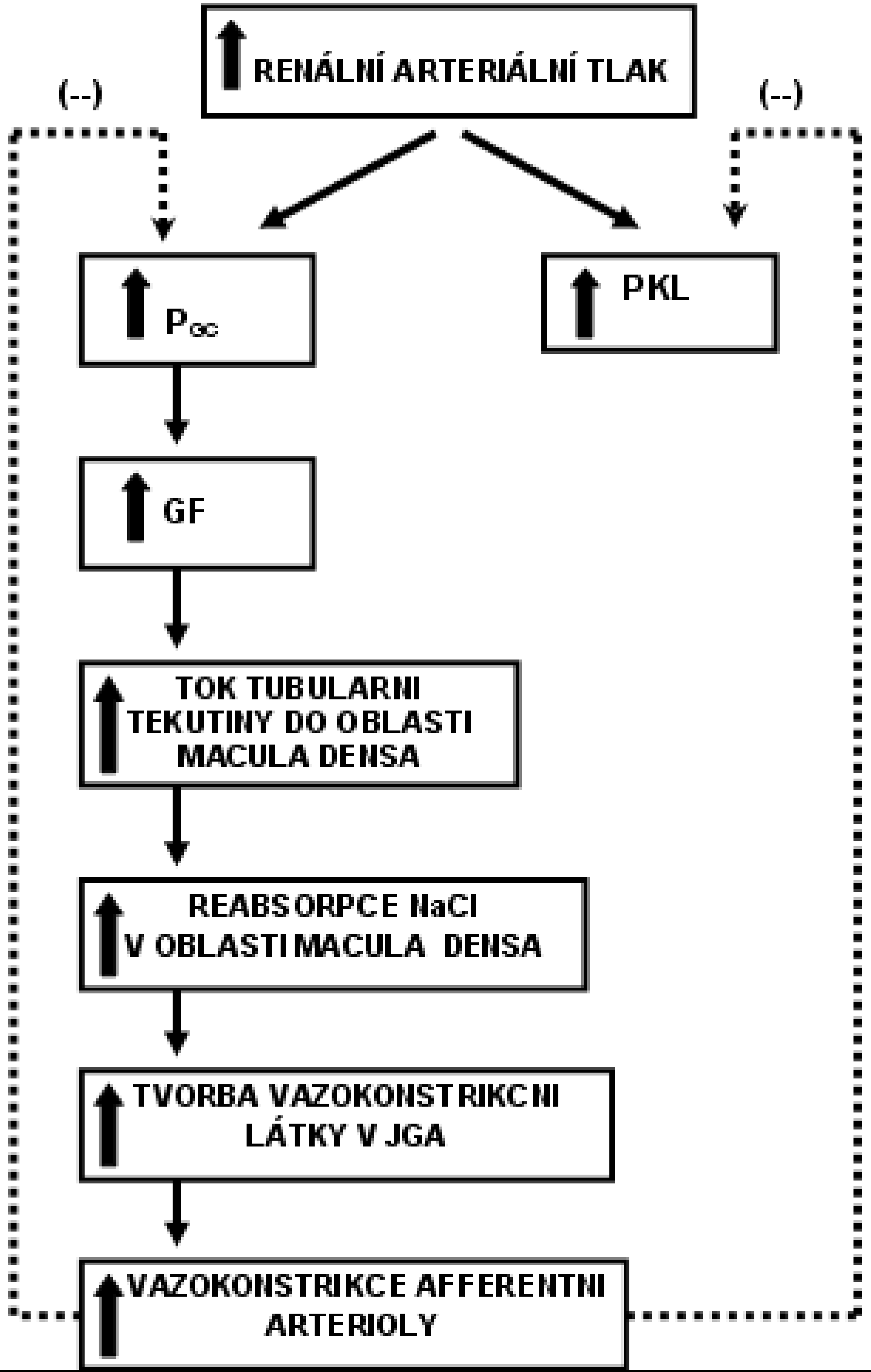

1600
1200
800
400
0
Renal blood flow (ml/min)
160
120
80
40
0
Glomerular filtration rate (ml/min)
Renal blood flow
Glomerular filtration rate
8
6
4
2
0
Urine output (ml/min)
50
100
150
200
Arterial pressure (mm Hg)

Autoregulation of Glomerular Filtration Rate and Renal Blood Flow

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


Proximal tubule
Cortex
Connecting tubule
Distal tubule
Bowman's capsule
Macula densa
Cortical collecting tubule
Medulla
Loop of Henle:
Thick segment of ascending limb
Thin segment of ascending limb
Descending limb
Medullary collecting tubule
Collecting duct


Glomerular epithelium
Juxtaglomerular cells
Afferent arteriole
Efferent arteriole
Internal elastic lamina
Macula densa
Smooth muscle fiber
Distal tubule
Basement membrane



↑ RENÁLNÍ ARTERIÁLNÍ TLAK

(--)

(--)

↑ P_{GC}

↑ PKL

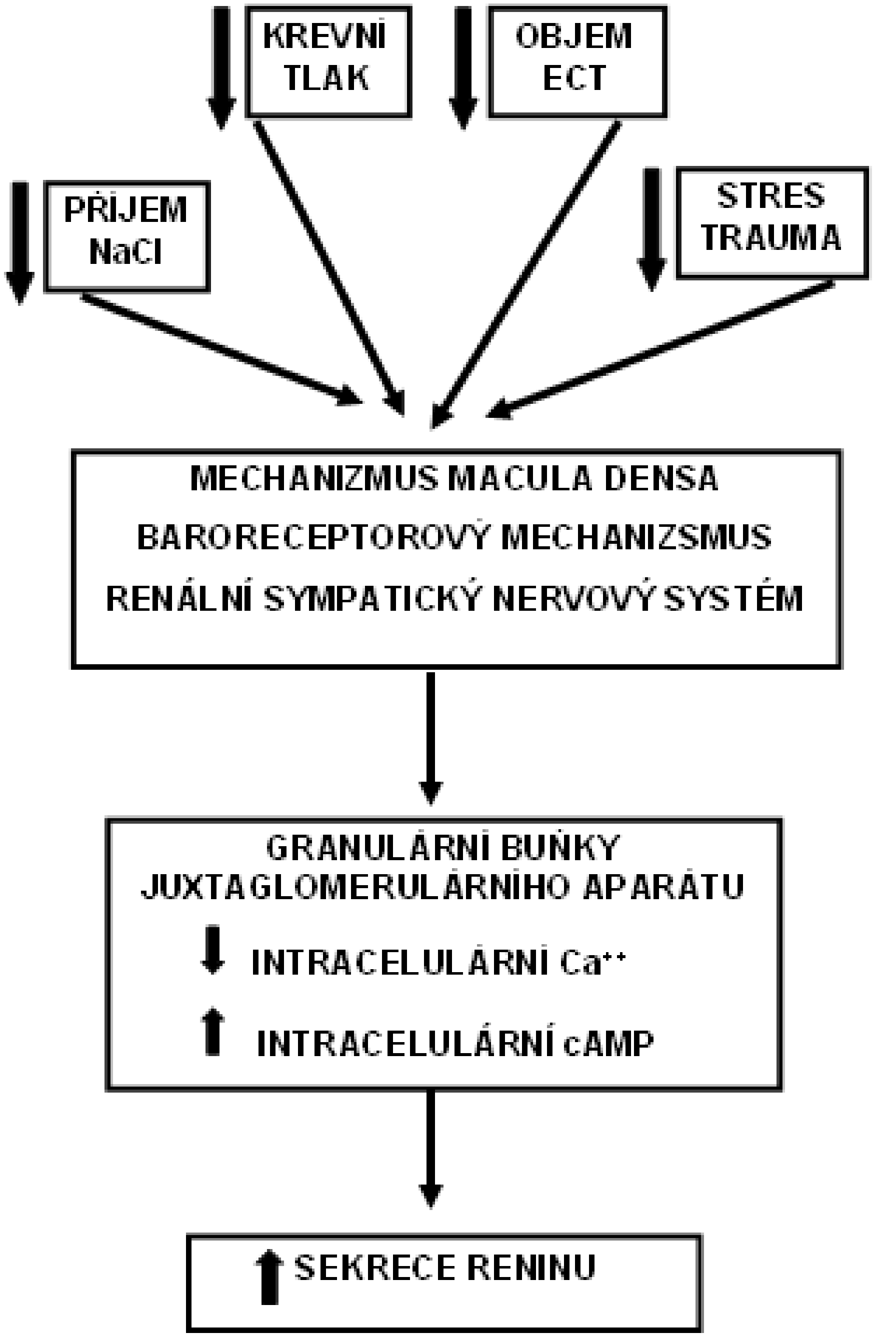
↑ GF

↑ TOK TUBULARNI TEKUTINY DO OBLASTI MACULA DENSA

↑ REABSORPCE NaCl V OBLASTI MACULA DENSA

↑ TVORBA VAZOKONSTRIKCNI LÁTKY V JGA

↑ VAZOKONSTRIKCE AFFERENTNI ARTERIOLY



↓ KREVNÍ TLAK

↓ OBJEM ECT

↓ PŘÍJEM NaCl

↓ STRES TRAUMA

MECHANIZMUS MACULA DENSA

BARORECEPTOROVÝ MECHANIZSMUS

RENÁLNÍ SYMPATICKÝ NERVOVÝ SYSTÉM

GRANULÁRNÍ BUŇKY JUXTAGLOMERULÁRNÍHO APARÁTU

↓ INTRACELULÁRNÍ Ca^{++}

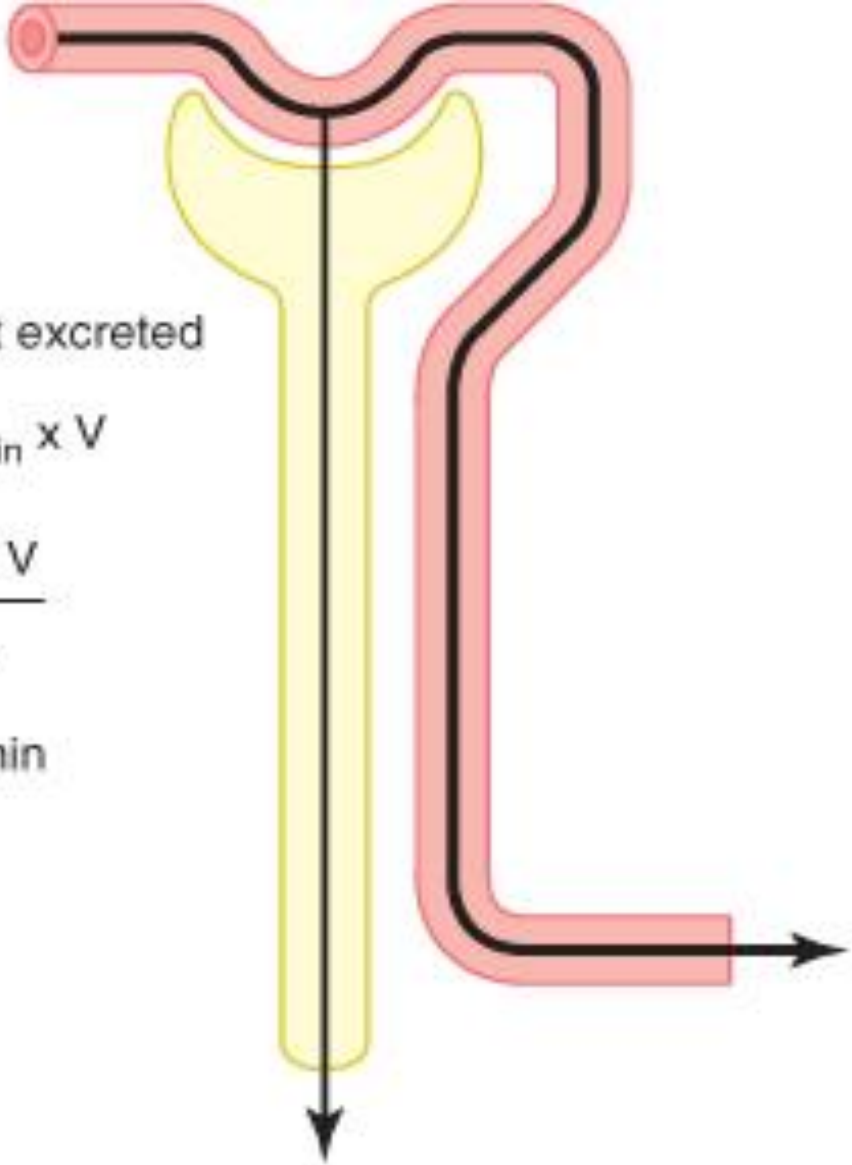
↑ INTRACELULÁRNÍ cAMP

↑ SEKRECE RENINU

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_{inulin} = 1 mg/ml



Amount filtered = Amount excreted

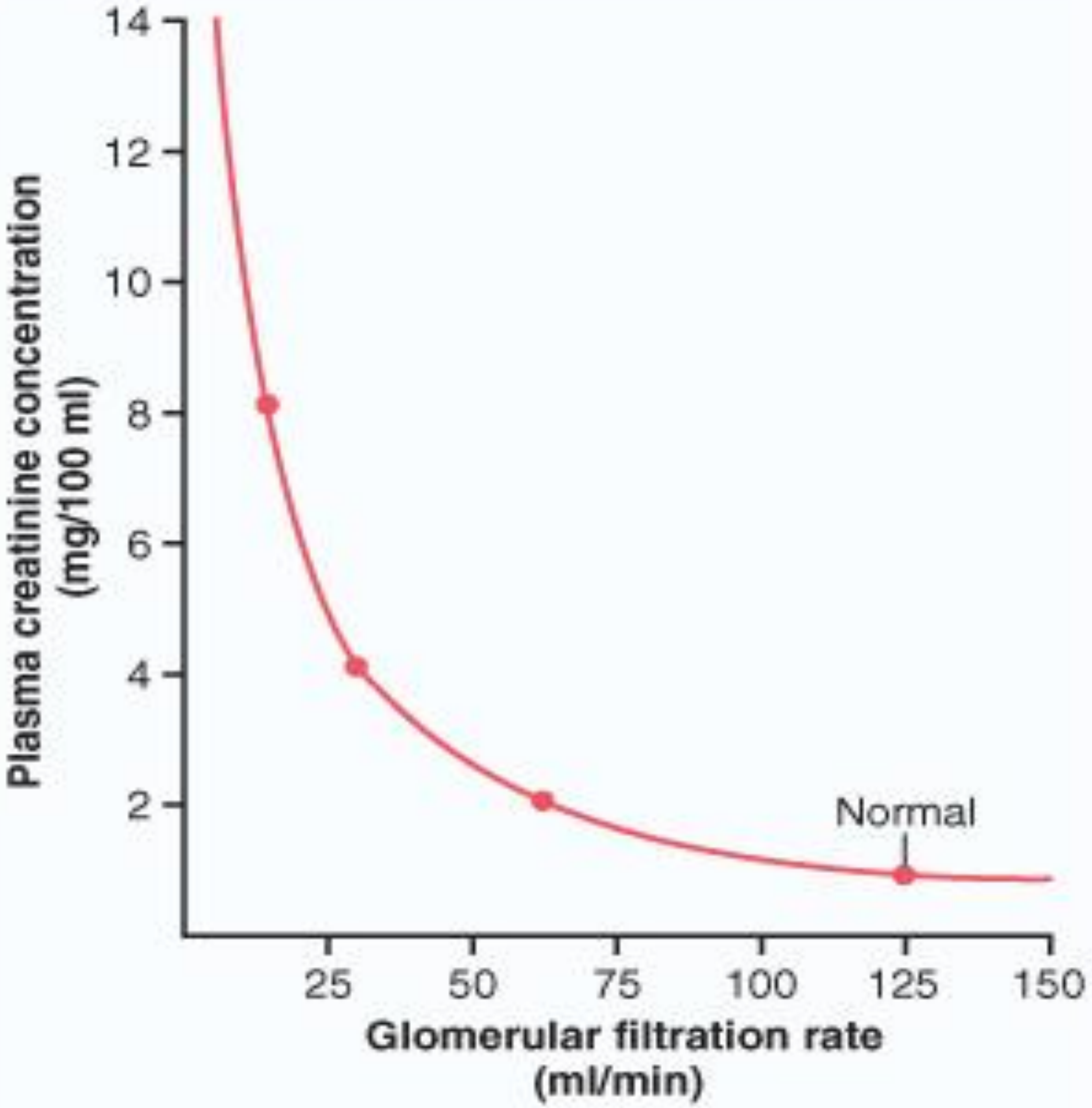
$$GFR \times P_{inulin} = U_{inulin} \times V$$

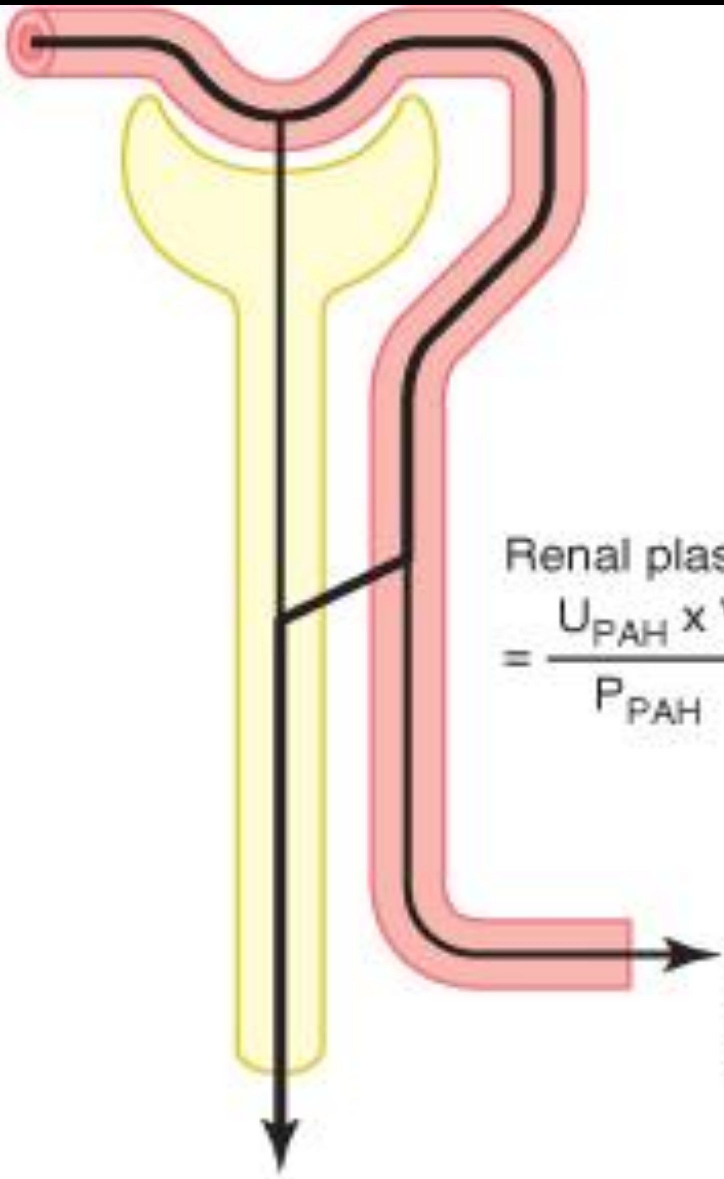
$$GFR = \frac{U_{inulin} \times V}{P_{inulin}}$$

GFR = 125 ml/min

U_{inulin} = 125 mg/ml

V = 1 ml/min


Plasma creatinine concentration (mg/100 ml)
14
12
10
8
6
4
2
Normal
25
50
75
100
125
150
Glomerular filtration rate (ml/min)



$P_{PAH} = 0.01$ mg/ml

Renal plasma flow

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

Renal venous PAH = 0.001 mg/ml

$U_{PAH} = 5.85$ mg/ml

V = 1 ml/min

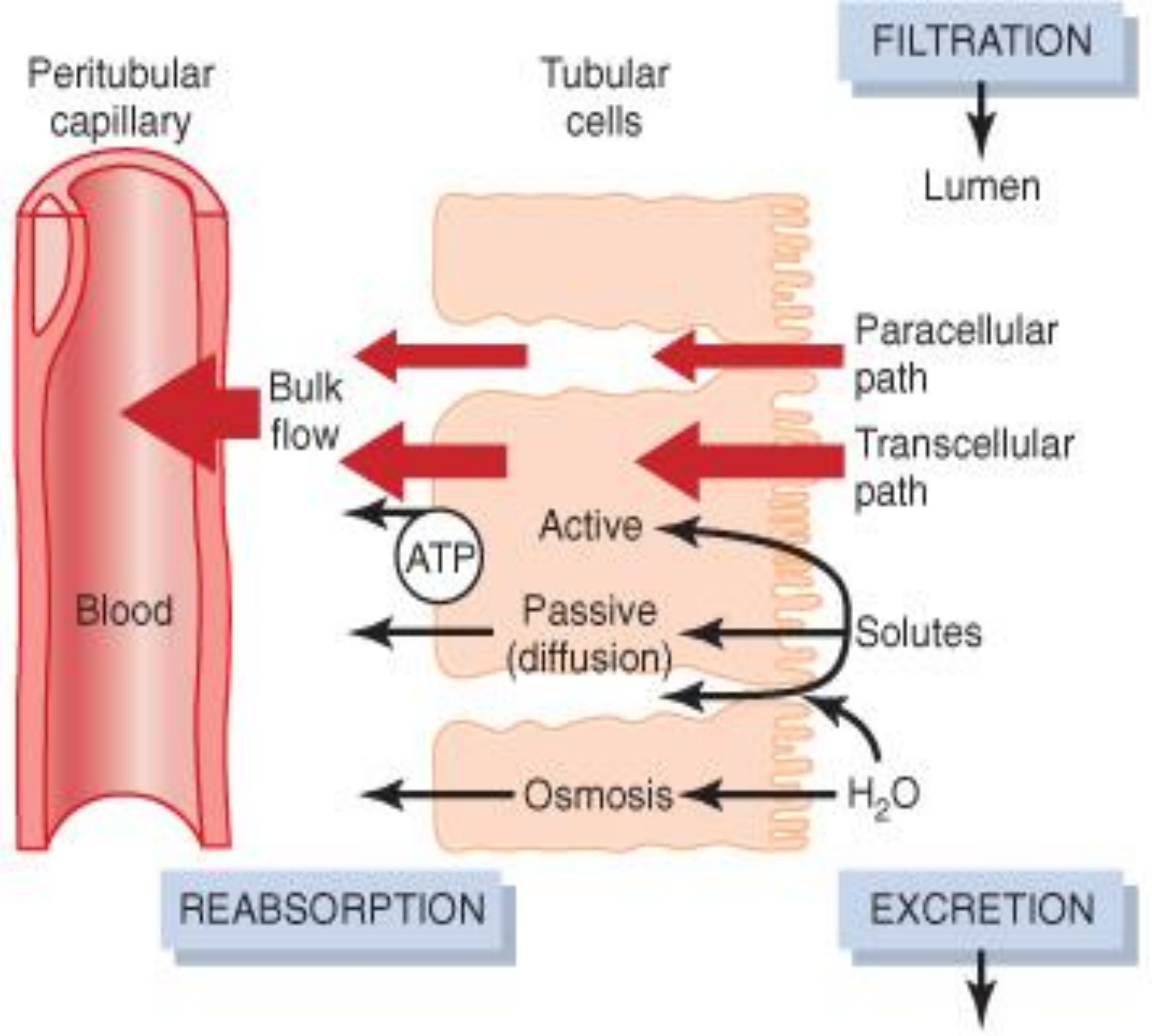
Tubular Processing of the Glomerular Filtrate

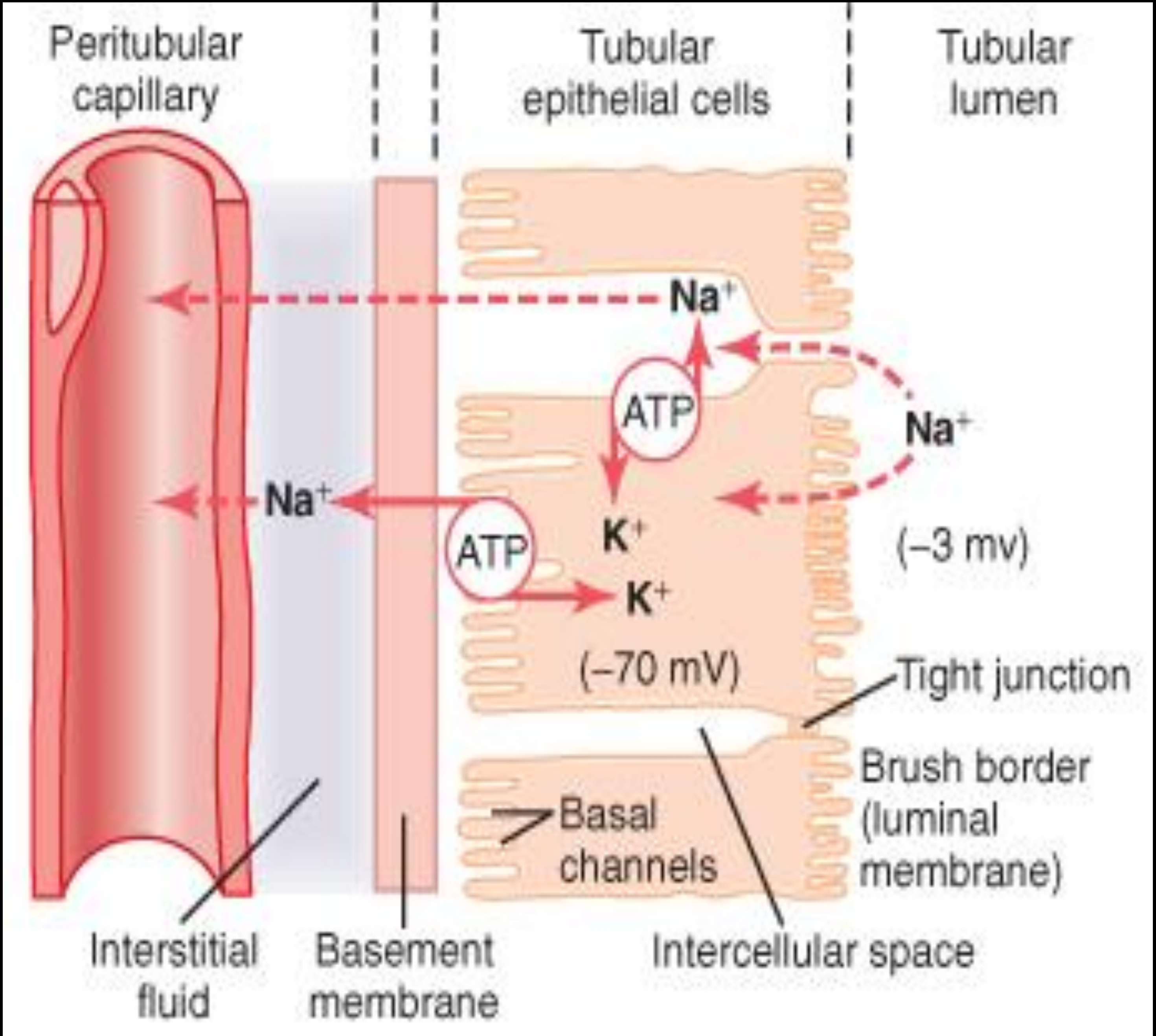
Urinary excretion = Glomerular Filtration – Tubular reabsorption
+ Tubular Secretion

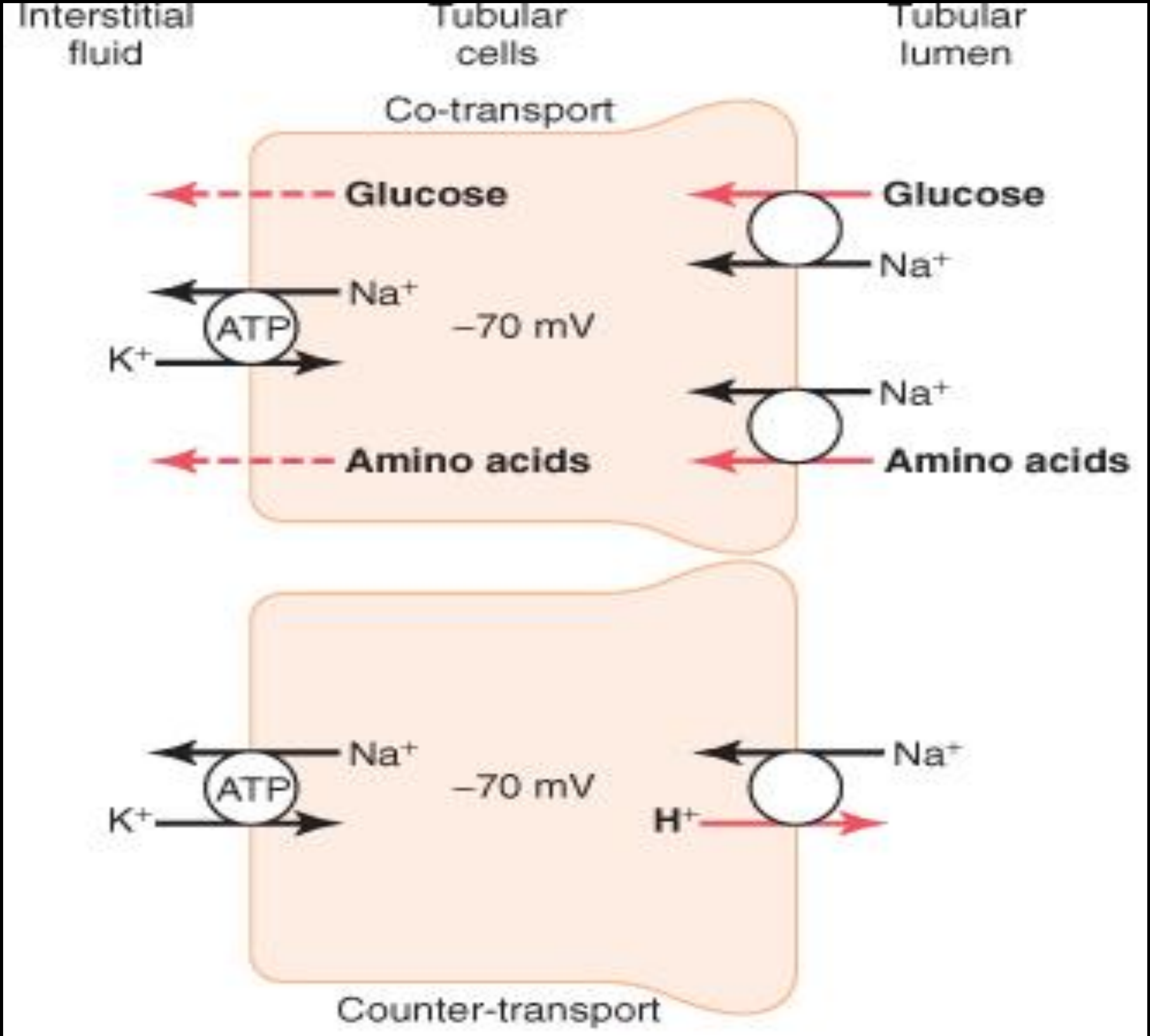
1. **The processes of glomerular filtration and tubular reabsorption are quantitatively very large relative to urinary excretion for many substances.**
2. **Unlike glomerular filtration, tubular reabsorption is highly selective.**

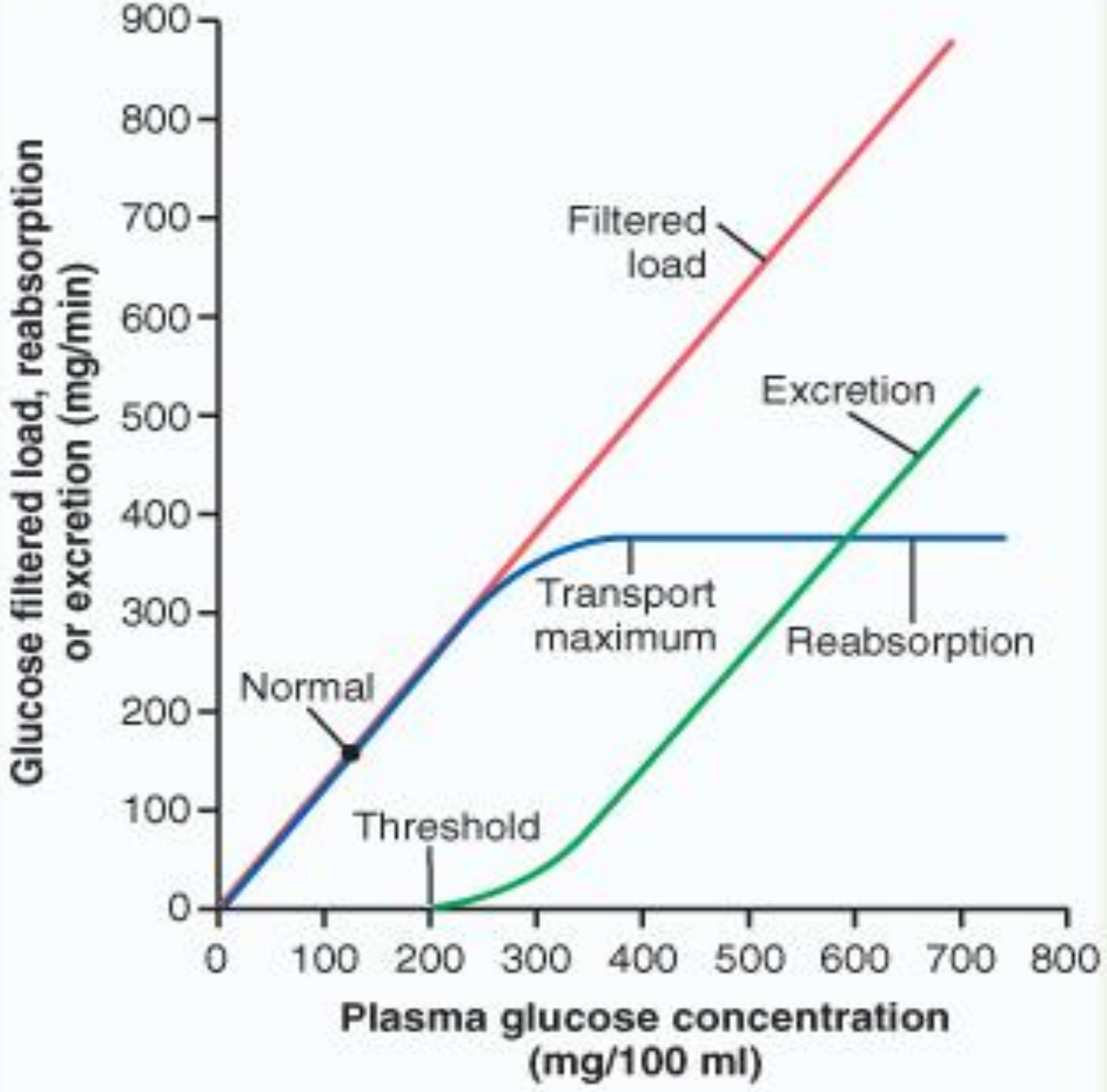
Filtration, Reabsorption and Excretion Rates of Different Substances by the Kidneys

	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


FILTRATION
Peritubular capillary
Tubular cells
Lumen
Paracellular path
Bulk flow
Transcellular path
Active
ATP
Blood
Passive (diffusion)
Solutes
Osmosis
H_2O
REABSORPTION
EXCRETION

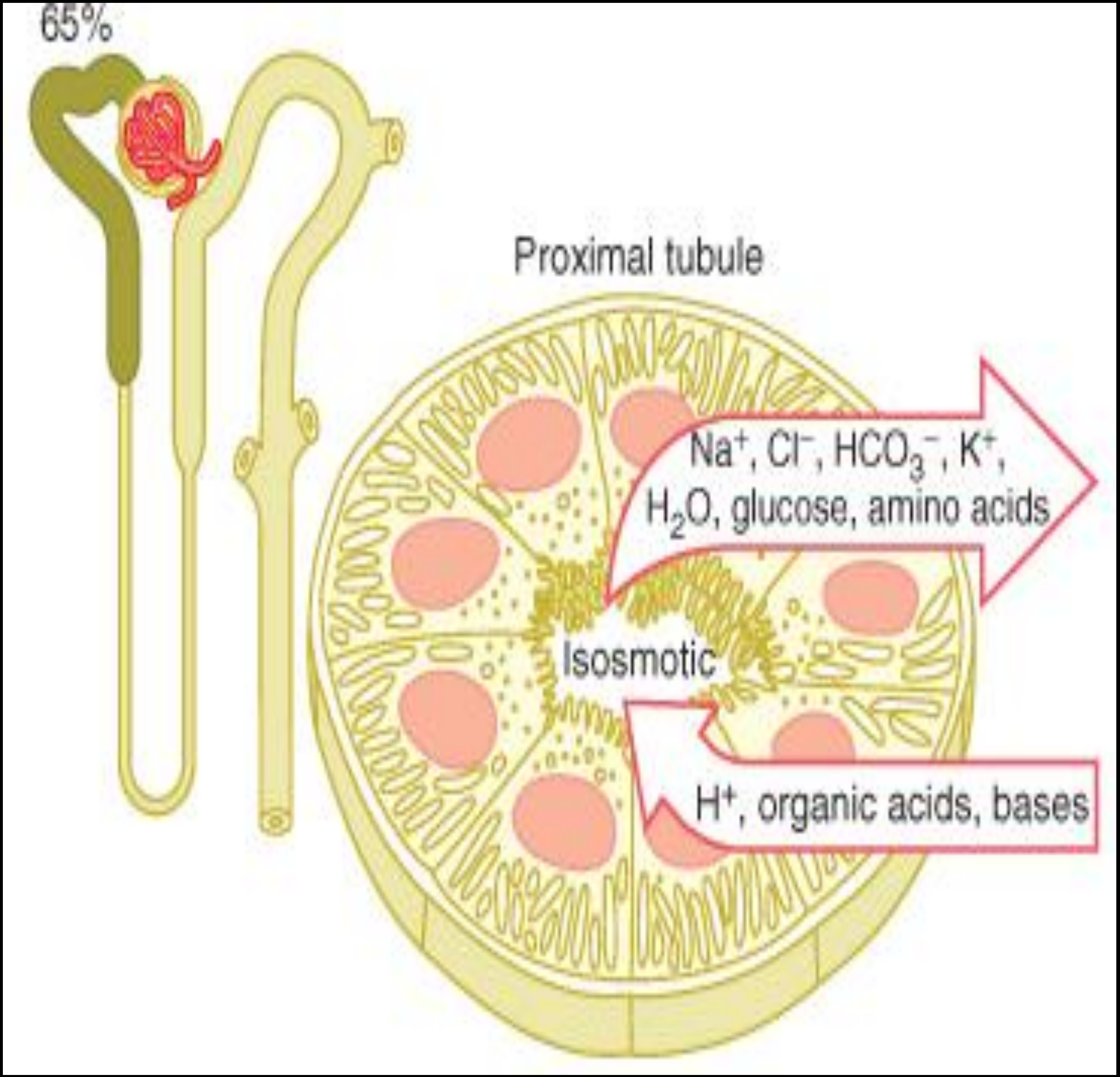

Peritubular capillary
Tubular epithelial cells
Tubular lumen
Na+
ATP
Na+
Na+
ATP
K+
K+
(−3 mv)
(−70 mV)
Tight junction
Brush border (luminal membrane)
Basal channels
Interstitial fluid
Basement membrane
Intercellular space

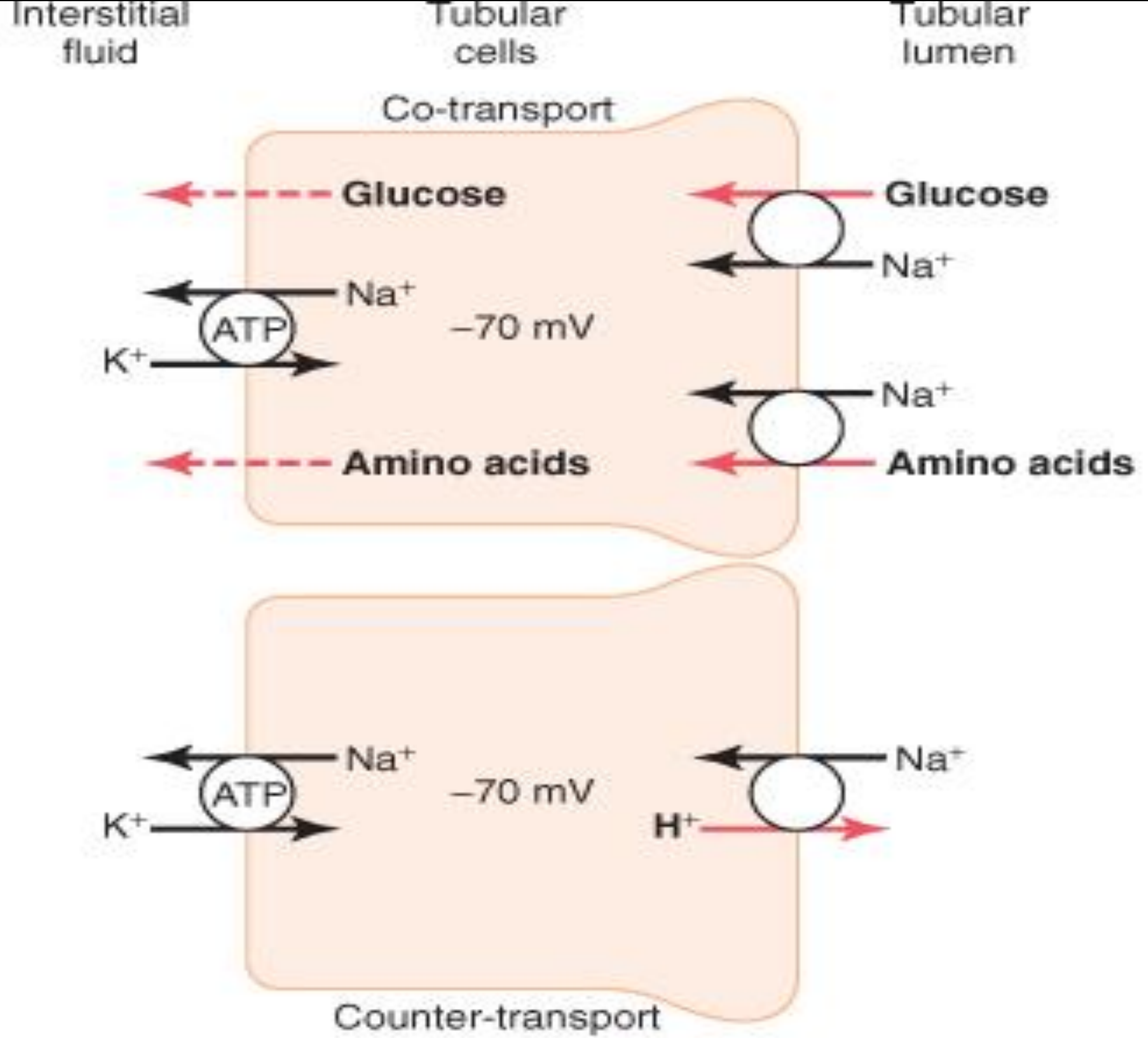

Interstitial fluid
Tubular cells
Tubular lumen
Co-transport
Glucose
Glucose
Na+
Na+
ATP
K+
–70 mV
Na+
Amino acids
Amino acids
Na+
ATP
K+
–70 mV
Na+
H+
Counter-transport


Glucose filtered load, reabsorption or excretion (mg/min)
900
800
700
600
500
400
300
200
100
0
Filtered load
Excretion
Transport maximum
Reabsorption
Normal
Threshold
0
100
200
300
400
500
600
700
800
Plasma glucose concentration (mg/100 ml)

Comparison of sodium and water reabsorption along the tubule

	Percent of filtered load reabsorbed (%)	
Tubular segment	**Sodium**	**Water**
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 *(during water-loading)* >24 *(during dehydration)*


65%
Proximal tubule
Na^+, Cl^-, HCO_3^-, K^+,
H_2O, glucose, amino acids
Isosmotic
H^+, organic acids, bases



Interstitial fluid

Tubular cells

Tubular lumen

Co-transport

Glucose

Glucose

Na^+

Na^+

ATP

K^+

–70 mV

Na^+

Amino acids

Amino acids

Na^+

ATP

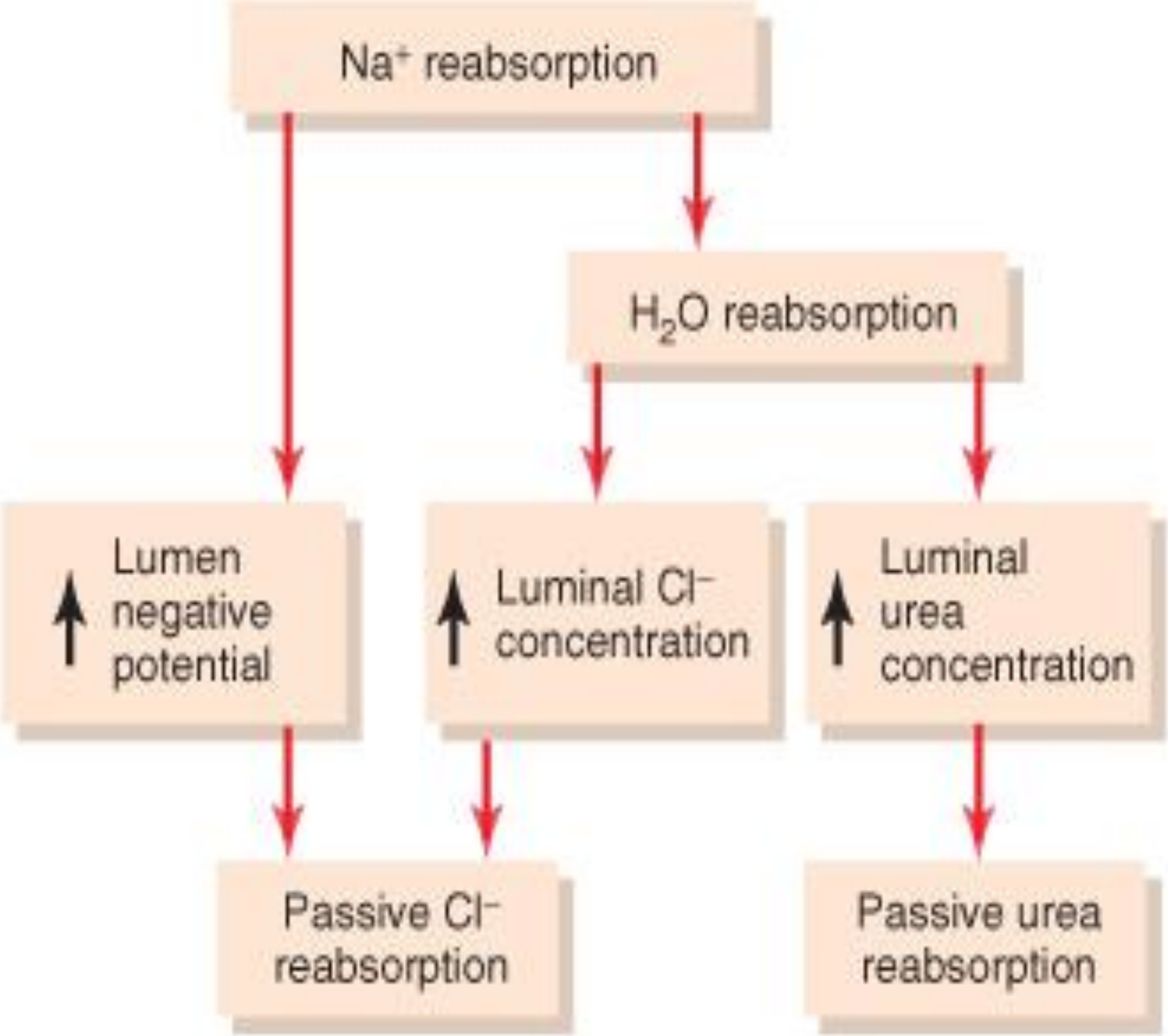
K^+

–70 mV

Na^+

H^+

Counter-transport



Na^+ reabsorption

H_2O reabsorption

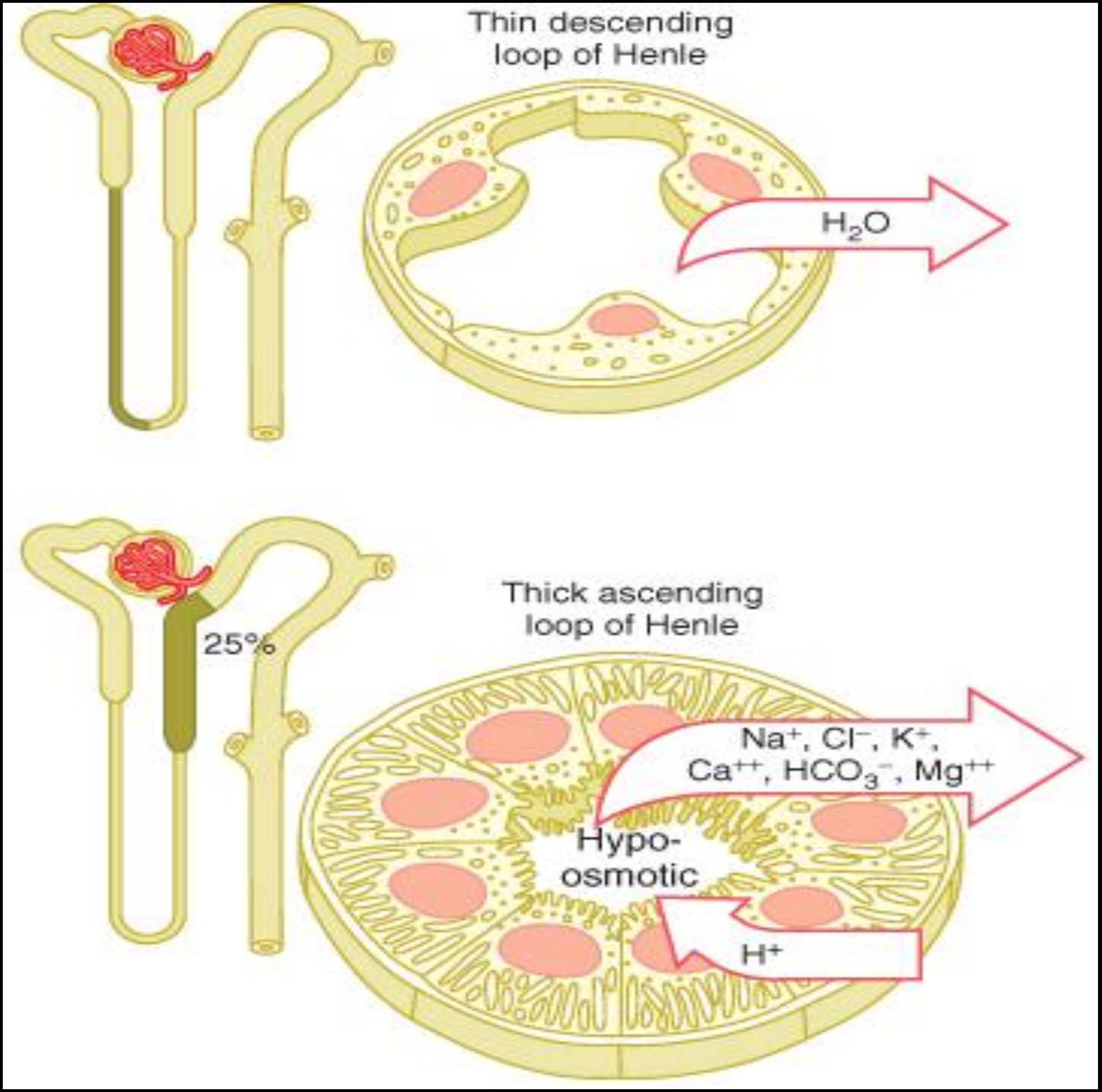
↑ Lumen negative potential

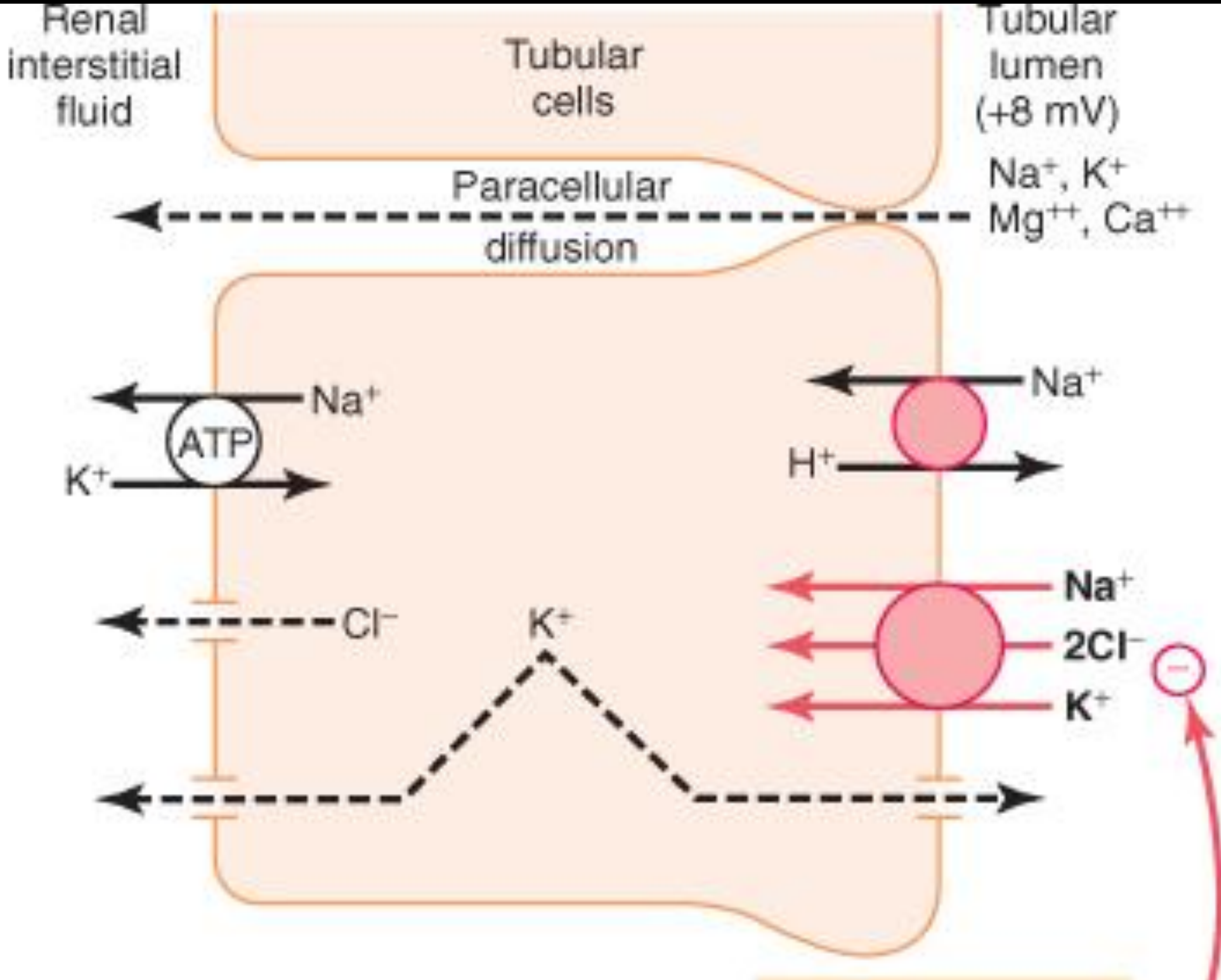
↑ Luminal Cl^- concentration

↑ Luminal urea concentration

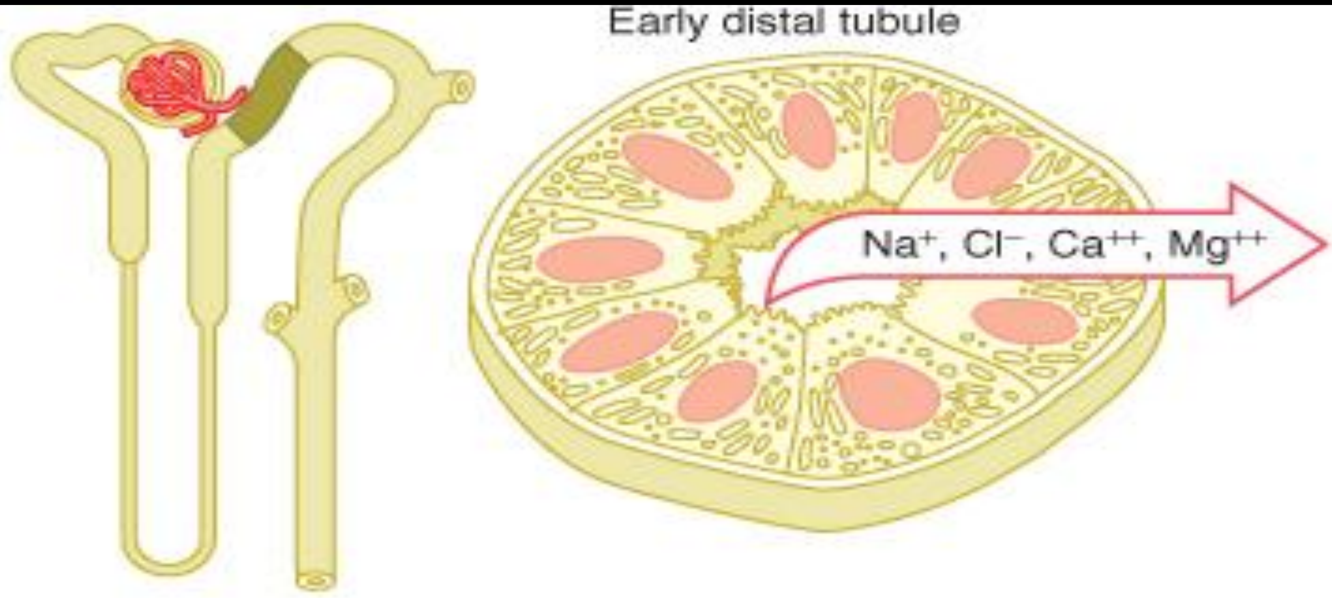
Passive Cl^- reabsorption

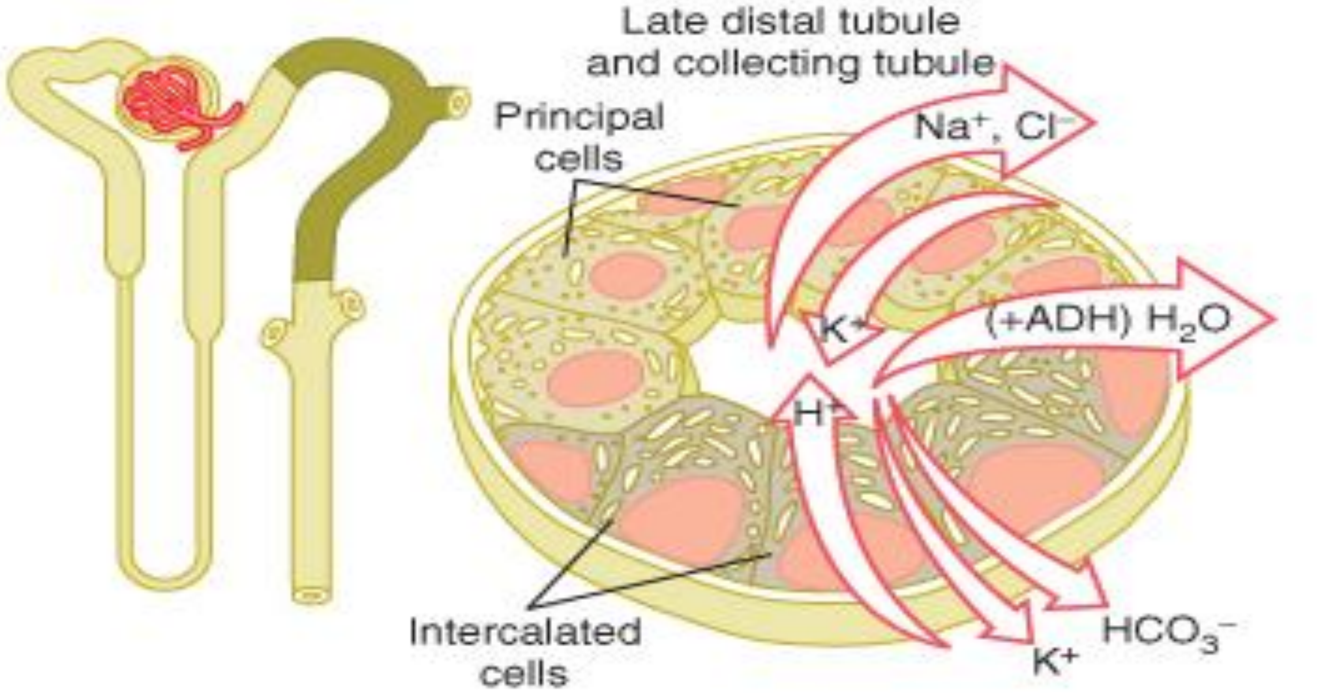
Passive urea reabsorption

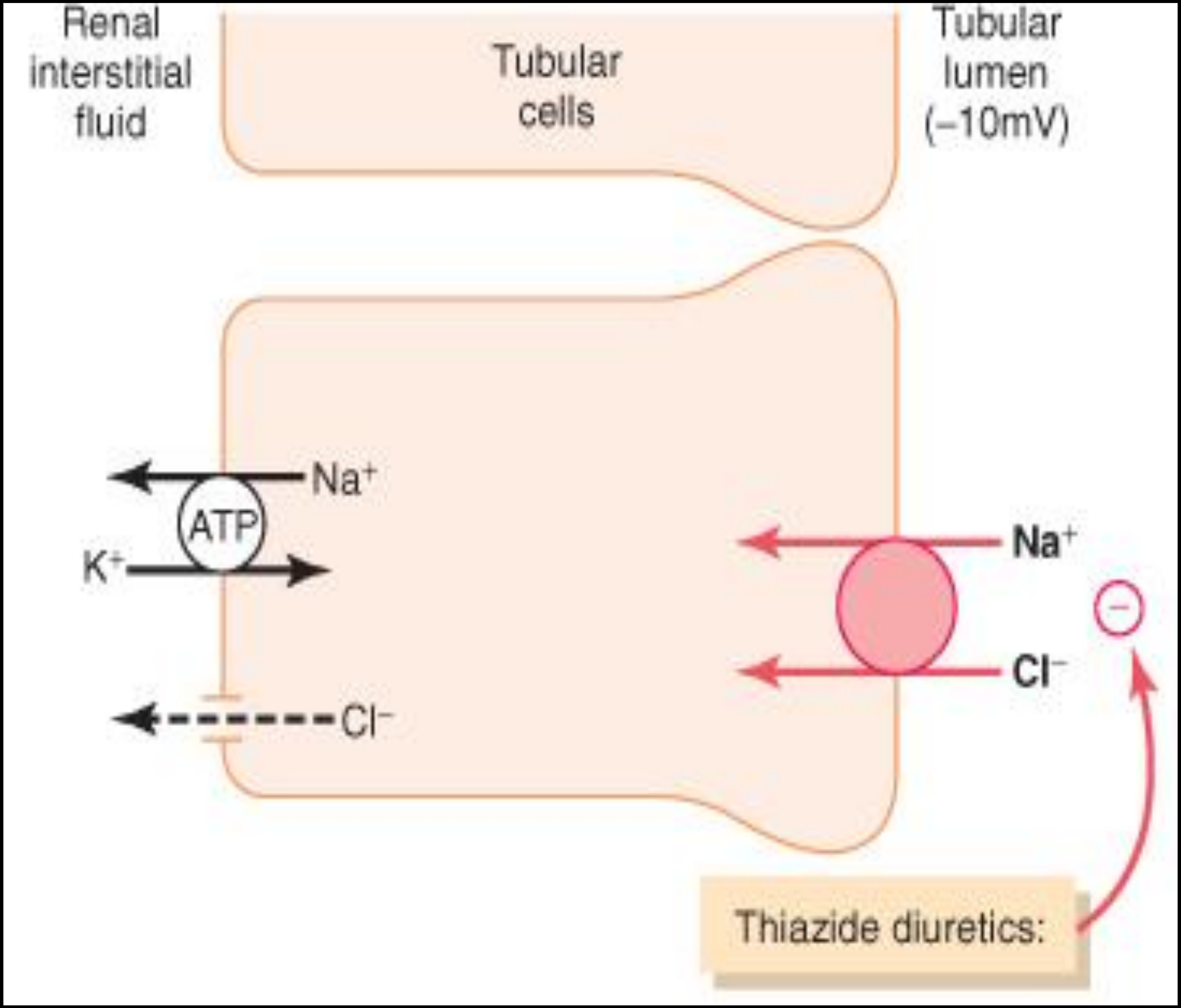

Thin descending loop of Henle
H_2O
25%
Thick ascending loop of Henle
Na^+, Cl^-, K^+, Ca^{++}, HCO_3^-, Mg^{++}
Hypo-osmotic
H^+

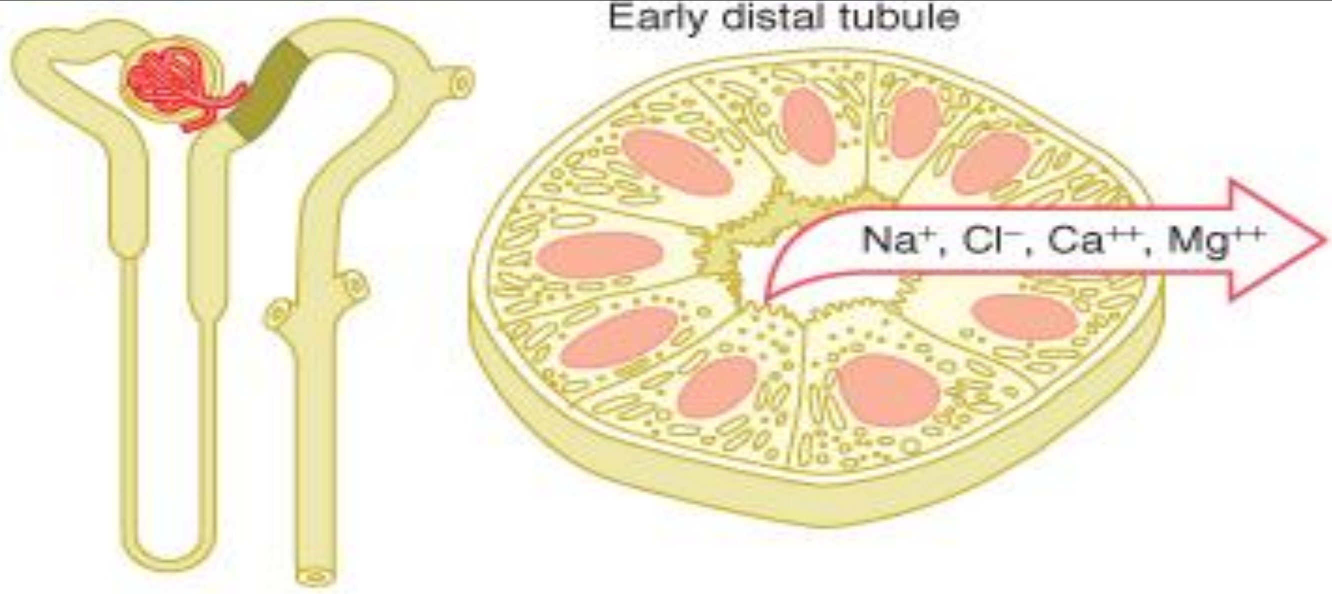


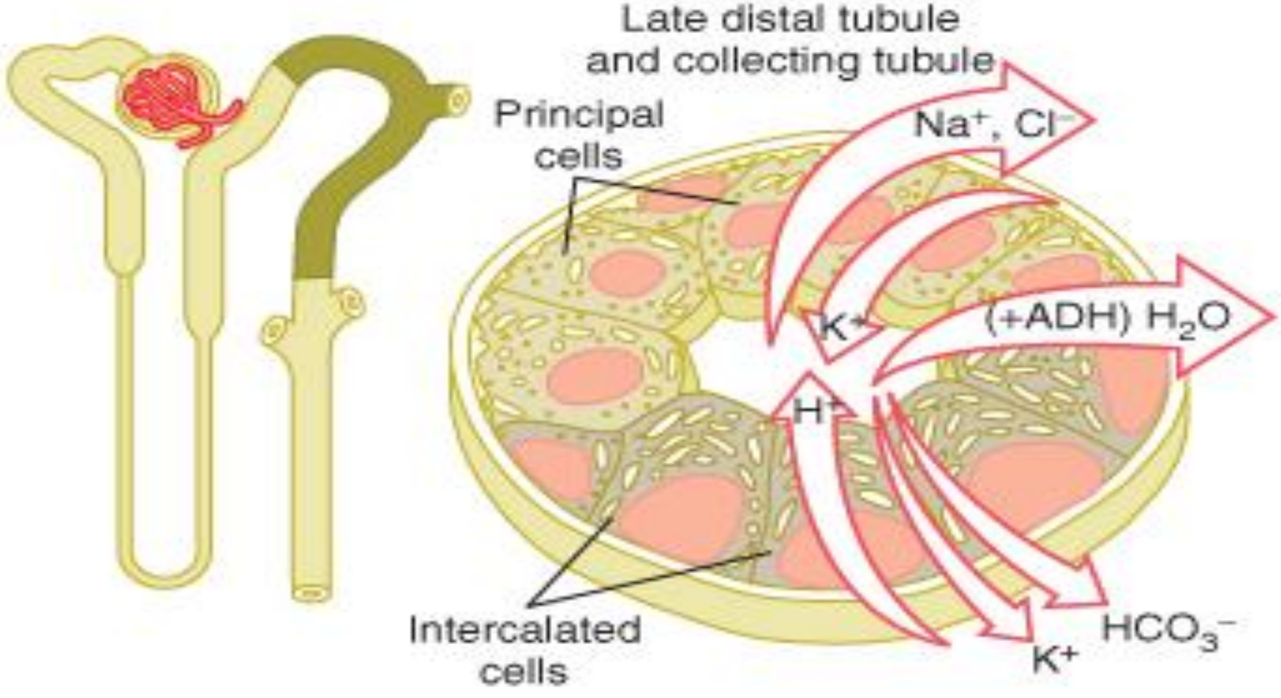
Loop diuretics
- **Furosemide**
- **Ethacrynic acid**
- **Bumetanide**

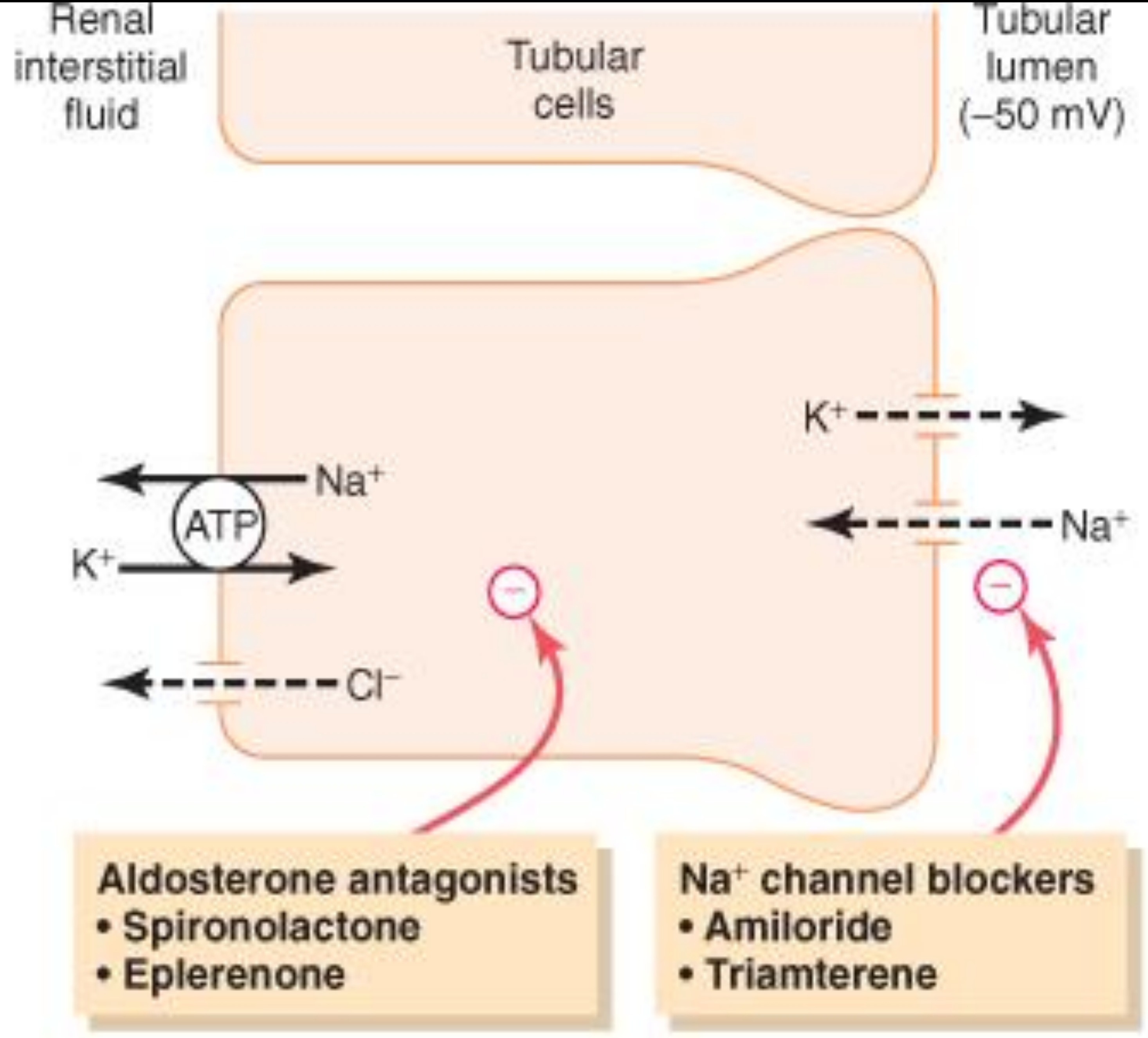

Early distal tubule
Na^+, Cl^-, Ca^{++}, Mg^{++}


Late distal tubule and collecting tubule
Principal cells
Na^+, Cl^-
K^+
(+ADH) H_2O
H^+
Intercalated cells
K^+
HCO_3^-


Renal interstitial fluid
Tubular cells
Tubular lumen (–10mV)
Na+
ATP
K+
Cl−
Na+
Cl−
−
Thiazide diuretics:

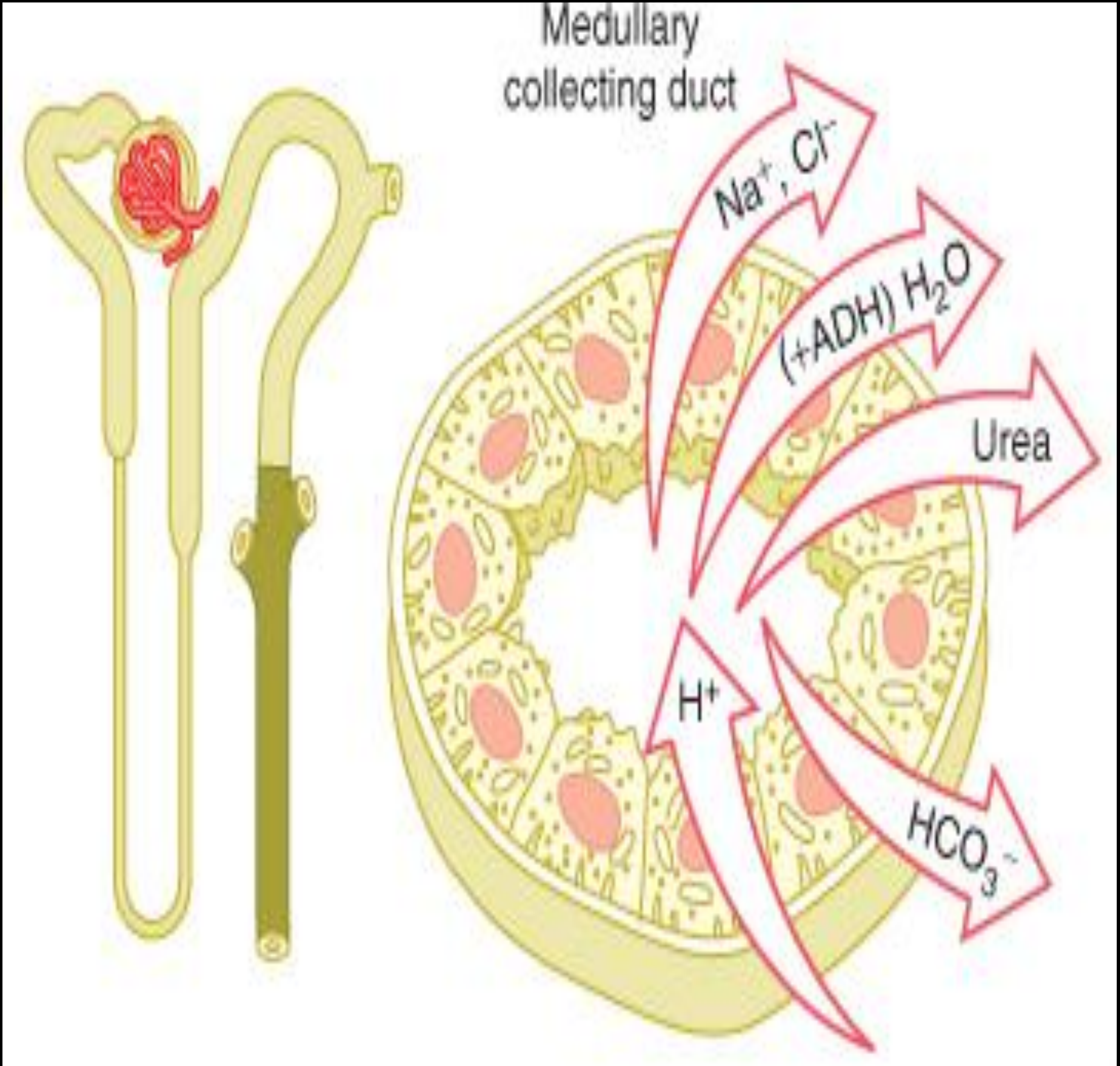

Early distal tubule
Na^+, Cl^-, Ca^{++}, Mg^{++}

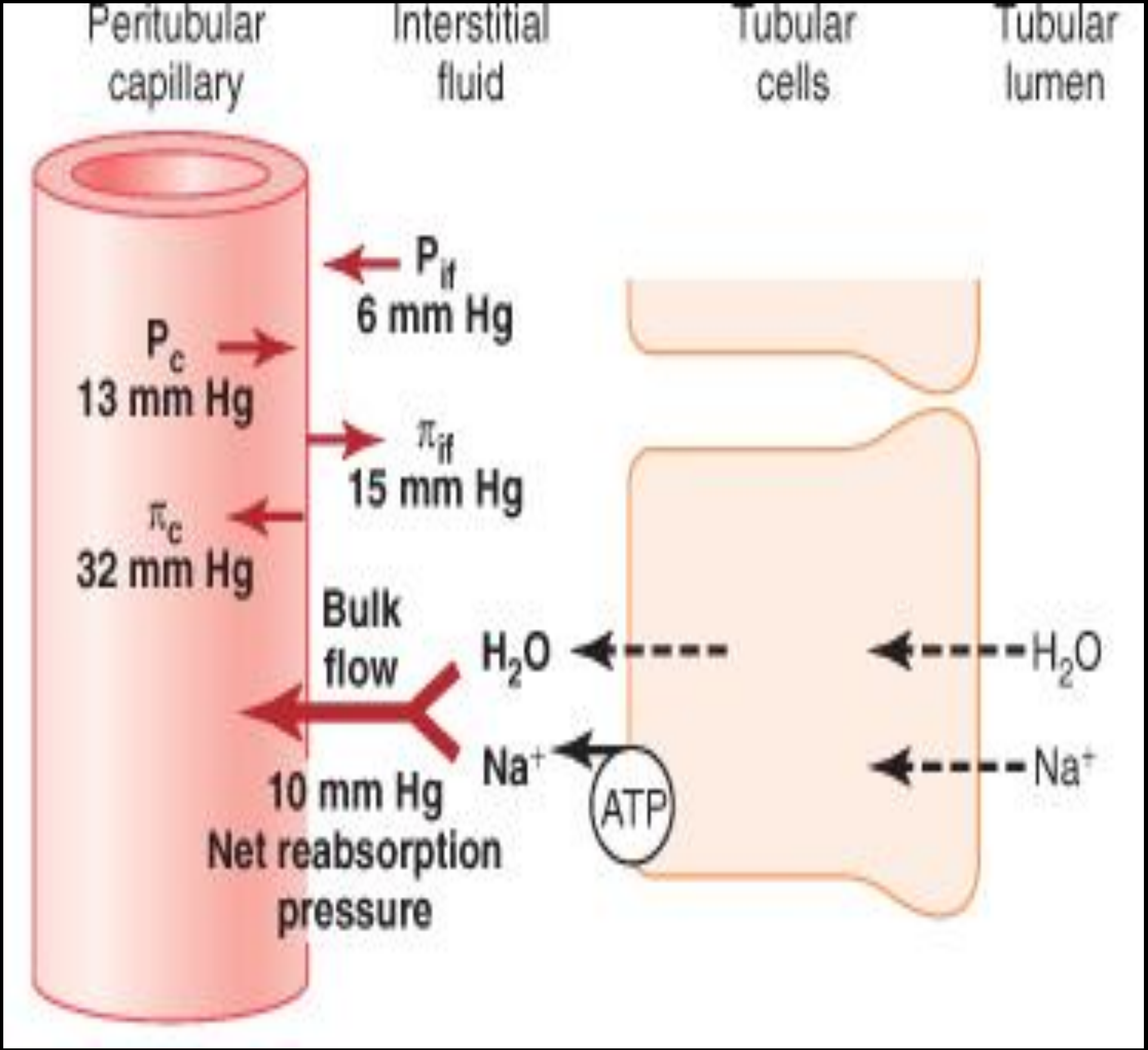

Late distal tubule
and collecting tubule
Principal
cells
Na^+, Cl^-
K^+
(+ADH) H_2O
H^+
Intercalated
cells
K^+
HCO_3^-

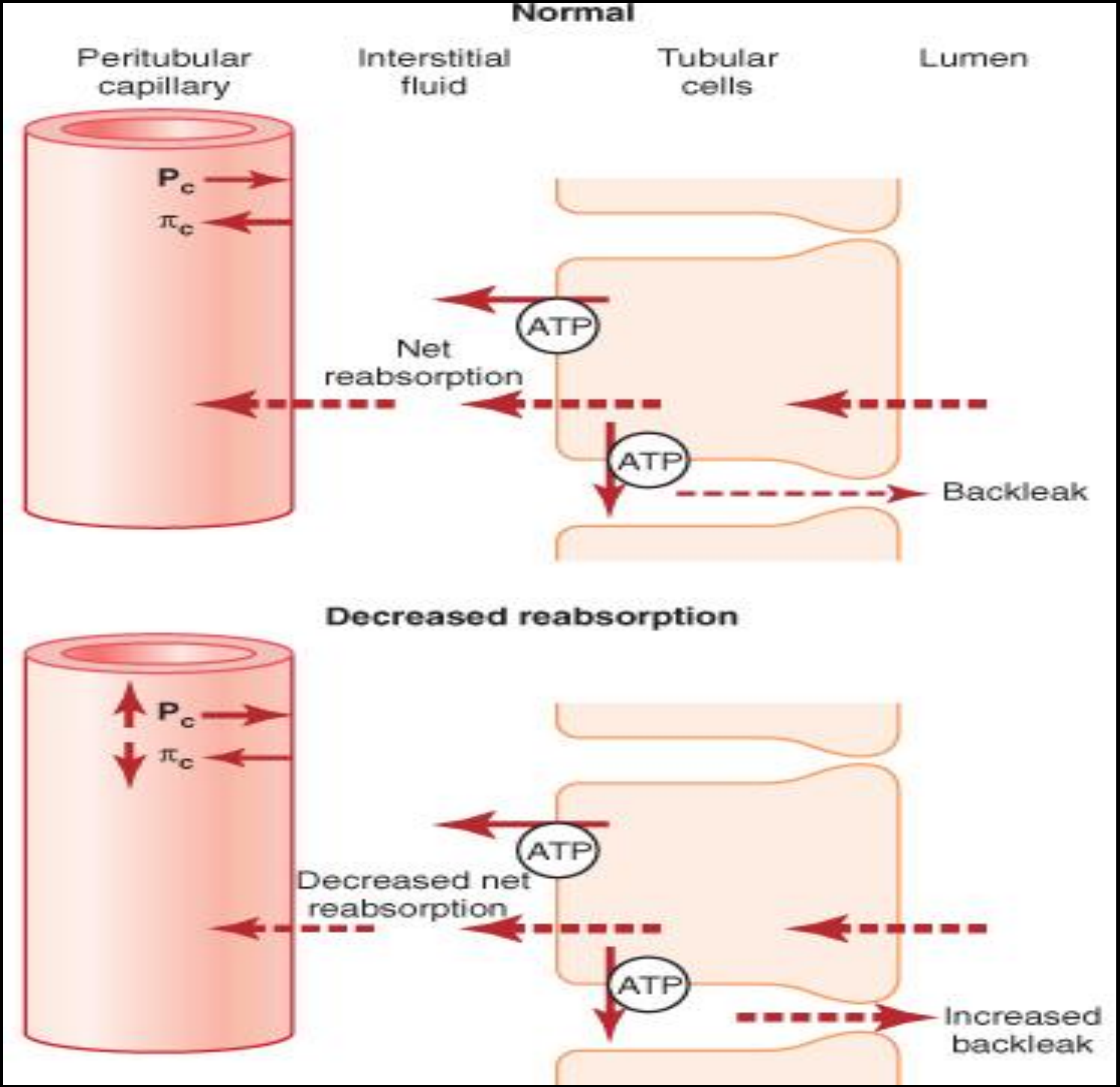


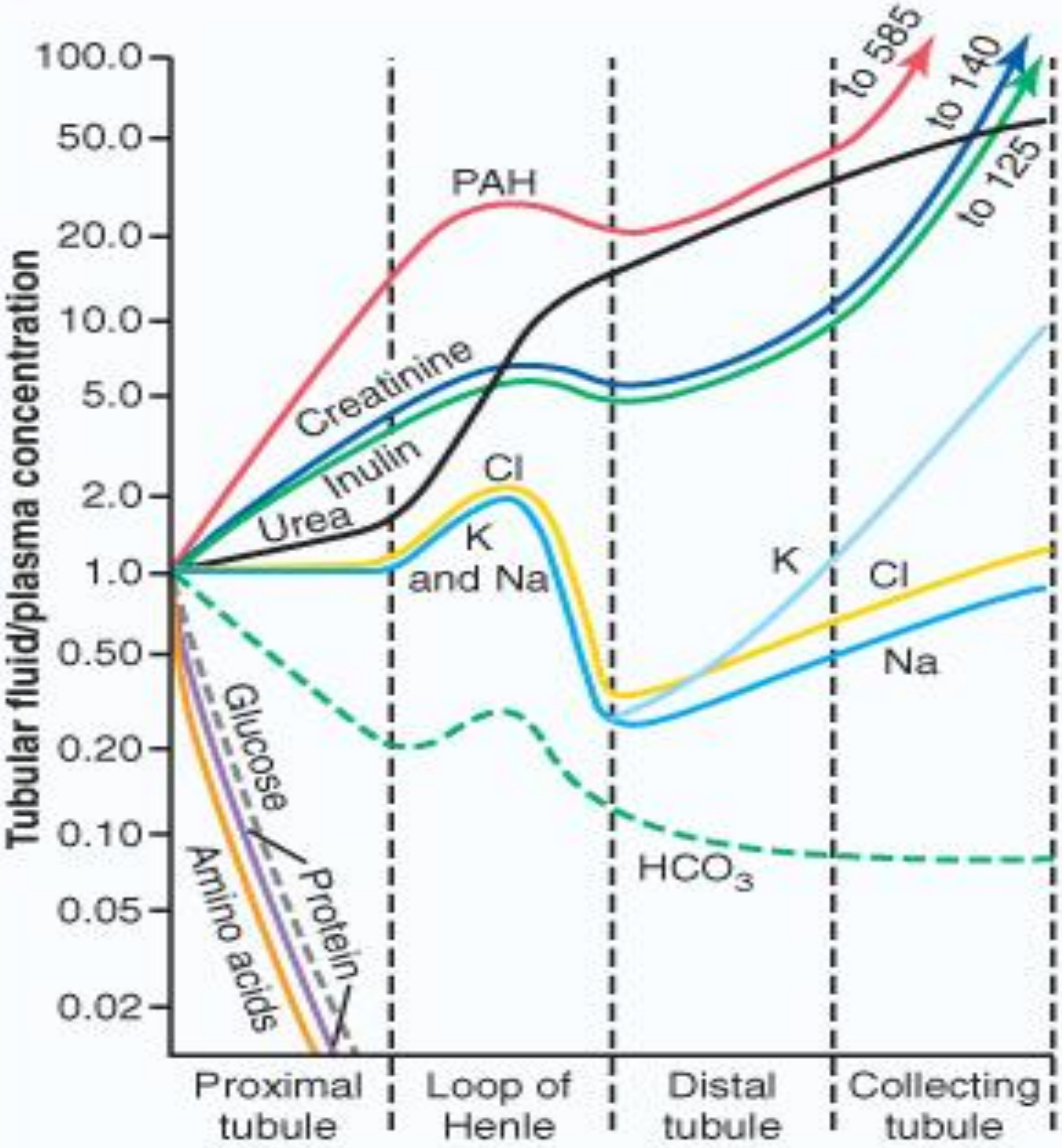
Aldosterone antagonists
- **Spironolactone**
- **Eplerenone**

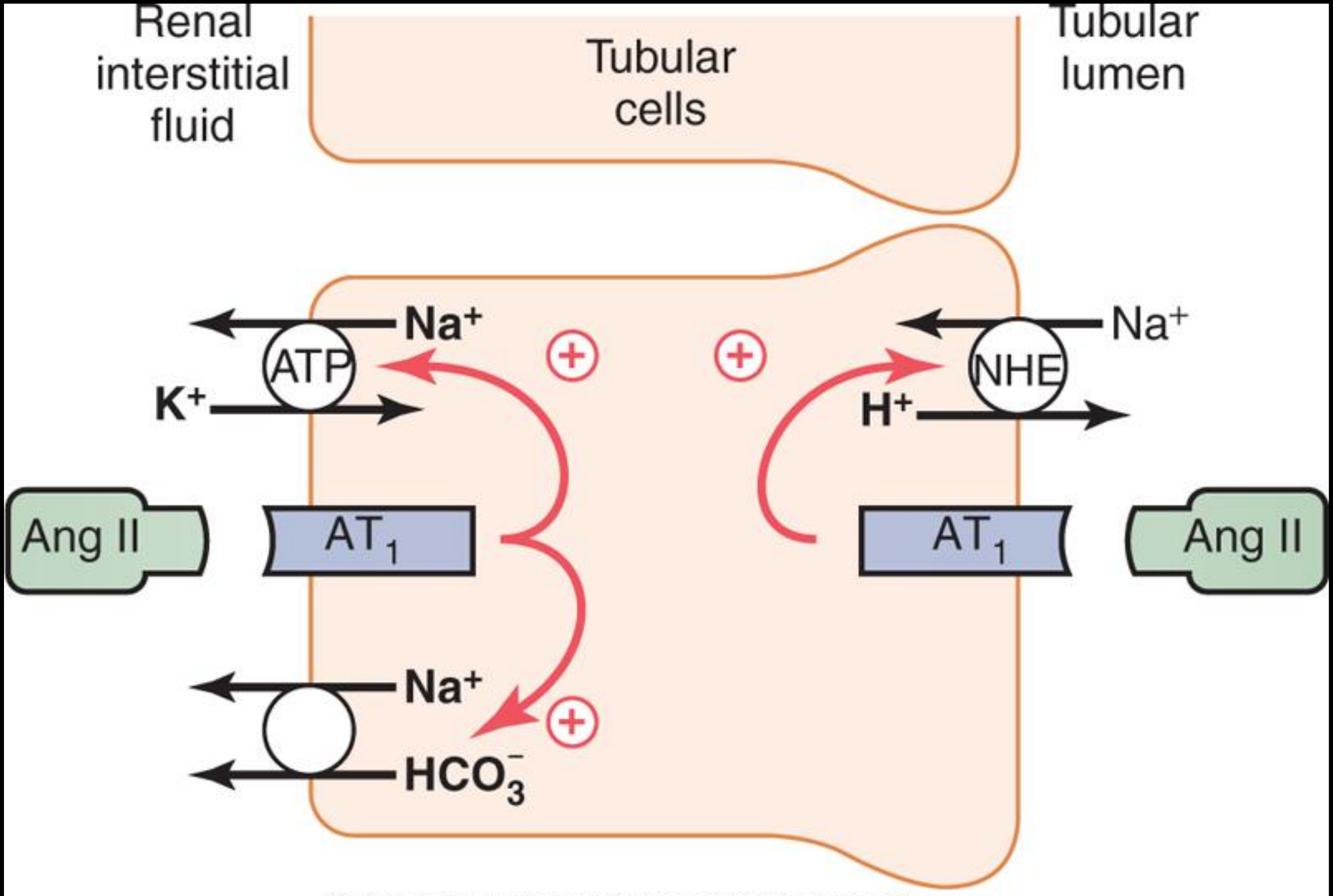
Na⁺ channel blockers
- **Amiloride**
- **Triamterene**


Medullary collecting duct
Na^+, Cl^-
(+ADH) H_2O
Urea
H^+
HCO_3^-


Peritubular capillary
Interstitial fluid
Tubular cells
Tubular lumen
P_{if}
6 mm Hg
P_c
13 mm Hg
π_{if}
15 mm Hg
π_c
32 mm Hg
Bulk flow
H_2O
H_2O
Na^+
Na^+
ATP
10 mm Hg
Net reabsorption pressure


Normal
Peritubular capillary
Interstitial fluid
Tubular cells
Lumen
P_c
π_c
ATP
Net reabsorption
ATP
Backleak
Decreased reabsorption
P_c
π_c
ATP
Decreased net reabsorption
ATP
Increased backleak


Tubular fluid/plasma concentration
100.0
50.0
20.0
10.0
5.0
2.0
1.0
0.50
0.20
0.10
0.05
0.02
to 585
to 140
to 125
PAH
Creatinine
Inulin
Urea
Cl
K
and Na
K
Cl
Na
HCO3
Glucose
Protein
Amino acids
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule



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

Renal Regulation of Potassium Balance

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

E_{ion} = the electrical potential (mV)
R = natural gas constant
T = the absolute temperature (^{0}K)
z = the valence of the ion
F = the Faraday constant (96 500 colombs/mol)
$C_{1\ (in)}$ = the concentration of the ion inside the cell (mmol/L)
$C_{2\ (out)}$ = the concentration of the ion outside the cell (mmol/L)
2.3 RT/F = 60 mV at 37^{0}C

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

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

$$= 60\ mV \times 1$$

= 60 mV (or -60 mV, cell interior negative)

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

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

$$= 60\ mV \times 1.40$$

= 84 mV (or -84 mV, cell interior negative)

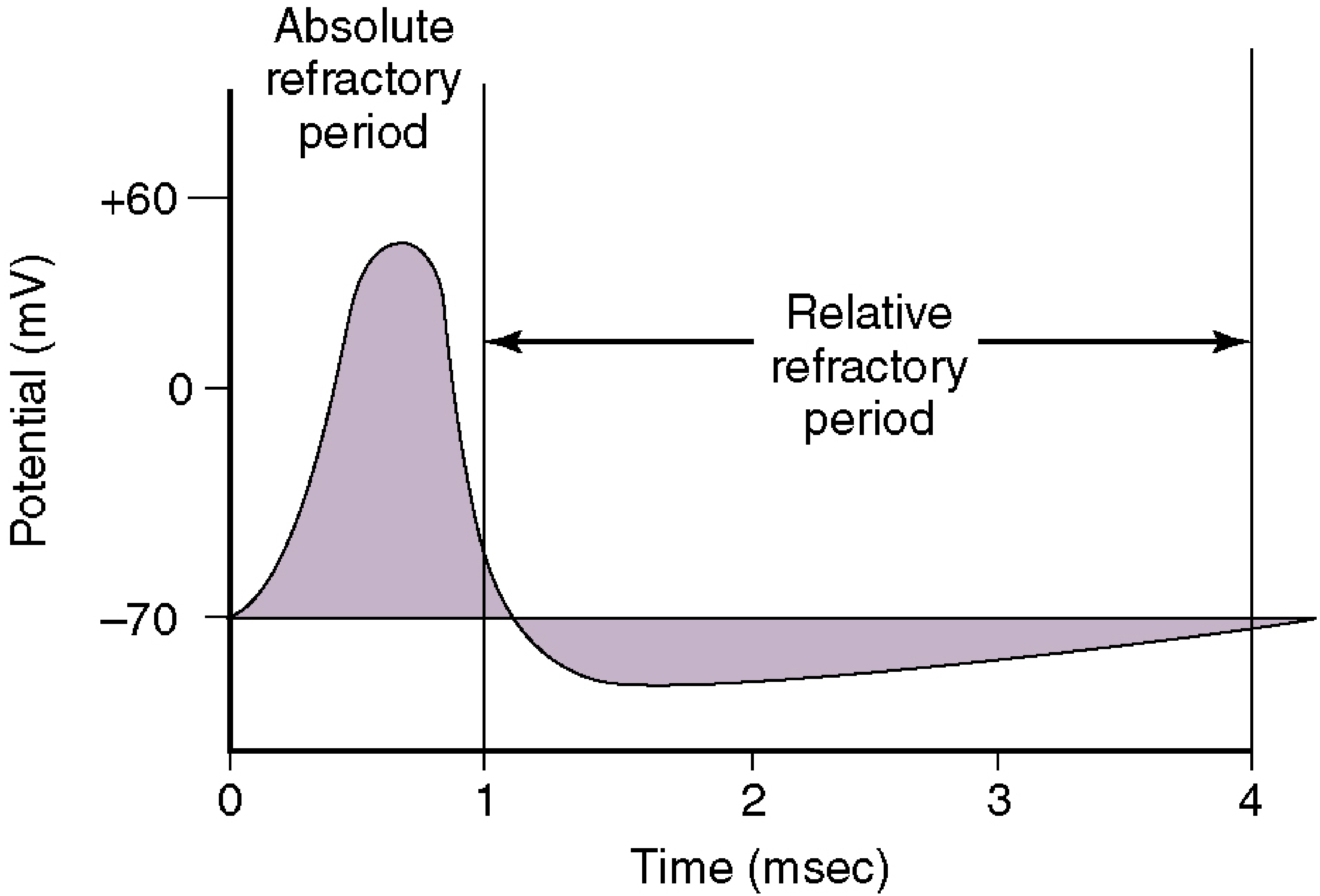
$$E_{ion} = \frac{60\ mV}{1} \log_{10} \frac{100}{1}$$

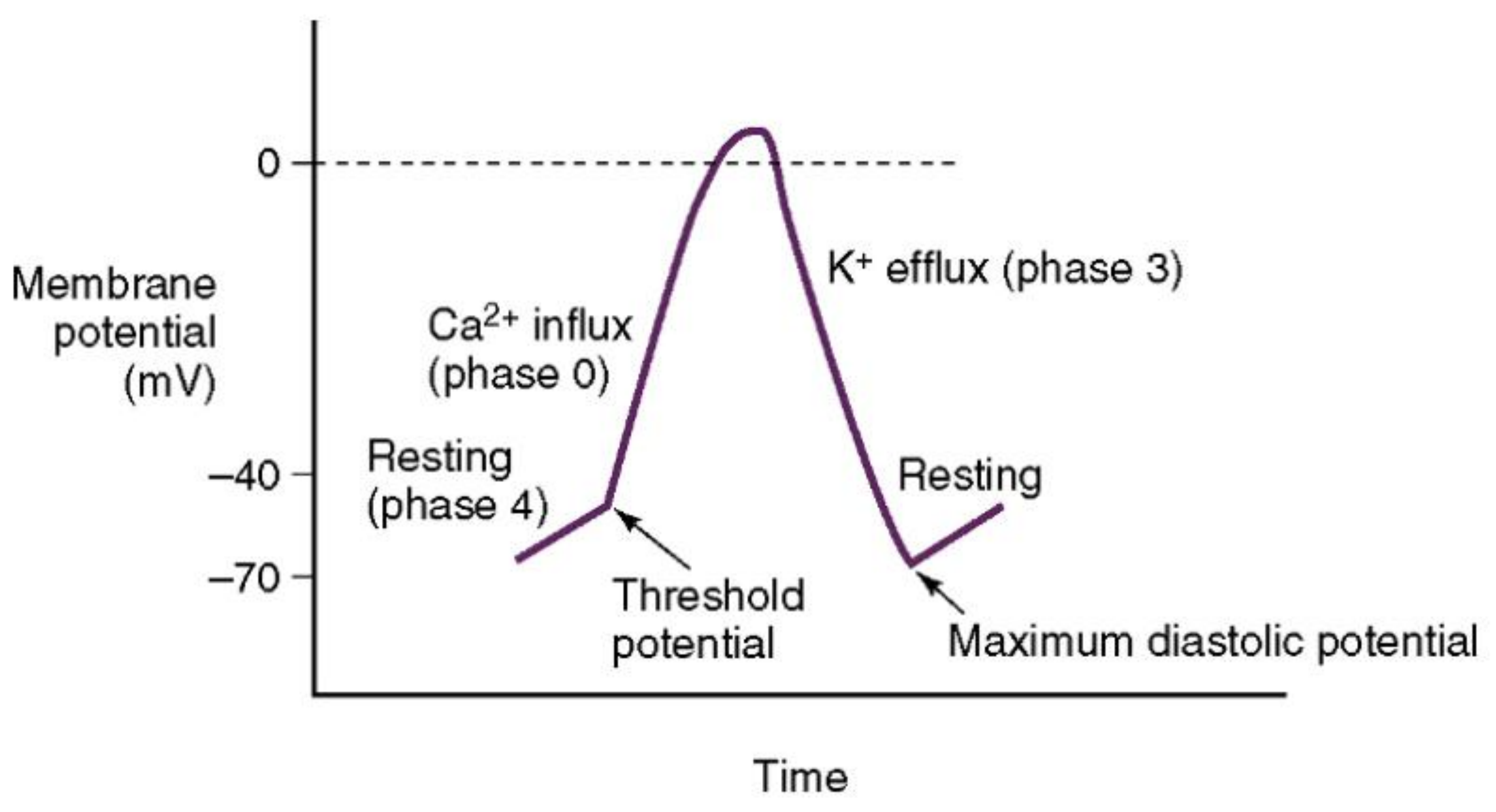
$$= 60\ mV \times \log_{10} 100$$

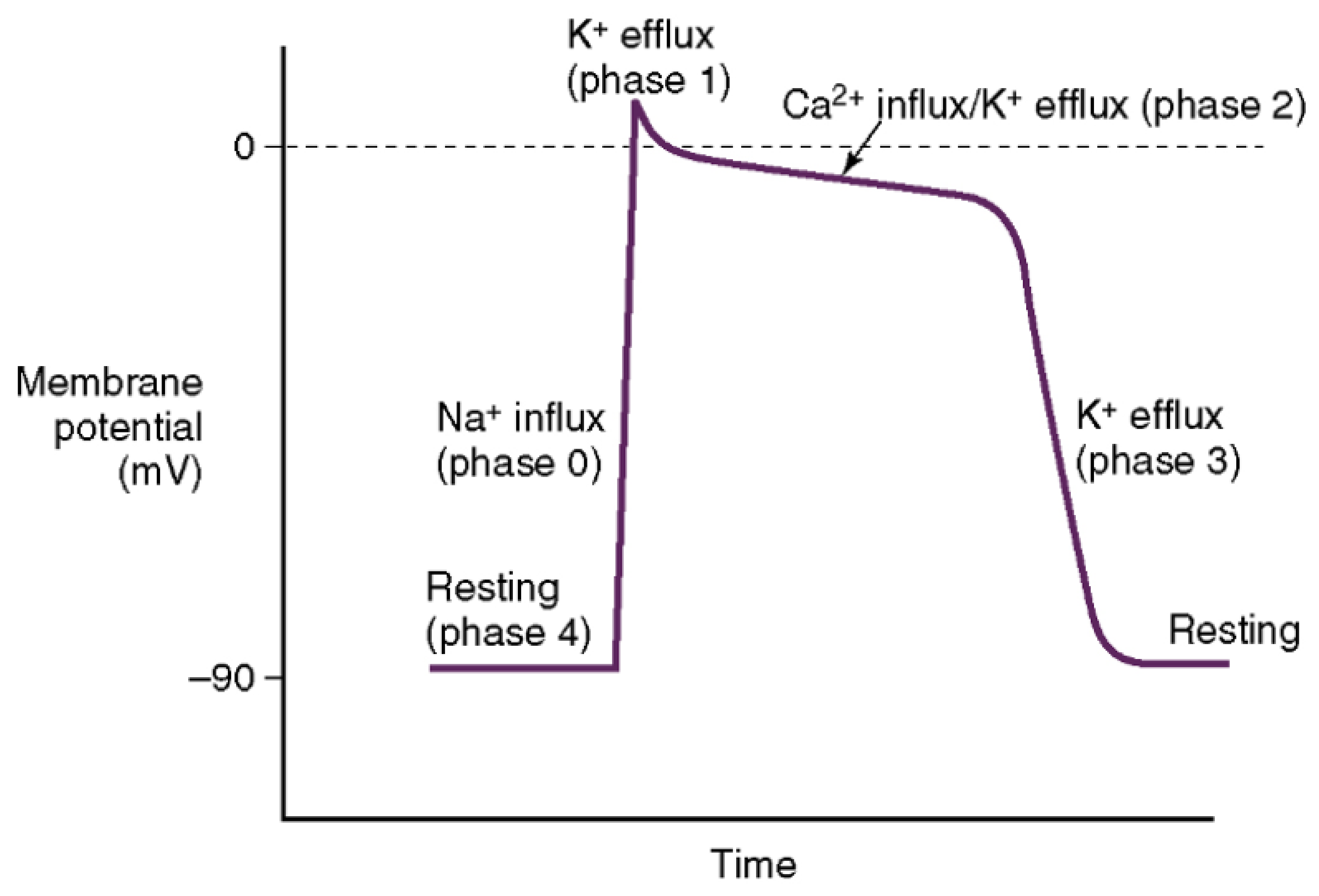
$$= 60\ mV \times 2$$

= 120 mV (or -120 mV, cell interior negative)

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


Absolute refractory period
Relative refractory period
+60
0
–70
Potential (mV)
0
1
2
3
4
Time (msec)


0
Membrane
potential
(mV)
−40
−70
Ca2+ influx
(phase 0)
K+ efflux (phase 3)
Resting
(phase 4)
Resting
Threshold
potential
Maximum diastolic potential
Time


K+ efflux (phase 1)
Ca2+ influx/K+ efflux (phase 2)
0
Membrane potential (mV)
Na+ influx (phase 0)
K+ efflux (phase 3)
Resting (phase 4)
Resting
–90
Time

Hyperkalemia

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

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

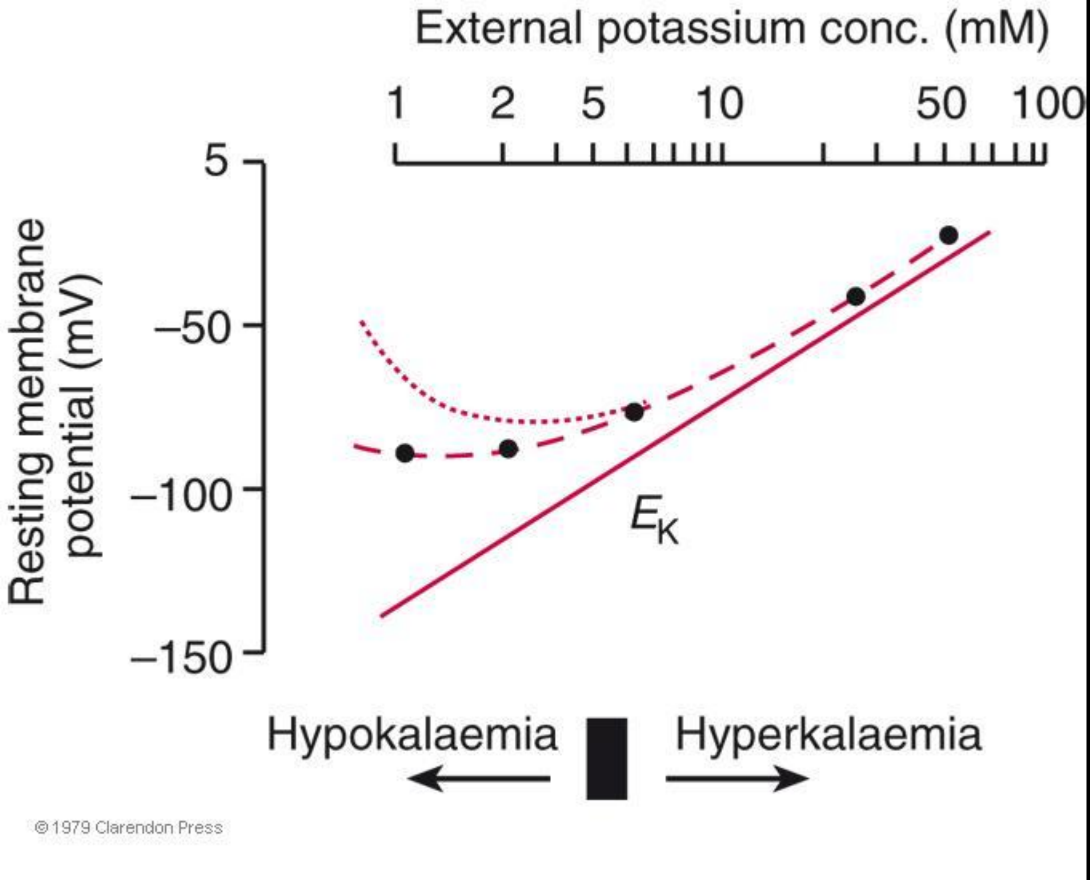
2.3 ET/F (60 mV at 37^0 C)

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

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

$$= 60 \times 1.4$$

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



© 1979 Clarendon Press

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

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

$$= 60 \times 2$$

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

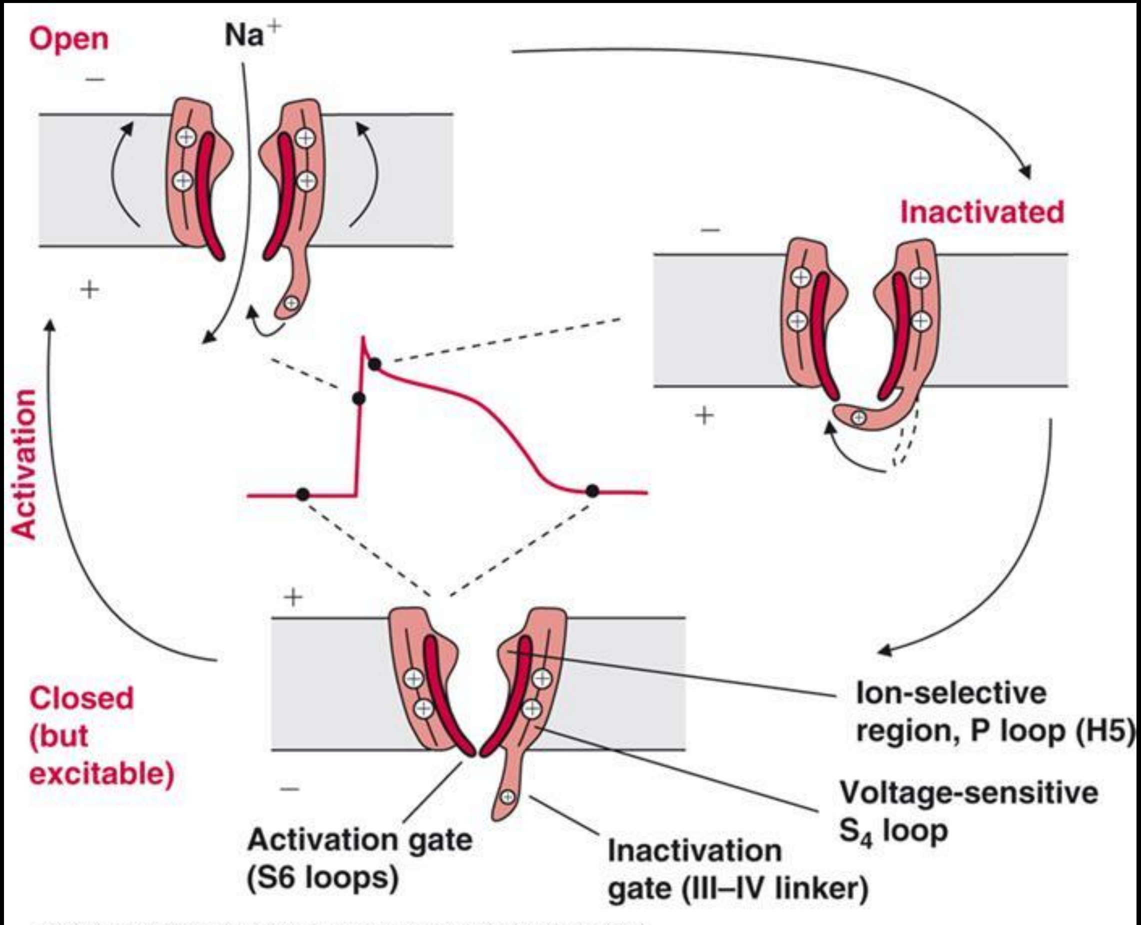
$$E_K = -\frac{60}{1} \log_{10} \frac{[100]}{[10]}$$

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

$$= 60 \times 1$$

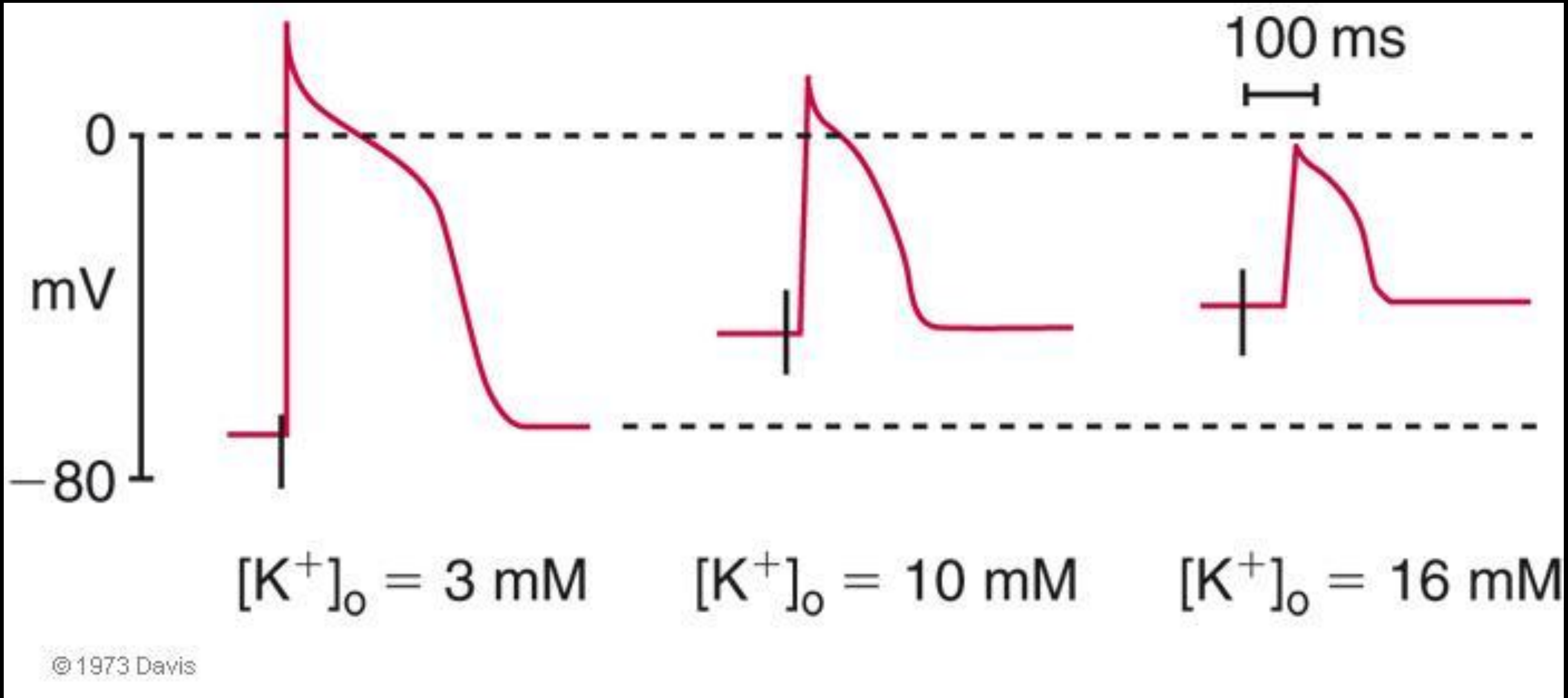
$$= 60 \text{ mV (or -60 mV)}$$

Reduced resting membrane potential
diminishes the action potential, because
the low resting potential prevents many
Na^+ channels from reseting from the
Inactivated state to the closed-but –activatable state

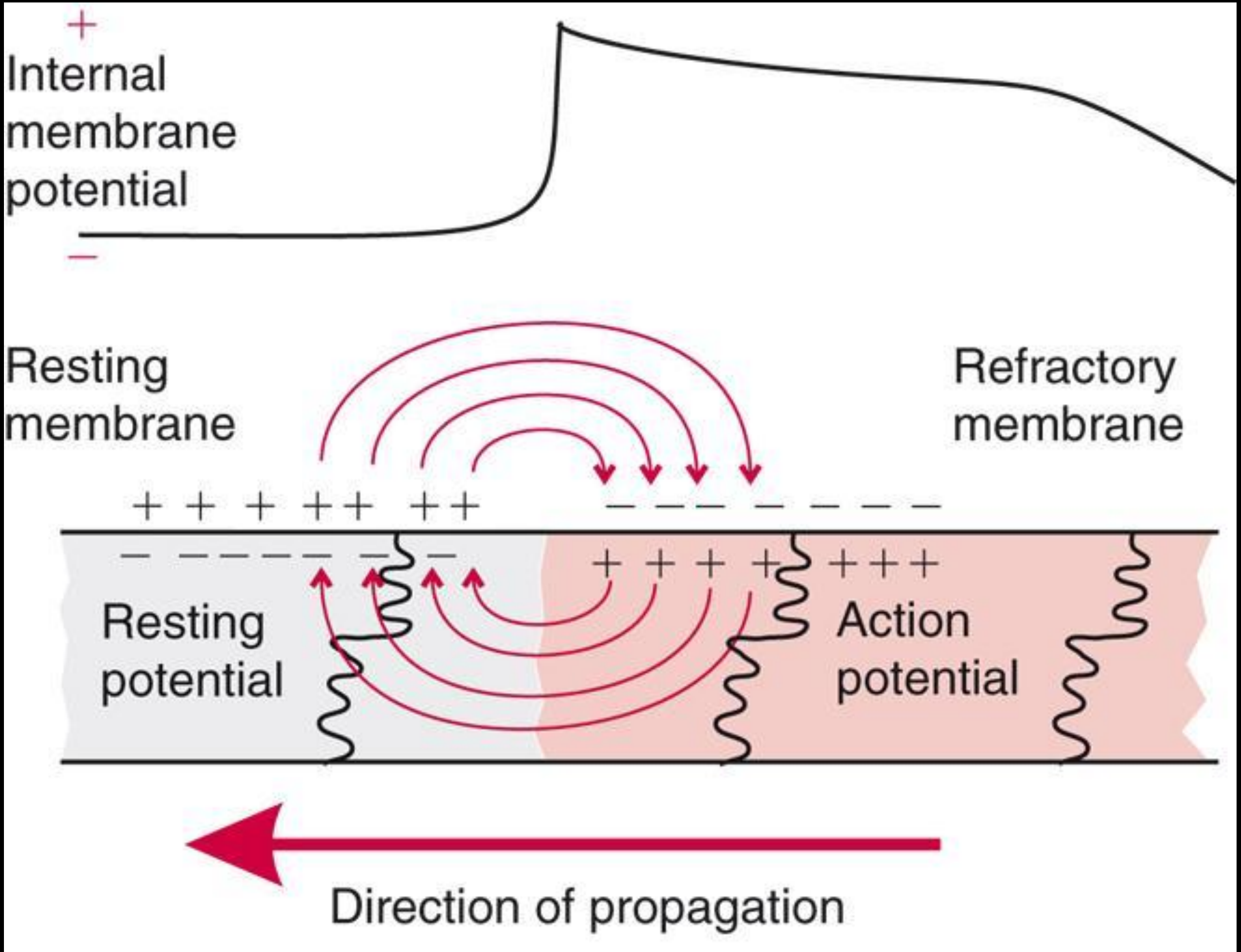


An Introduction to Cardiovascular Physiology/Hodder Arnold © 2010 JR Levick

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 $I_{ca\text{-}L}$



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/fibrilation.



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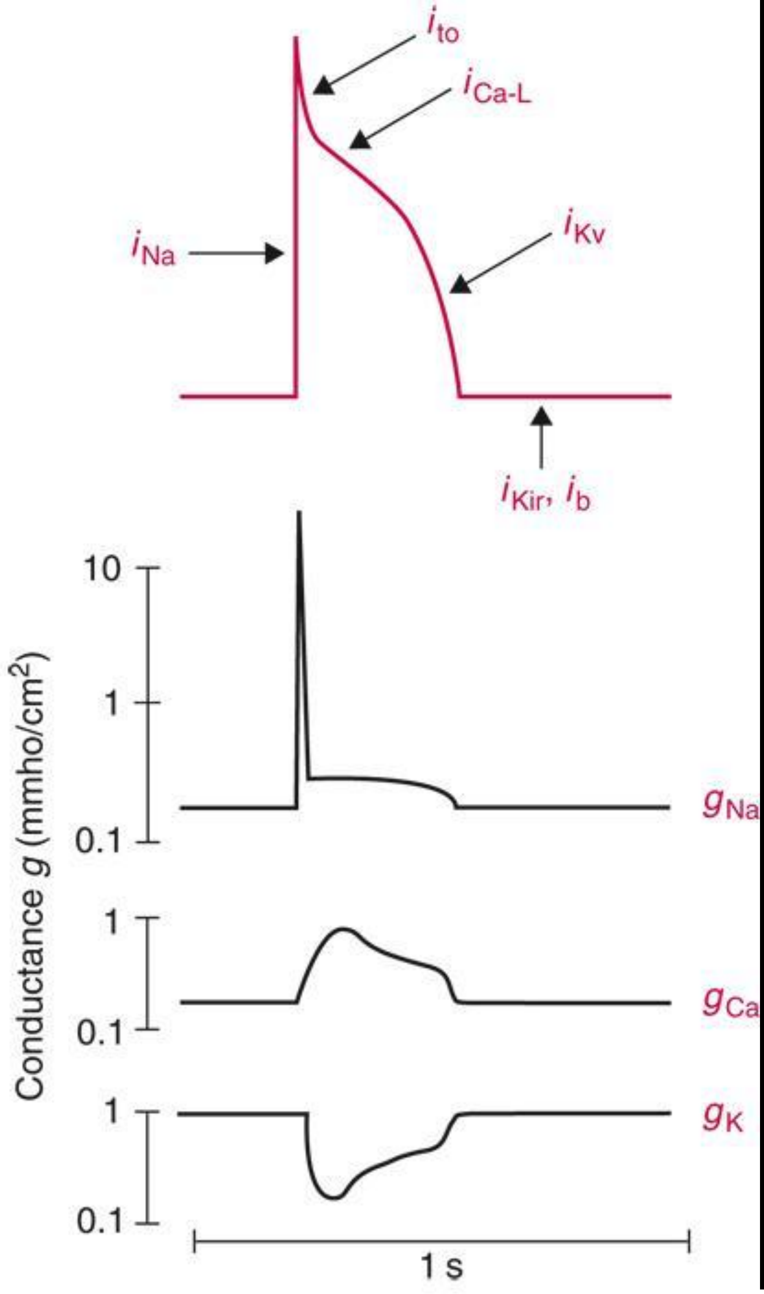
The raised extracellular K^+ also stimulates the $3Na^+$-$2K^+$ pump, enhances the activity of K^+ channels K_{ir} and K_v, causing early repolarization.

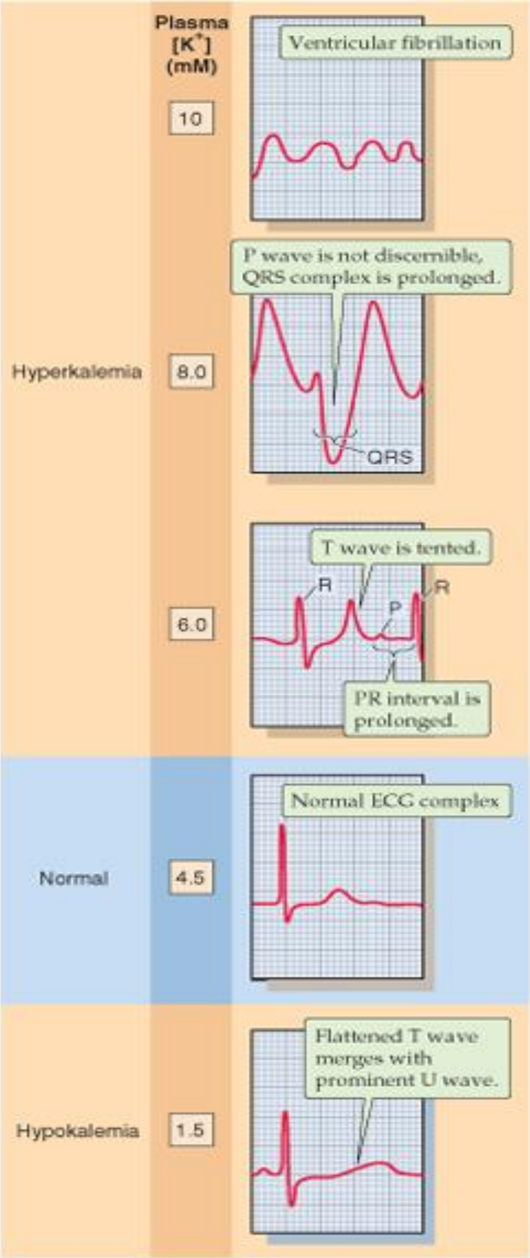
Wide QRS is likely due to slow electrical propagation in the ventricle

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

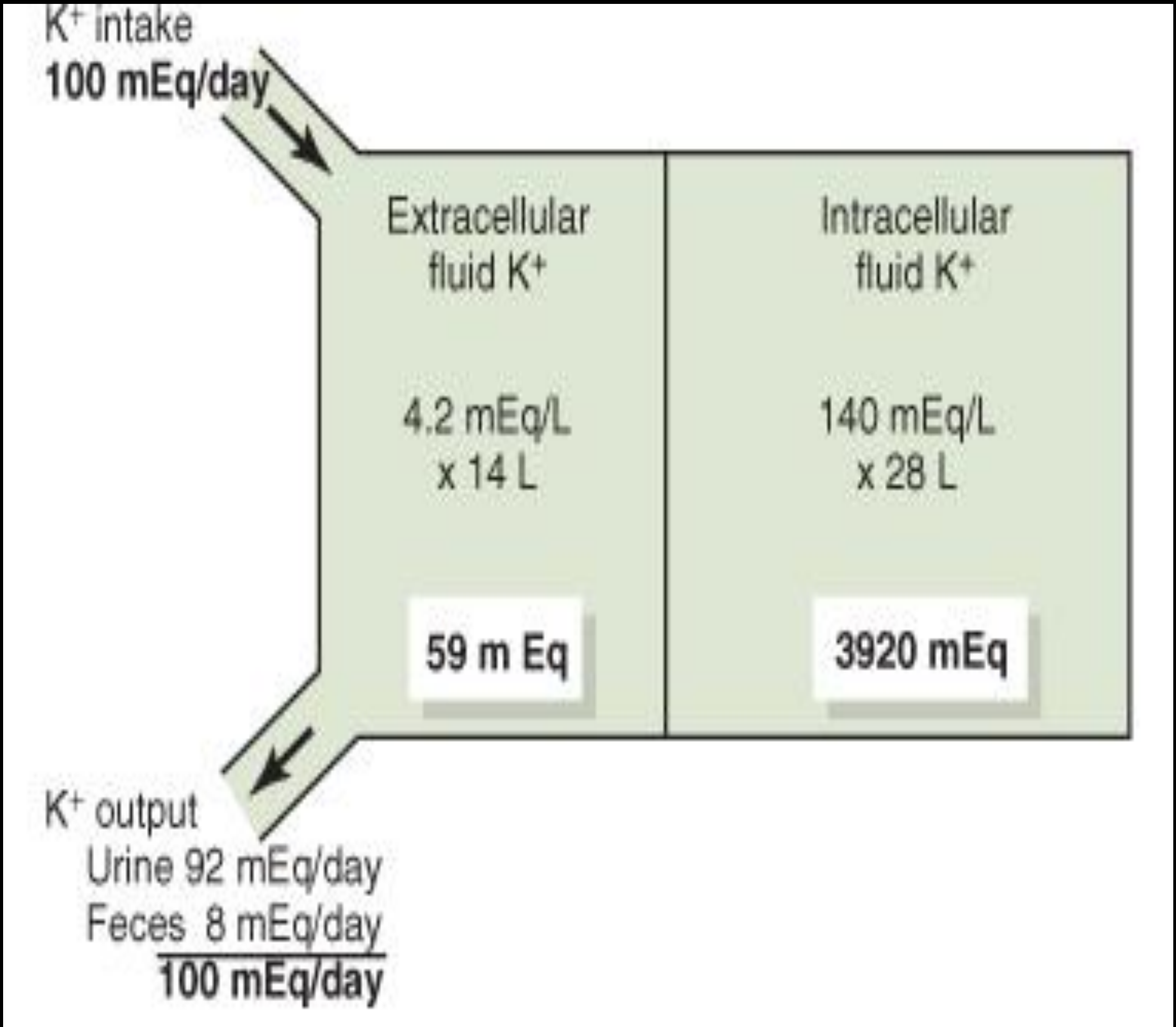
Hypokalemia

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 myocates.
Prolongation of the subepicardial action potentials leads to flattened or even Inverted T wawes, which are called a U wawe.





Boron & Boulpaep: Medical Physiology, 2nd Edition.



K+ intake
100 mEq/day

Extracellular
fluid K+

4.2 mEq/L
x 14 L

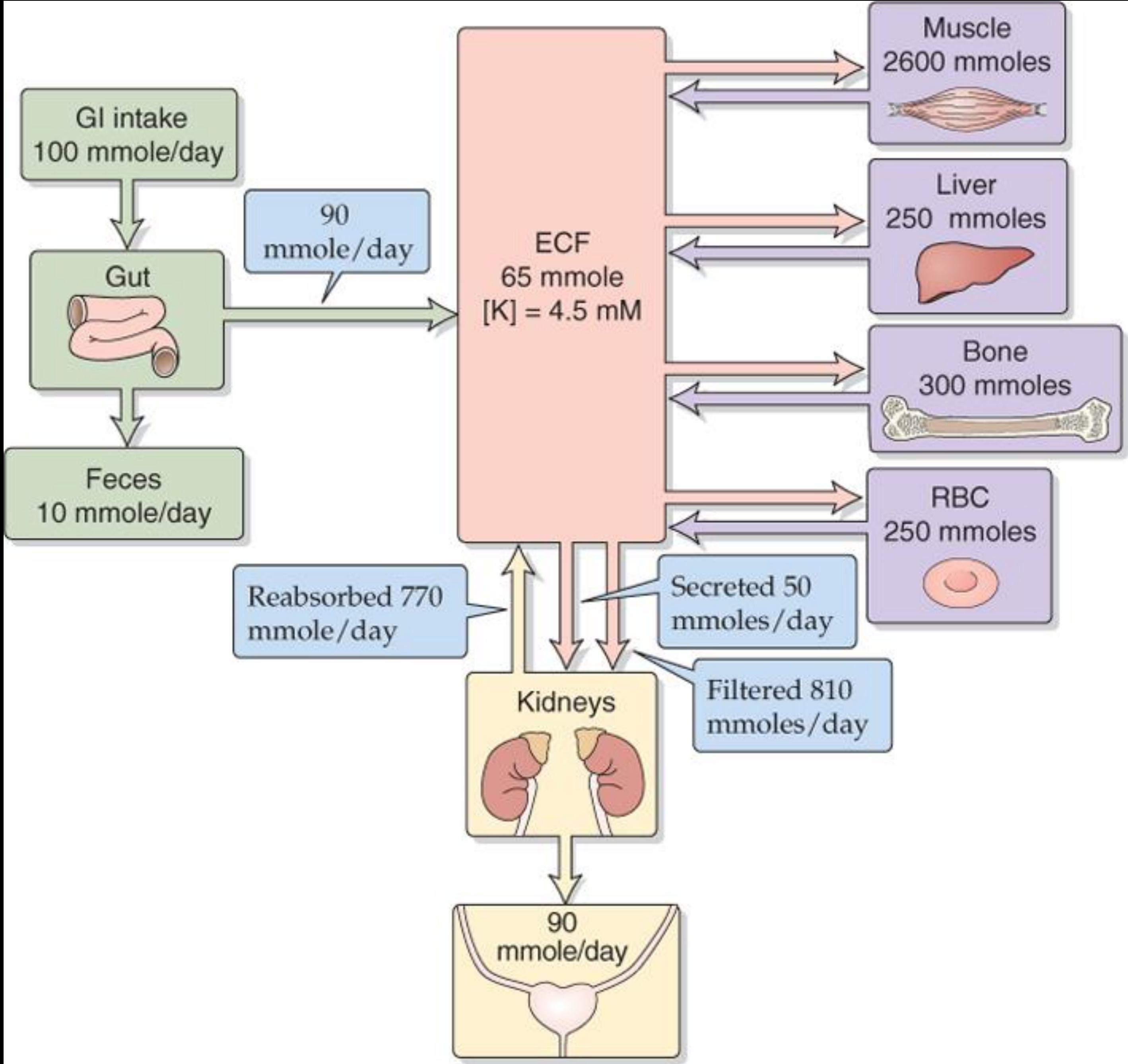
59 m Eq

Intracellular
fluid K+

140 mEq/L
x 28 L

3920 mEq

K+ output
Urine 92 mEq/day
Feces 8 mEq/day
100 mEq/day



GI intake
100 mmole/day

Gut

90
mmole/day

Feces
10 mmole/day

ECF
65 mmole
[K] = 4.5 mM

Muscle
2600 mmoles

Liver
250 mmoles

Bone
300 mmoles

RBC
250 mmoles

Reabsorbed 770
mmole/day

Secreted 50
mmoles/day

Filtered 810
mmoles/day

Kidneys

90
mmole/day

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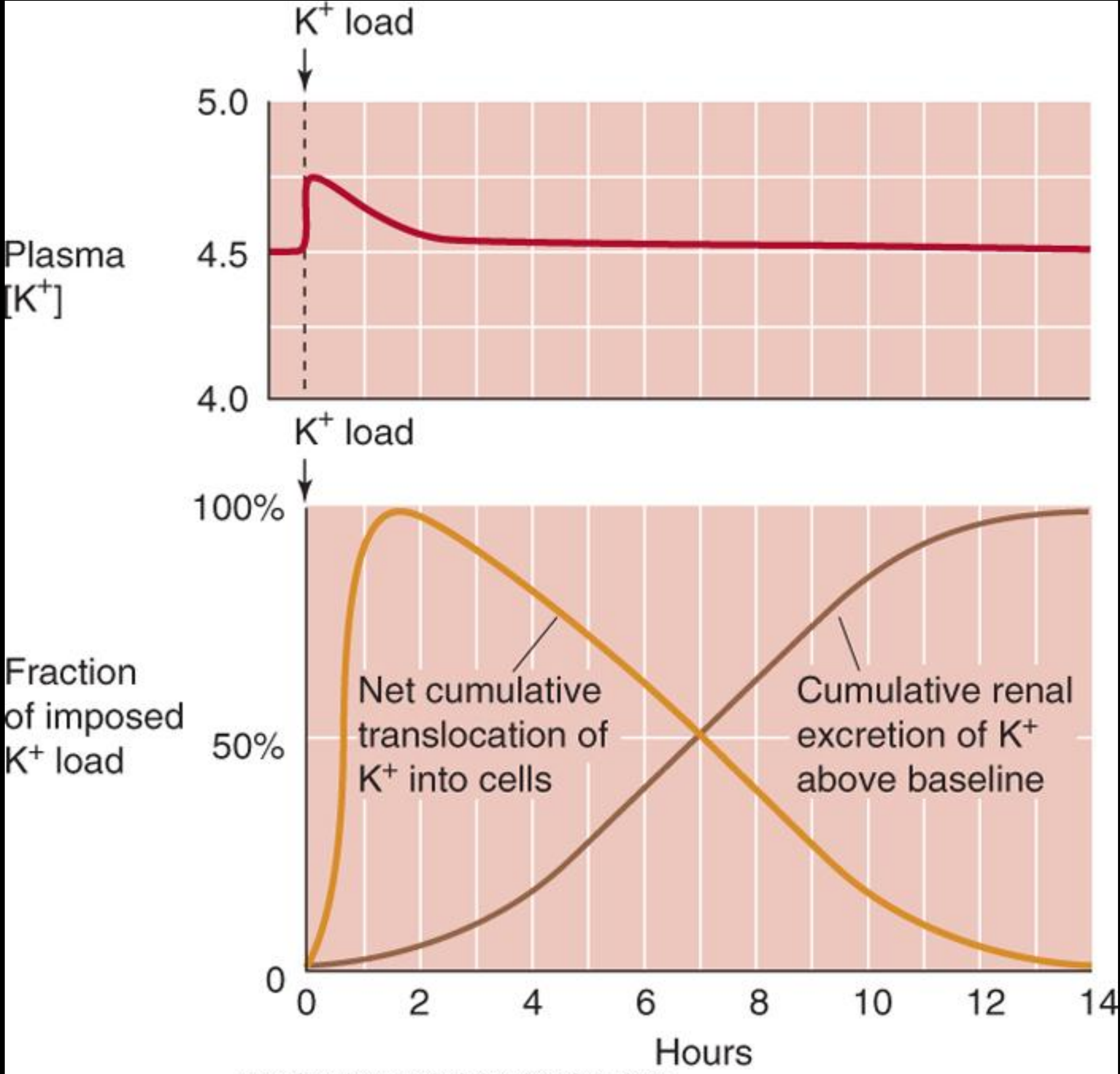
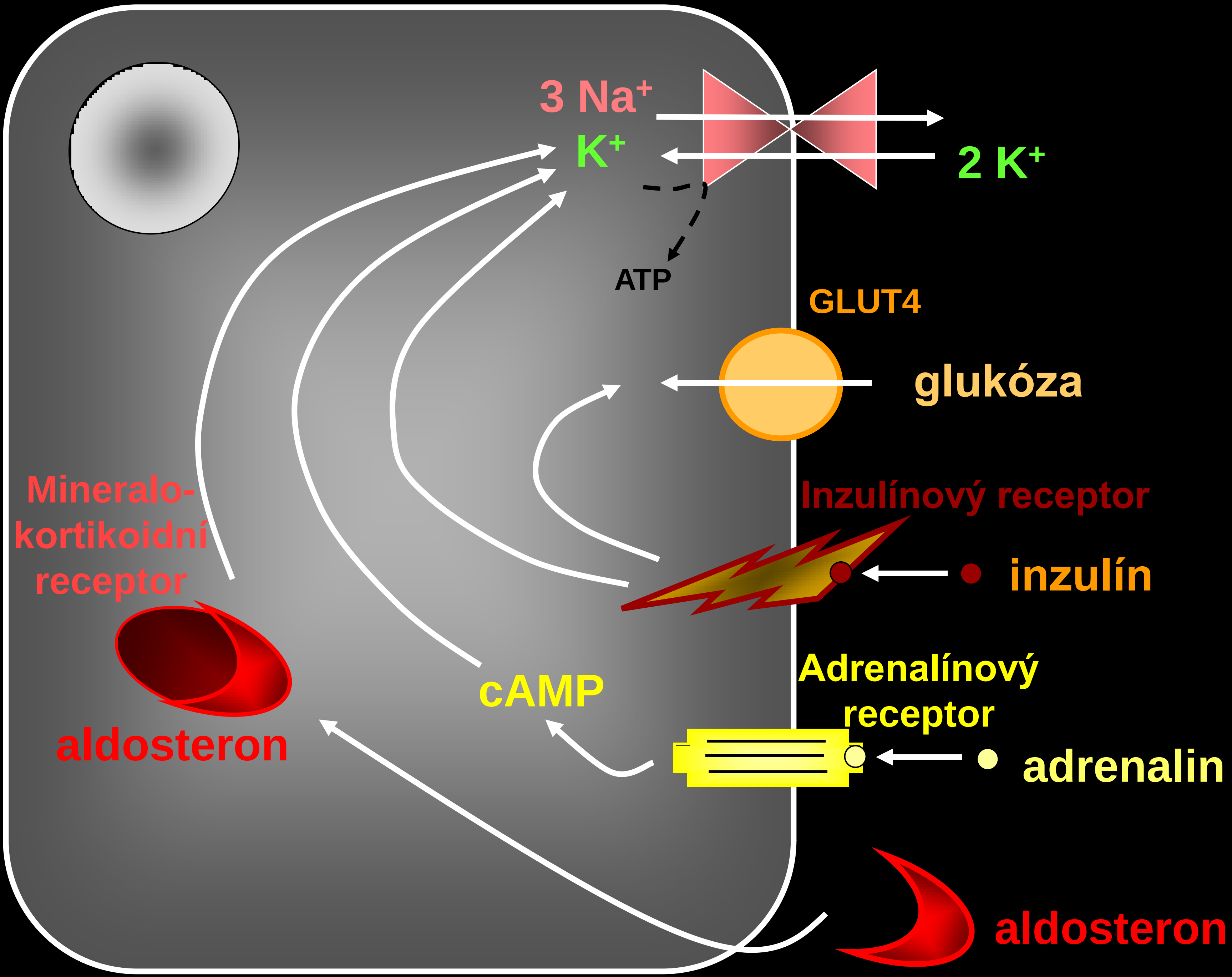
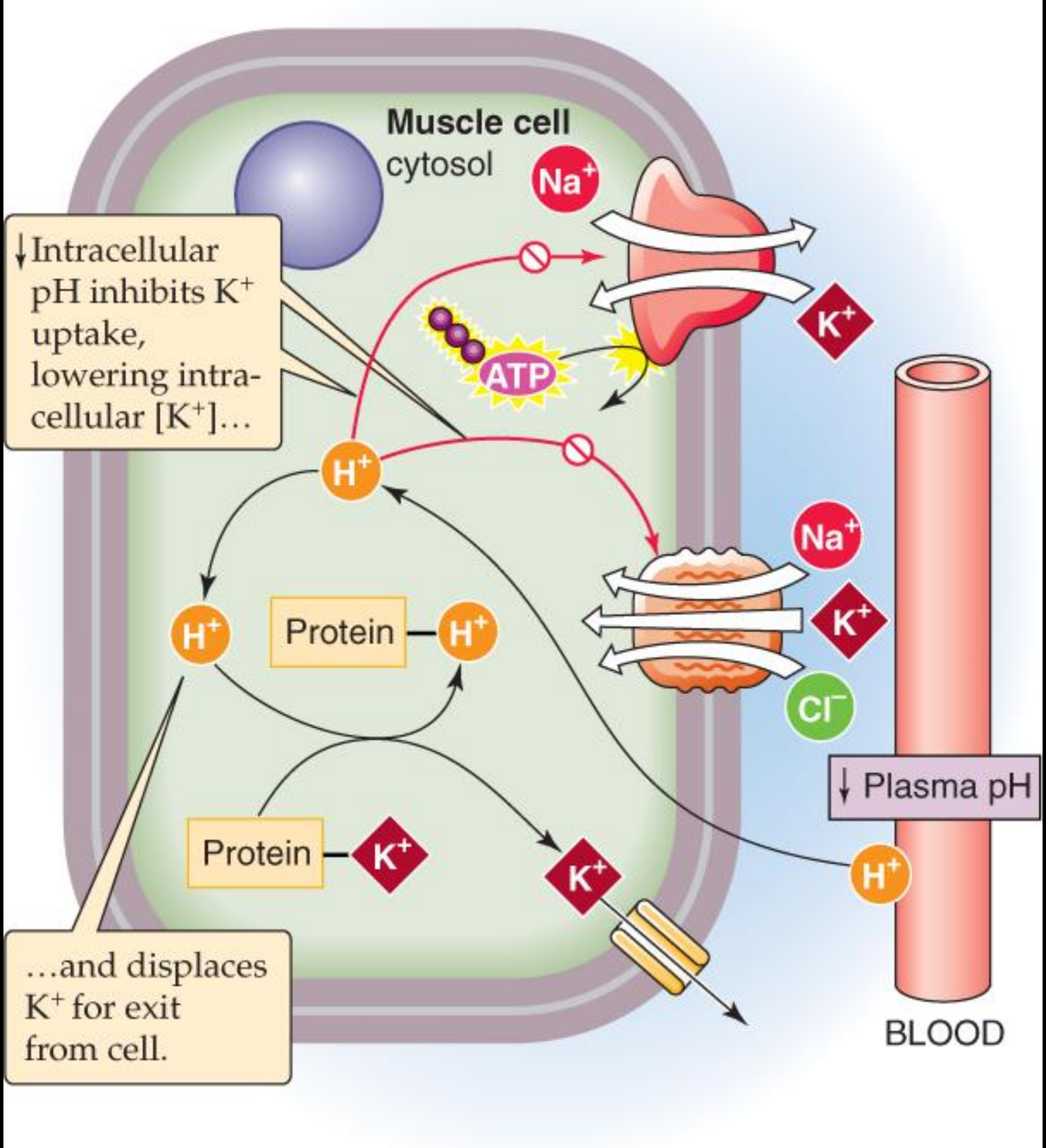


Boron & Boulpaep: Medical Physiology, 2nd Edition.


3 Na⁺
K⁺
2 K⁺
ATP
GLUT4
glukóza
Inzulínový receptor
inzulín
Adrenalínový receptor
adrenalin
cAMP
Mineralo-kortikoidní receptor
aldosteron
aldosteron



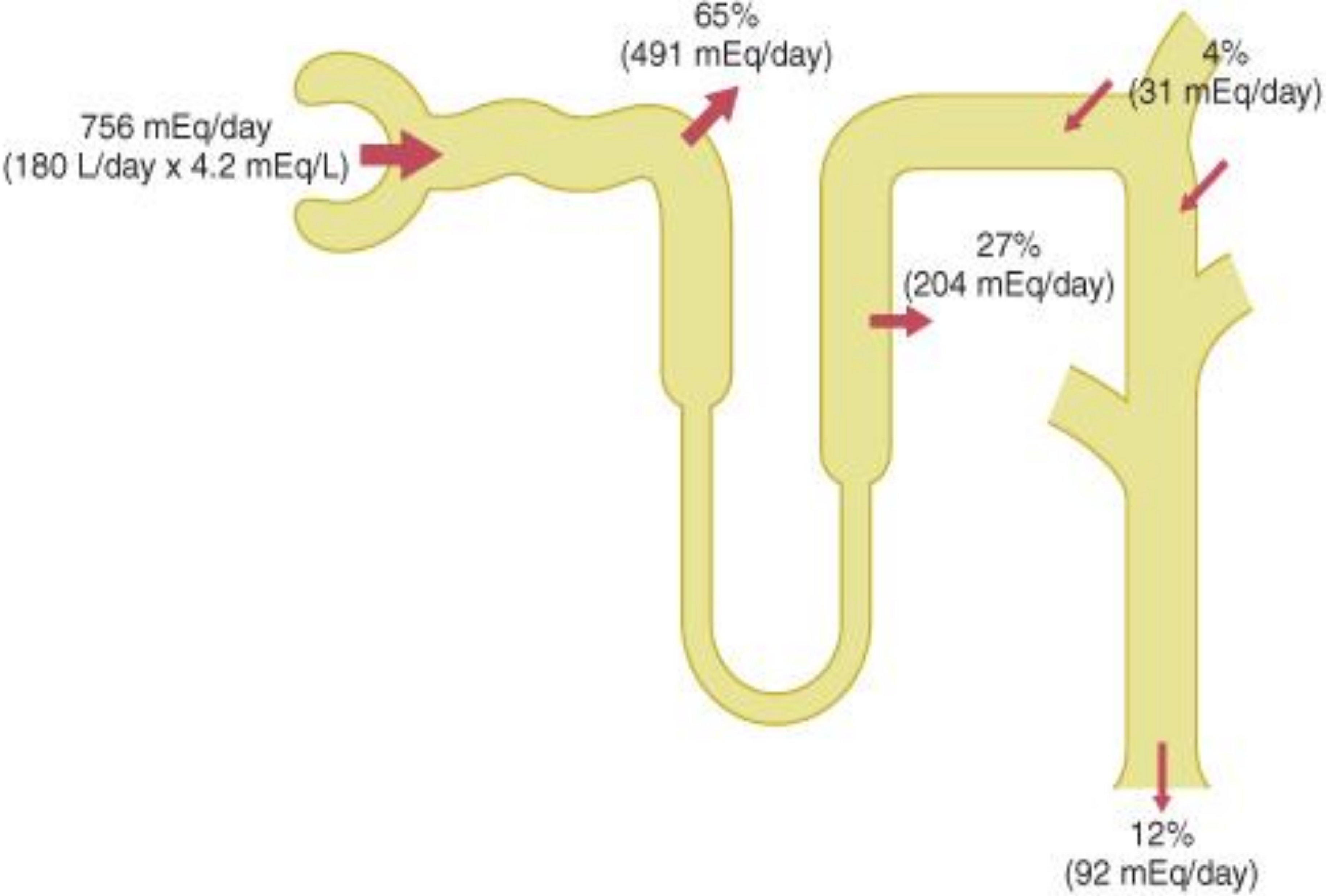
↓ Intracellular pH inhibits K$^+$ uptake, lowering intracellular [K$^+$]…

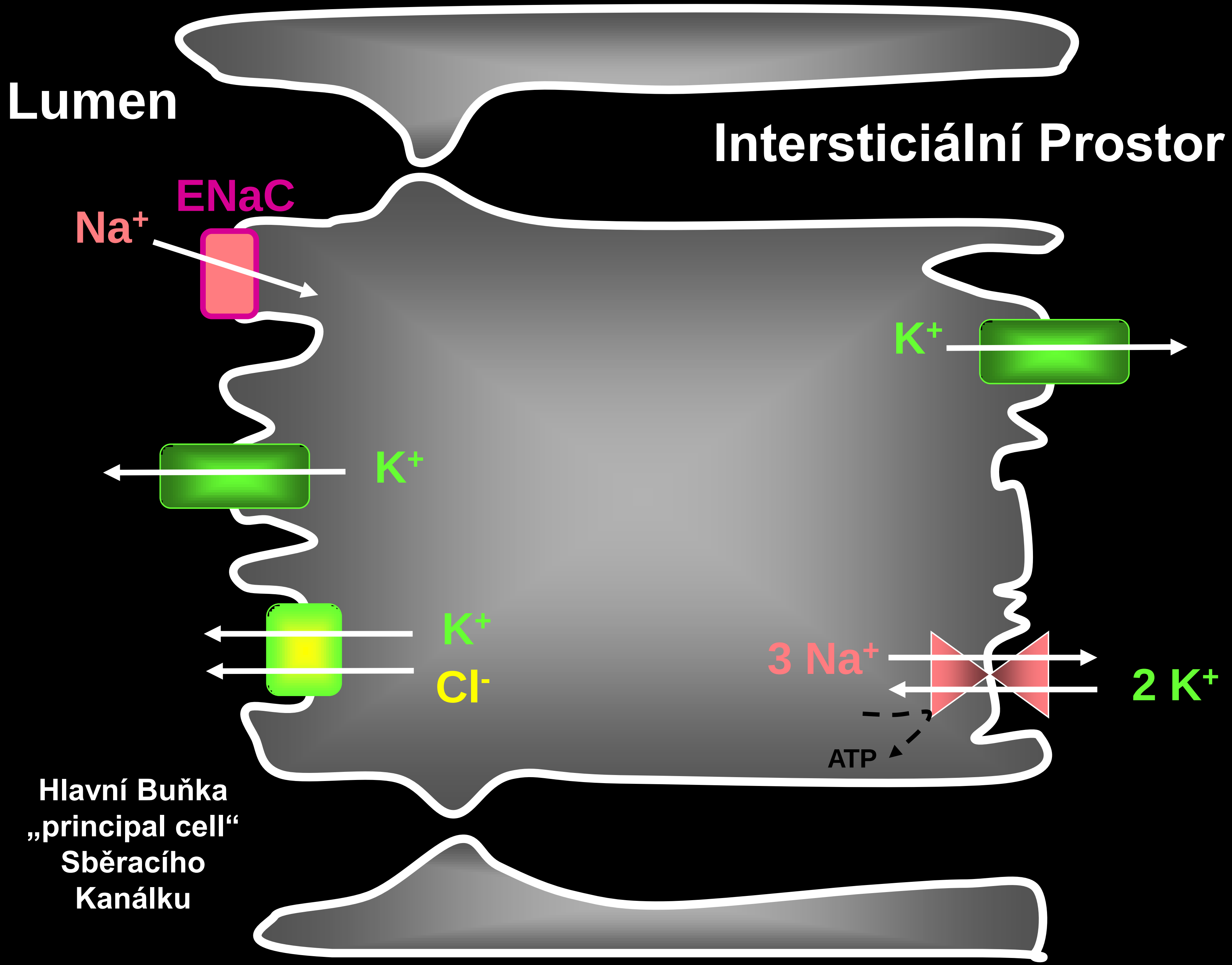
…and displaces K$^+$ for exit from cell.

Boron & Boulpaep: Medical Physiology, 2nd Edition.

Summary of tubular potassium transport

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


756 mEq/day
(180 L/day x 4.2 mEq/L)
65%
(491 mEq/day)
4%
(31 mEq/day)
27%
(204 mEq/day)
12%
(92 mEq/day)

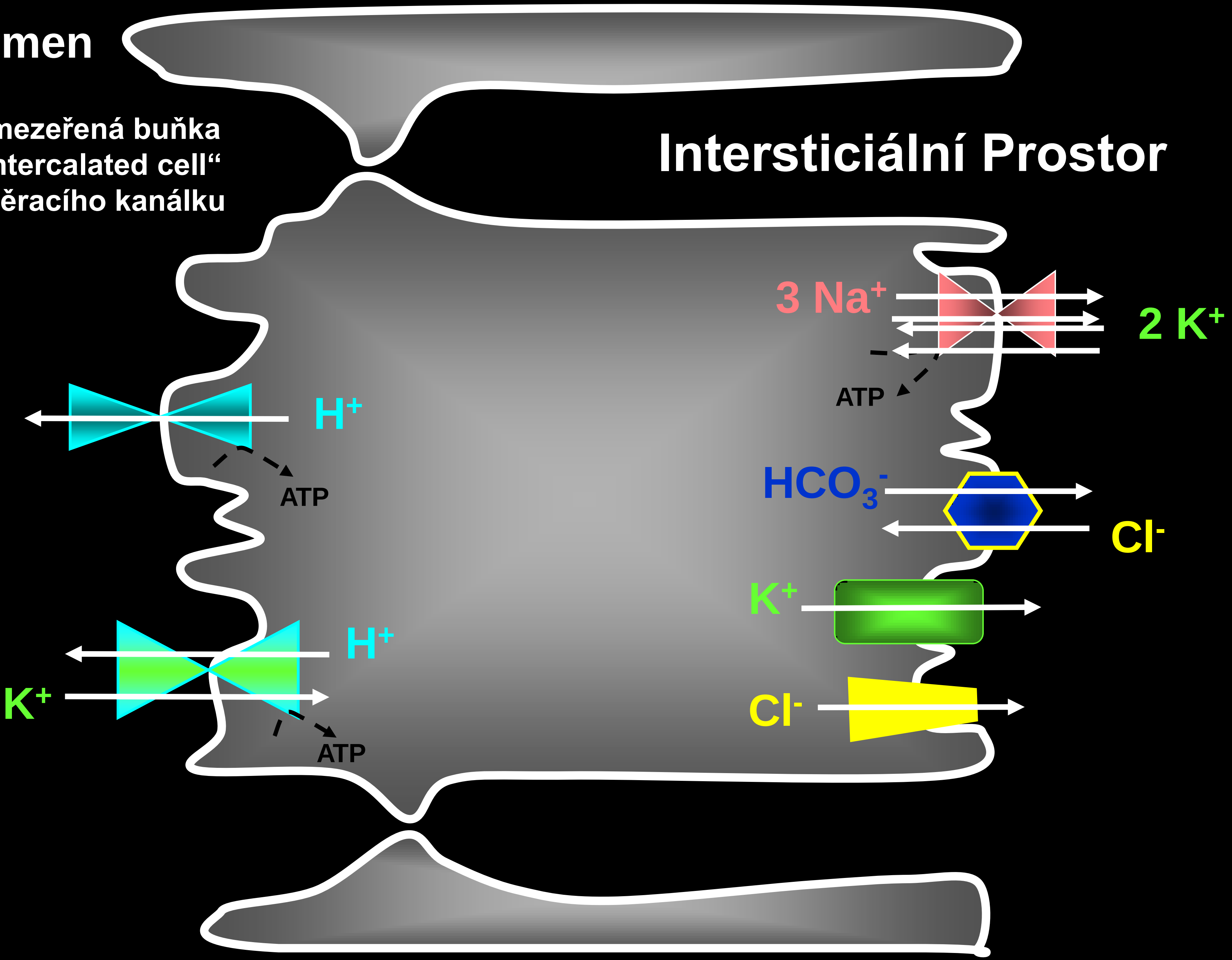


**Hlavní Buňka
„principal cell“
Sběracího
Kanálku**

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 Potasium ions from inside the cells through the basolateral membrane.

Ad.2:

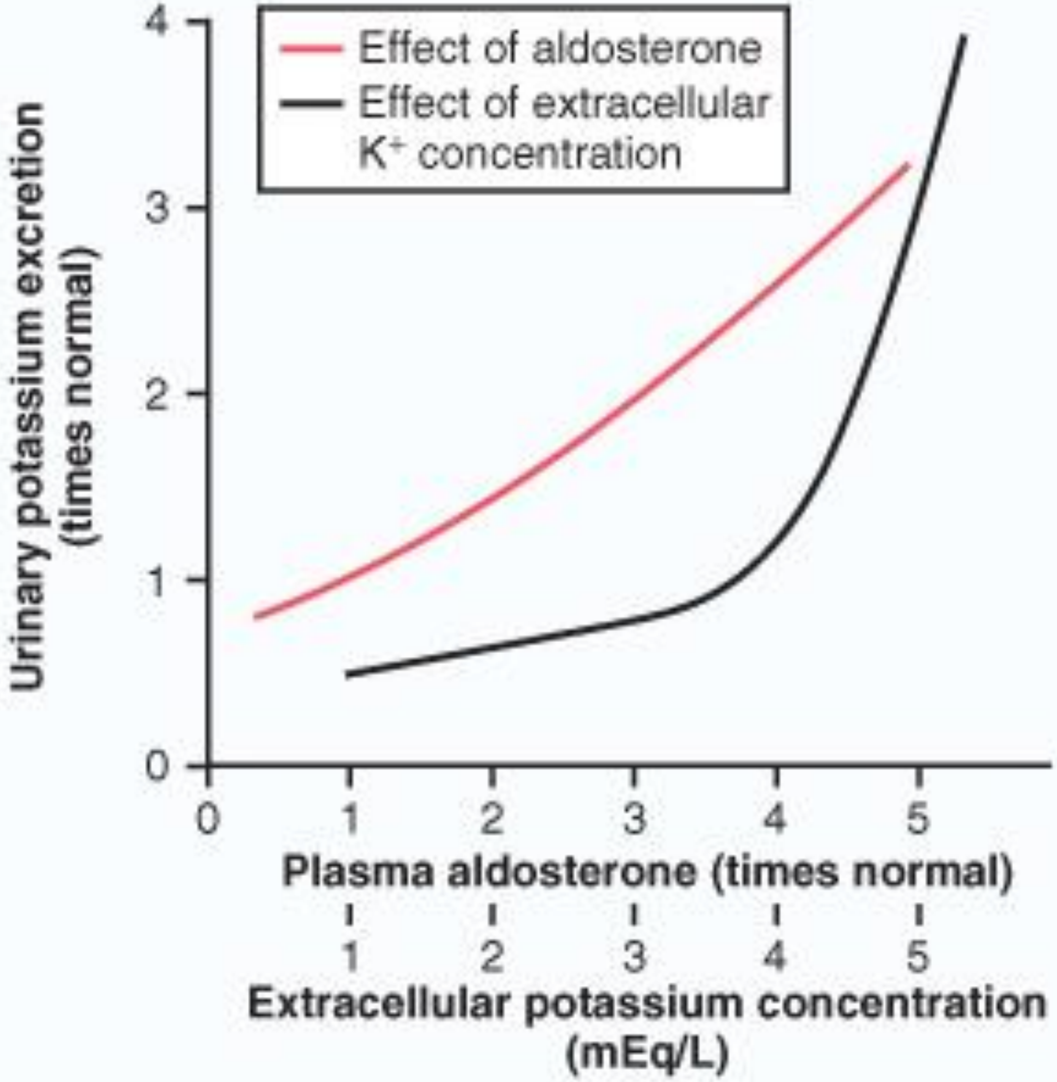
The luminal membrane pathway that allows potassium to exit the cell must be open and this is the function of aldosterone. It also stimulates Na-K-ATPase.

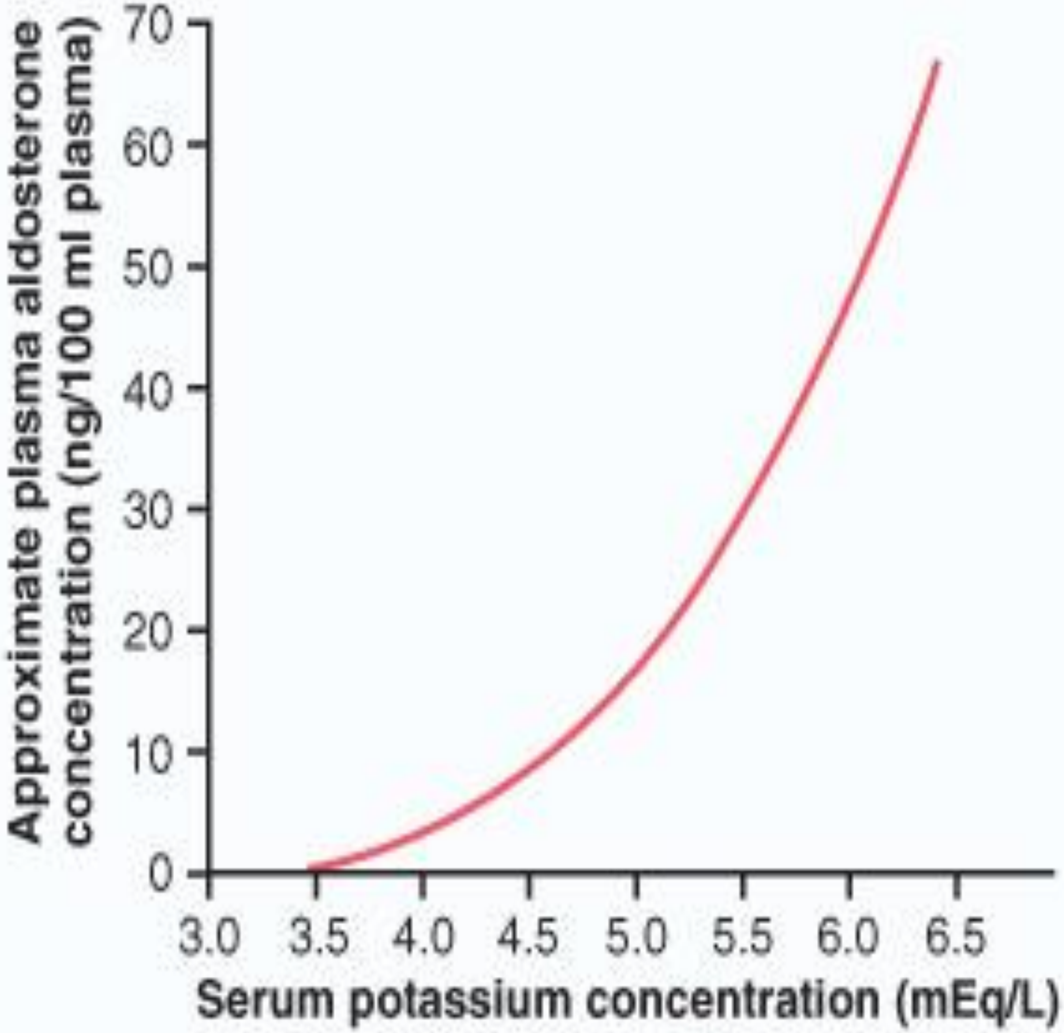
Ad.3:

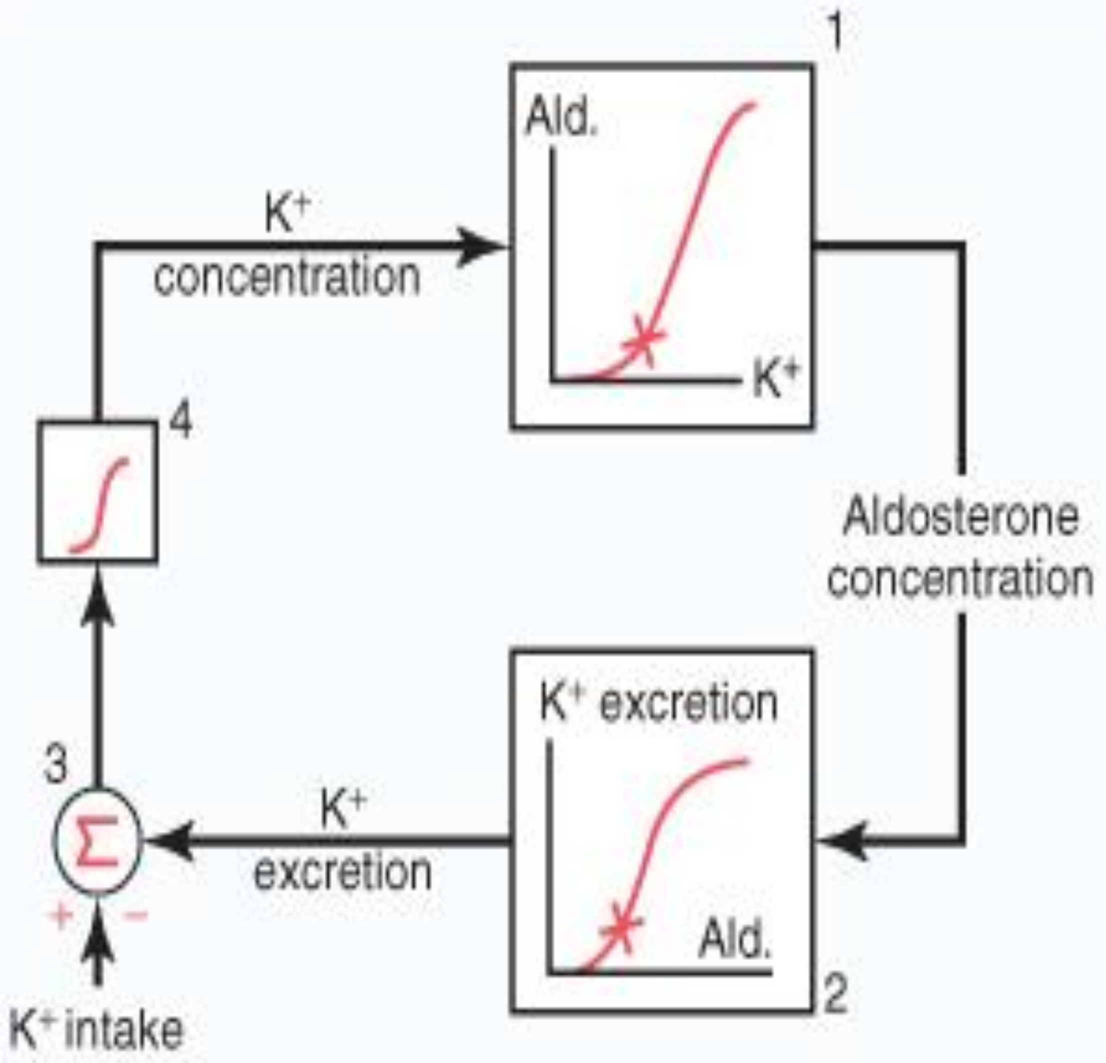
With an increased delivery of sodium to the cortical collecting duct, more sodium enters principal cells, and more potassium is secreted.

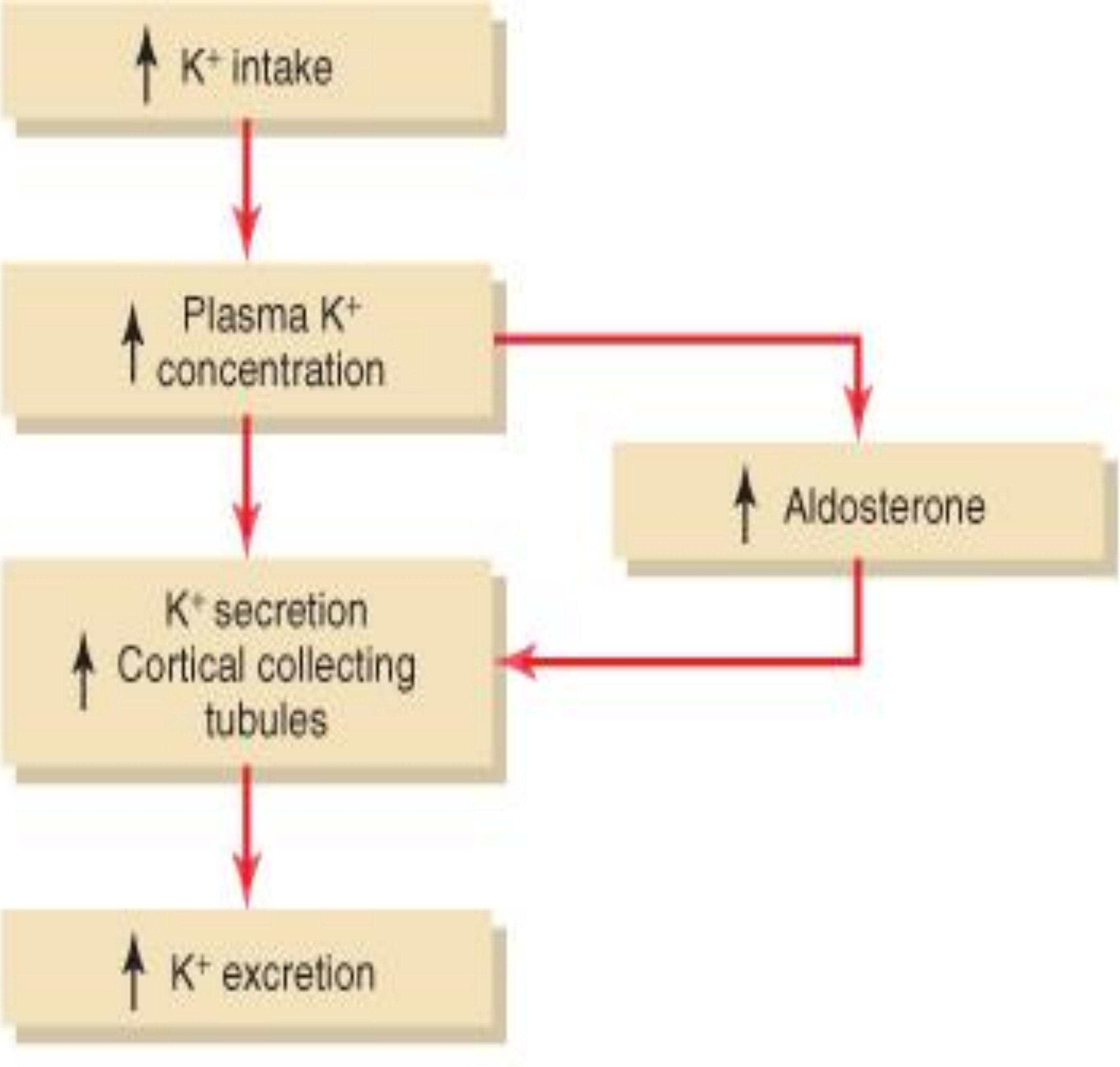
4. Acute acidosis decreases potassium secretion

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.


Effect of aldosterone
Effect of extracellular K+ concentration
Urinary potassium excretion (times normal)
0
1
2
3
4
0
1
2
3
4
5
Plasma aldosterone (times normal)
1
2
3
4
5
Extracellular potassium concentration (mEq/L)


Approximate plasma aldosterone concentration (ng/100 ml plasma)
70
60
50
40
30
20
10
0
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
Serum potassium concentration (mEq/L)


1
Ald.
K+
K+
concentration
4
Aldosterone
concentration
K+ excretion
Ald.
2
3
Σ
K+
excretion
+
−
K+ intake



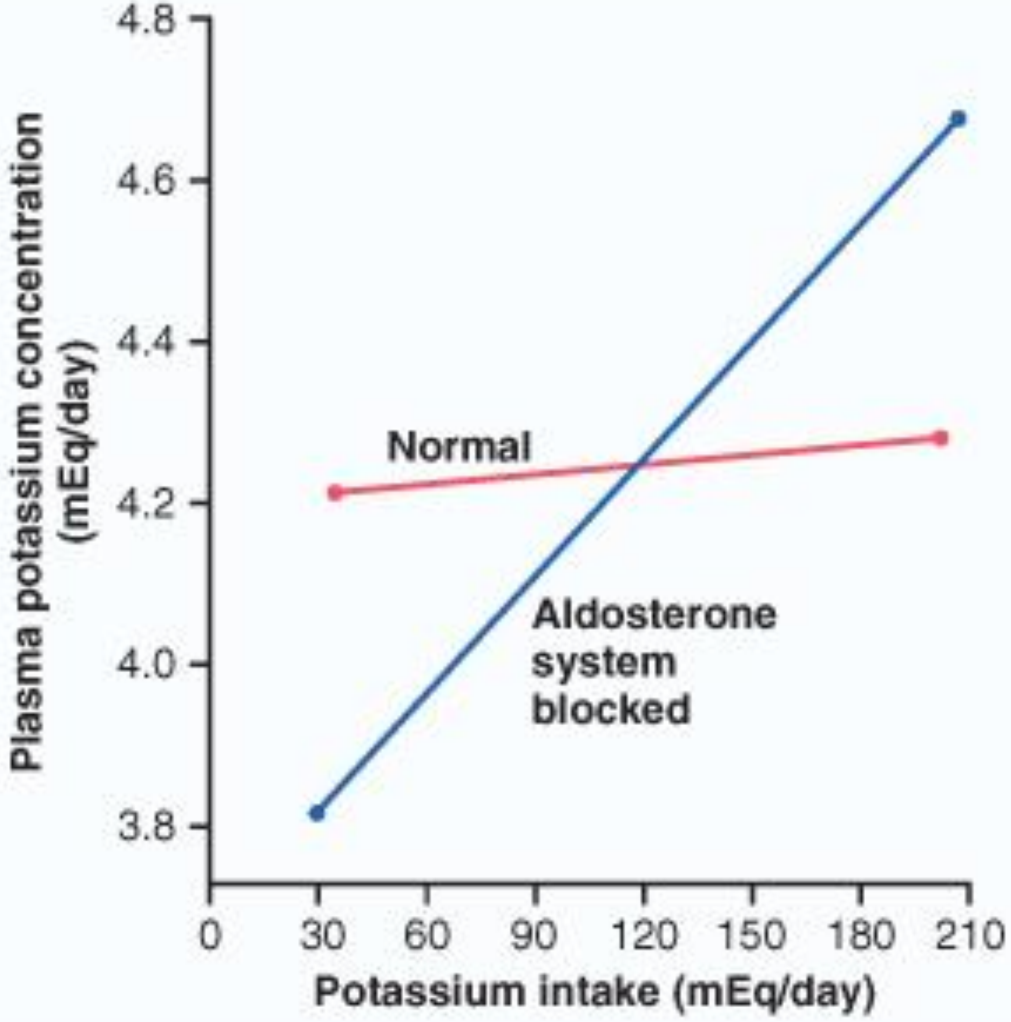
↑ K^+ intake

↑ Plasma K^+ concentration

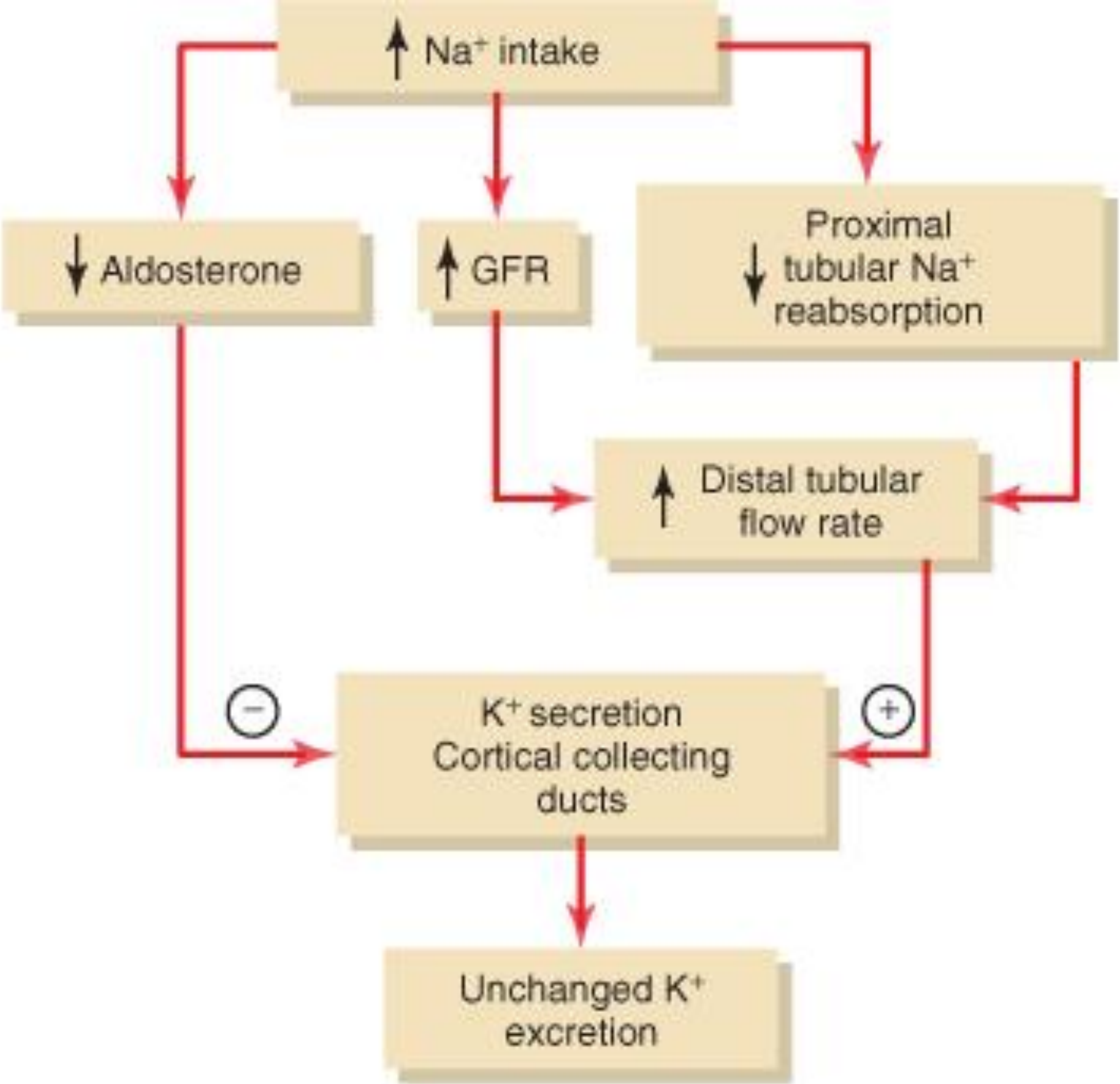
↑ Aldosterone

↑ K^+ secretion Cortical collecting tubules

↑ K^+ excretion



4.8
4.6
4.4
4.2
4.0
3.8
Plasma potassium concentration (mEq/day)
Normal
Aldosterone system blocked
0
30
60
90
120
150
180
210
Potassium intake (mEq/day)



↑ Na^+ intake

↓ Aldosterone

↑ GFR

Proximal ↓ tubular Na^+ reabsorption

↑ Distal tubular flow rate

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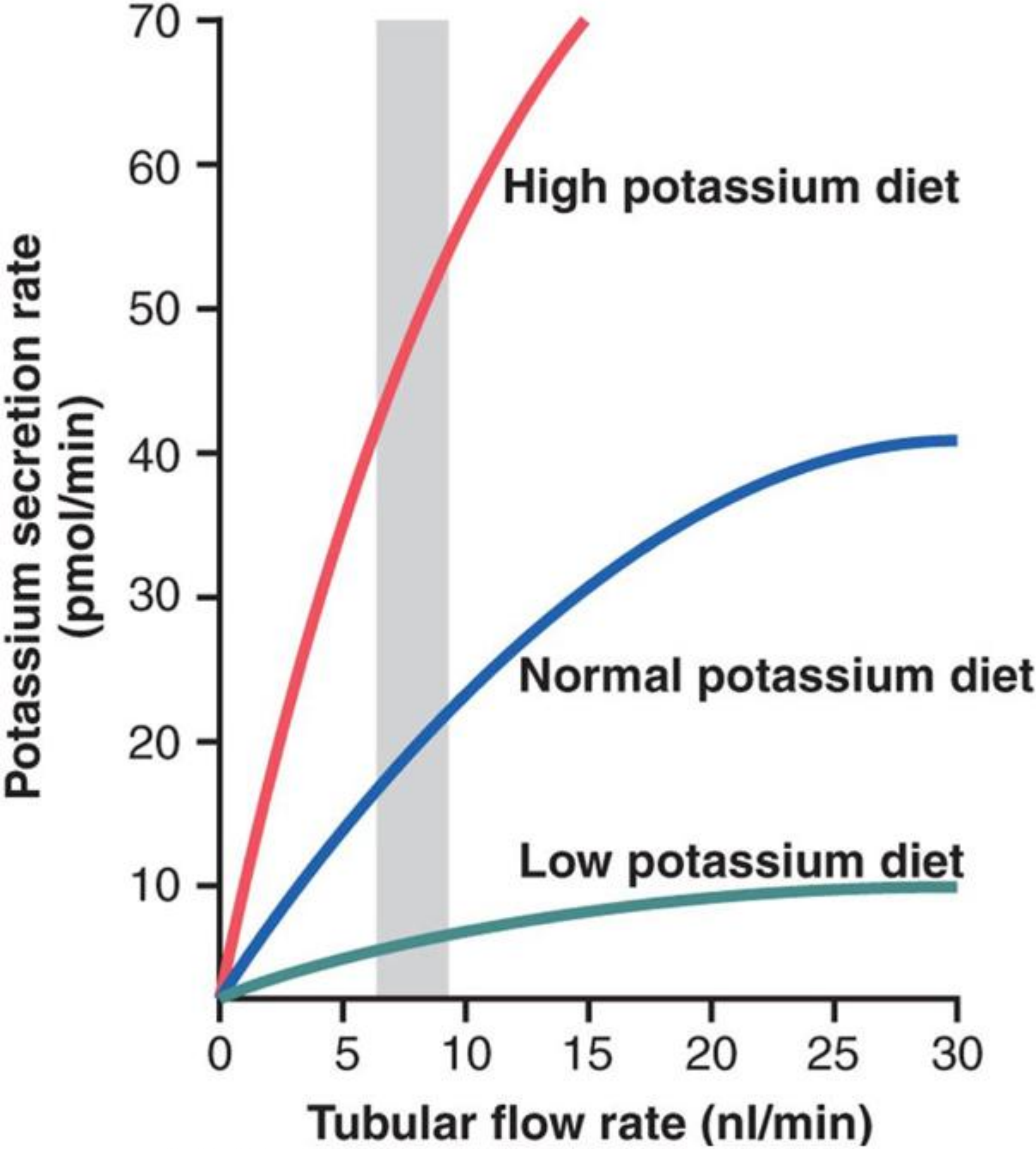
⊕

K^+ secretion Cortical collecting ducts

Unchanged K^+ excretion



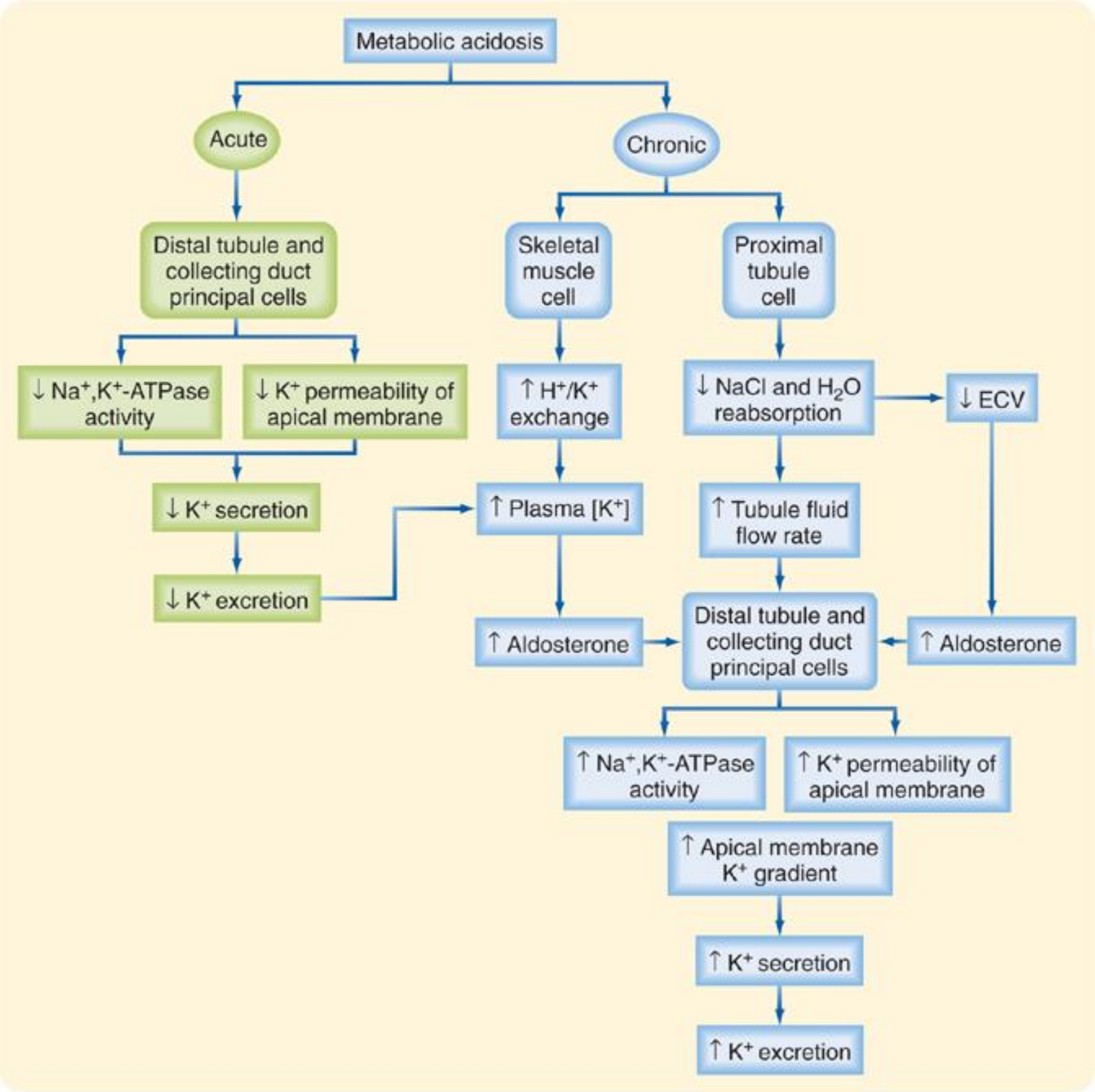
Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

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.



Metabolic acidosis

Acute

Distal tubule and collecting duct principal cells

↓ Na^+,K^+-ATPase activity

↓ K^+ permeability of apical membrane

↓ K^+ secretion

↓ K^+ excretion

Chronic

Skeletal muscle cell

↑ H^+/K^+ exchange

↑ Plasma $[K^+]$

↑ Aldosterone

Proximal tubule cell

↓ NaCl and H_2O reabsorption

↓ ECV

↑ Tubule fluid flow rate

↑ Aldosterone

Distal tubule and collecting duct principal cells

↑ Na^+,K^+-ATPase activity

↑ K^+ permeability of apical membrane

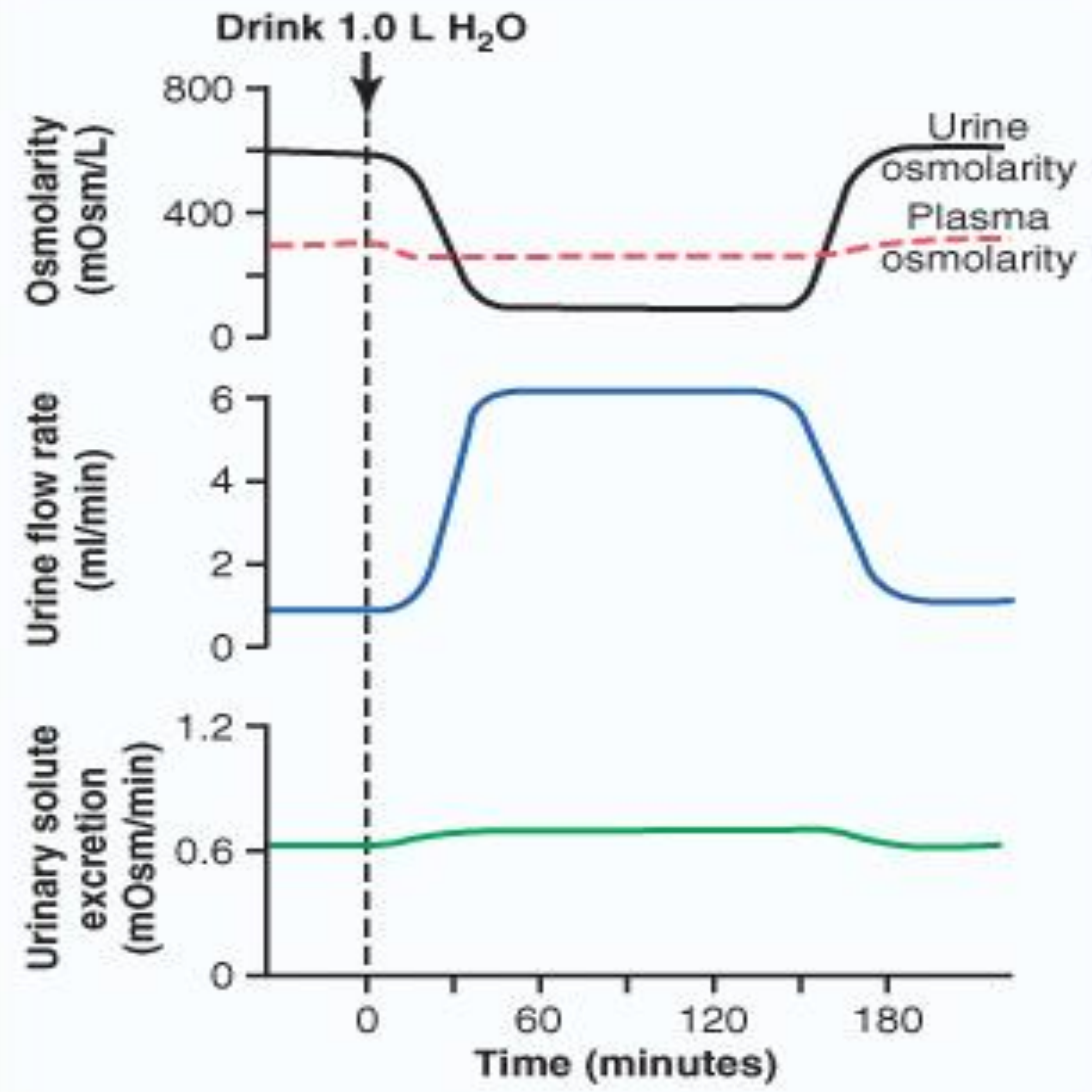
↑ Apical membrane K^+ gradient

↑ K^+ secretion

↑ K^+ excretion

Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.

Regulation of Extracellular Fluid Osmolarity and Sodium Concentration


Drink 1.0 L H_2O
Osmolarity (mOsm/L)
800
400
0
Urine osmolarity
Plasma osmolarity
Urine flow rate (ml/min)
6
4
2
0
Urinary solute excretion (mOsm/min)
1.2
0.6
0
0
60
120
180
Time (minutes)

Obligatory urine volume

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

Proč nepít mořskou vodu?

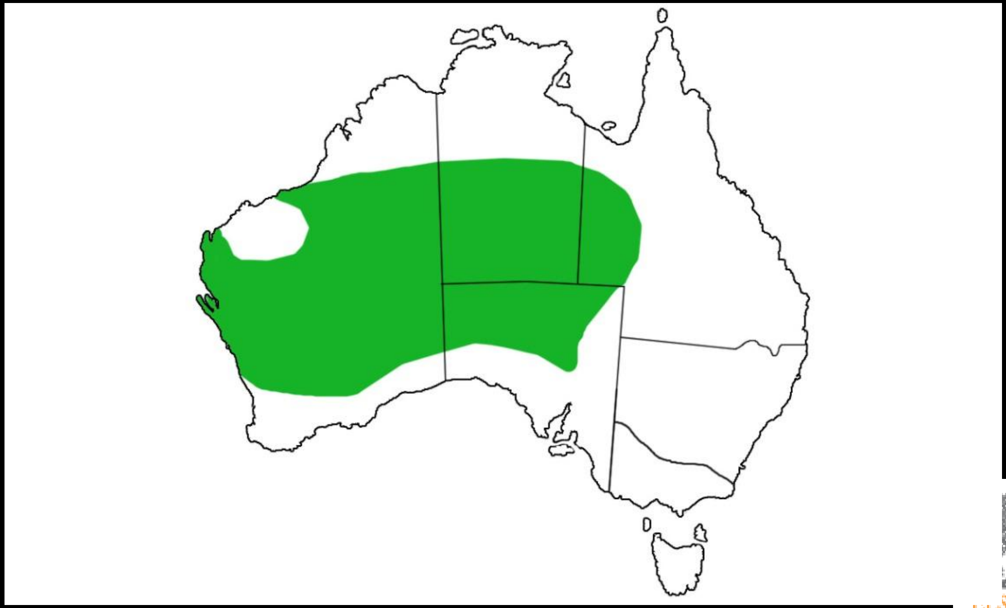
1 L mořské vody = 1 200 mOsm = příjem 1 200 mOsm/L
Organizmus se musí denně zbavit minimálně 600 mOsm denně
To znamená, že musíme vyloučit 1800 mOsm, což i při tvorbě maximálně koncentrované moči (1200 mOsm/l) musíme vyloučit 1.5 L.
Z toho vyplývá, že máme minimální ztrátu 500 ml.

Australian hopping mouse

Notomys alexis

Klokanomyš spinifexová

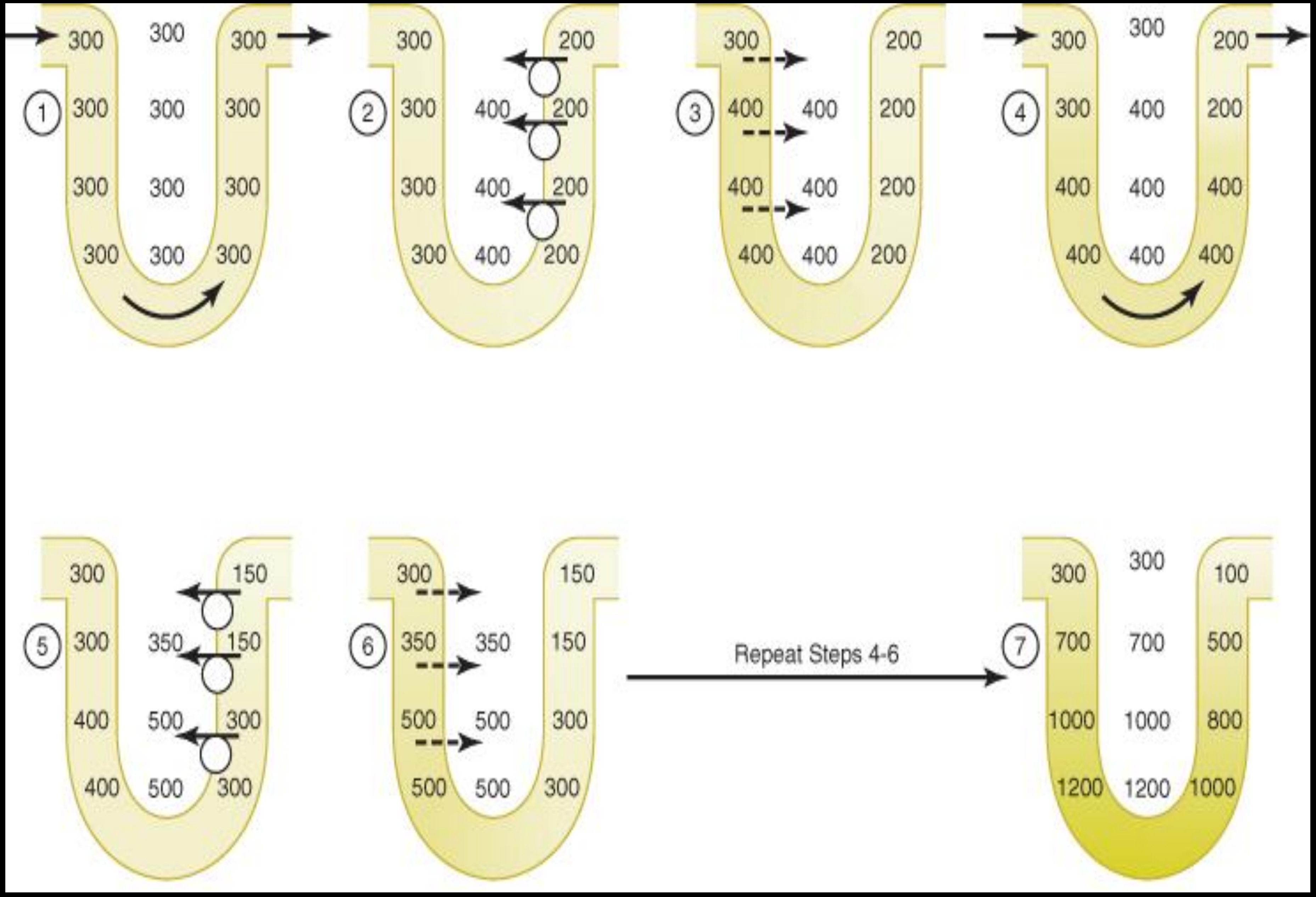
Can concentrate urine to 10 000 mOsm/L

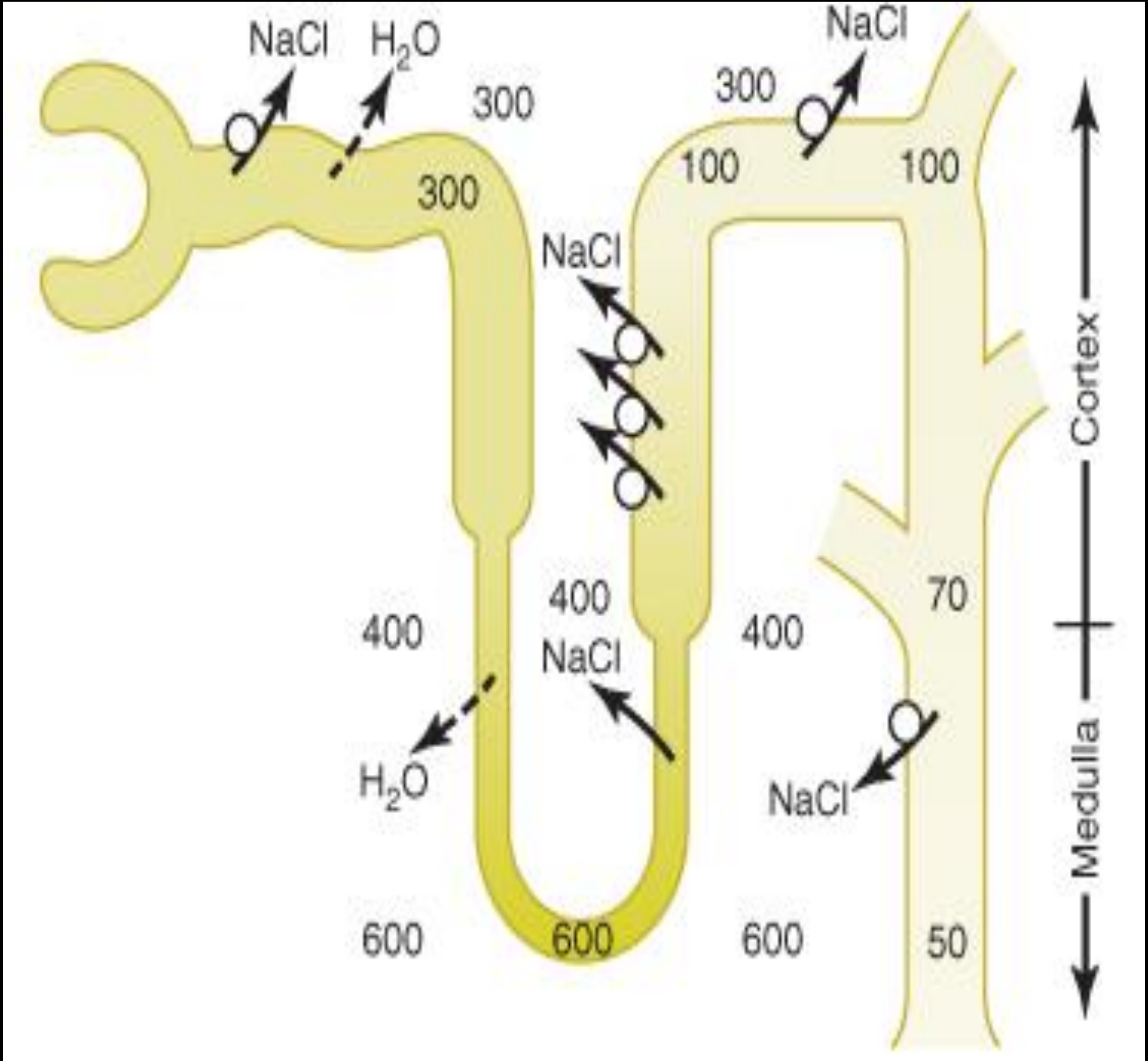


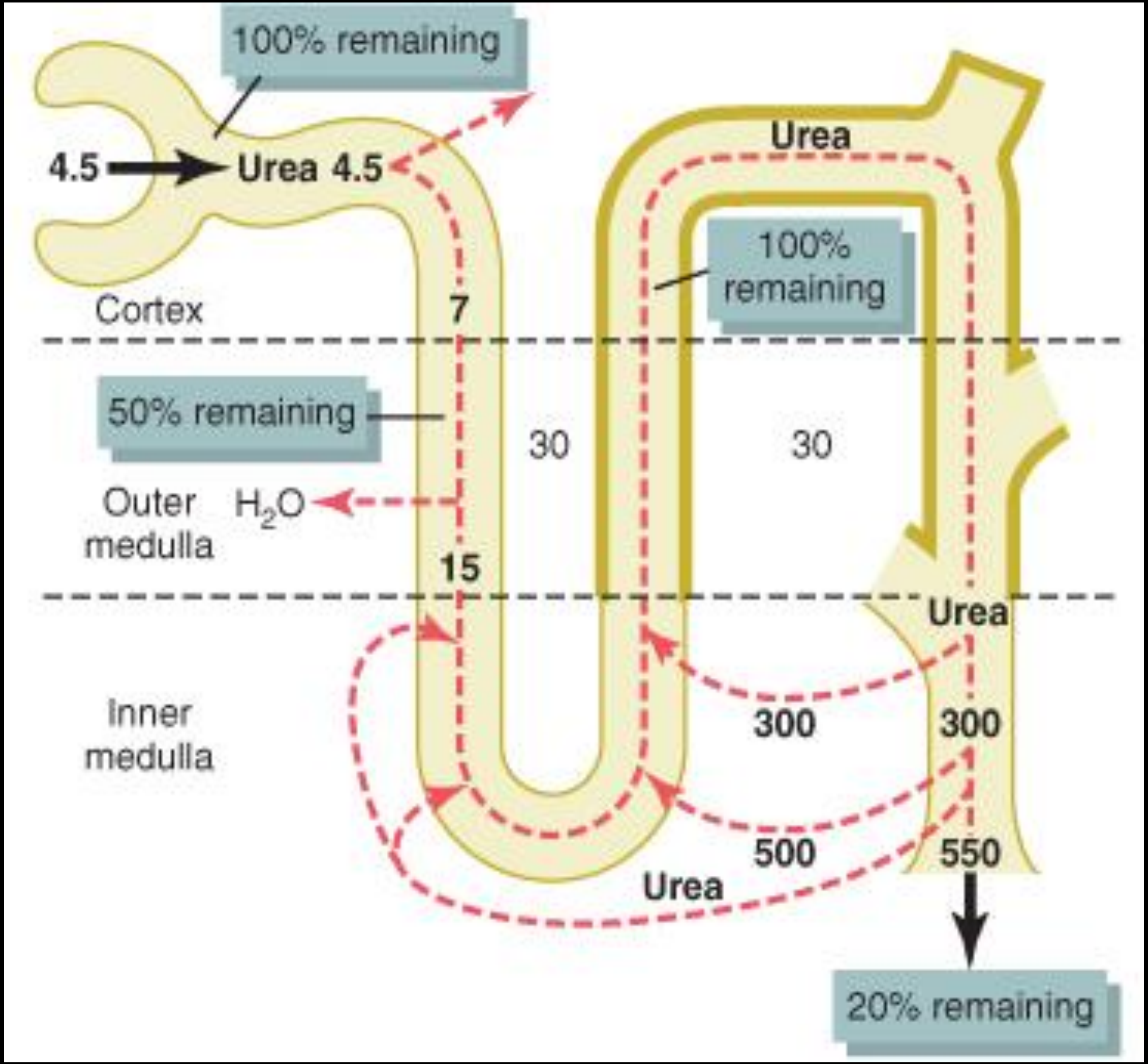
Requirement for Excreting a Concentrated Urine

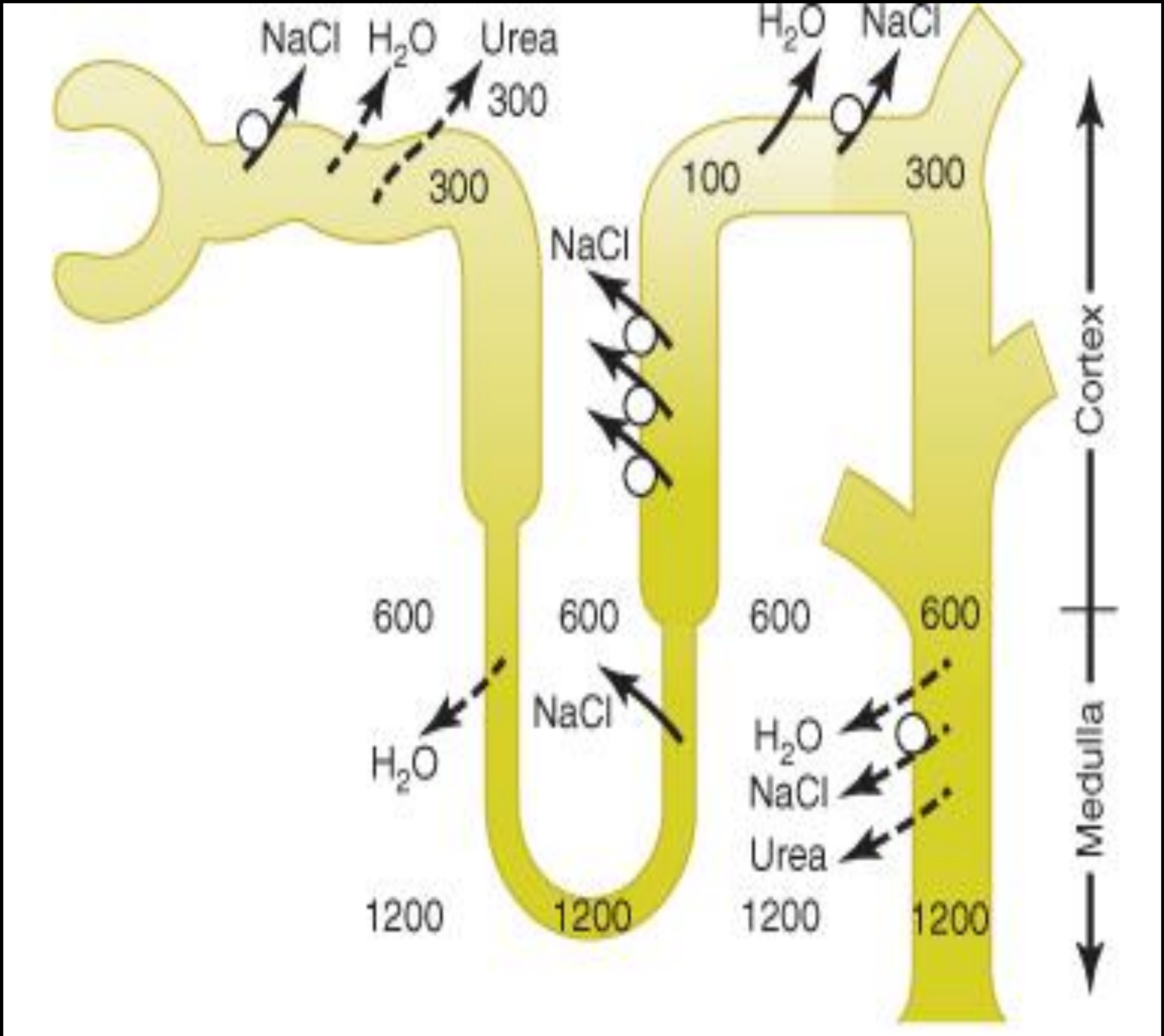
1. High level of ADH (antidiuretic hormone)
2. High osmolarity of the renal medullary interstitial fluid

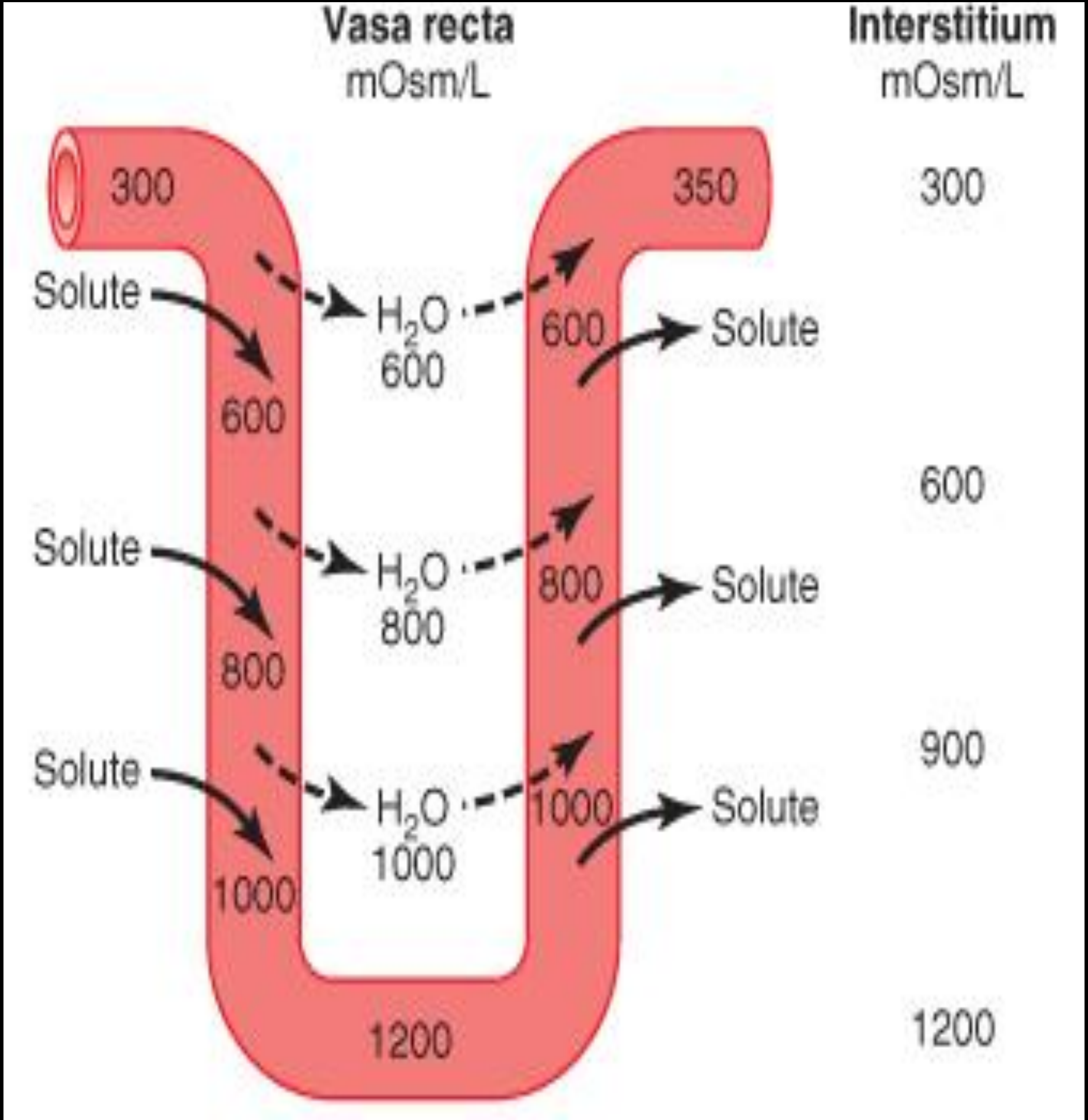
		Permeability		
	Active NaCl Transport	H_20	NaCl	Urea
Proximal Tubule	++	++	+	+
Thin descending limb	0	++	+	+
Thin ascending limb	0	0	+	+
Thick ascending limb	++	0	0	0
Distal tubule	+	+ADH	0	0
Cortical collecting tubule	+	+ADH	0	0
Inner medullary collecting duct	+	+ADH	0	++ADH

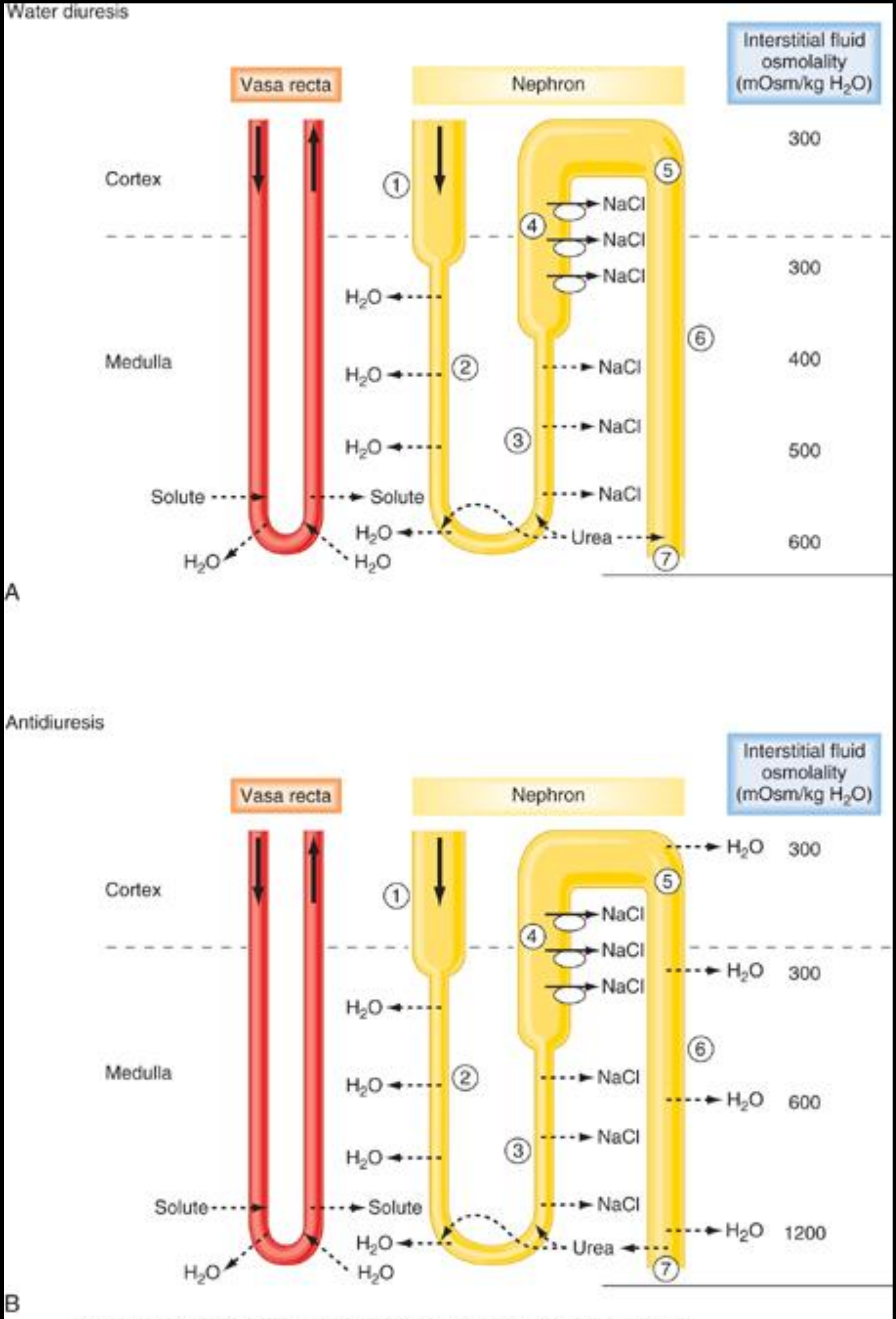

1
300
300
300
300
300
300
300
300
300
300
300
300
2
300
200
300
400
200
300
400
200
300
400
200
3
300
200
400
400
200
400
400
200
400
400
200
4
300
300
200
300
400
200
400
400
400
400
400
400
5
300
150
300
350
150
400
500
300
400
500
300
6
300
150
350
350
150
500
500
300
500
500
300
Repeat Steps 4-6
7
300
300
100
700
700
500
1000
1000
800
1200
1200
1000


NaCl
H_2O
300
300
NaCl
300
100
100
NaCl
400
400
NaCl
400
400
70
H_2O
NaCl
600
600
600
50
Cortex
Medulla

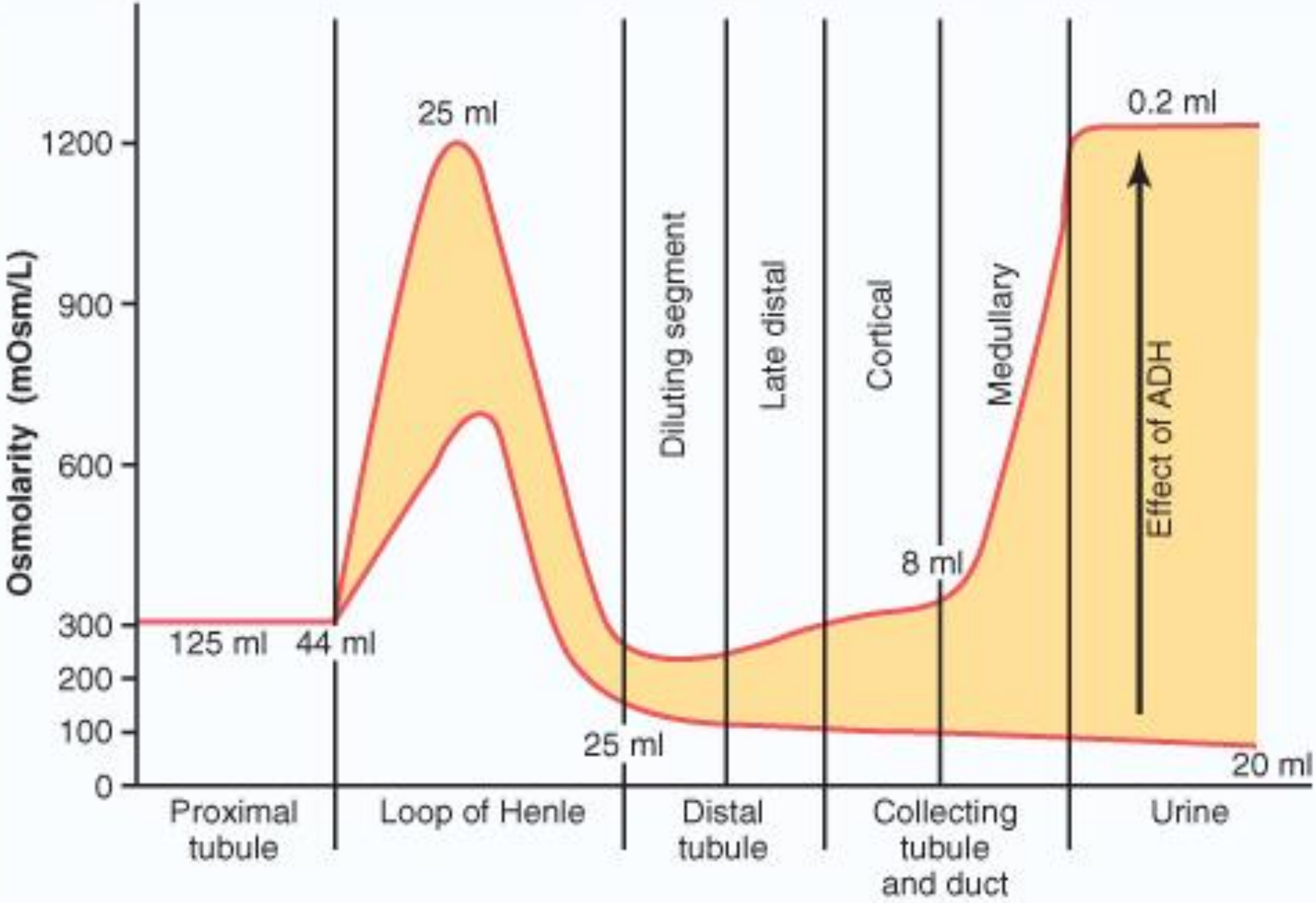

100% remaining
4.5
Urea 4.5
Urea
100% remaining
Cortex
7
50% remaining
30
30
Outer medulla
H_2O
15
Urea
Inner medulla
300
300
500
550
Urea
20% remaining


NaCl
H2O
Urea
300
300
H2O
NaCl
100
300
NaCl
600
600
600
600
H2O
NaCl
H2O
NaCl
Urea
1200
1200
1200
1200
Cortex
Medulla


Vasa recta
mOsm/L
Interstitium
mOsm/L
300
350
300
Solute
H_2O
600
600
Solute
600
600
Solute
H_2O
800
800
Solute
800
900
Solute
H_2O
1000
1000
Solute
1000
1200
1200



Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.


Osmolarity (mOsm/L)
1200
900
600
300
200
100
0
25 ml
0.2 ml
125 ml
44 ml
25 ml
8 ml
20 ml
Diluting segment
Late distal
Cortical
Medullary
Effect of ADH
Proximal tubule
Loop of Henle
Distal tubule
Collecting tubule and duct
Urine

$$V = C_{Osm} + C_{H20}$$

V = urine flow

C_{osm} = osmolal clearance

C_{H2O} = free water clearance

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

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

P_{osm} = plasma osmolarity, 300 mOsm/L
U_{osm} = urine osmolarity, 600 mOsml/L
V = urine flow, 1 ml/min (0.001 L/min)

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

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

Free-water clearance (C_{H20}): is calculated as the difference between urine flow and C_{osm}

$$C_{H20} = V - C_{osm} = V - \frac{U_{osm} \times V}{P_{osm}}$$

$$C_{H20} = 1 \text{ ml/min} - 2 \text{ ml/min} = -1 \text{ ml/min}$$

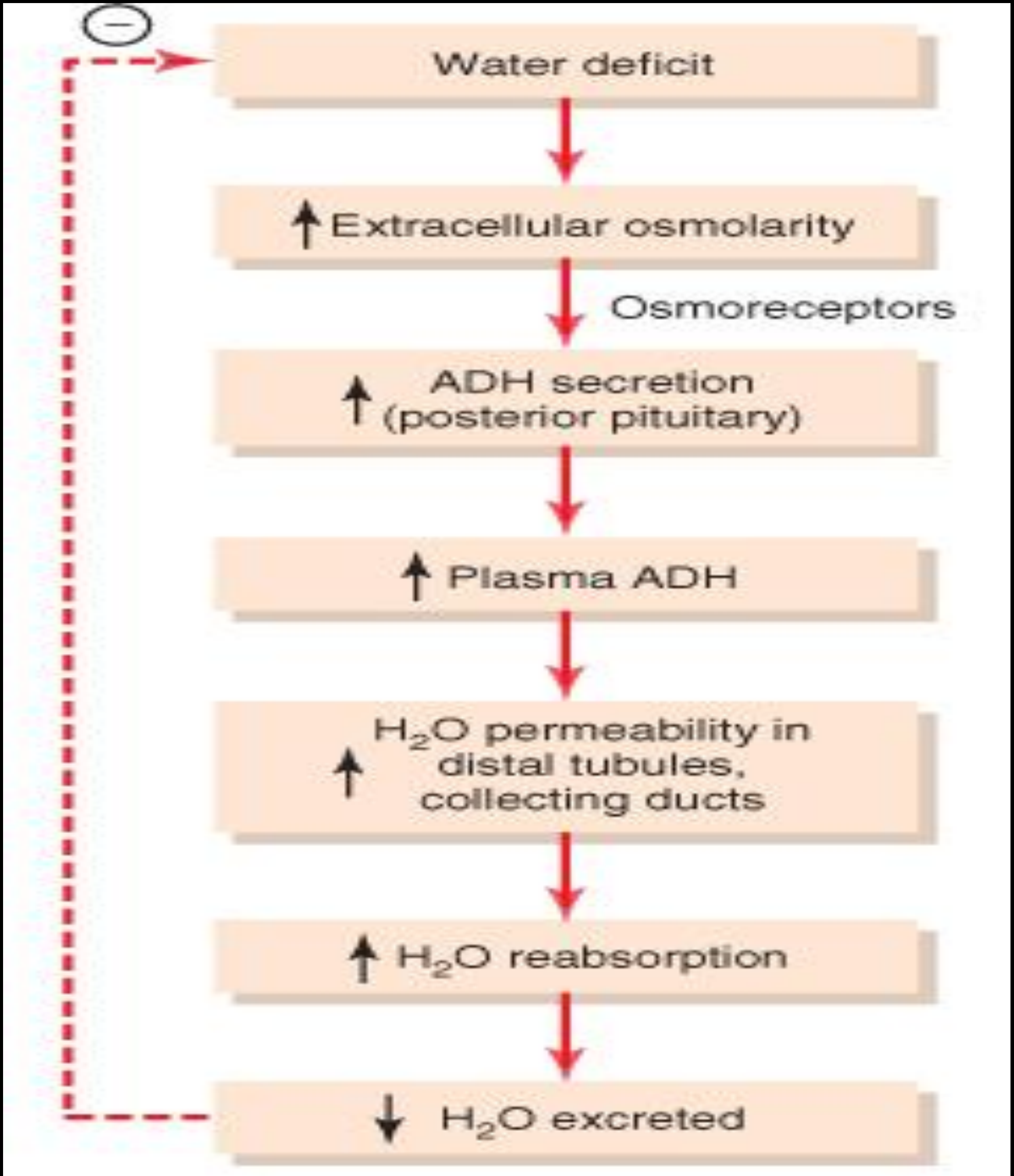
When C_{H20} is positive, excess water is being excreted by the kidneys, when C_{H20} is negative excess solutes ,are being removed from the plasma by the kidneys and water is being conserved.

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

Estimating plasma osmolarity from plasma sodium concentration

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

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



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Water deficit

↑ Extracellular osmolarity

Osmoreceptors

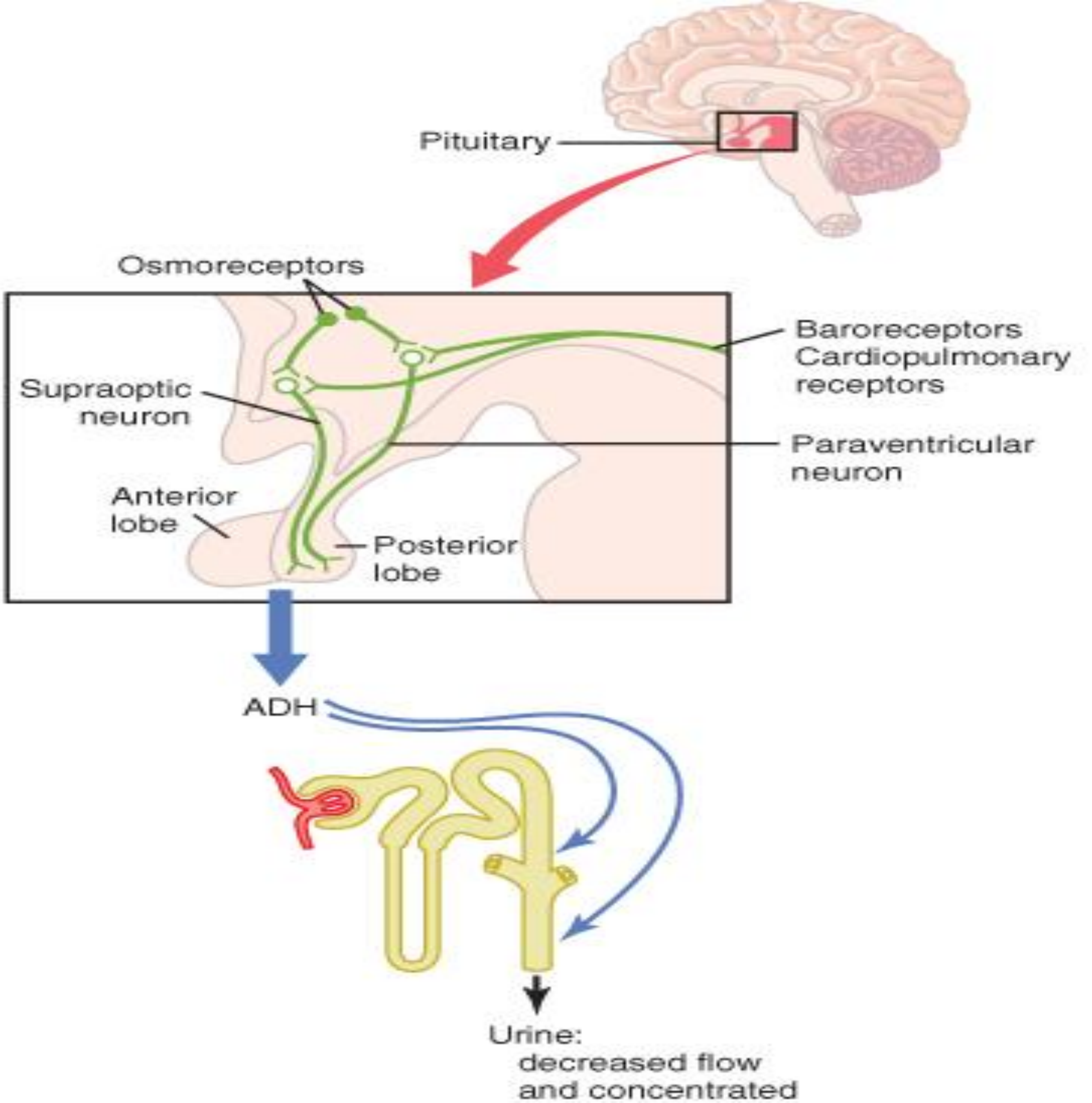
↑ ADH secretion (posterior pituitary)

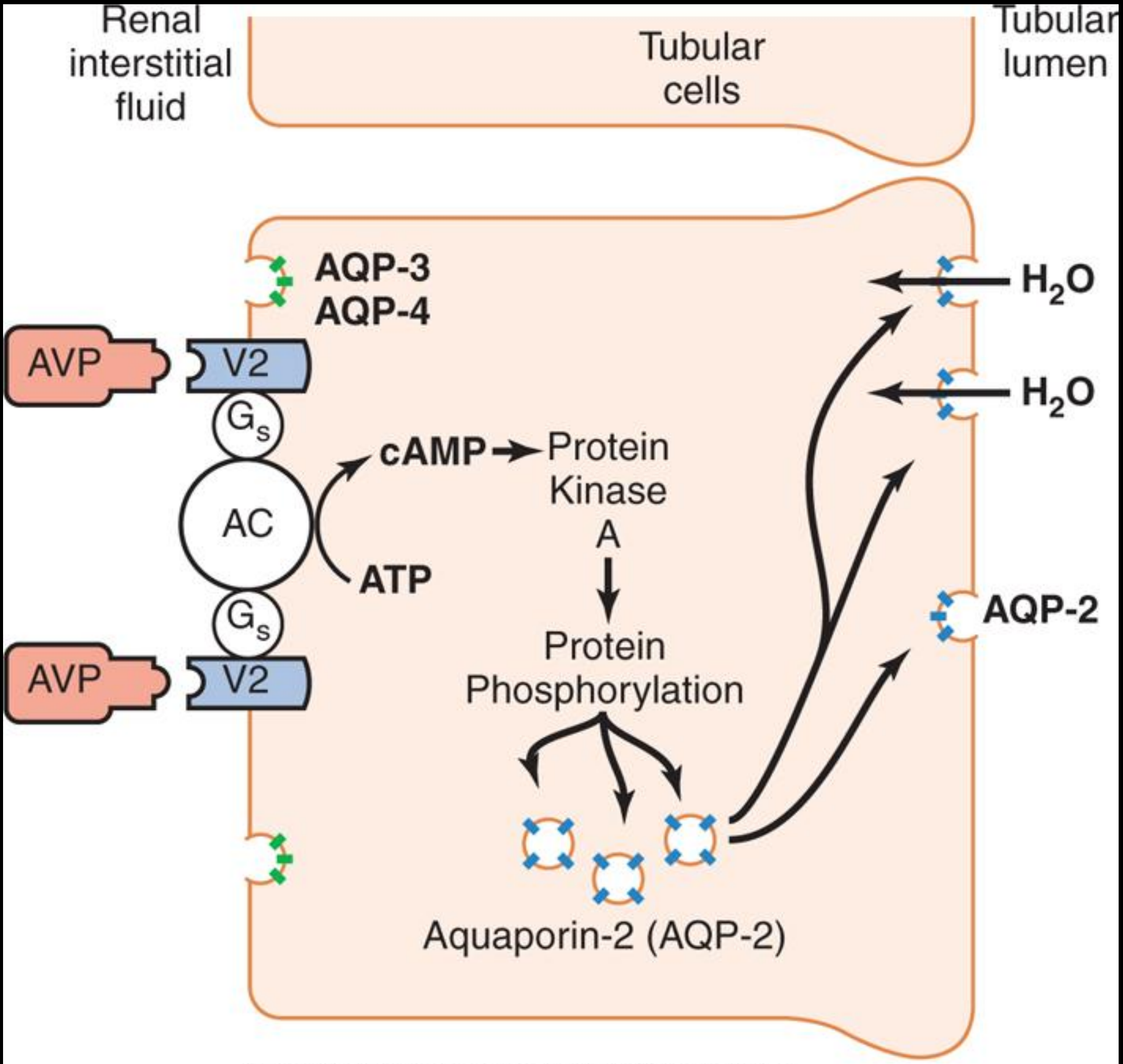
↑ Plasma ADH

↑ H_2O permeability in distal tubules, collecting ducts

↑ H_2O reabsorption

↓ H_2O excreted


Pituitary
Osmoreceptors
Baroreceptors
Cardiopulmonary
receptors
Supraoptic
neuron
Paraventricular
neuron
Anterior
lobe
Posterior
lobe
ADH
Urine:
decreased flow
and concentrated



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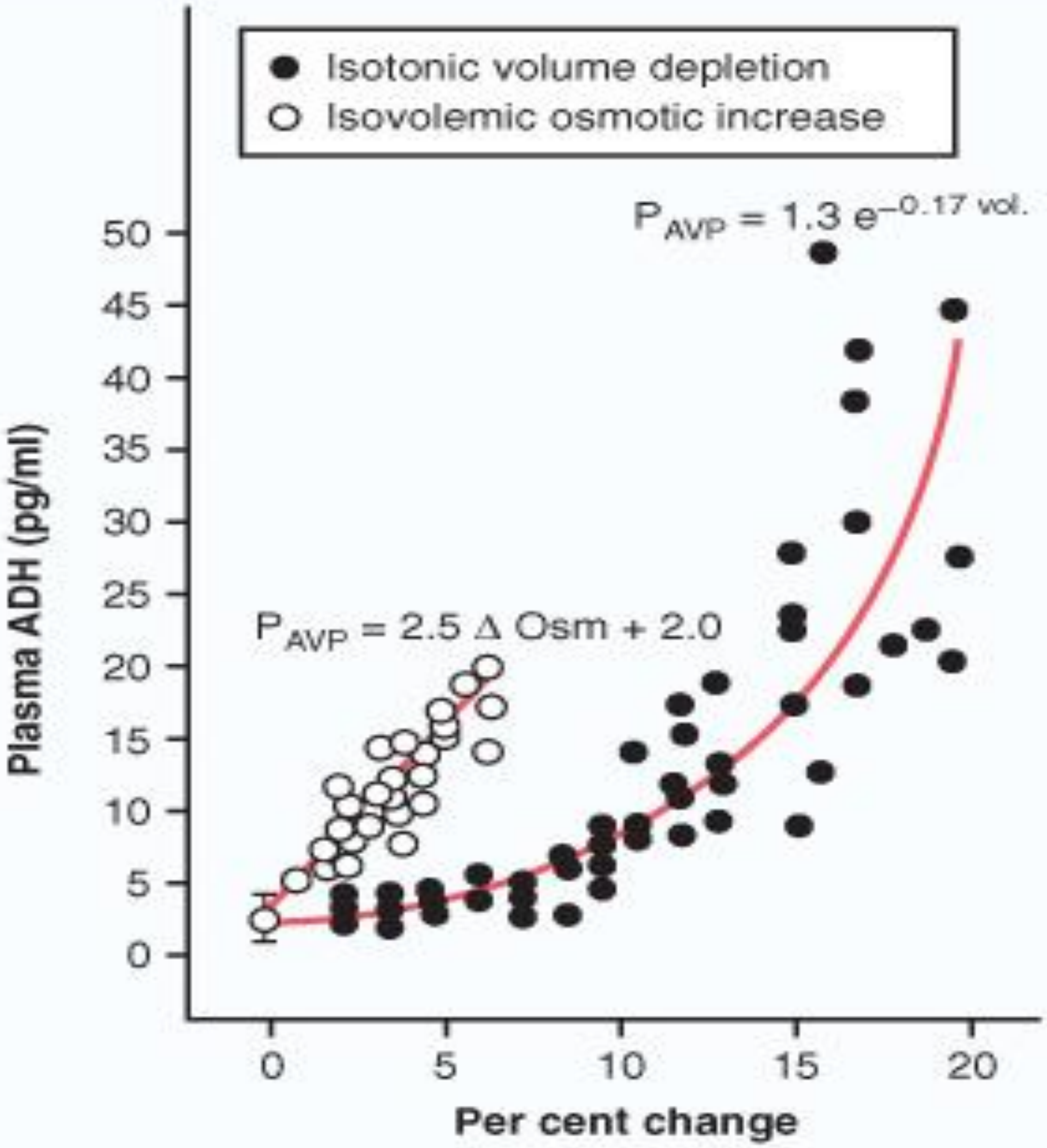
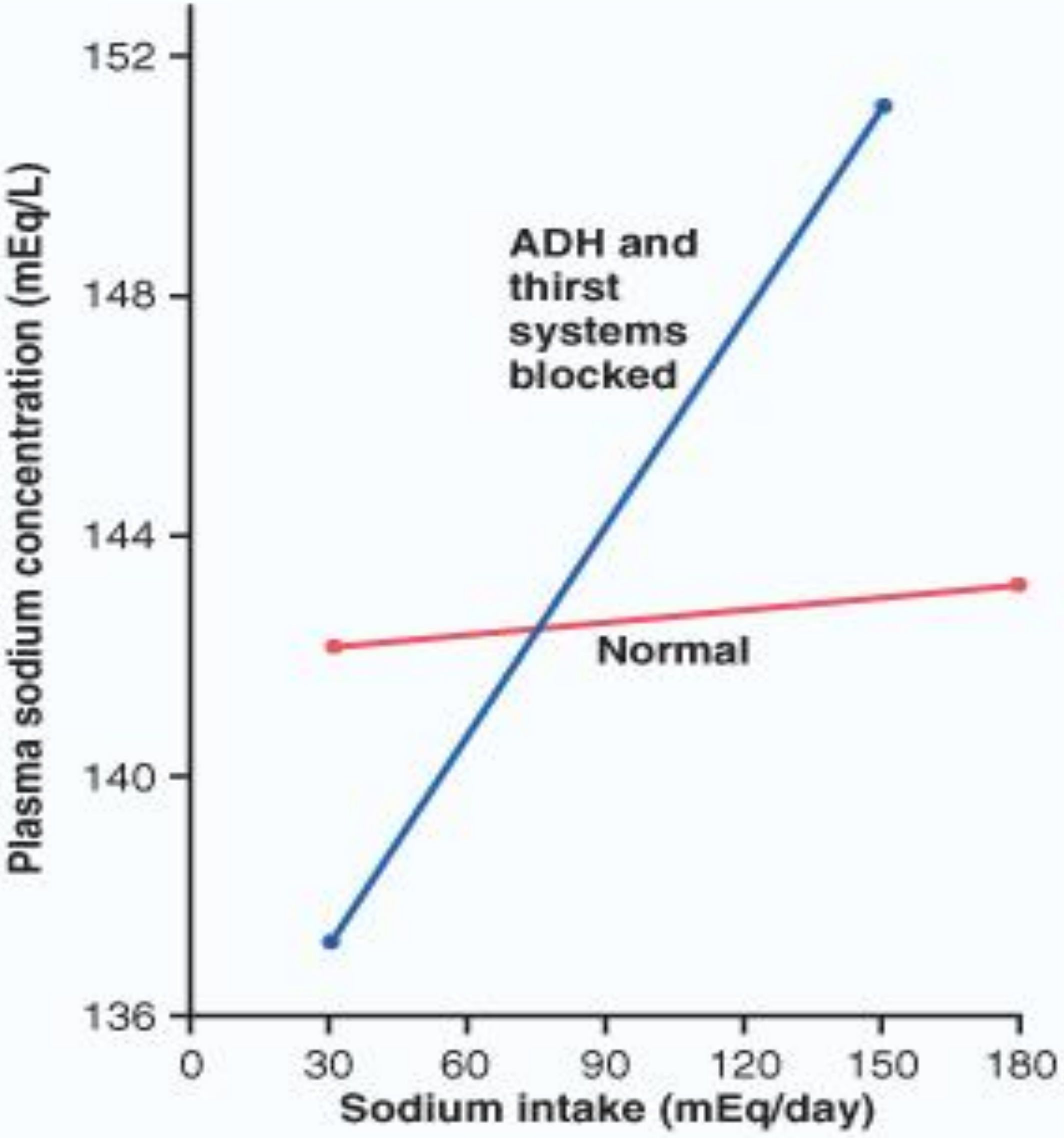
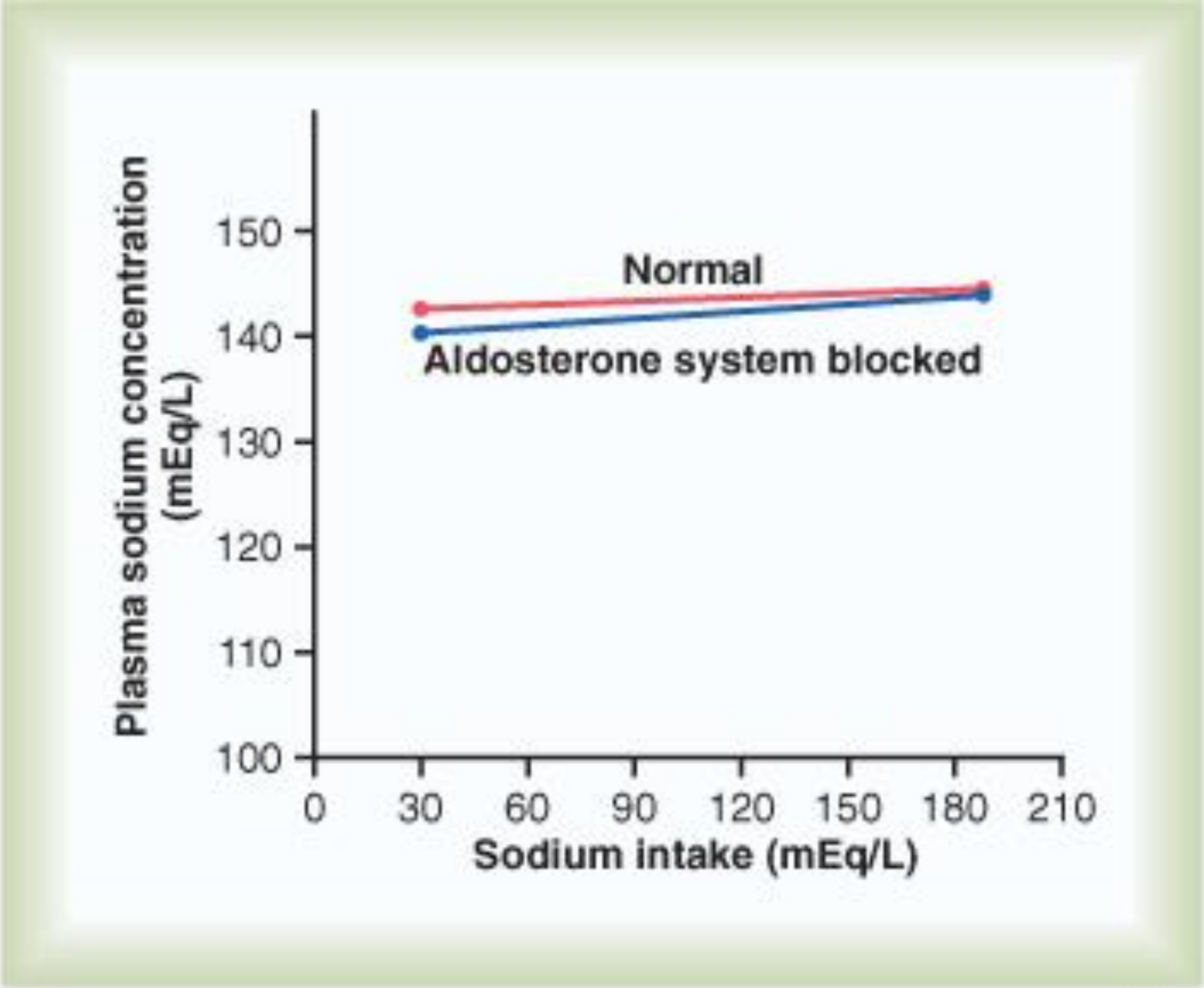
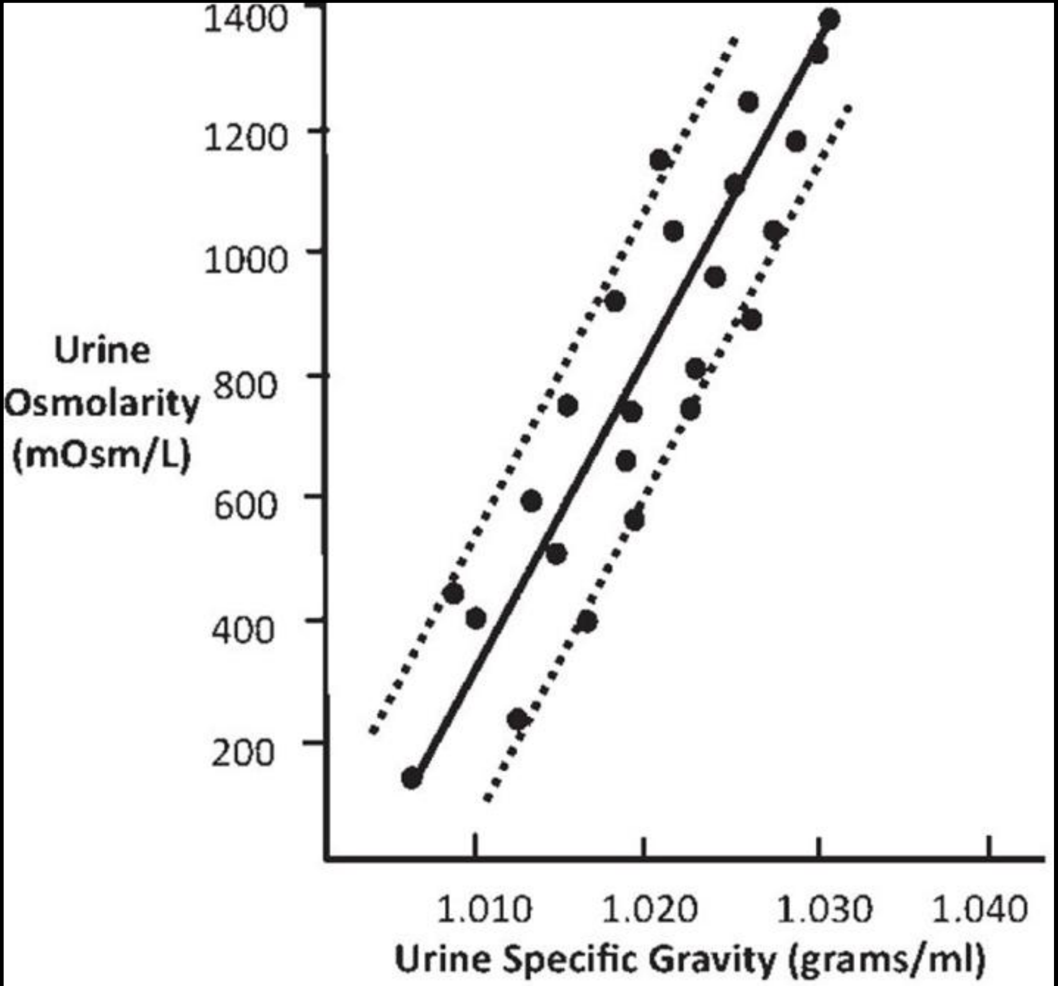

● Isotonic volume depletion
○ Isovolemic osmotic increase
$P_{AVP} = 1.3\ e^{-0.17\ vol.}$
$P_{AVP} = 2.5\ \Delta\ Osm + 2.0$
Plasma ADH (pg/ml)
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
Per cent change


Plasma sodium concentration (mEq/L)
152
148
144
140
136
ADH and thirst systems blocked
Normal
0
30
60
90
120
150
180
Sodium intake (mEq/day)


Plasma sodium concentration (mEq/L)
150
140
130
120
110
100
Normal
Aldosterone system blocked
0
30
60
90
120
150
180
210
Sodium intake (mEq/L)



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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.** ($HCl – H^+ Cl^-$) ($H_2CO_3 \longrightarrow H^+ \ HCO_3^-$)

A **base** is an ion or a molecule that can accept a hydrogen ion.
(HPO_4^{2-} is base because it can accept hydrogen ion to form $H_2PO_4^-$)

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^+ in solution (HCl)
A **week acid** have less tendency to dissociate its ions and, therefore release H^+ (H_2CO_3)

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 mmol/L, H^+ = 0.00004 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_2 (Merely a Potential Acid)

1. Complete oxidation of neutral carbohydrated and fat → $CO_2 + H_2O$
2. Oxidation of most neutral amino acids → Urea + $CO_2 + H_2O$

B. Reactions producing nonvolatile acids

1. Oxidation of sulfur-containing amino acids → Urea + $CO_2 + H_2O + H_2SO_4$ → $2H^+ + SO_4^{2-}$
   (examples: methionine, cysteine)
2. Metabolism of phosphorous-containing compounds → H_3PO_4 → $H^+ + H_2PO_4^{2-}$
3. Oxidation of cationic amino acids → Urea + $CO_2 + H_2O + H^+$
   (examples: lysine+, arginin+)
4. Production of nonmetabolizable organic acids → HA → $H^+ + A^-$
   (examples: uric acid, oxalic acid)
5. Incomplete oxidation of carohydrate and fat → HA → $H^+ + A^-$
   (examples: lactic acid, ketoacidosis)

C. Reactions producing nonvaletile bases

1. Oxidation of anionic amino acids → Urea + $CO_2 + H_2O + HCO_3^-$
   (examples: glutamate$^-$, aspartate$^-$)
2. Oxidation of organic anions → $CO_2 + H_2O + HCO_3^-$
   (examples: lactate$^-$, acetate$^-$)

Buffering of Hydrogen Ions in the Body Fluids

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

$$\text{Buffer} + H^+ \leftrightarrows \text{H Buffer}$$

In this example, a free H^+ combines with the buffer to form a weak acid (H Buffer)

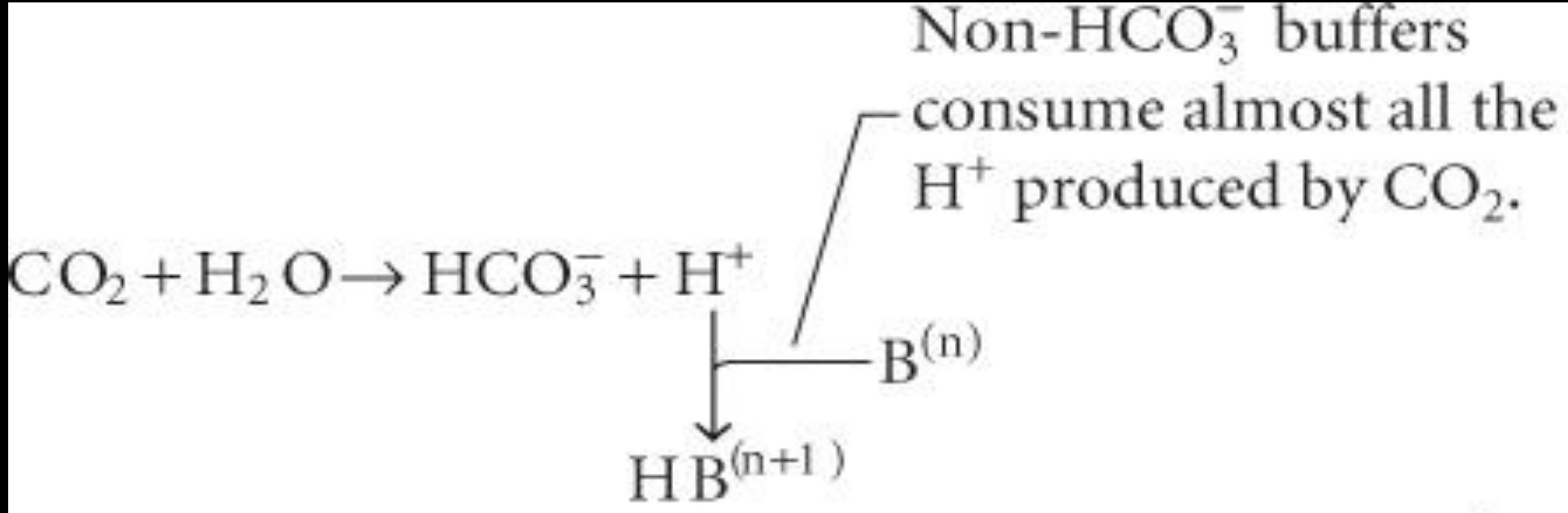
Bicarbonate Buffer System

$$\uparrow H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow CO_2 + H_2O$$

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

$$\begin{array}{ccccc} \downarrow CO_2 \;+ H_2O & \longrightarrow & H_2CO_3 & \longrightarrow & \uparrow HCO_3^- \quad + H^+ \\ & & + & & + \\ & & NaOH & & Na \end{array}$$

The weak base $NaHCO_3^-$ replaces the strong base NaOH. At the same time the concentration of H_2CO_3 decreases (because it reacts with NaOH), causing more CO_2 to combine with H_2O, in order to replace the H_2CO_3.
The net result is a tendency for the CO_2 levels in the blood to decrease, but it is prevented by the decreased ventilation.
The rise in blood HCO_3^- is compensated by increased renal excretion of HCO3-.



$$CO_2 + H_2O \rightarrow HCO_3^- + \underset{\substack{\downarrow \leftarrow B^{(n)} \\ HB^{(n+1)}}}{H^+}$$

Non-HCO_3^- buffers consume almost all the H^+ produced by CO_2.

(28-28)

Henderson-Hasselbalch Equation:

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times pCO_2}$$

1. Increase in bicarbonate ion concentration causes the pH to rise.
2. Increase in pCO_2 causes the pH to decrease.

1. Bicarbonate concentration is regulated mainly by the kidneys.
2. pCO_2 concentration is regulated by the rate of respiration.

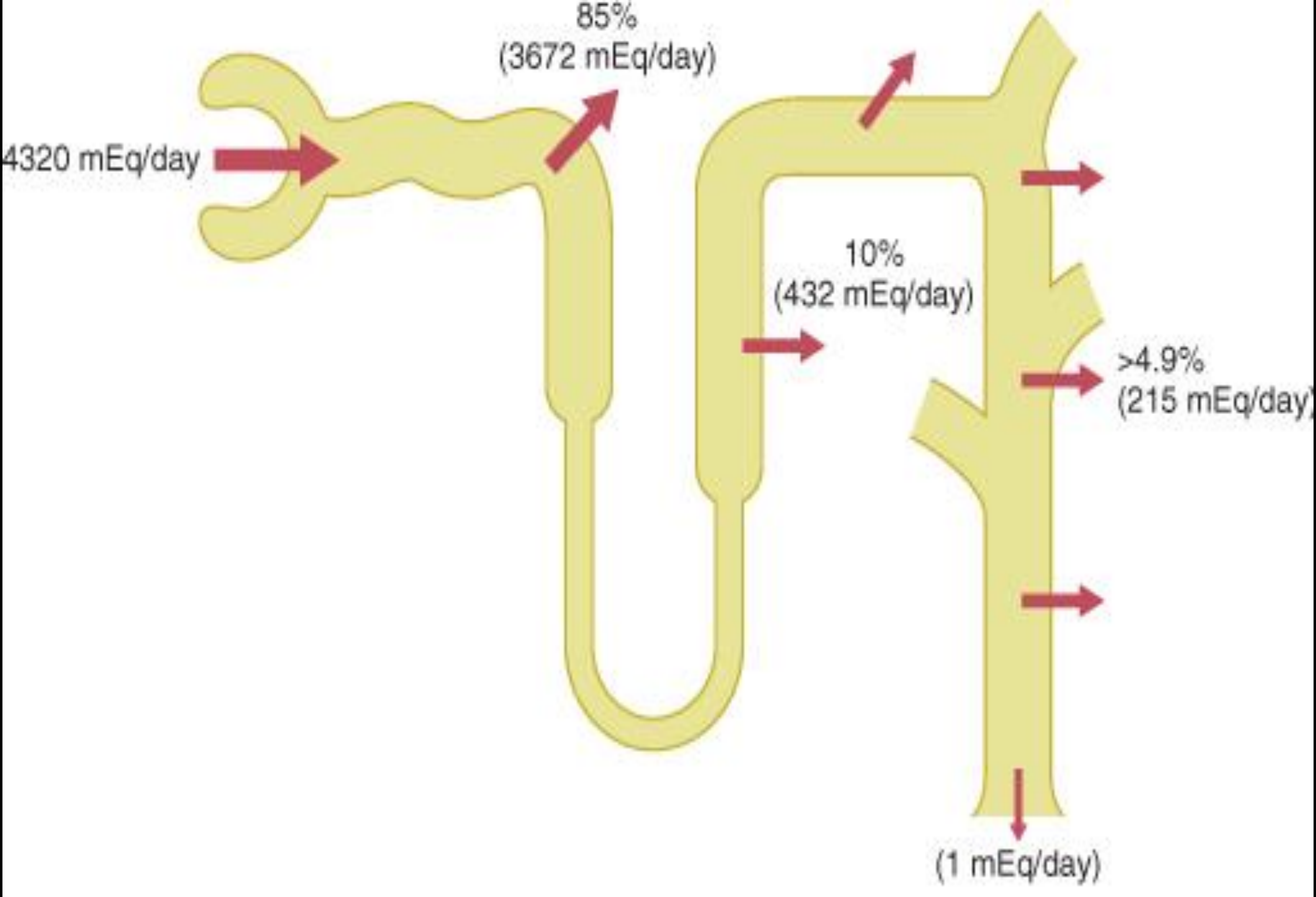
1. When disturbances of acid-base balance results from a primary changes in extracellular fluid bicarbonate concentrations are referred to as metabolic acid-base disorders.
2. When disturbances of acid base balance results from a primary changes in pCO_2 are referred as respiratory acid-base disorders.

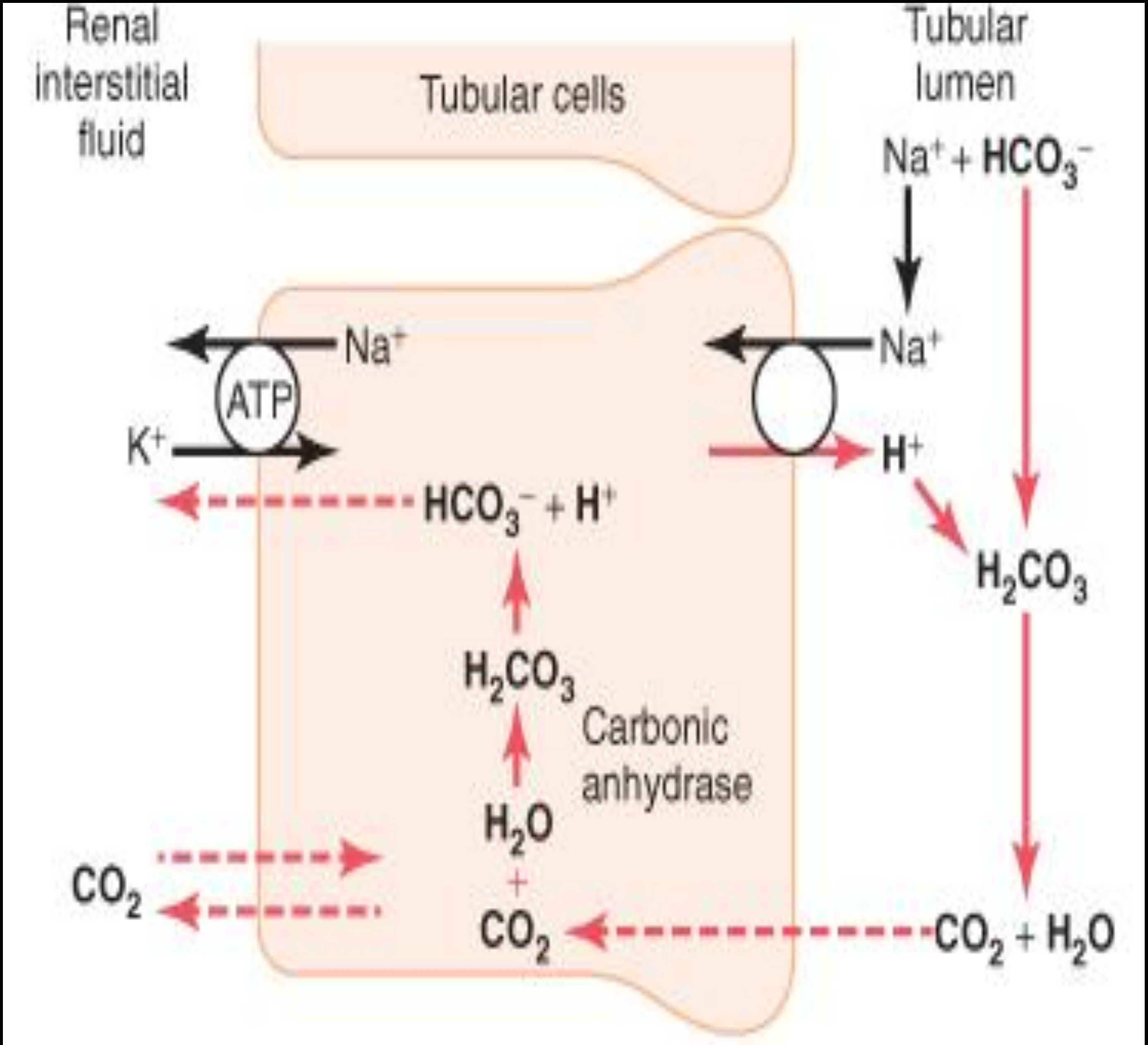
The kidneys regulate extracellular fluid H^+ concentrations thought three fundamental mechanisms:

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

Ad. 1.

180 L/day x 24 mmol/L = 4320 mmol of HCO_3^-


4320 mEq/day
85%
(3672 mEq/day)
10%
(432 mEq/day)
>4.9%
(215 mEq/day)
(1 mEq/day)



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

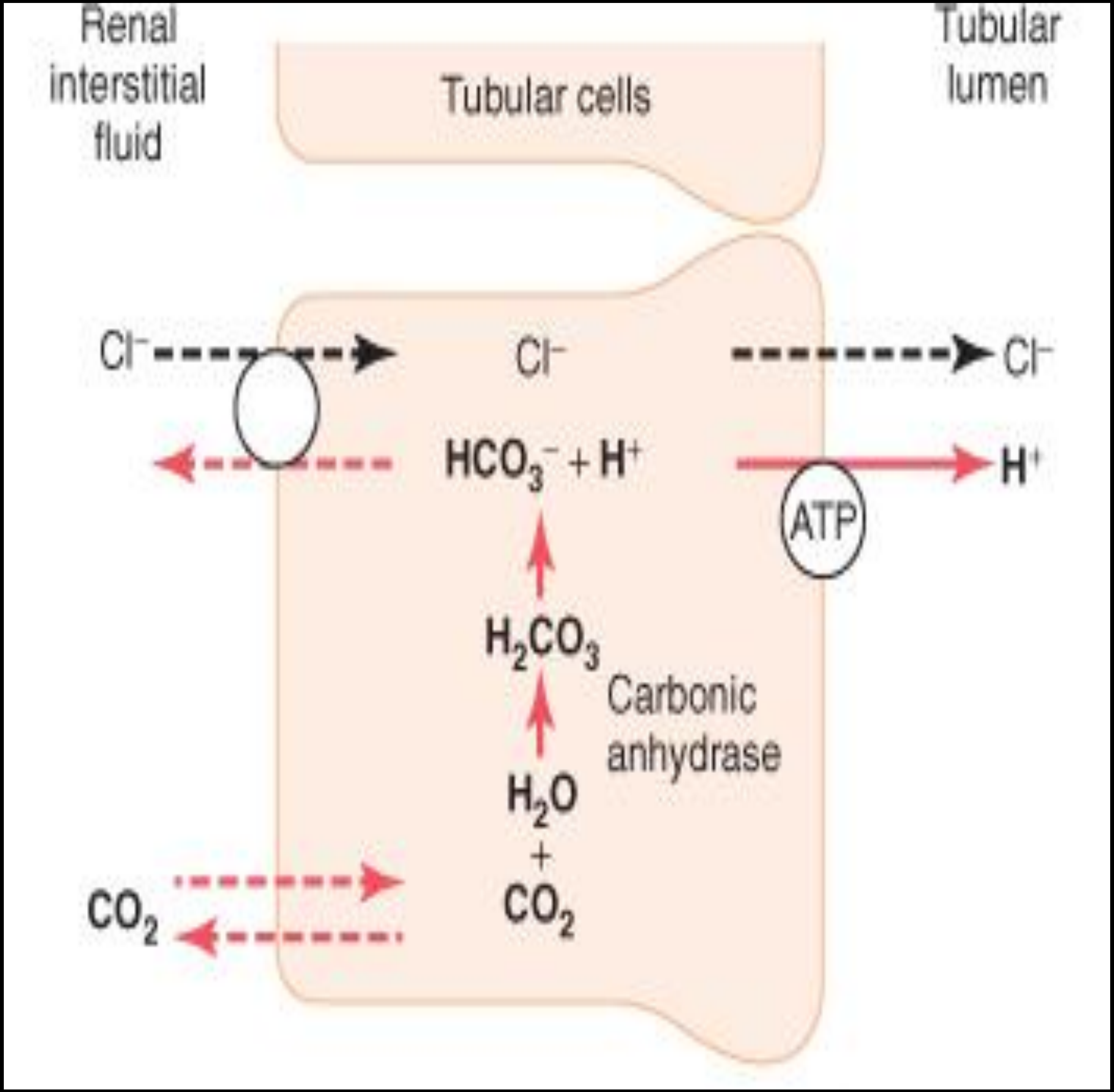
Thus, each time a hydrogen ion is formed in the tubular epithelial cells,
a bicarbonate ion is also formed and released back into the blood.
The net effect of these reactions is a „reabsorption“ of bicarbonate, although
the bicarbonate ions that actually enter the extracellular fluid are not the same.

The transport of HCO_3^- accros the basolateral membrane is facilitated by:

1. Na^+-HCO_3^- co-transporter
2. Cl^--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.

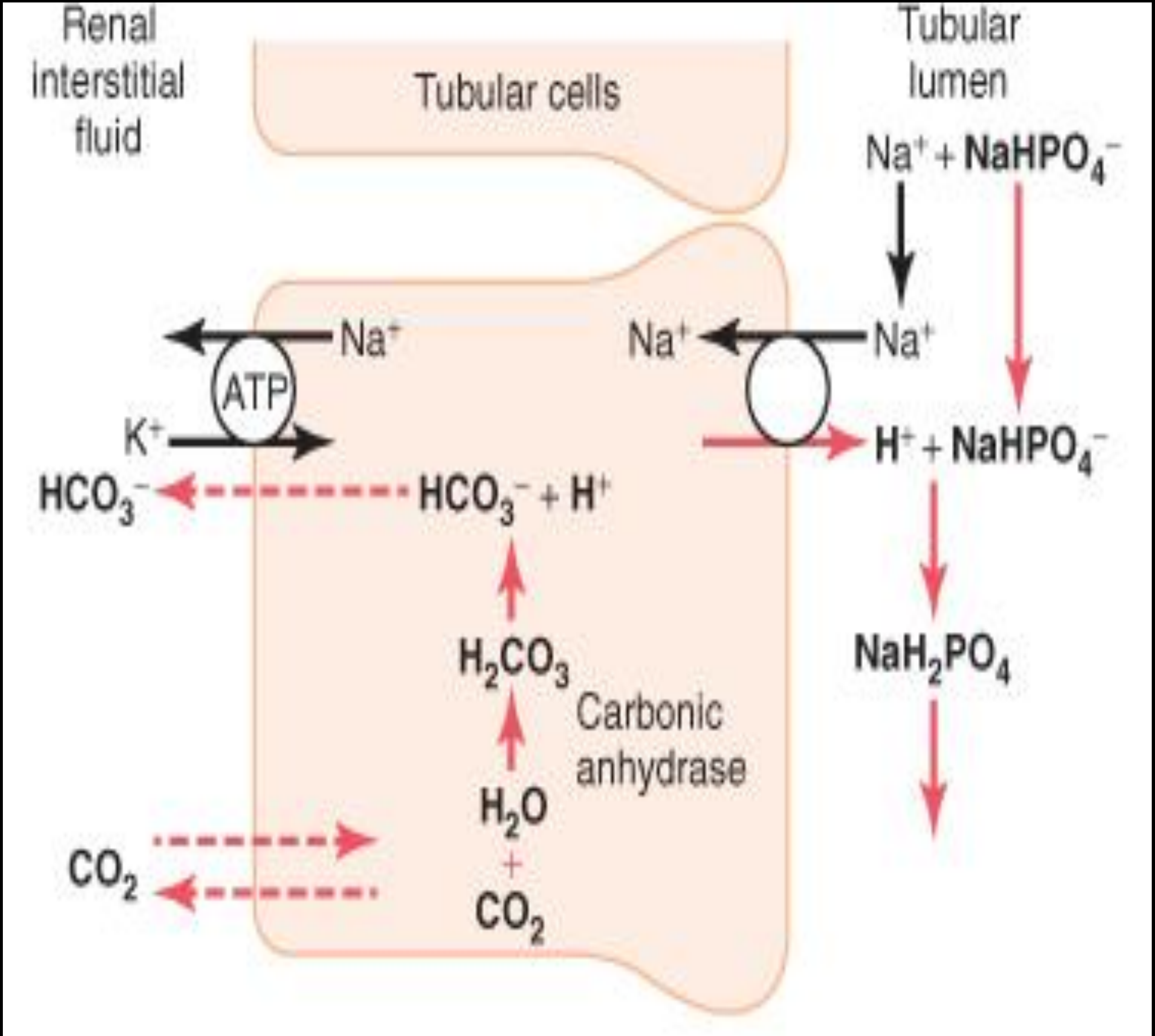
In the proximal tubules, hydrogen ion concentration can increase only about threefold (compared to the filtered load), in the collecting tubule the hydrogen concentration can be increased as 900-fold.



Late distal tubule and collecting tubules (intercalated cells)

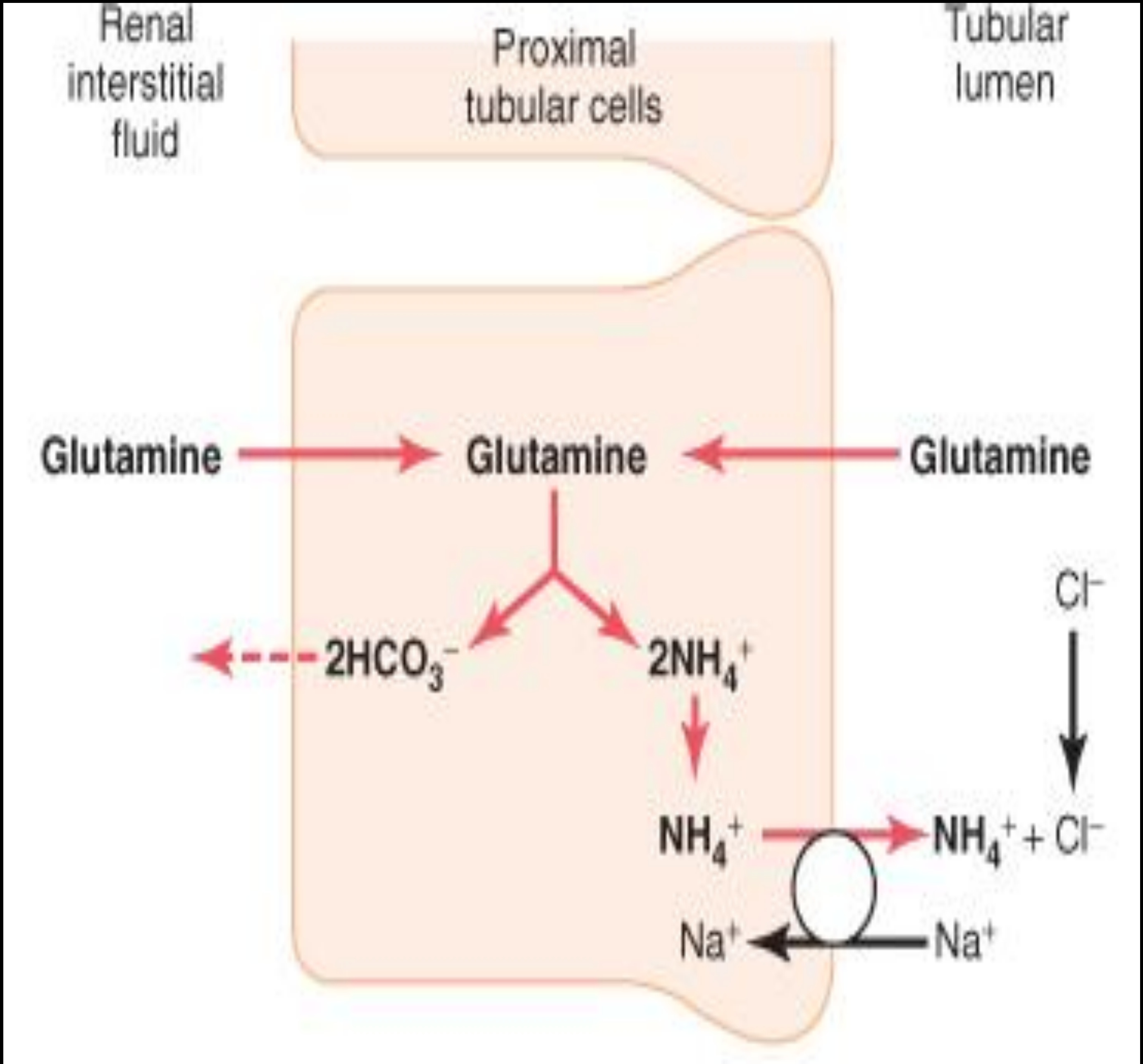
Phosphate and Ammonia Buffers

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.

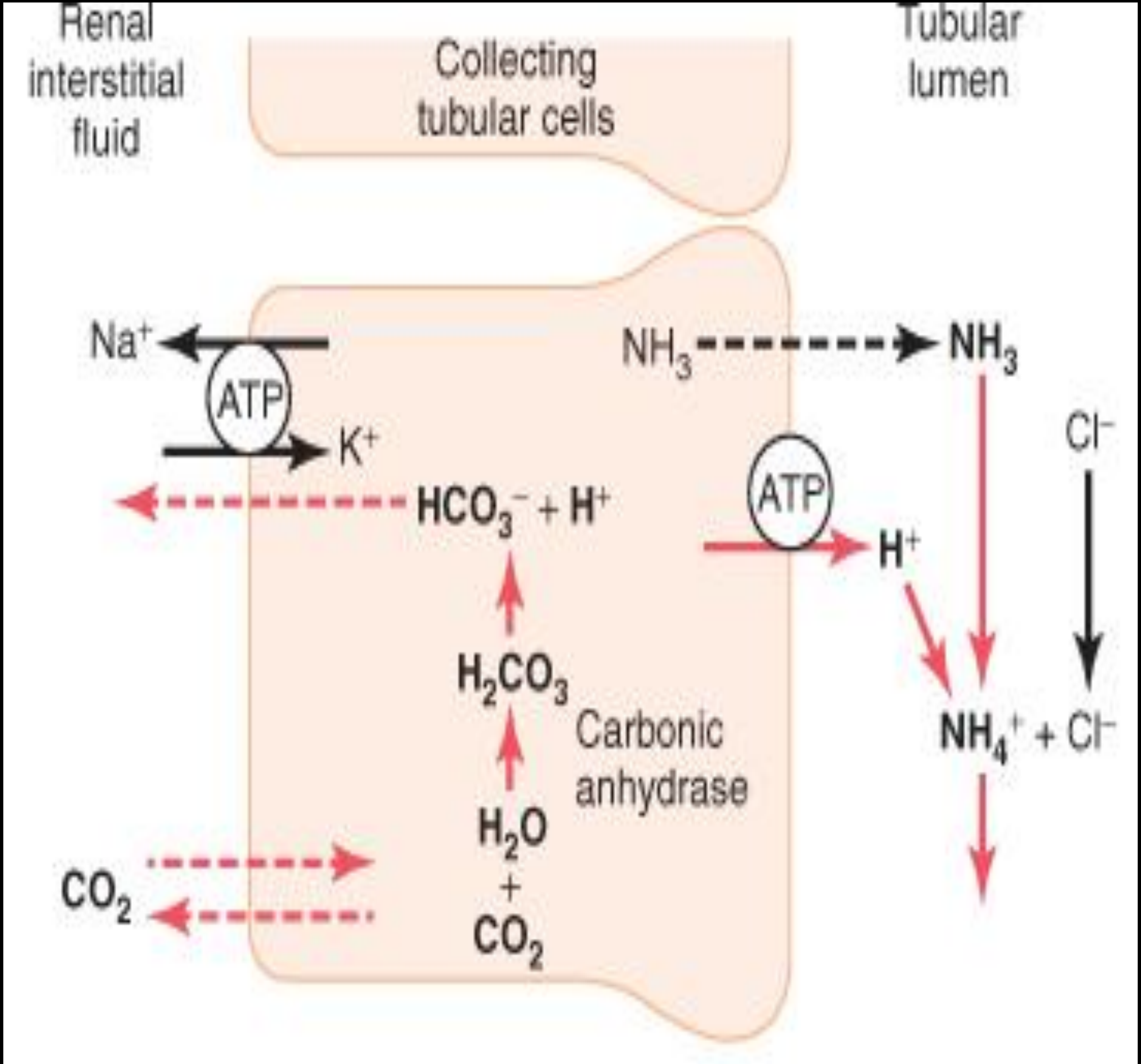

Renal interstitial fluid
Tubular cells
Tubular lumen
$Na^+ + NaHPO_4^-$
Na^+
ATP
K^+
Na^+
Na^+
$H^+ + NaHPO_4^-$
HCO_3^-
$HCO_3^- + H^+$
H_2CO_3
Carbonic anhydrase
NaH_2PO_4
H_2O
+
CO_2
CO_2

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.

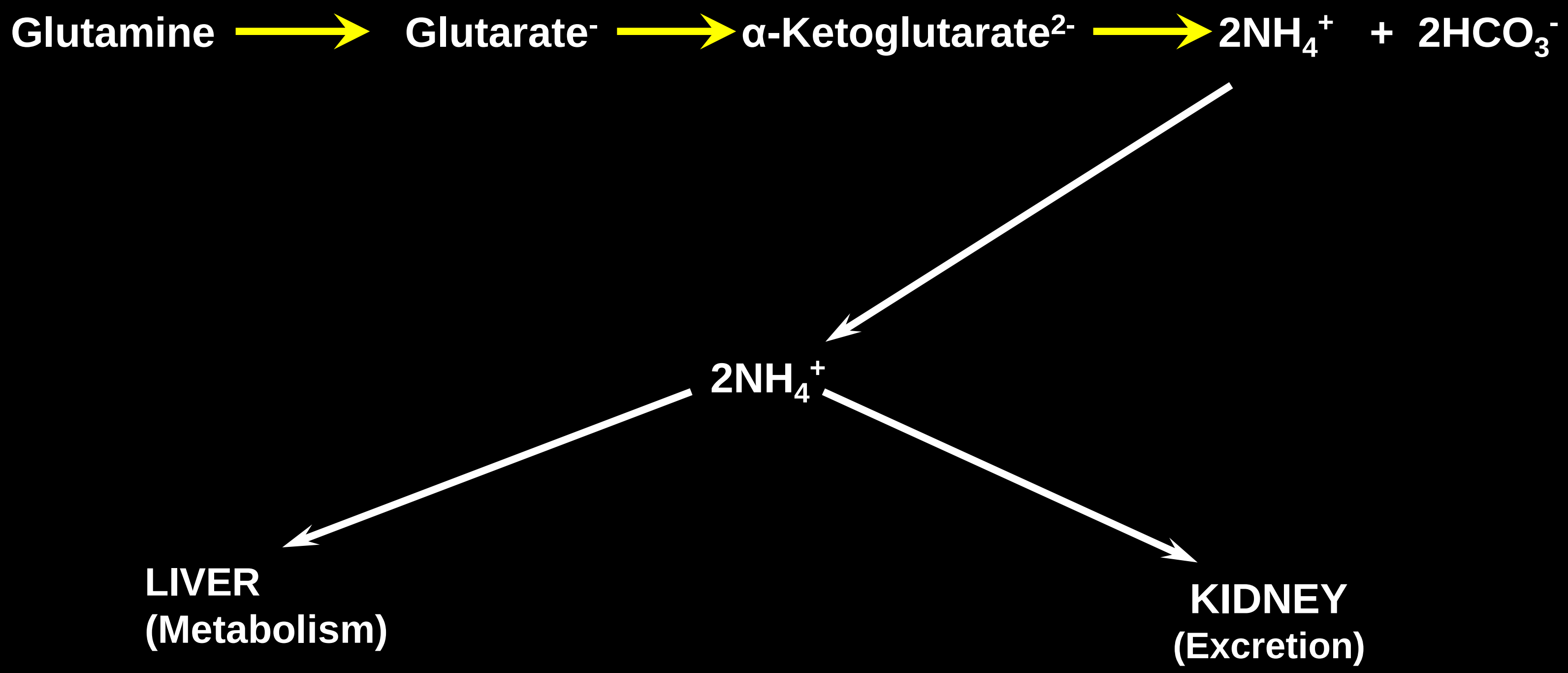
A second buffer system in the tubular fluid that is even more important quantitatively than the phosphate buffer system is composed of ammonia (NH_3) and the ammonium ion (NH_4^+).



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



Collecting duct



Glutamine $\rightarrow$ Glutarate$^-$ $\rightarrow$ α-Ketoglutarate^{2-} $\rightarrow$ $2NH_4^+ + 2HCO_3^-$

$2NH_4^+$

LIVER
(Metabolism)

KIDNEY
(Excretion)

$2NH_4^+ + CO_2 \rightarrow \text{Urea} + H_20 + 2H^+$

Loss of $2HCO_3^-$ by buffering of $2H^+$

Save $2HCO_3^-$ by excretion of $2NH_4^+$

Under conditions of chronic acidosis, the rate of 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 NH_4^+.

Quantifying Renal Acid-Base Excretion

Net acid excretion = NH^+_4 excretion + Urinary titratable acid – bicarbonate excretion

Titratable acid represents the nonbicarbonate, non-NH_4^+ buffer excreted in the urine (phosphate and other organic buffers)

The most important stimuli for increasing H^+ secretion by the tubules are:

1. **An increase in pCO_2 of extracellular fluid.**
2. **An in H^+ concentration in extracellular fluid.**

TK = SV x PCR

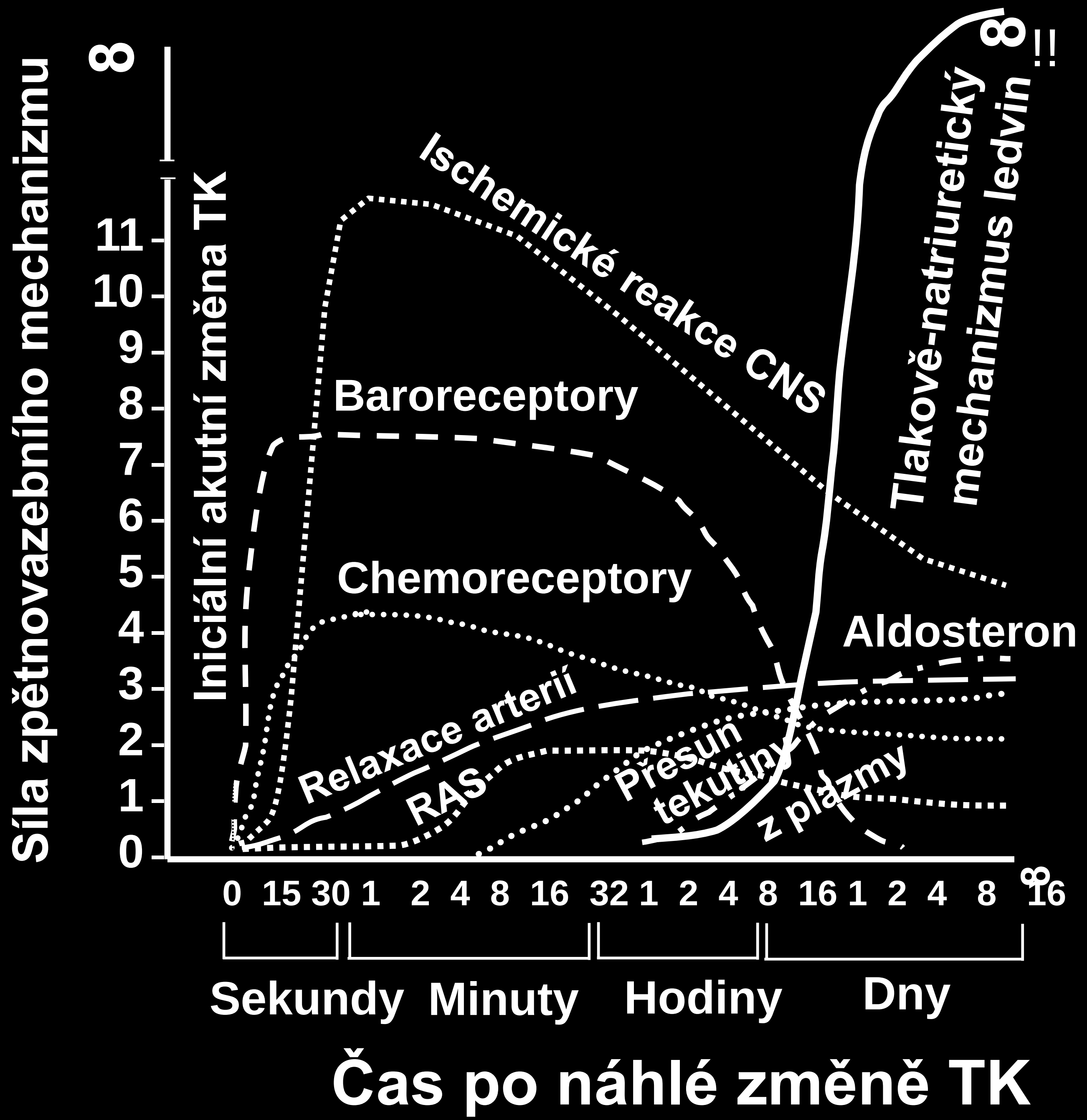
TK = arteriální krevní tlak

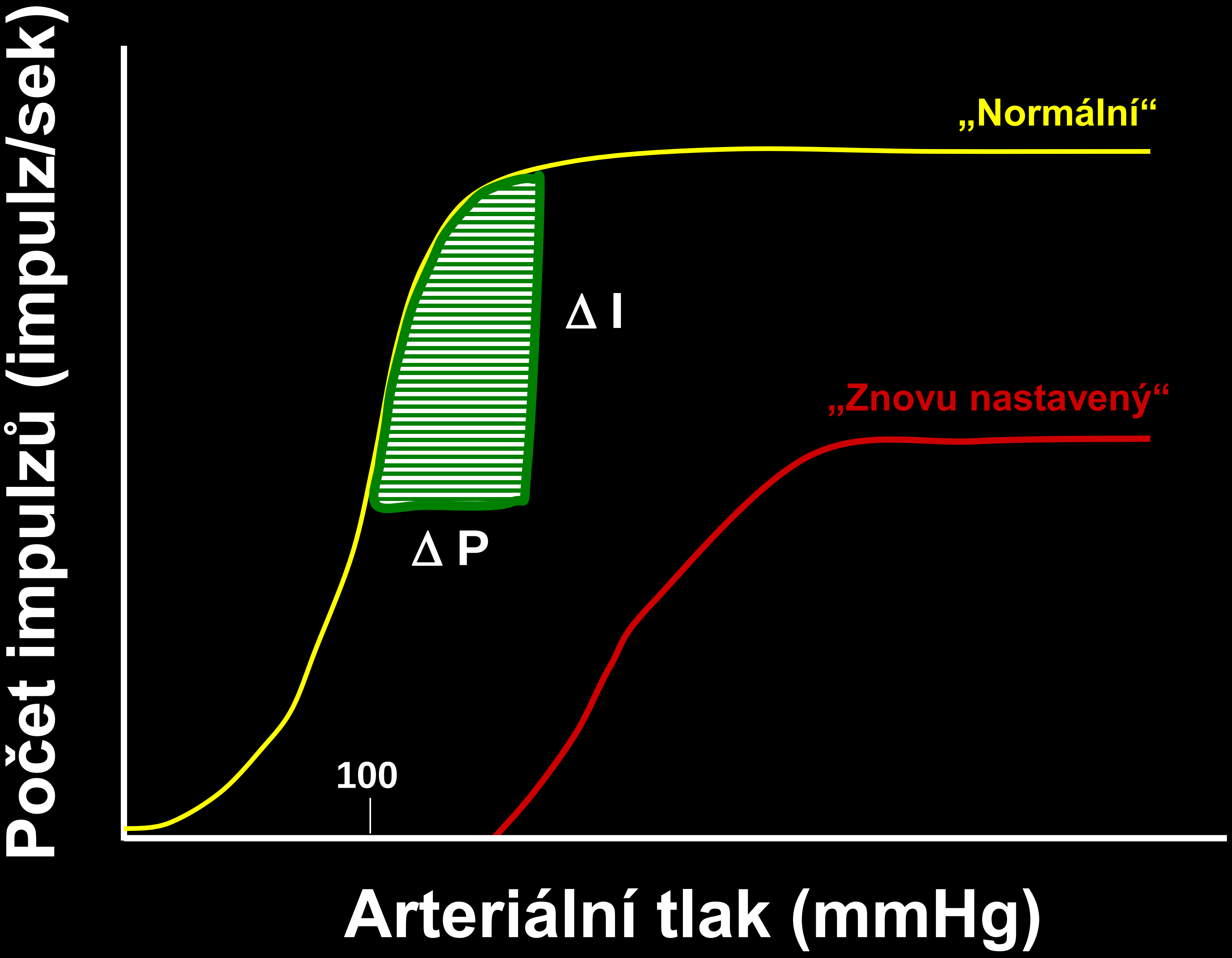
SV = srdeční výdej

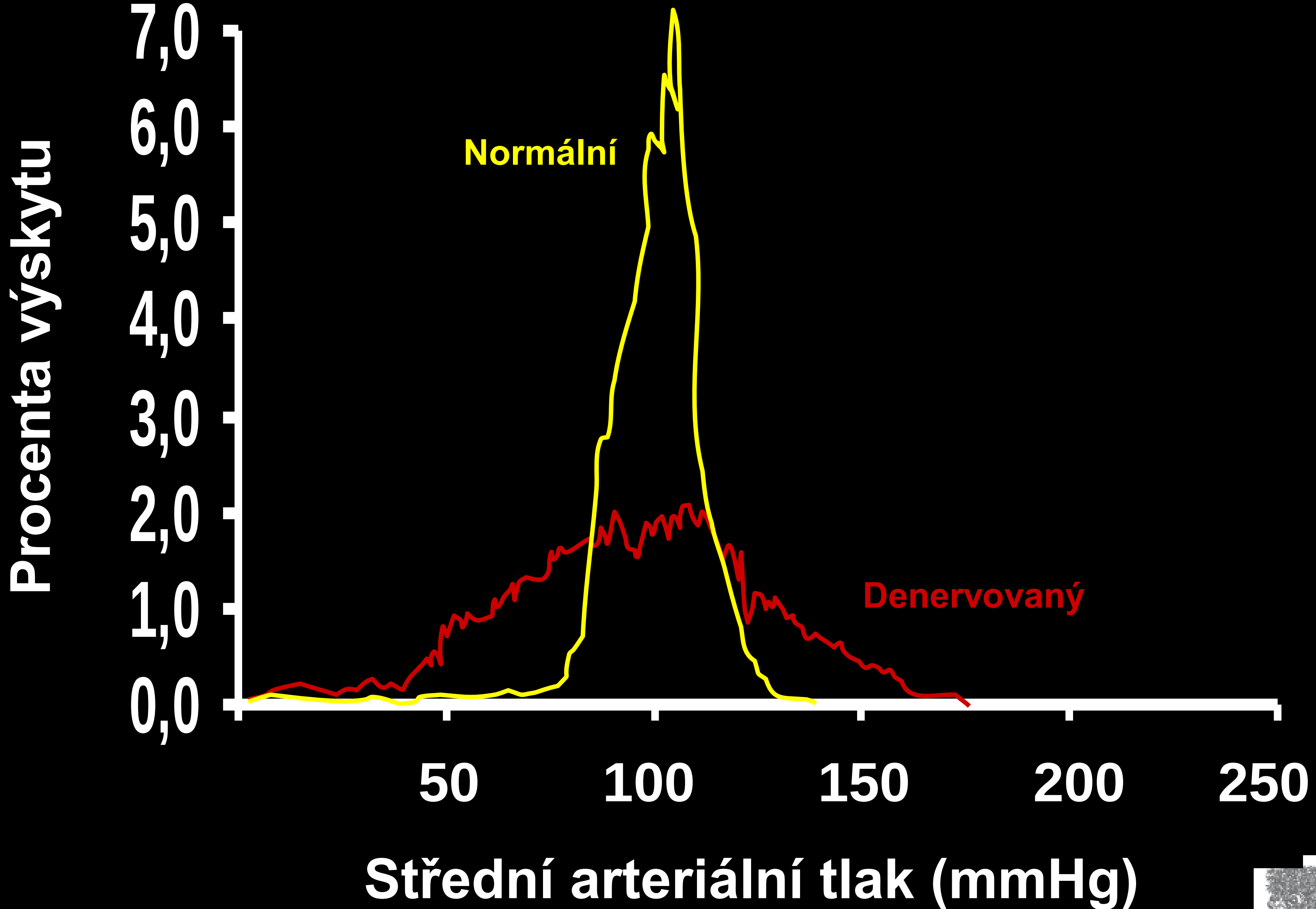
PCR = periferní cévní rezistence

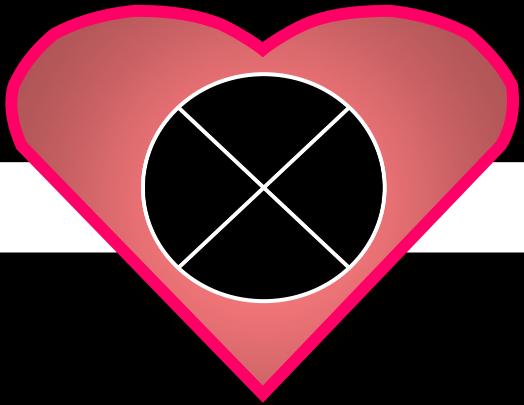
Akutní mechanizmy regulace krevního tlaku

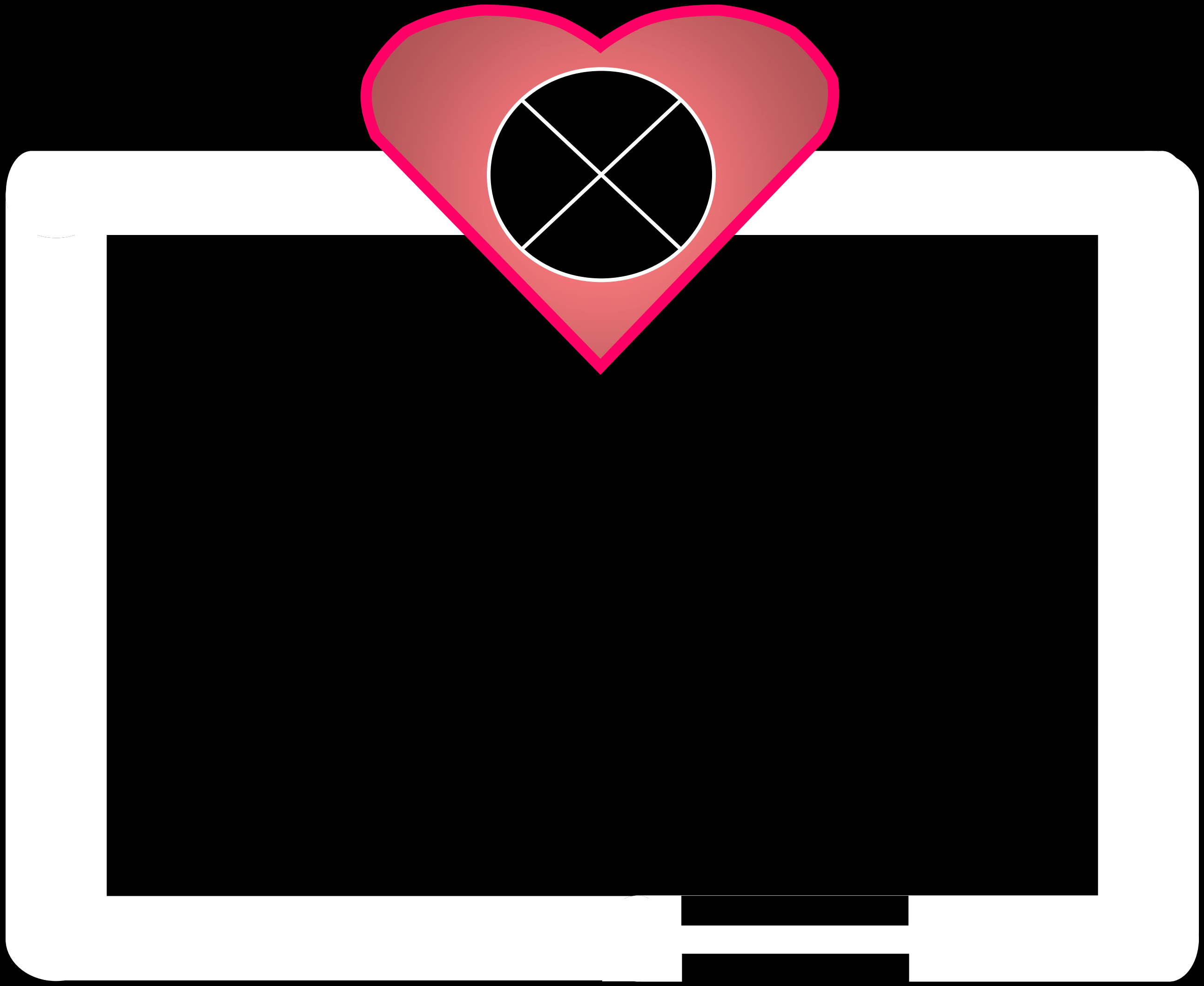
1. Arteriální baroreflex
2. Arteriální chemoreceptory
3. Bainbridgeův reflex
4. Ischemické receptory CNS

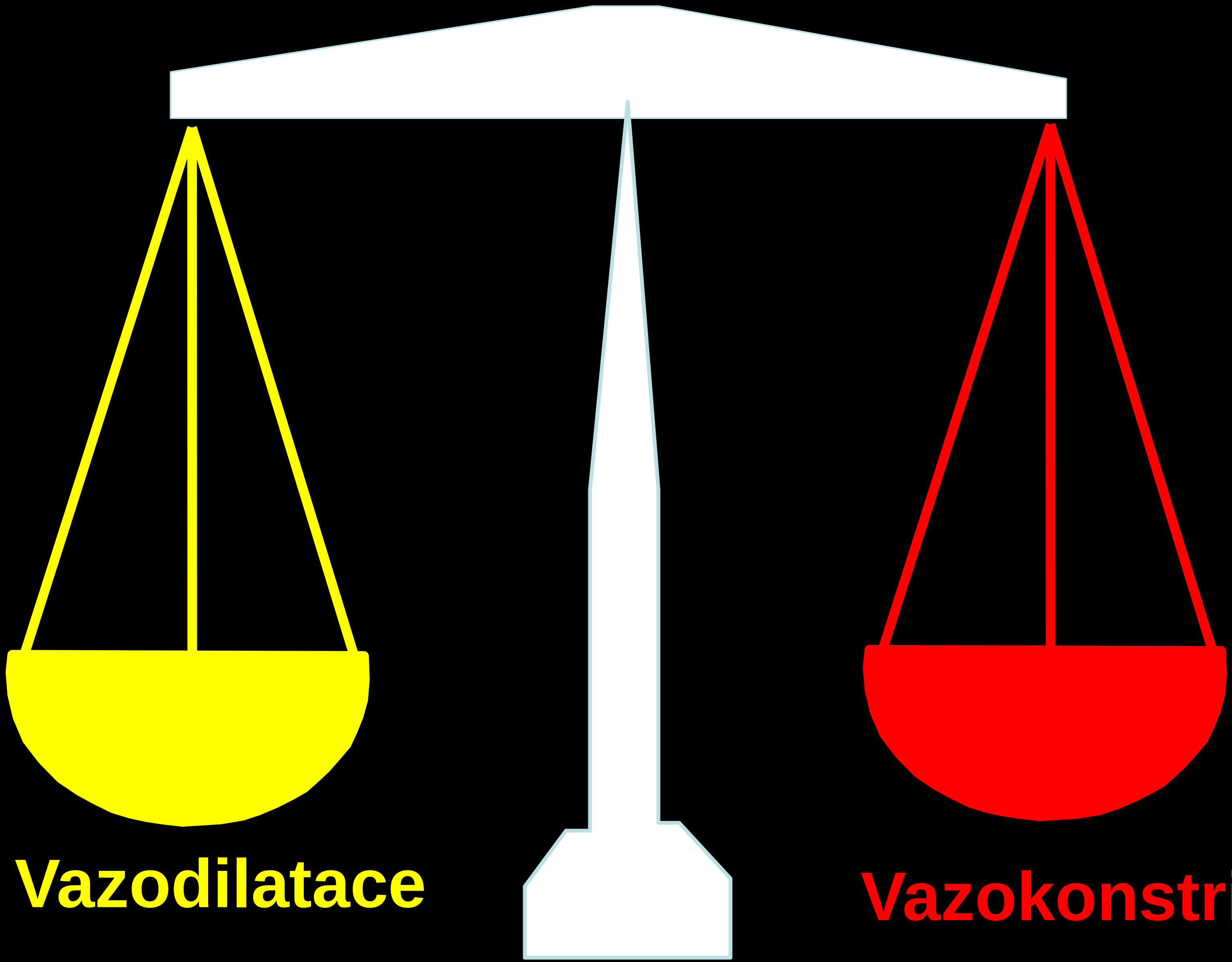

Síla zpětnovazebního mechanizmu
∞
11
10
9
8
7
6
5
4
3
2
1
0
Iniciální akutní změna TK
Ischemické reakce CNS
Baroreceptory
Chemoreceptory
Relaxace arterií
RAS
Přesun tekutiny z plazmy
Aldosteron
Tlakově-natriuretický mechanizmus ledvin
∞ !!
0 15 30 1 2 4 8 16 32 1 2 4 8 16 1 2 4 8 16 ∞
Sekundy
Minuty
Hodiny
Dny
Čas po náhlé změně TK


Počet impulzů (impulz/sek)
„Normální“
ΔI
„Znovu nastavený“
ΔP
100
Arteriální tlak (mmHg)


Procenta výskytu
7,0
6,0
5,0
4,0
3,0
2,0
1,0
0,0
Normální
Denervovaný
50
100
150
200
250
Střední arteriální tlak (mmHg)







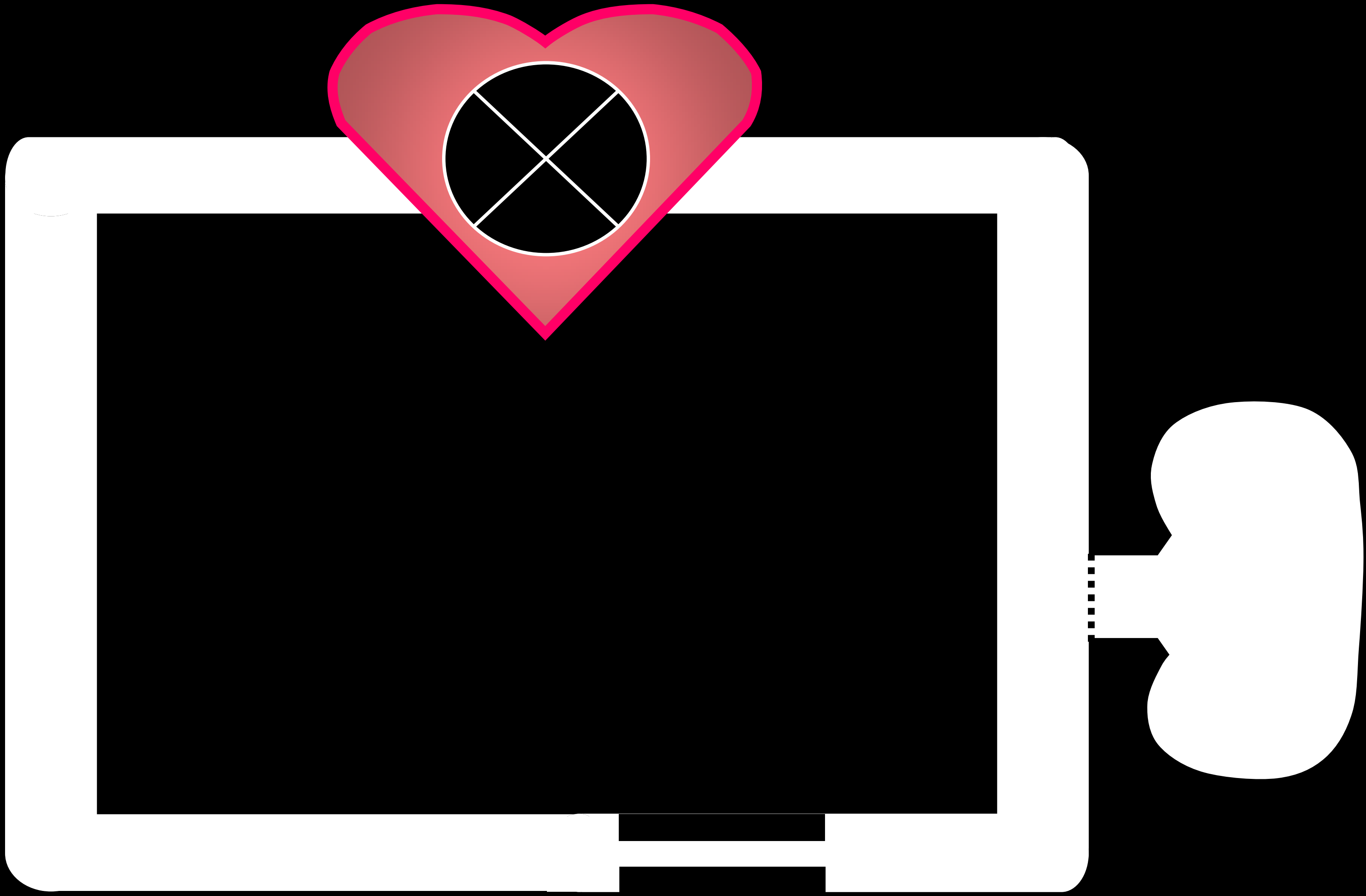
Vazodilatace

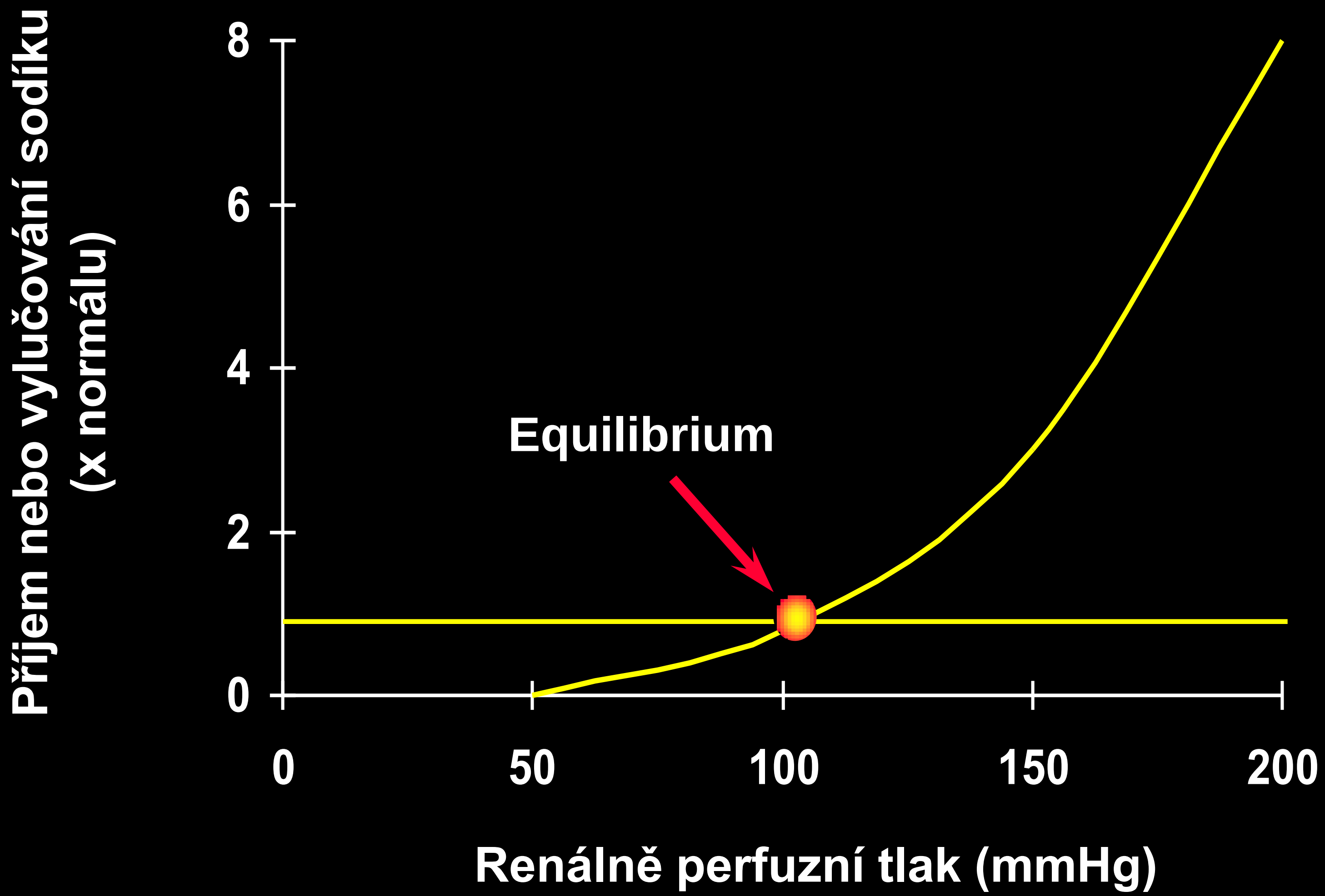
Vazokonstrikce

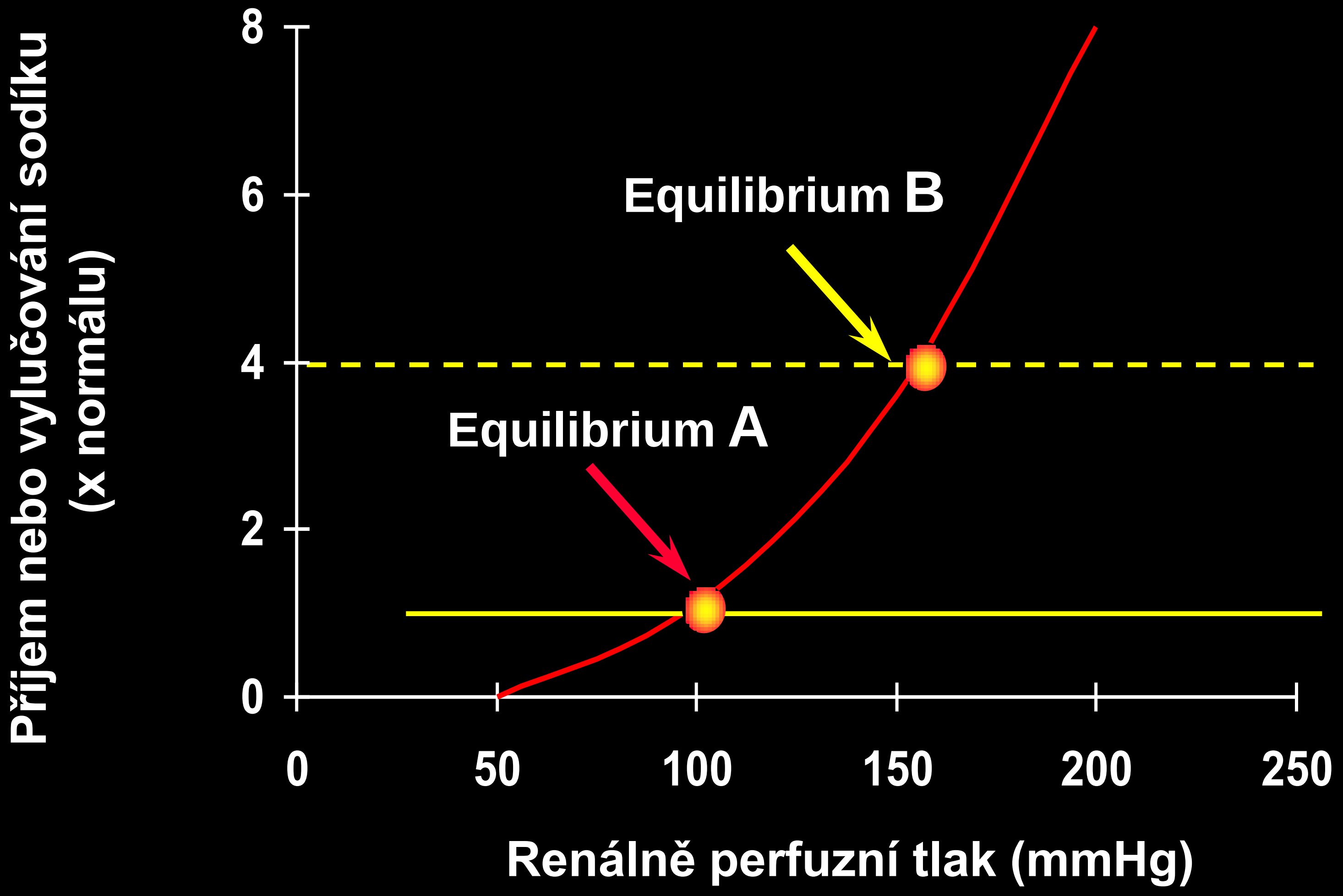
“The first slide of the lecturer, who was an intrepid young cardiovascular physiologist, was Figure 1 from Guyton and Coleman´s epic paper. It was clear that the audience was already becoming nervous. There was some whispering, shuffling, and a sense of unease.

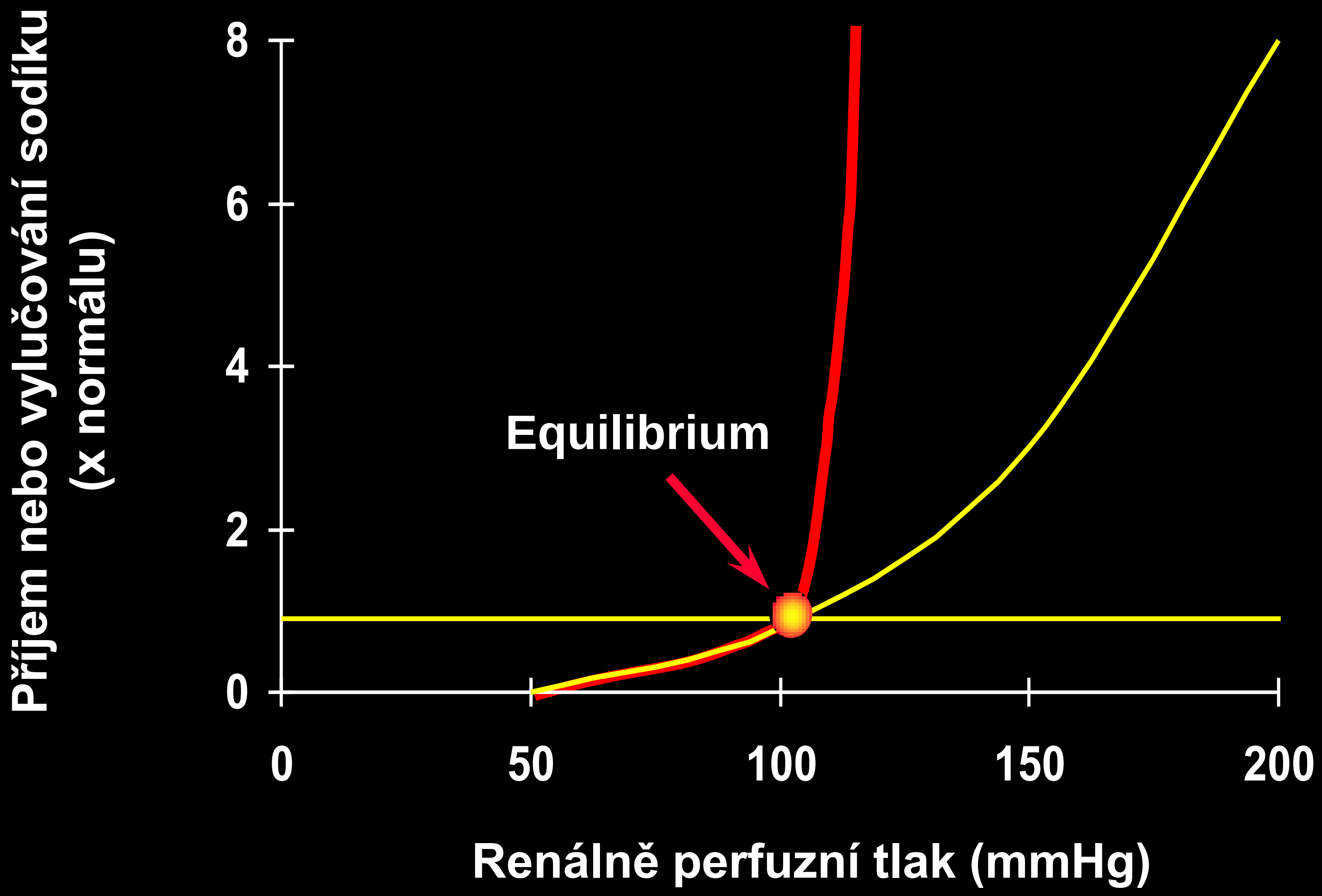
The lecturer´s second slide was met with a more definite response. There was derision, laughter, and spontaneous comments from the audience…..
I witnessed, for the only time in my academic life,
a lecturer being chased from the podium by the audience”

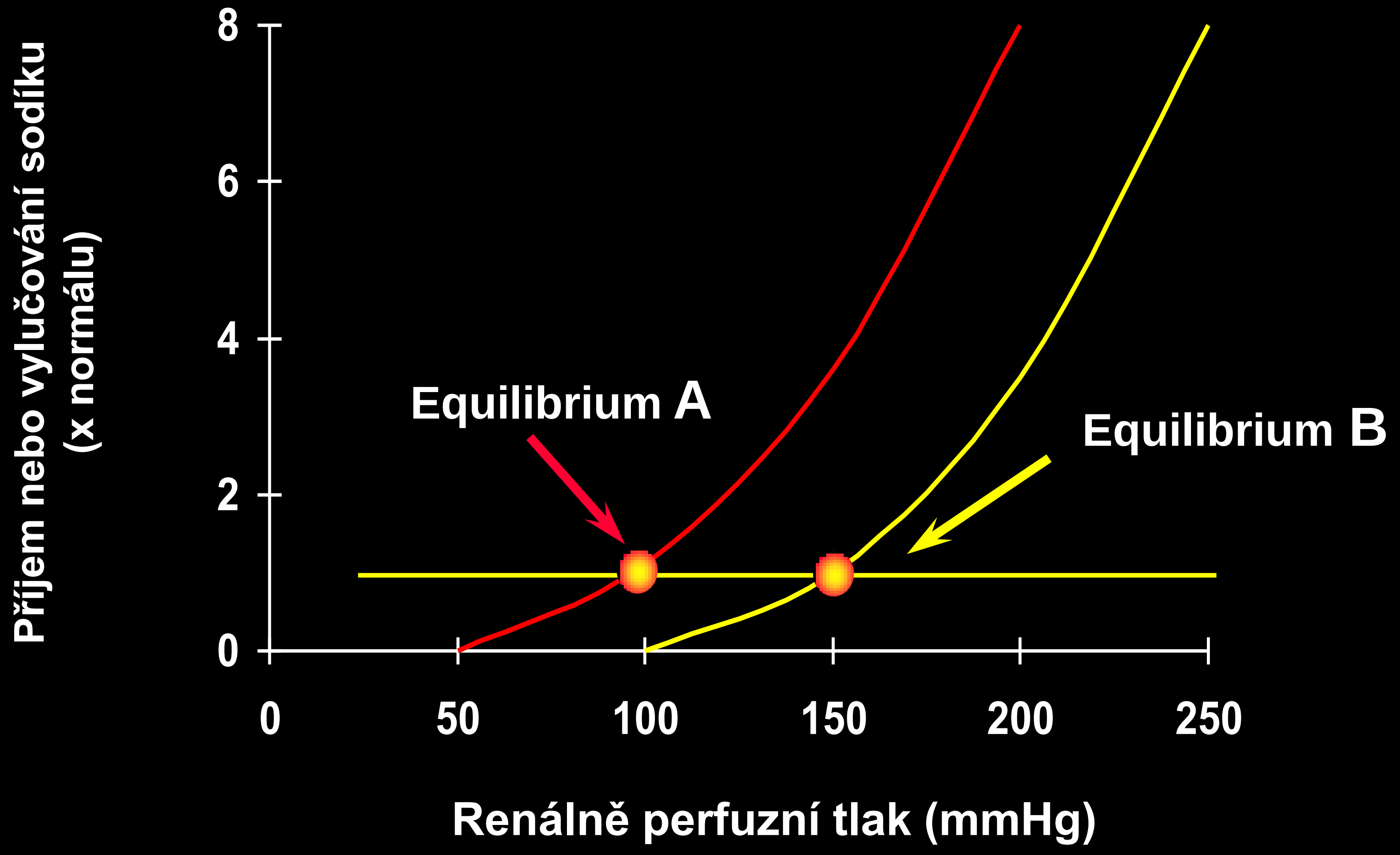
Christopher S. Wilcox

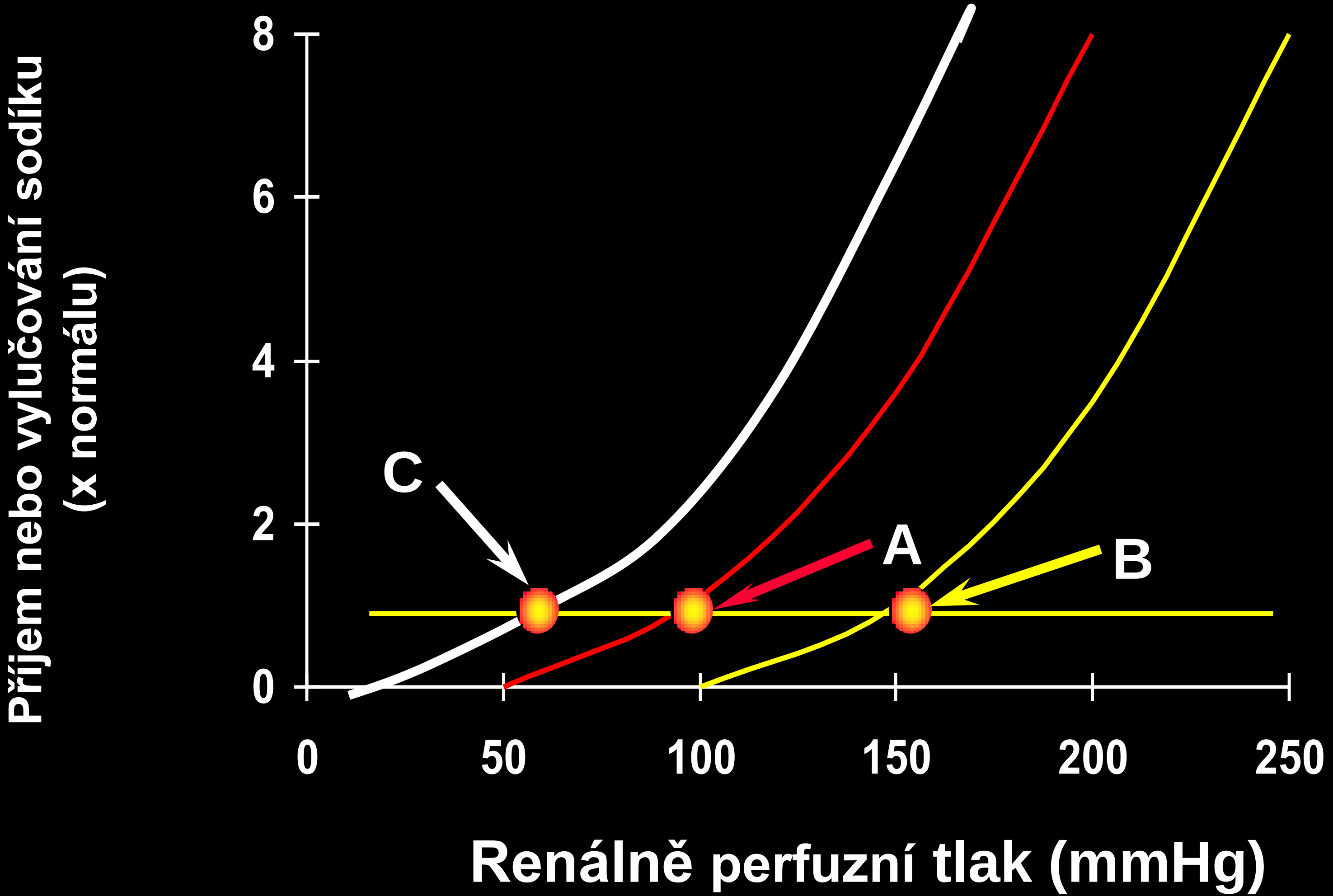


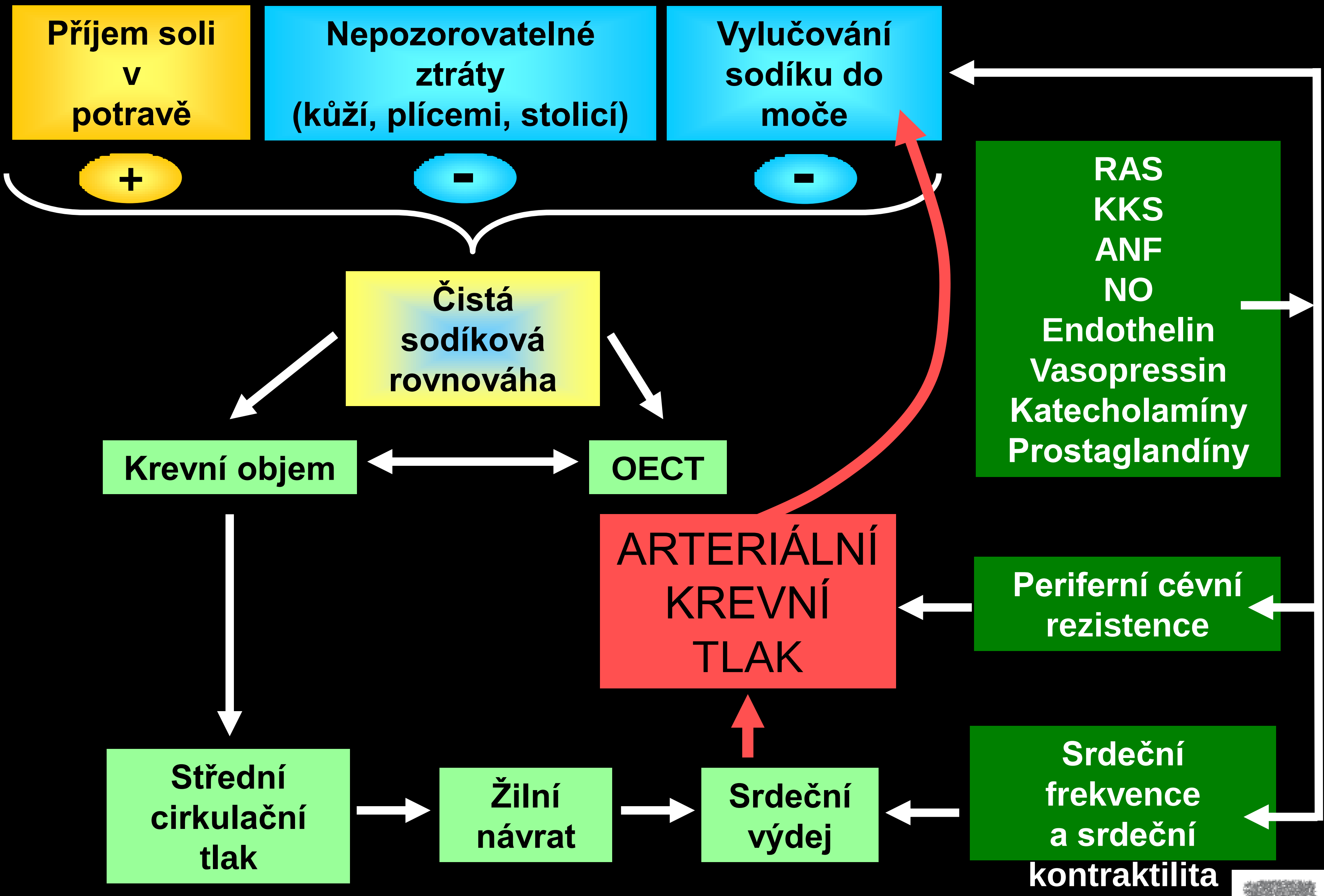

Příjem nebo vylučování sodíku
(x normálu)
8
6
4
2
0
Equilibrium
0
50
100
150
200
Renálně perfuzní tlak (mmHg)


Příjem nebo vylučování sodíku
(x normálu)
8
6
4
2
0
Equilibrium B
Equilibrium A
0
50
100
150
200
250
Renálně perfuzní tlak (mmHg)


Příjem nebo vylučování sodíku
(x normálu)
8
6
4
2
0
Equilibrium
0
50
100
150
200
Renálně perfuzní tlak (mmHg)


Příjem nebo vylučování sodíku
(x normálu)
8
6
4
2
0
0
50
100
150
200
250
Equilibrium A
Equilibrium B
Renálně perfuzní tlak (mmHg)


Příjem nebo vylučování sodíku
(x normálu)
8
6
4
2
0
0
50
100
150
200
250
C
A
B
Renálně perfuzní tlak (mmHg)



Příjem soli v potravě

Nepozorovatelné ztráty (kůží, plícemi, stolicí)

Vylučování sodíku do moče

+

-

-

Čistá sodíková rovnováha

Krevní objem

OECT

ARTERIÁLNÍ KREVNÍ TLAK

RAS
KKS
ANF
NO
Endothelin
Vasopressin
Katecholamíny
Prostaglandíny

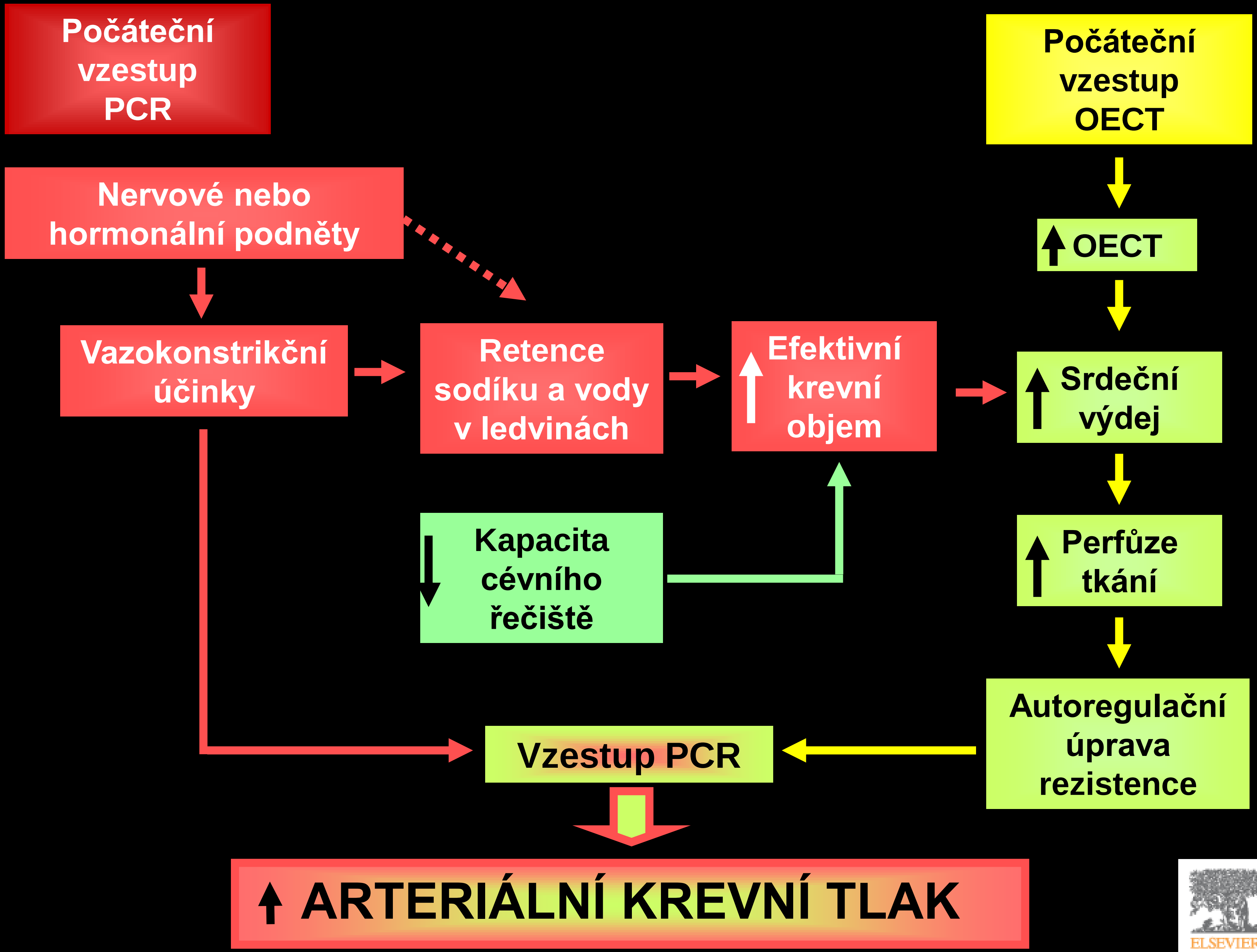
Periferní cévní rezistence

Střední cirkulační tlak

Žilní návrat

Srdeční výdej

Srdeční frekvence a srdeční kontraktilita



Počáteční vzestup PCR

Počáteční vzestup OECT

Nervové nebo hormonální podněty

↑ OECT

Vazokonstrikční účinky

Retence sodíku a vody v ledvinách

↑ Efektivní krevní objem

↑ Srdeční výdej

↓ Kapacita cévního řečiště

↑ Perfůze tkání

Autoregulační úprava rezistence

Vzestup PCR

↑ ARTERIÁLNÍ KREVNÍ TLAK

Formy Hypertenze

A. Esentiální (Primární) Hypertenze

B. Sekundární Hypertenze

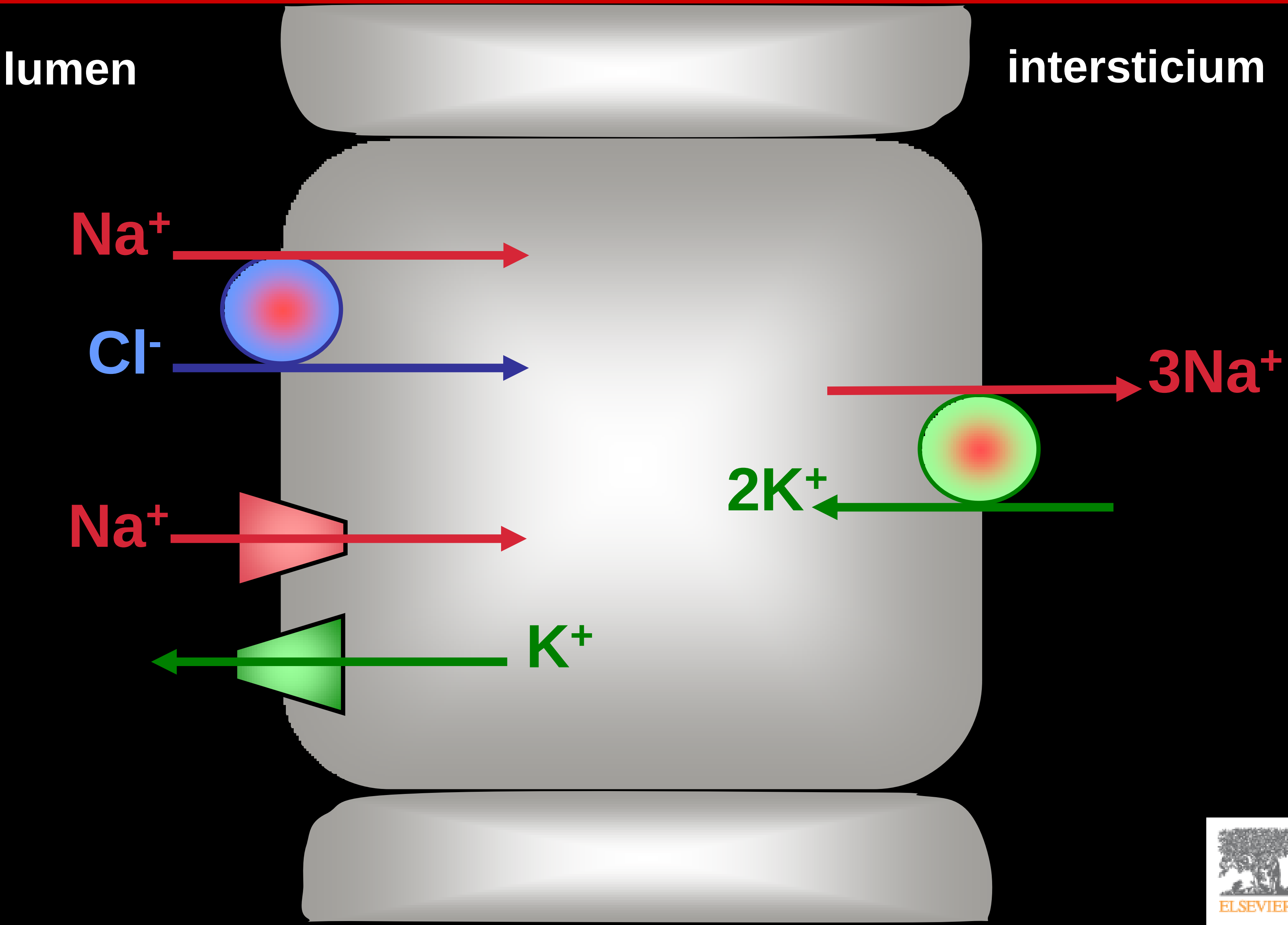
1. Renovaskulární Hypertenze
2. Renální (parenchymatózní) Hypertenze
3. Endokrinně Podmíněné Formy Hypertenze
    - a/ Primární hyperaldosteronismus
    - b/ Pseudohyperaldosterinismus - Liddleuv syndrom
    - c/ Pseudohyperaldosterinismus - způsobený defektem 11-ßH
    - d/ Hyperaldosterinismus ovlivnitelný glukokortikoidy
    - e/ Cushingův sysndrom
    - f/ Feochromocytom

Primární hyperaldosteronismus

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

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

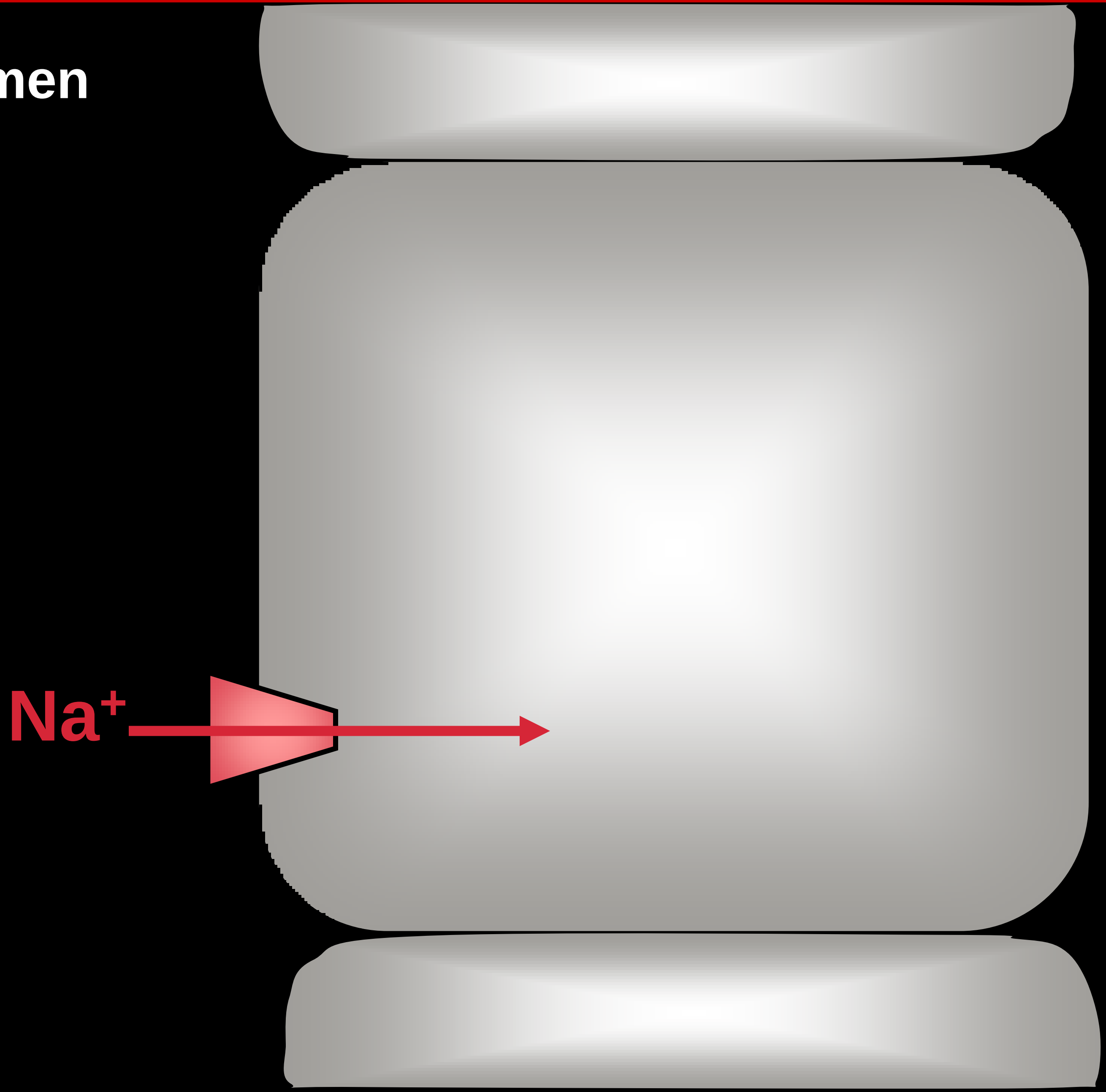
Primární hyperaldosteronismus



Liddleuv syndrom - pseudohyperaldosteronis

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

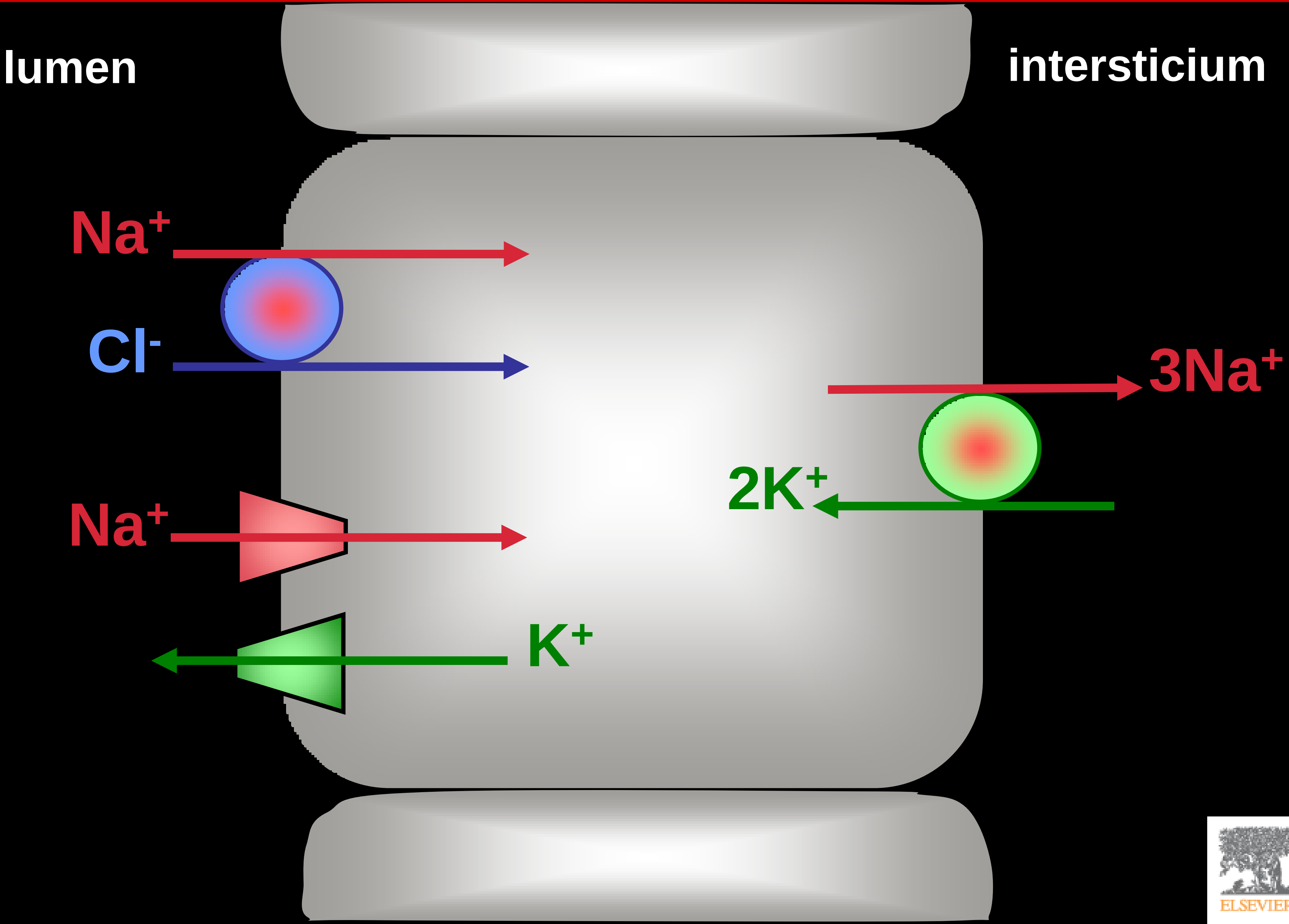
Liddleúv syndrom - pseudohyperaldosterinismus



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-ß-HSD, která mění kortizol na kortizon, což sekundárně způsobí, že v okolí těchto buněk je lokálně dostupný pouze aldoster

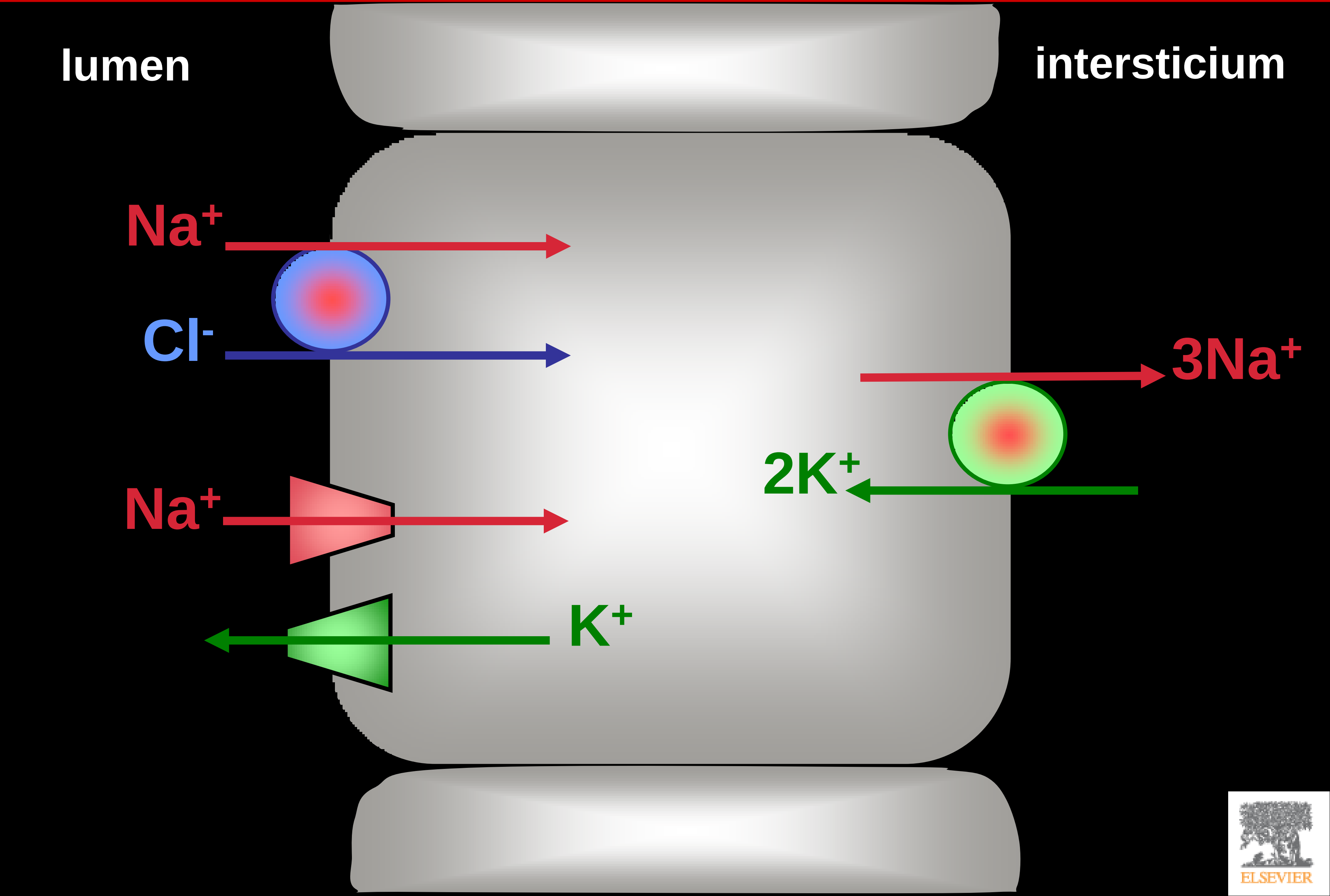

lumen
intersticium
Na+
Cl-
Na+
K+
3Na+
2K+

Pseudohyperaldosteronismus

příznivě ovlivnitelný glukokortikoidy

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

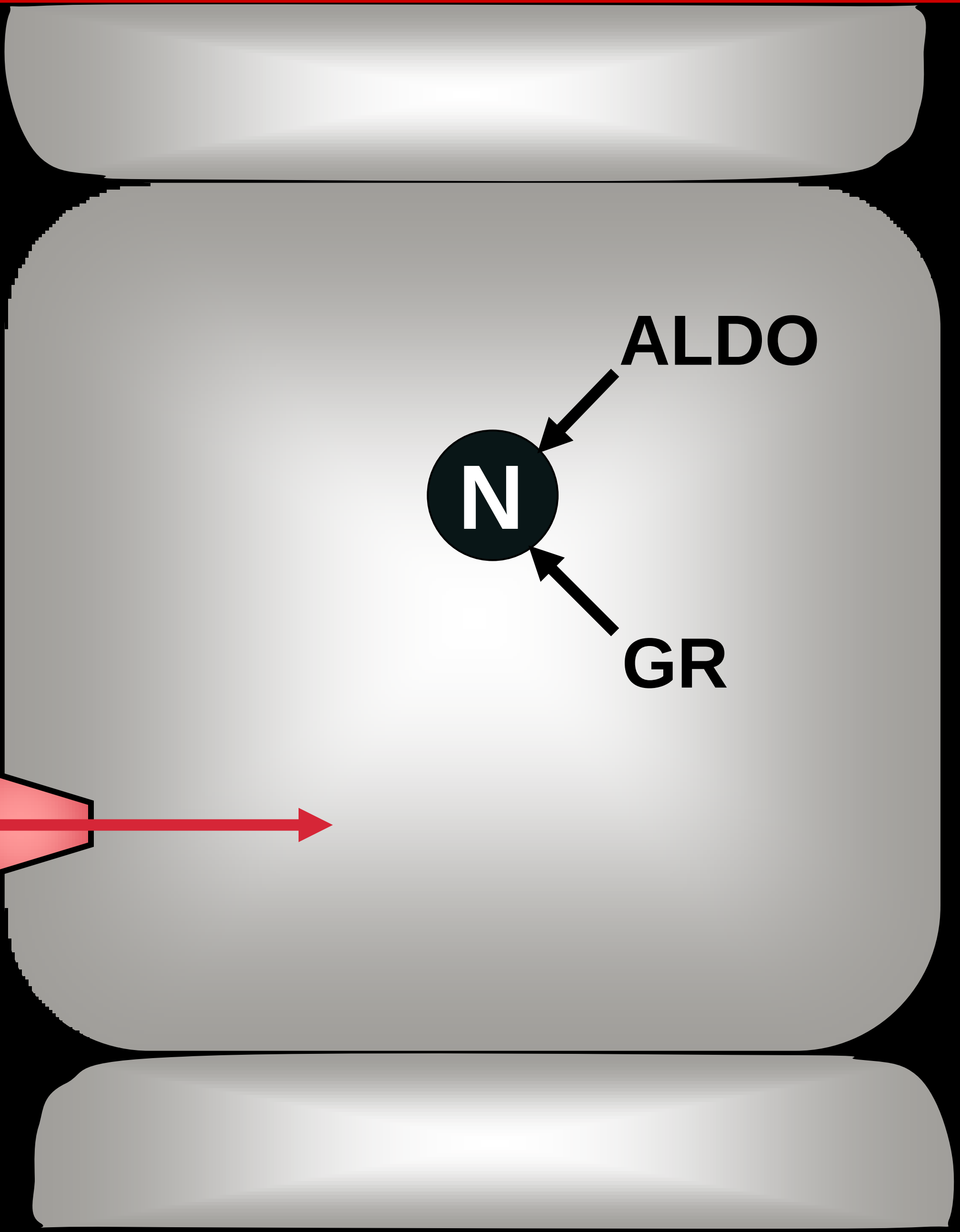
Hyperaldosterinismus – ovlivněný glukokortikoidy



Cushingův syndrom

případě nadměrného (farmakologického) podávání glukokortikodi
tak i funkční 11-ß-HSD není schopna „odbourat“ všechen kortizol
a dochází k aktivaci mineralokortikoidních receptorů

Cushingův syndrom



lumen

intersticium

ALDO

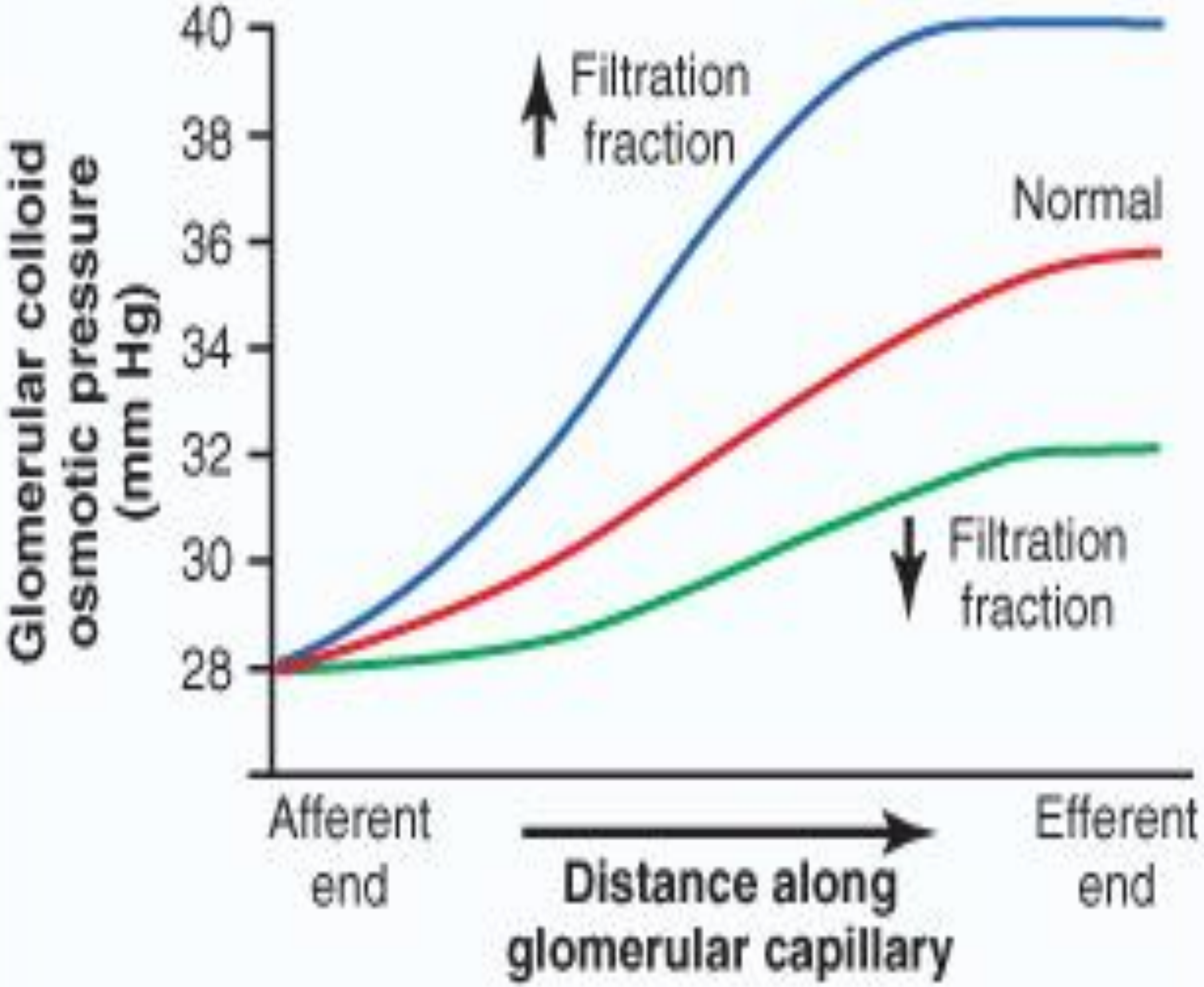
N

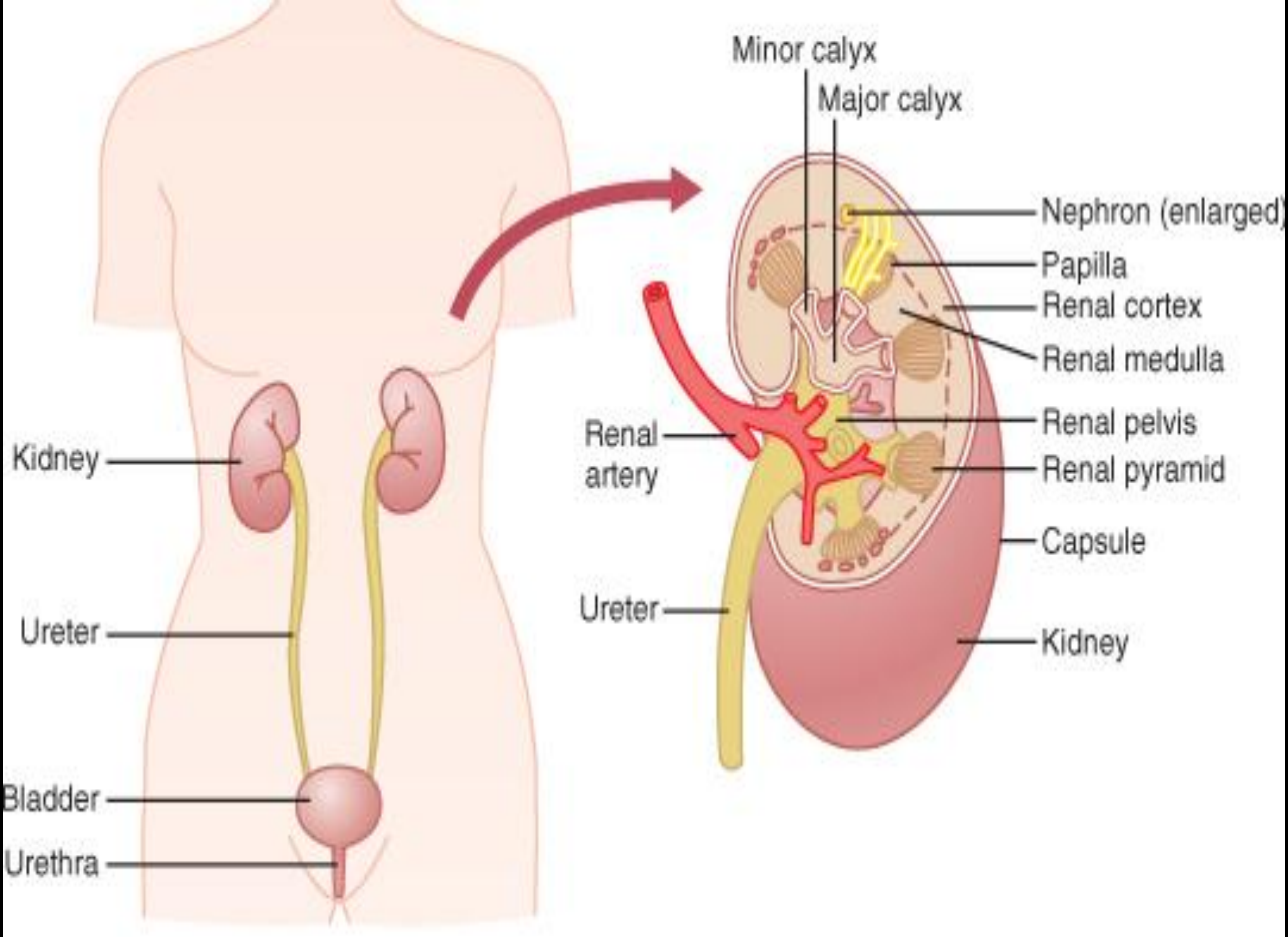
GR

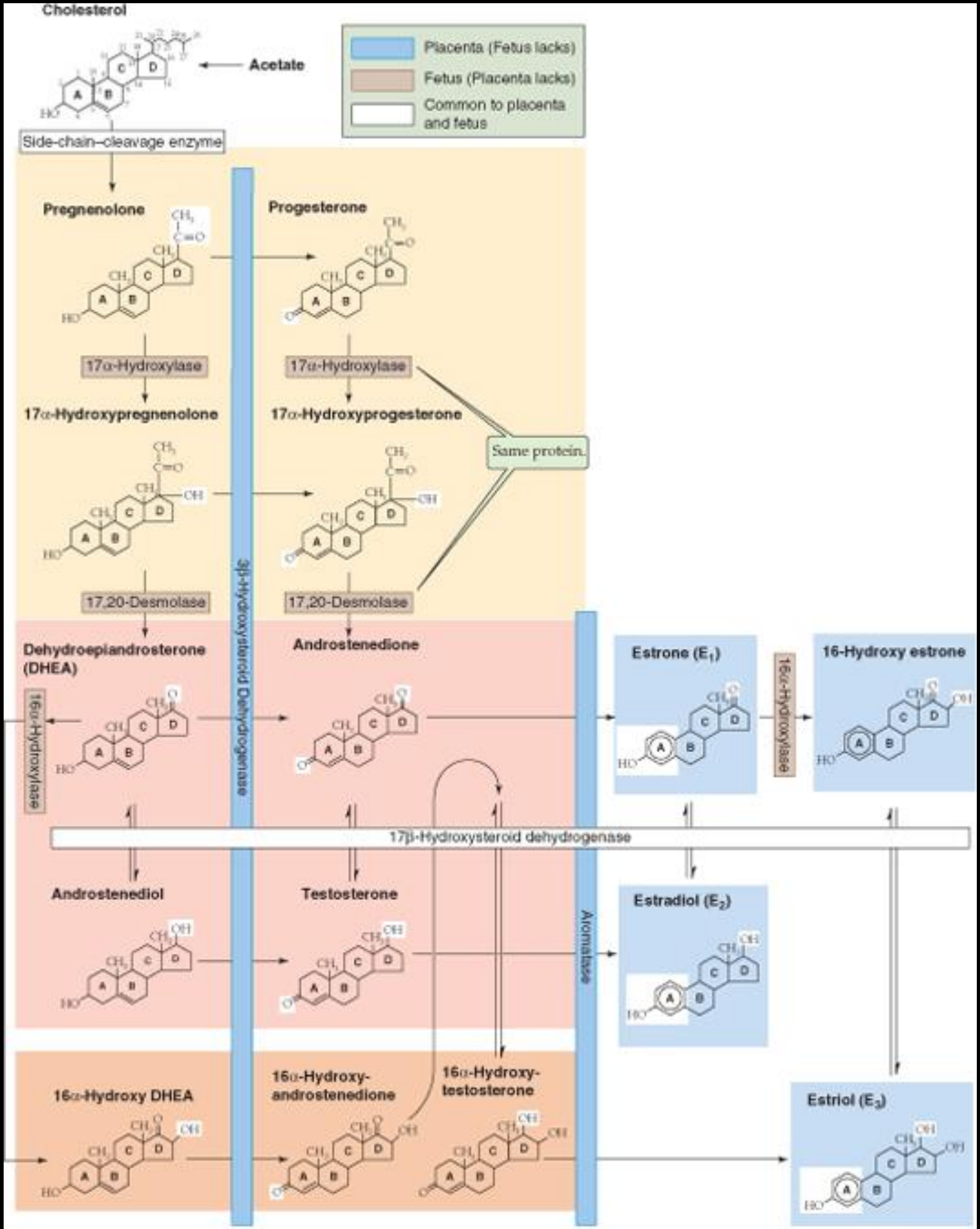
Na^+

Feochromocytom

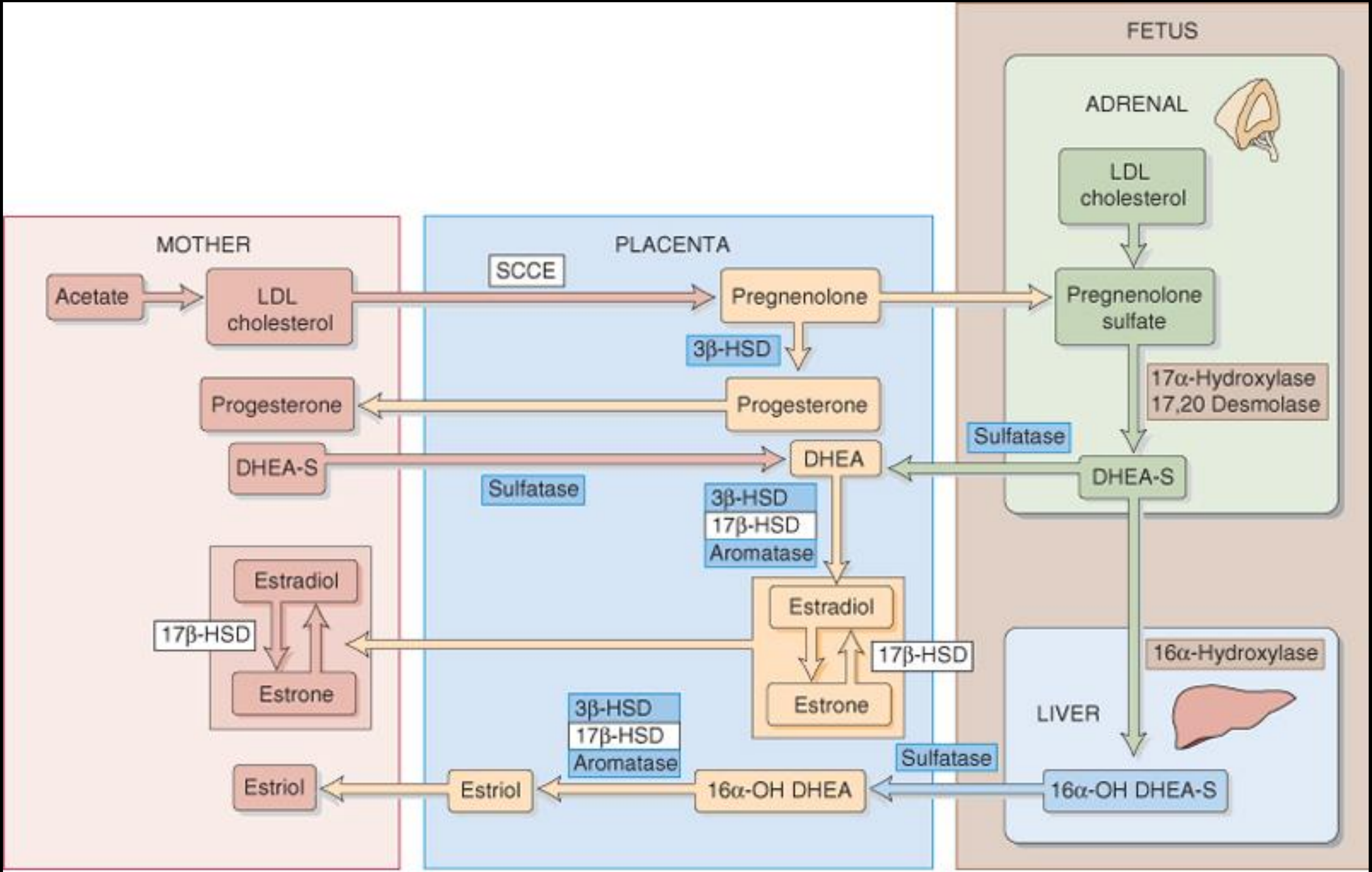
Nádor dřeně nadledvin produkuje enormní množství katecholaminů


Glomerular colloid osmotic pressure (mm Hg)
40
38
36
34
32
30
28
↑ Filtration fraction
Normal
↓ Filtration fraction
Afferent end
Distance along glomerular capillary
Efferent end


Minor calyx
Major calyx
Nephron (enlarged)
Papilla
Renal cortex
Renal medulla
Renal pelvis
Renal pyramid
Capsule
Kidney
Renal artery
Ureter
Kidney
Ureter
Bladder
Urethra



Boron & Boulpaep: Medical Physiology, 2nd Edition.



MOTHER

Acetate

LDL cholesterol

Progesterone

DHEA-S

Estradiol

17β-HSD

Estrone

Estriol

PLACENTA

SCCE

Pregnenolone

3β-HSD

Progesterone

Sulfatase

DHEA

3β-HSD
17β-HSD
Aromatase

Estradiol

17β-HSD

Estrone

3β-HSD
17β-HSD
Aromatase

Estriol

16α-OH DHEA

Sulfatase

FETUS

ADRENAL

LDL cholesterol

Pregnenolone sulfate

17α-Hydroxylase
17,20 Desmolase

Sulfatase

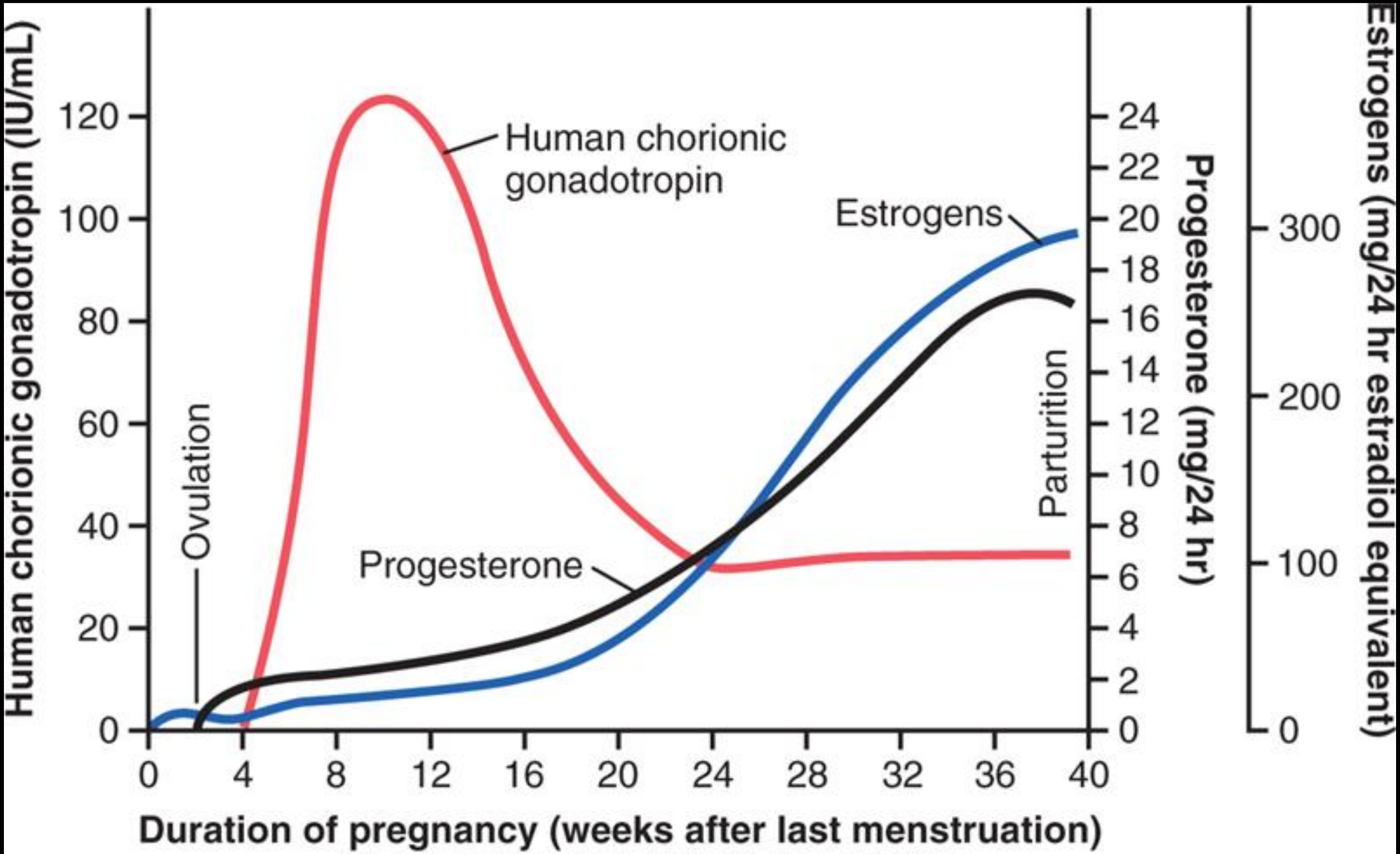
DHEA-S

16α-Hydroxylase

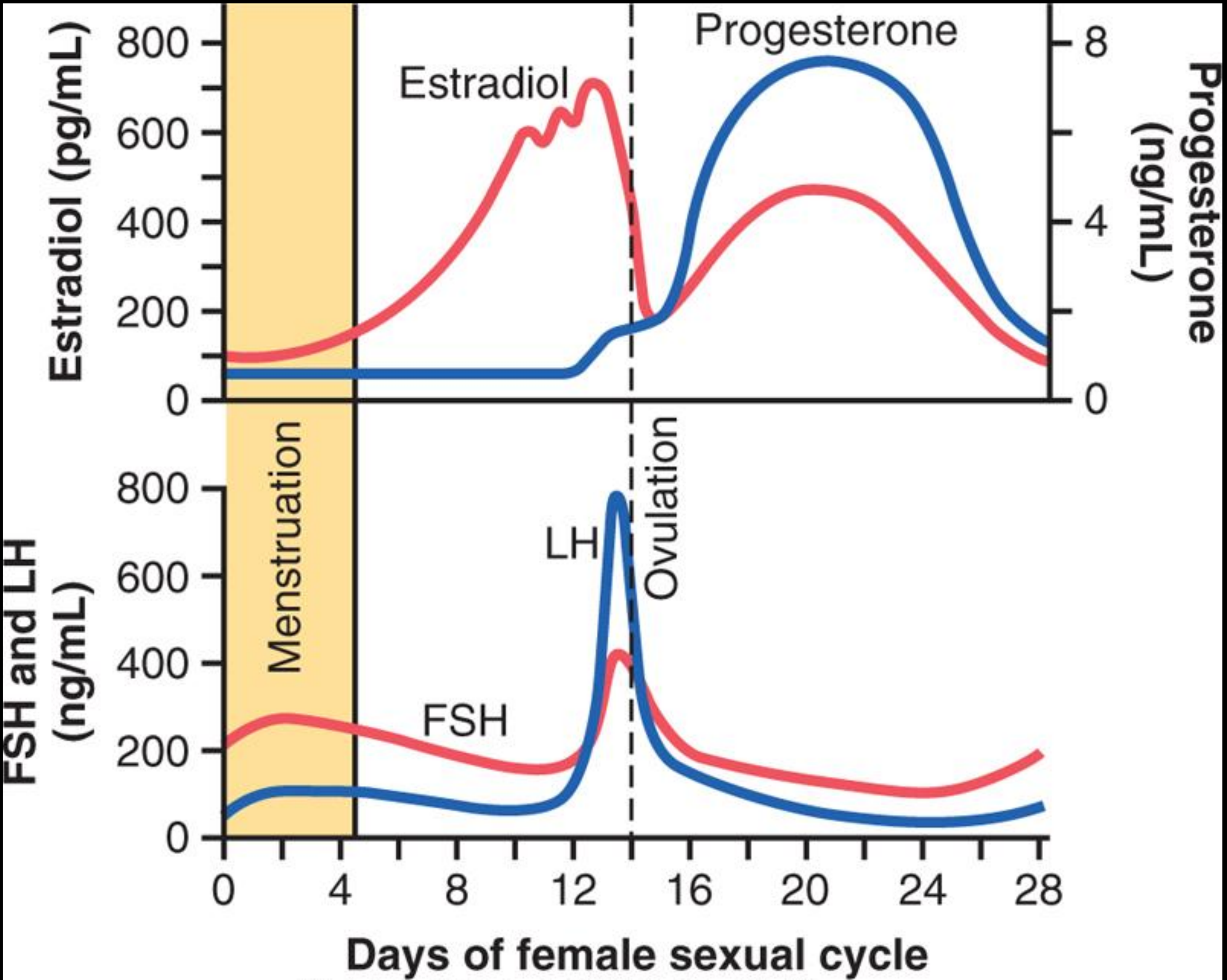
LIVER

16α-OH DHEA-S

Boron & Boulpaep: Medical Physiology, 2nd Edition.



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



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

Koncentrační mechanizmus ledvin

Organizmus se musí denně zbavit minimálně 600 mOsm denně

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

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

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

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_{vody}), což ve své podstatě není clearance, ale rozdíl mezi diurézou a osmotickou clearance.

Množství denní moči je určeno následující rovnicí:

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

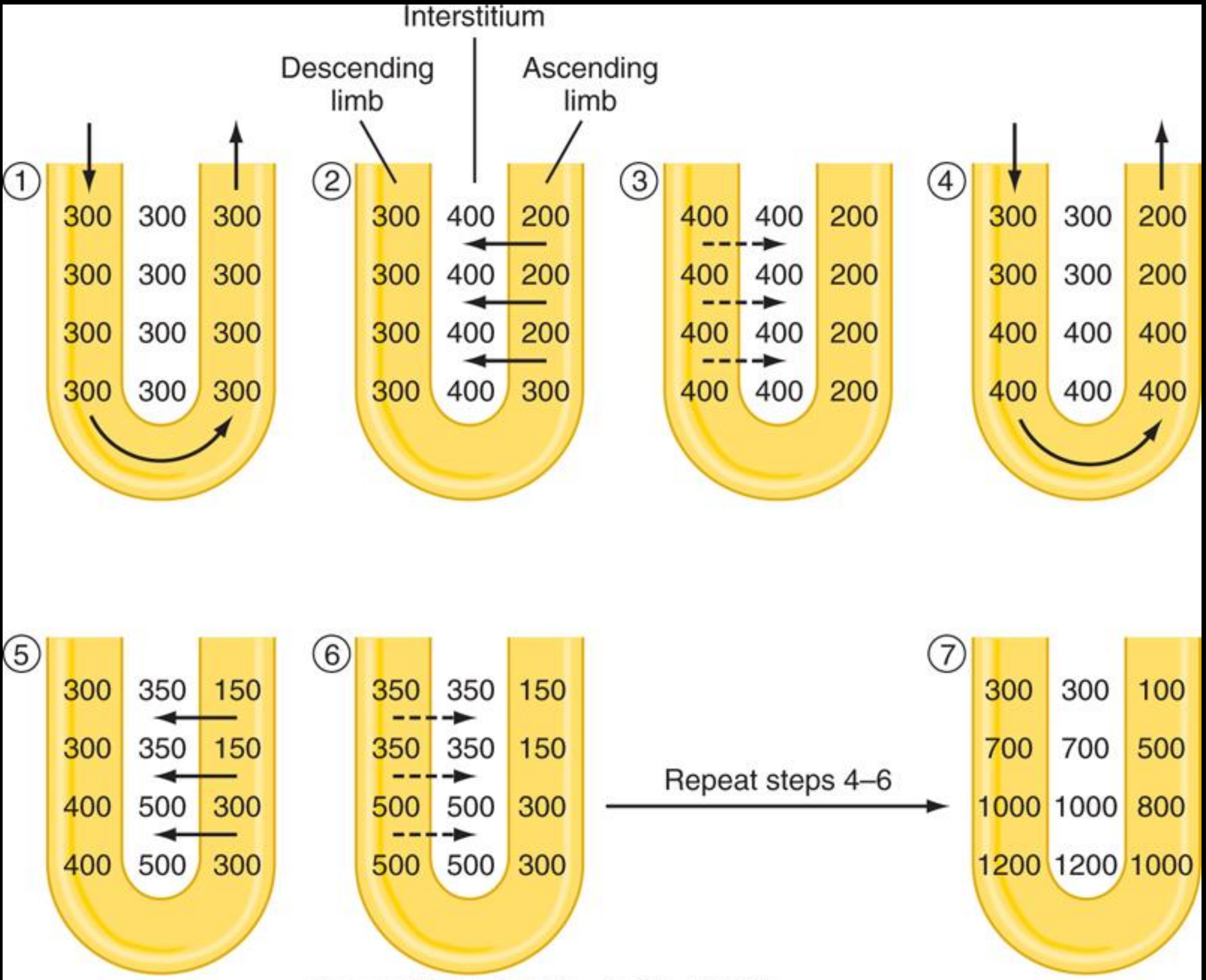
$C_{vody} = V - C_{osm}$

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

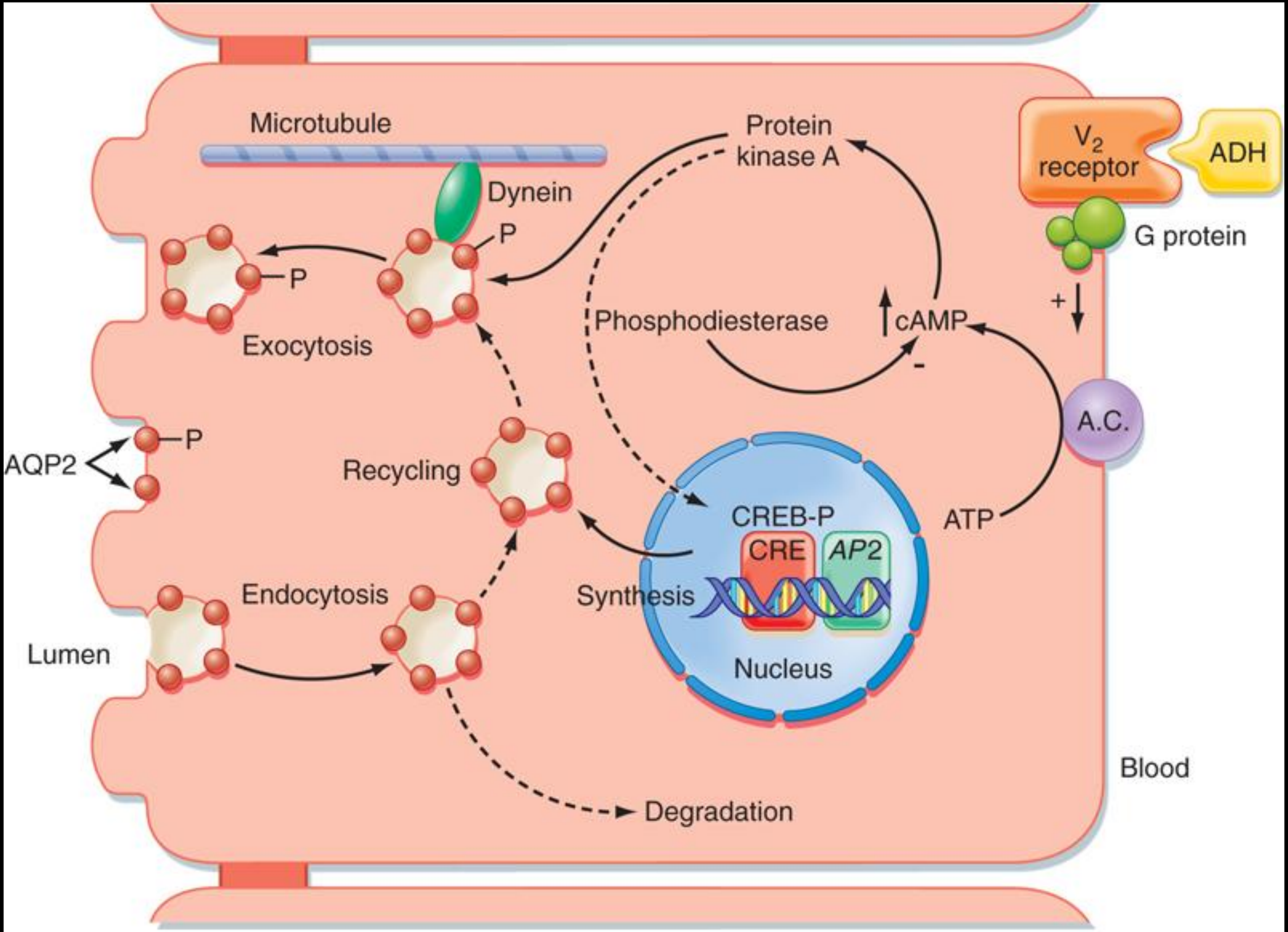
C_{vody} = 20 L/den – 2 L/den = 18 L/den

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

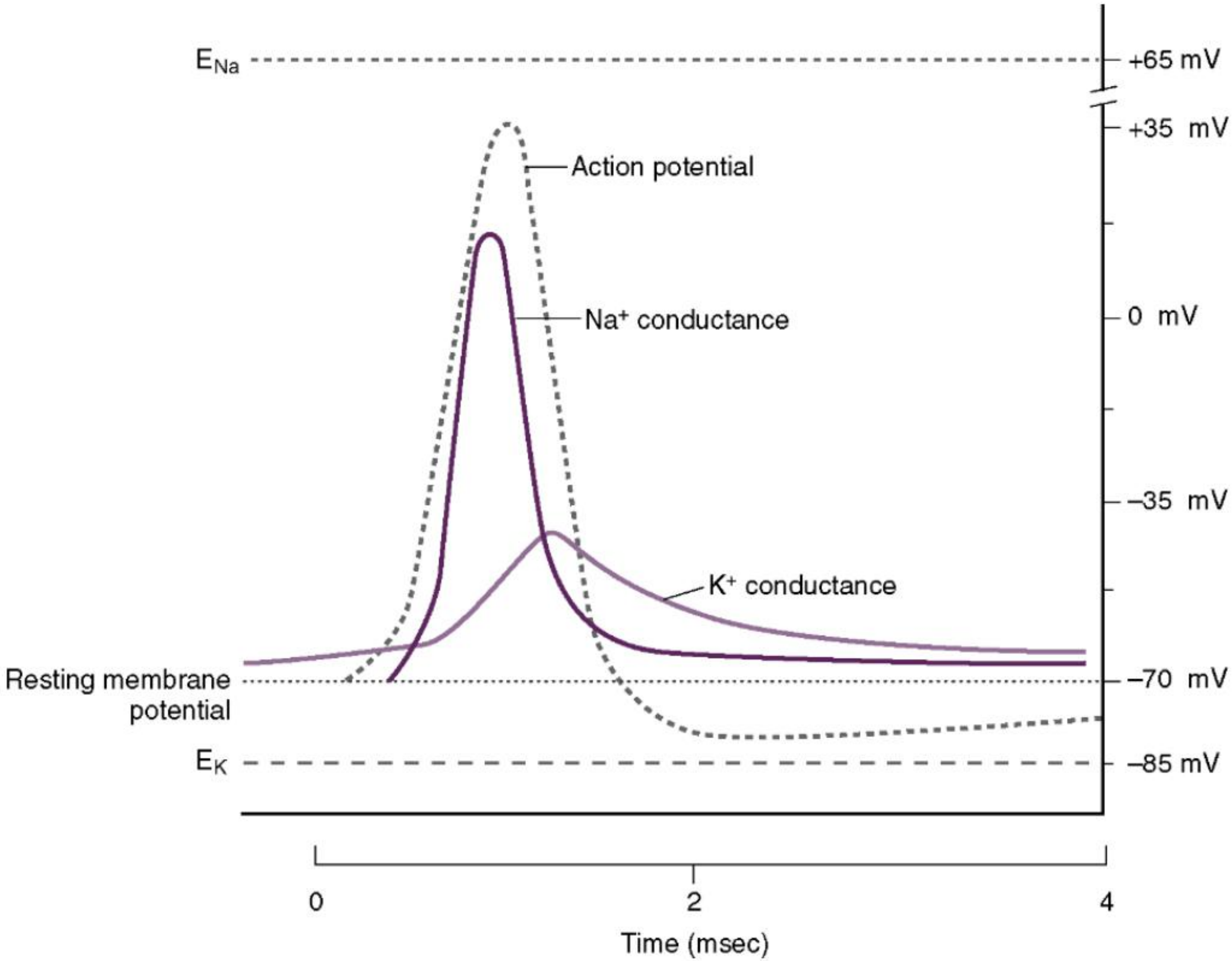
C_{vody} = 0,5 L/den – 2 L/den = -1,5 L/den

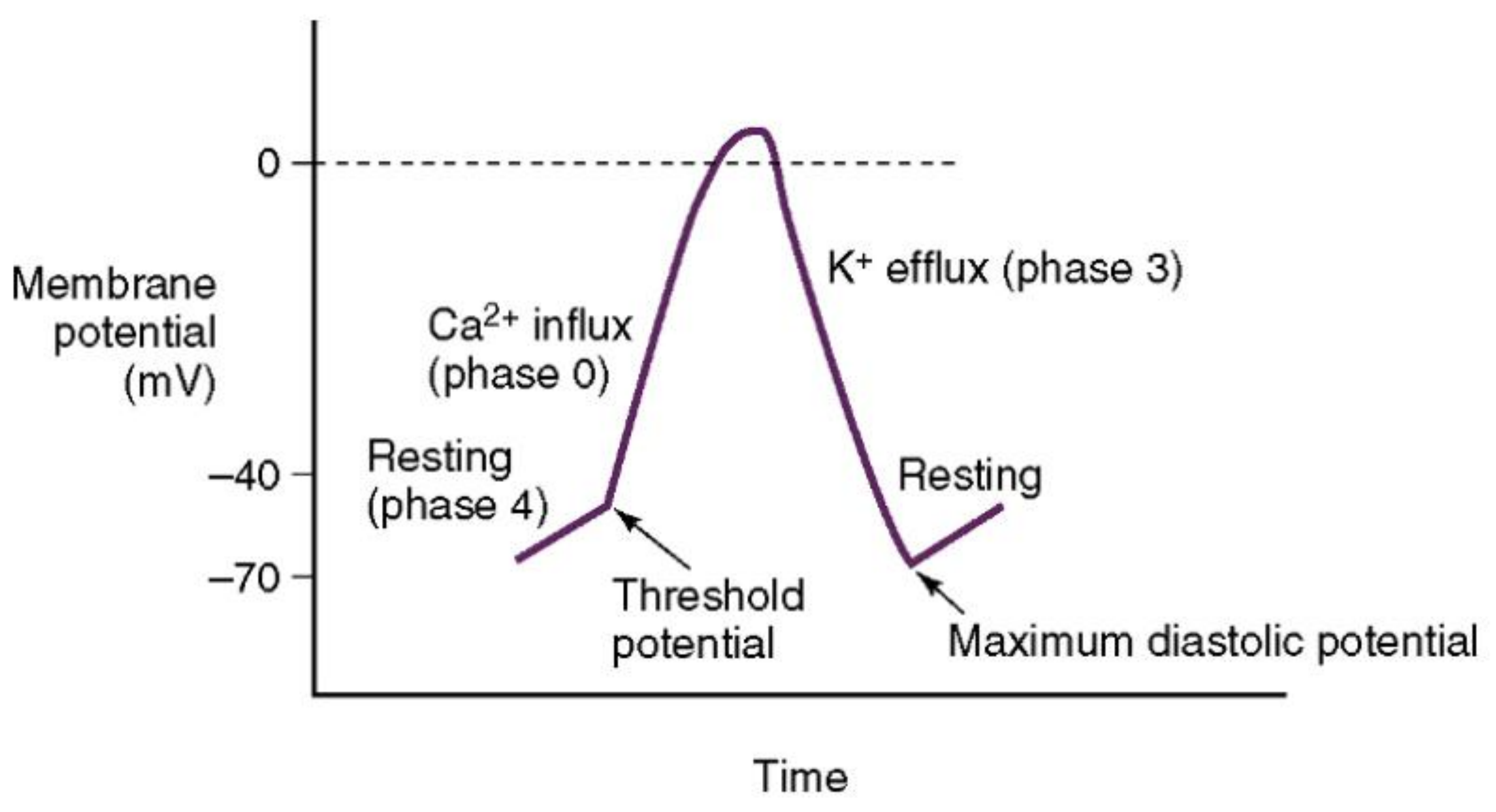


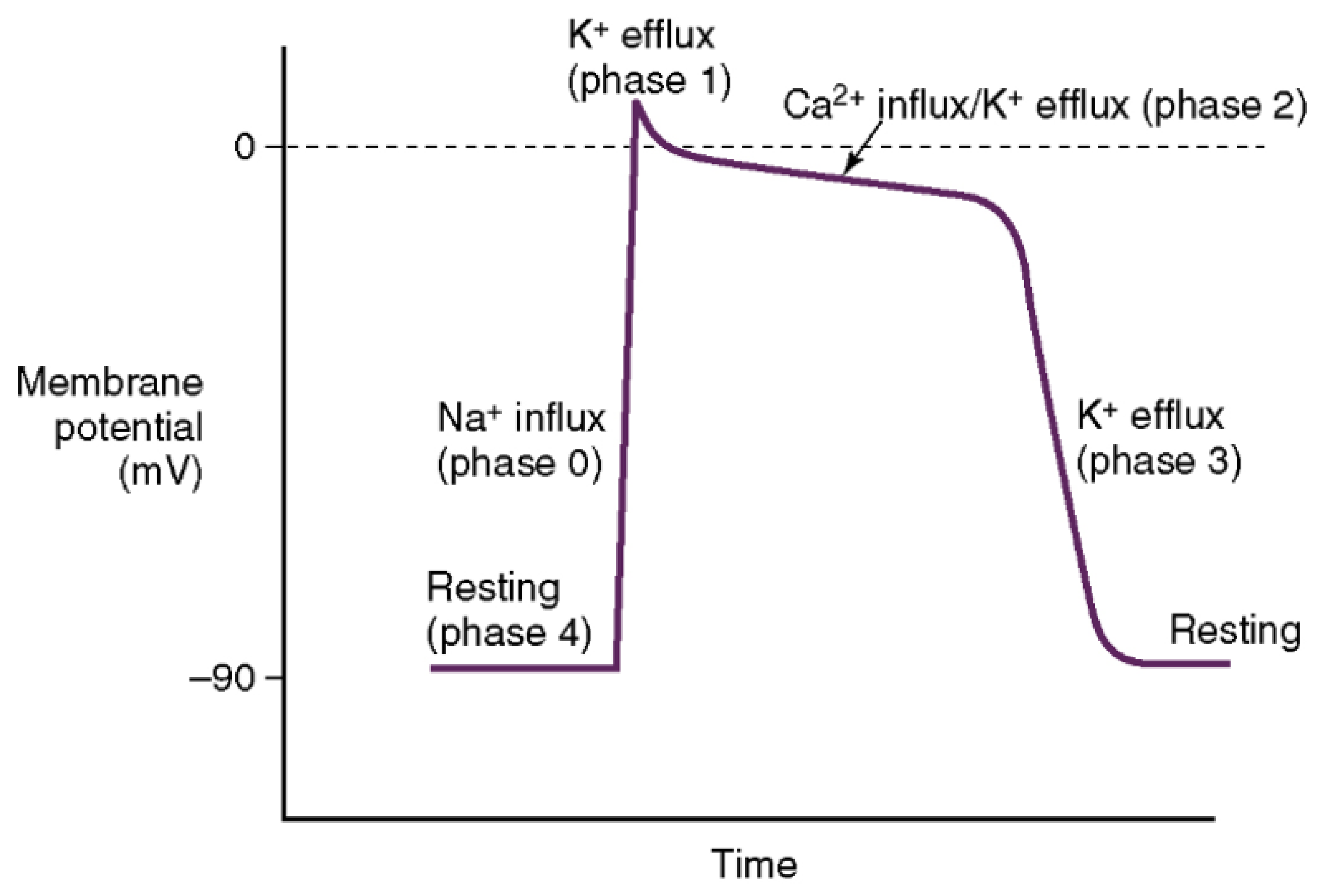
Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.

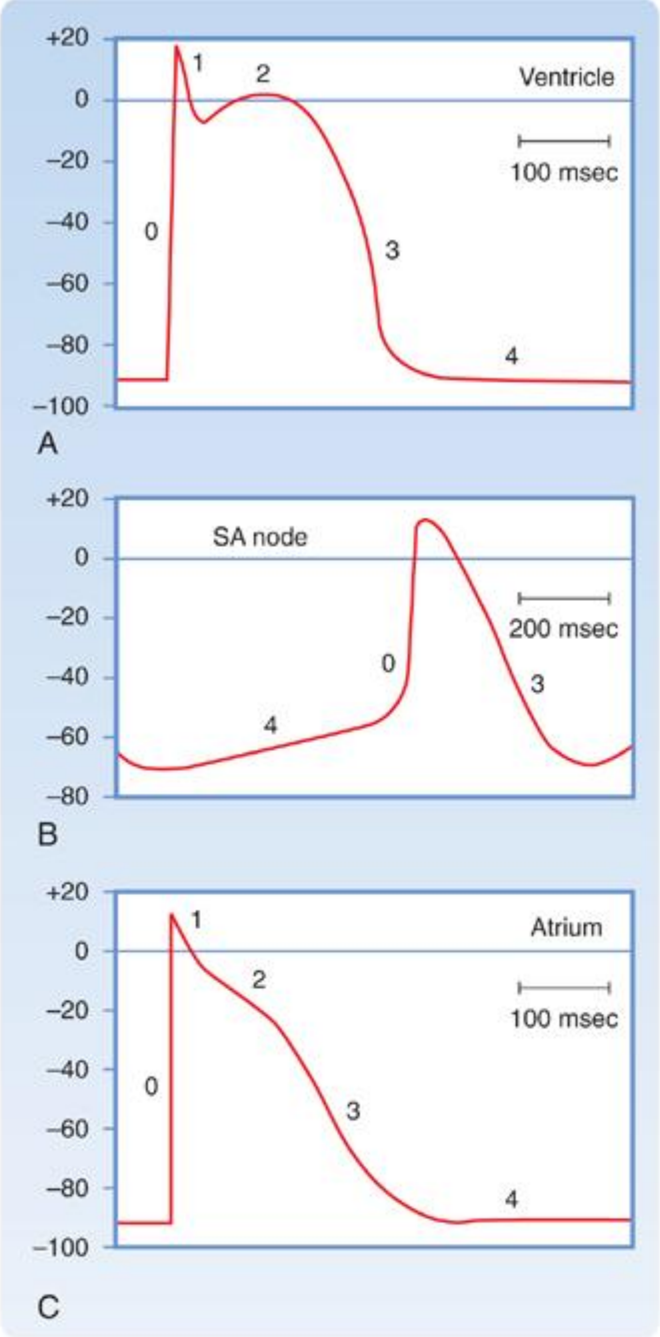


Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.

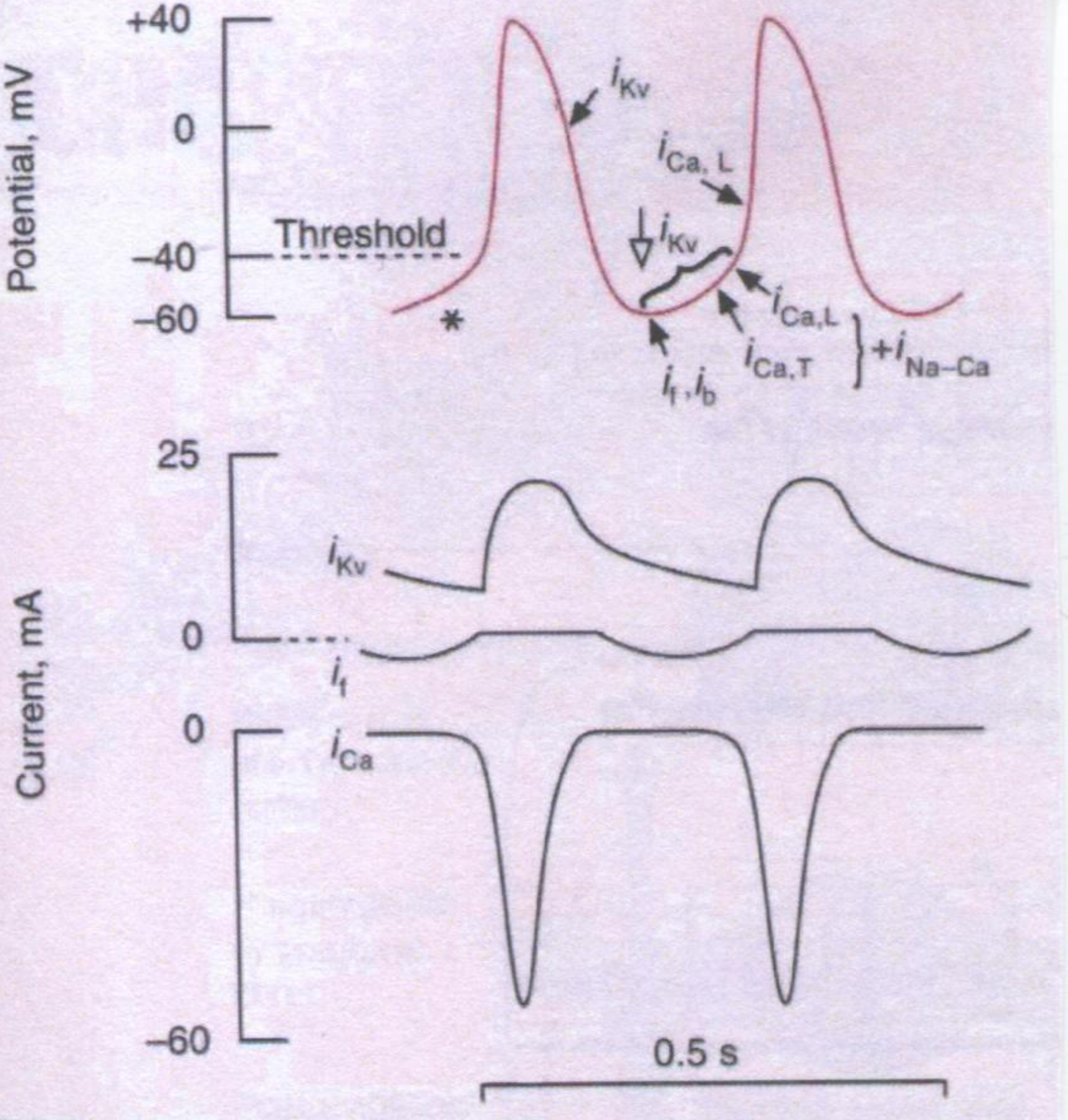

E_{Na}
+65 mV
+35 mV
Action potential
Na^+ conductance
0 mV
−35 mV
K^+ conductance
Resting membrane potential
−70 mV
E_K
−85 mV
0
2
4
Time (msec)


0
Membrane
potential
(mV)
−40
−70
Ca2+ influx
(phase 0)
K+ efflux (phase 3)
Resting
(phase 4)
Resting
Threshold
potential
Maximum diastolic potential
Time

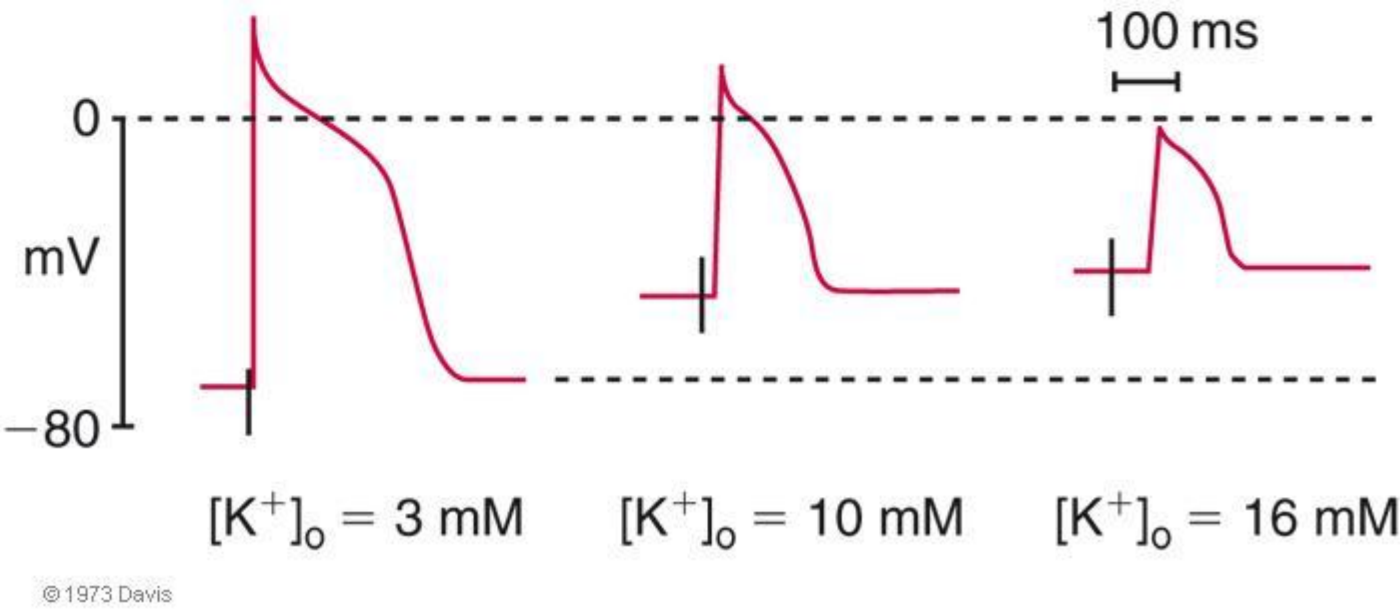

K+ efflux (phase 1)
Ca2+ influx/K+ efflux (phase 2)
0
Membrane potential (mV)
Na+ influx (phase 0)
K+ efflux (phase 3)
Resting (phase 4)
Resting
–90
Time

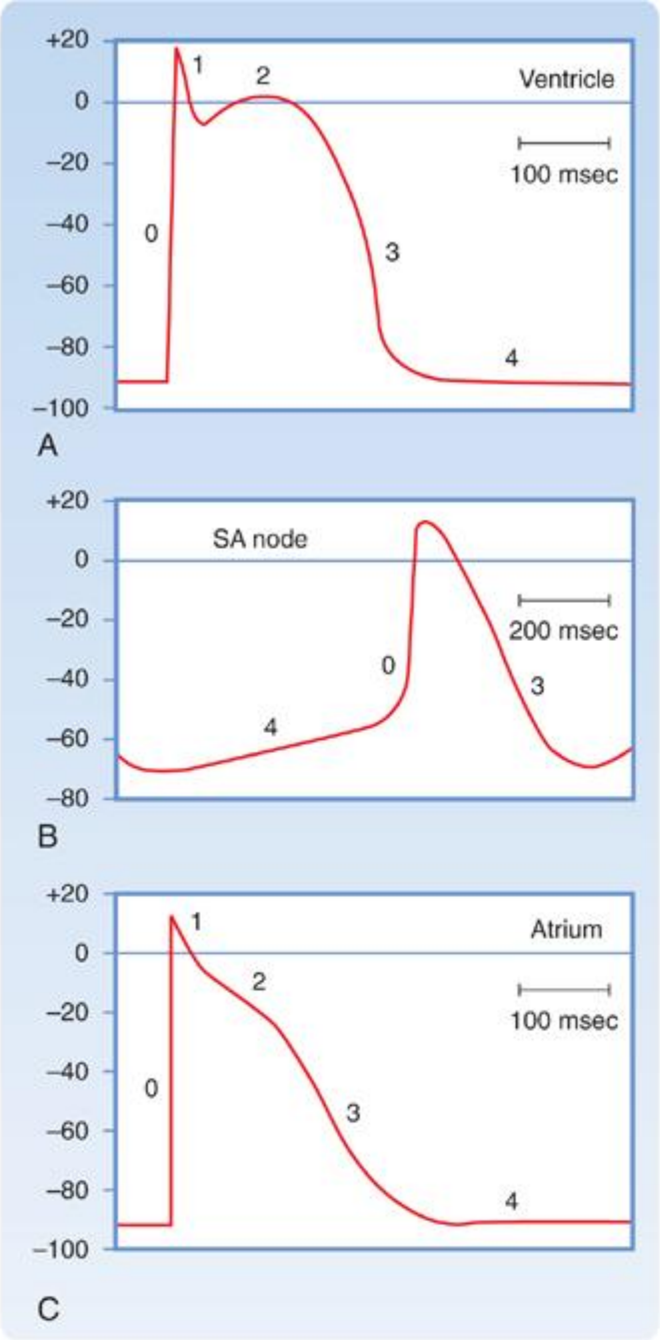


Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.

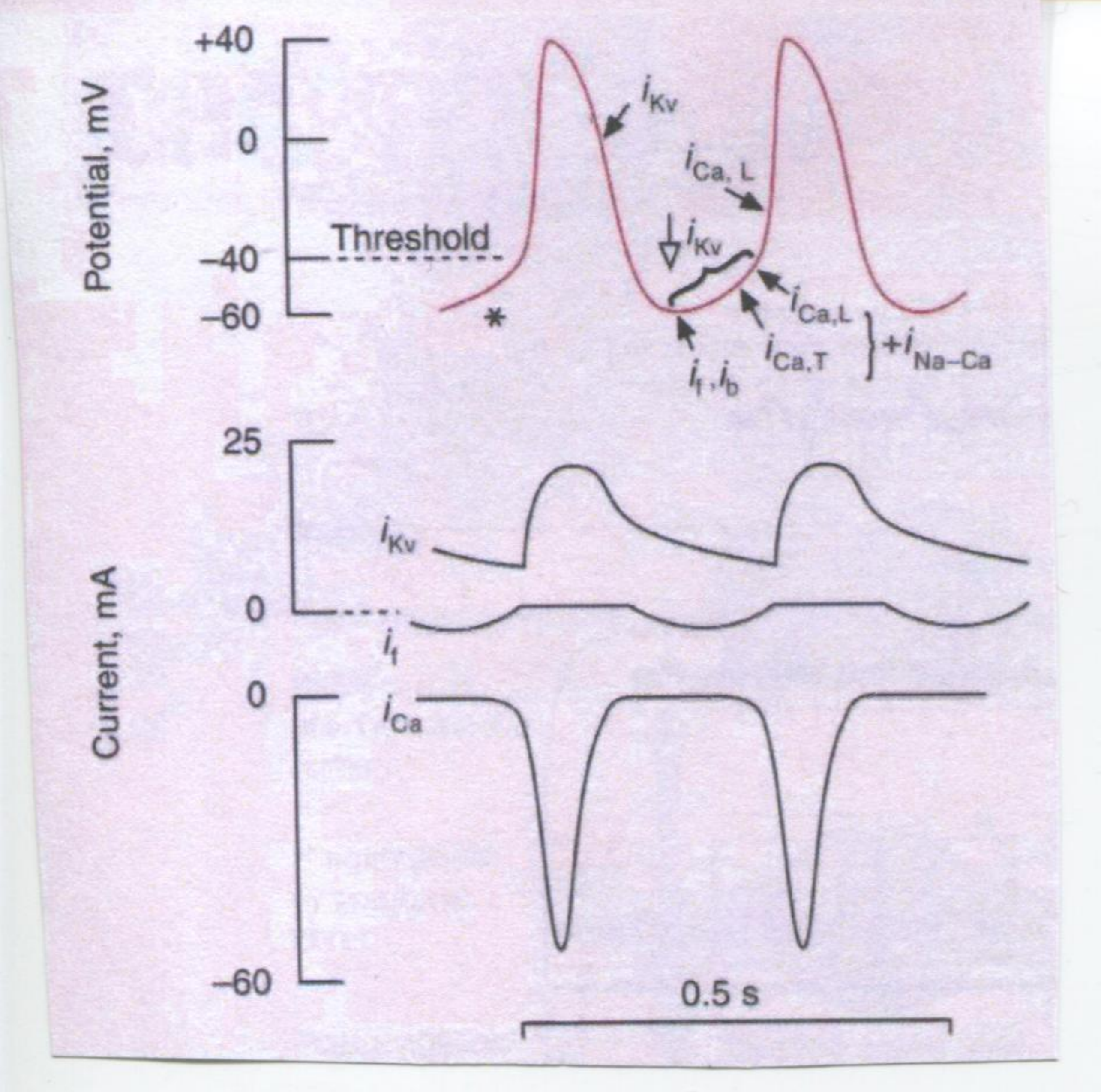


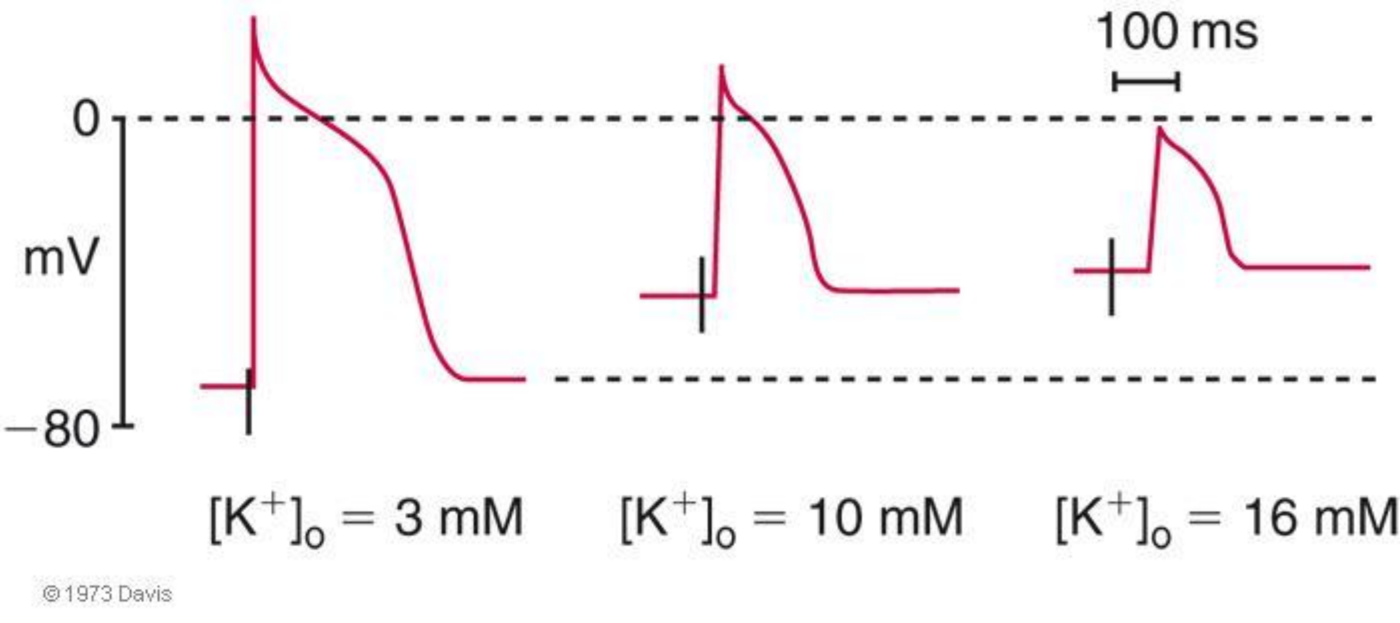
Potential, mV
+40
0
Threshold
–40
–60
*
i_{Kv}
$i_{Ca,L}$
i_{Kv}
$i_{Ca,L}$
$i_{Ca,T}$
$+i_{Na-Ca}$
i_f, i_b
Current, mA
25
i_{Kv}
0
i_f
0
i_{Ca}
–60
0.5 s

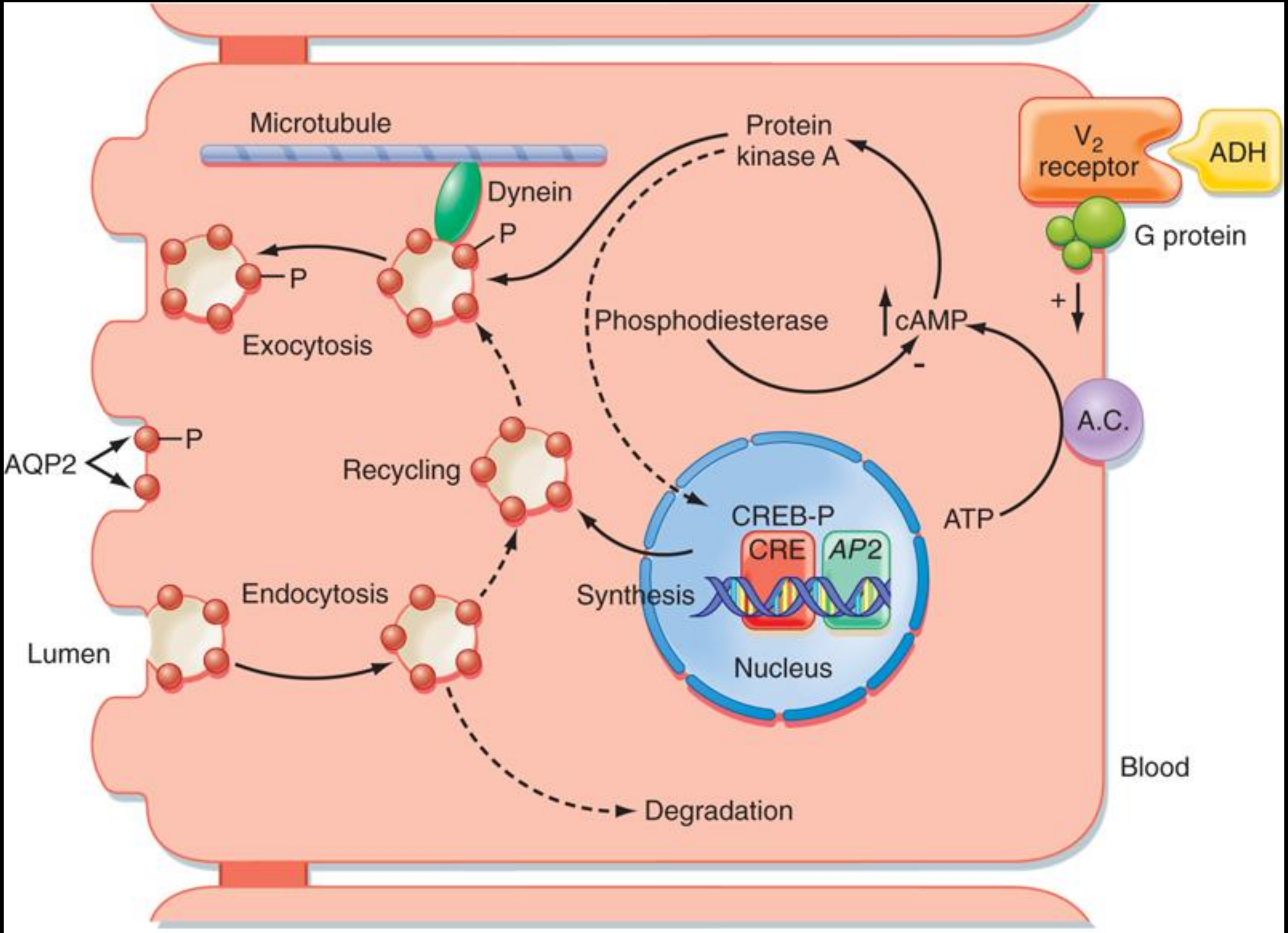

100 ms
0
mV
−80
$[K^+]_o$ = 3 mM
$[K^+]_o$ = 10 mM
$[K^+]_o$ = 16 mM



Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.


Potential, mV
+40
0
−40
−60
Threshold
*
i_{Kv}
$i_{Ca,L}$
i_{Kv}
$i_{Ca,L}$
$i_{Ca,T}$
$+i_{Na-Ca}$
i_f, i_b
Current, mA
25
i_{Kv}
0
i_f
0
i_{Ca}
−60
0.5 s

100 ms
0
mV
−80
$[K^+]_o$ = 3 mM
$[K^+]_o$ = 10 mM
$[K^+]_o$ = 16 mM



Koeppen and Stanton: Berne & Levy Physiology, 6th Edition.

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