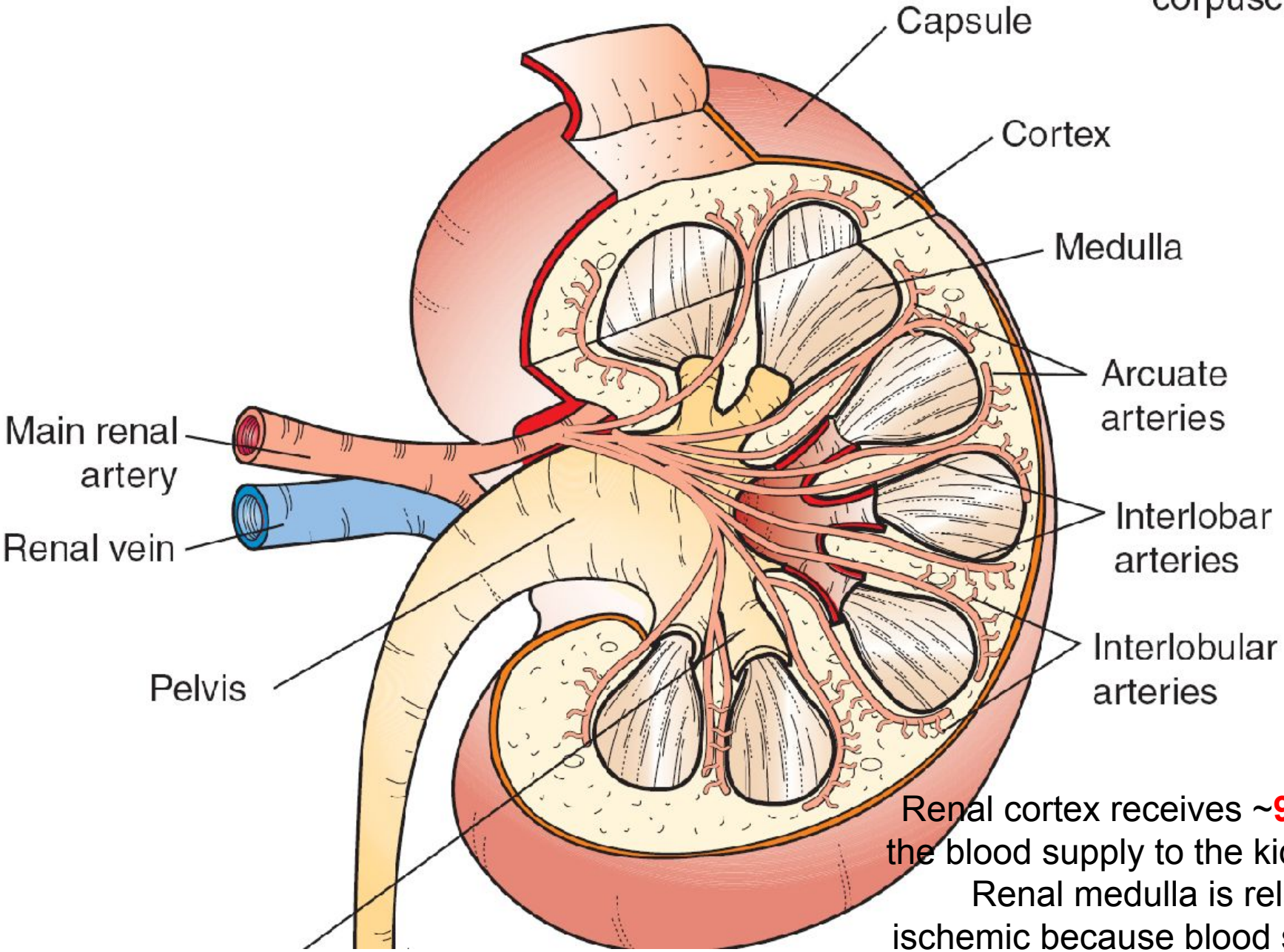


Renal cortex receives ~**90%** of the blood supply to the kidneys. Renal medulla is relatively ischemic because blood supply is reduced (**10%** of blood supply to the kidneys)

ПРОЦЕССЫ

- Фильтрация
- Реабсорбция
- Секреция

клубочек

каналец

ФУНКЦИИ

1. Поддержание водно-электролитного равновесия.
2. Выведение токсинов.
3. Регуляция обмена кальция и фосфора.
4. Поддержание кислотно-щелочного равновесия.
5. Стимуляция эритропоэза.

Фильтрация

СКФ= 90 – 120мл/мин

Легко фильтруются - < 70 кДА (~ 3,6 нм)

- большинство электролитов
- мочевина, креатинин (100%)
- глюкоза, ак, органические кислоты: мочевая, кетоновые тела и др.
- НМ протеины: инсулин (5808 Да), миоглобин (17 кДа)
- инулин, р-аминогиппуровая кислота

Плохо фильтруются

- альбумин (из-за заряда), глобулины (из-за ММ)
- липофильные вещества – т.к. транспортируются белками (непрямой билирубин, гормоны)

Оценка СКФ

- По клиренсу креатинина (проба Реберга - Тареева)
- По клиренсу инулина

<u>По специальным формулам:</u>

1. Шварца (у детей)
2. Кокрофта-Голта (оценивает клиренс креатинина)
3. MDRD (у пациентов с СД)
4. CKD-EPI (у пациентов с ССЗ)

+ уровень **цистатина С**

Name	Equation	Units	Comments
Clearance	$C_x = \frac{[U]_x \dot{V}}{[P]_x}$	mL/min	x is any substance
Clearance ratio	$\text{Clearance ratio} = \frac{C_x}{C_{inulin}}$	None	Also means fractional excretion of x
Renal plasma flow	$RPF = \frac{[U]_{PAH} \dot{V}}{[RA]_{PAH} - [RV]_{PAH}}$	mL/min	
Effective renal plasma flow	$\text{Effective RPF} = \frac{[U]_{PAH} \dot{V}}{[P]_{PAH}}$	mL/min	Underestimates RPF by 10%; equals C_{PAH}
Renal blood flow	$RBF = \frac{RPF}{1 - Hct}$	mL/min	1 minus Hct is fraction of blood volume that is plasma
Glomerular filtration rate	$GFR = \frac{[U]_{inulin} \dot{V}}{[P]_{inulin}}$	mL/min	Equals C_{inulin}
Filtration fraction	$FF = \frac{GFR}{RPF}$	None	
Filtered load	$\text{Filtered load} = GFR \times [P]_x$	mg/min	
Excretion rate	$\text{Excretion} = \dot{V} \times [U]_x$	mg/min	
Reabsorption or secretion rate	Reabsorption or secretion = Filtered load − Excretion	mg/min	If *positive,* net reabsorption If *negative,* net secretion
Free-water clearance	$C_{H_2O} = \dot{V} - C_{osm}$	mL/min	If *positive,* free water is excreted If *negative*, free water is reabsorbed

?

SAMPLE PROBLEM. In a 24-hour period, 1.44 L of urine is collected from a man receiving an infusion of inulin. In his urine, the [inulin] is 150 mg/mL and the [Na^+] is 200 mEq/L. In his plasma, the [inulin] is 1 mg/mL and the [Na^+] is 140 mEq/L. *What is the clearance ratio for Na^+, and what is the significance of its value?*

SOLUTION. The clearance ratio for Na^+ is the clearance of Na^+ relative to the clearance of inulin. The clearance equation for any substance is $C = [U] \times \dot{V}/[P]$. All of the values needed are provided in the description, although urine flow rate ($\dot{V}$) must be calculated.

$$\begin{aligned}\dot{V} &= \text{Urine volume/time}\\ &= 1.44\ \text{L/24 hr}\\ &= 1440\ \text{mL/1440 min}\\ &= 1.0\ \text{mL/min}\end{aligned}$$

$$\begin{aligned}C_{Na^+} &= \frac{[U]_{Na^+} \times \dot{V}}{[P]_{Na^+}}\\ &= \frac{200\ \text{mEq/L} \times 1\ \text{mL/min}}{140\ \text{mEq/L}}\\ &= 1.43\ \text{mL/min}\end{aligned}$$

$$\begin{aligned}C_{inulin} &= \frac{[U]_{inulin} \times \dot{V}}{[P]_{inulin}}\\ &= \frac{150\ \text{mg/mL} \times 1\ \text{mL/min}}{1\ \text{mg/mL}}\\ &= 150\ \text{mL/min}\end{aligned}$$

$$\begin{aligned}\frac{C_{Na^+}}{C_{inulin}} &= \frac{1.43\ \text{mL/min}}{150\ \text{mL/min}}\\ &= 0.01 \text{ or } 1\%\end{aligned}$$

The calculated clearance ratio for Na^+ of 0.01 (or 1%) provides a great deal of information about the renal handling of Na^+. Because Na^+ is freely filtered across the glomerular capillaries, it also must be extensively reabsorbed by the renal tubule, making its clearance much less than the clearance of inulin. The clearance ratio of 0.01 means that only 1% of the filtered Na^+ is excreted. Stated differently, 99% of the filtered Na^+ must have been reabsorbed.

FENa = [(UNa × PCr) ÷ (PNa ×UCr)] ×100

Variable	Prerenal	Intrinsic Renal	Postrenal
Urine osmolality (mOsm/kg)	> 500	< 350	< 350
Urine Na^+ (mEq/L)	< 20	> 40	> 40
FENa	< 1%	> 2%	> 1% (mild) > 2% (severe)
Serum BUN/Cr	> 20	< 15	> 15

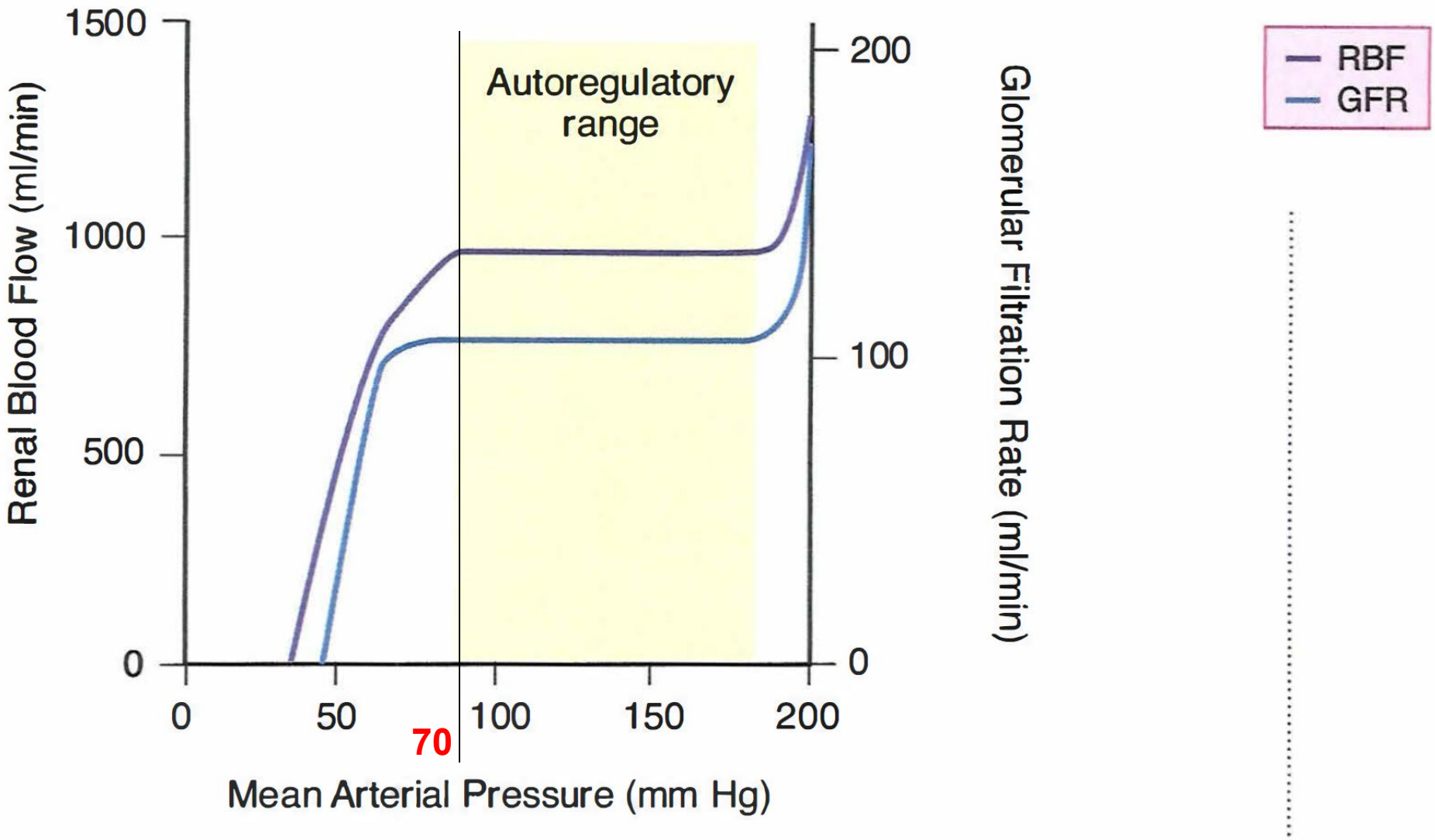
баро-
(аорты и каротидных телец)
волюмо-
(предсердия и полые вены)
осморецепторы
(гипоталамус)
Macula densa

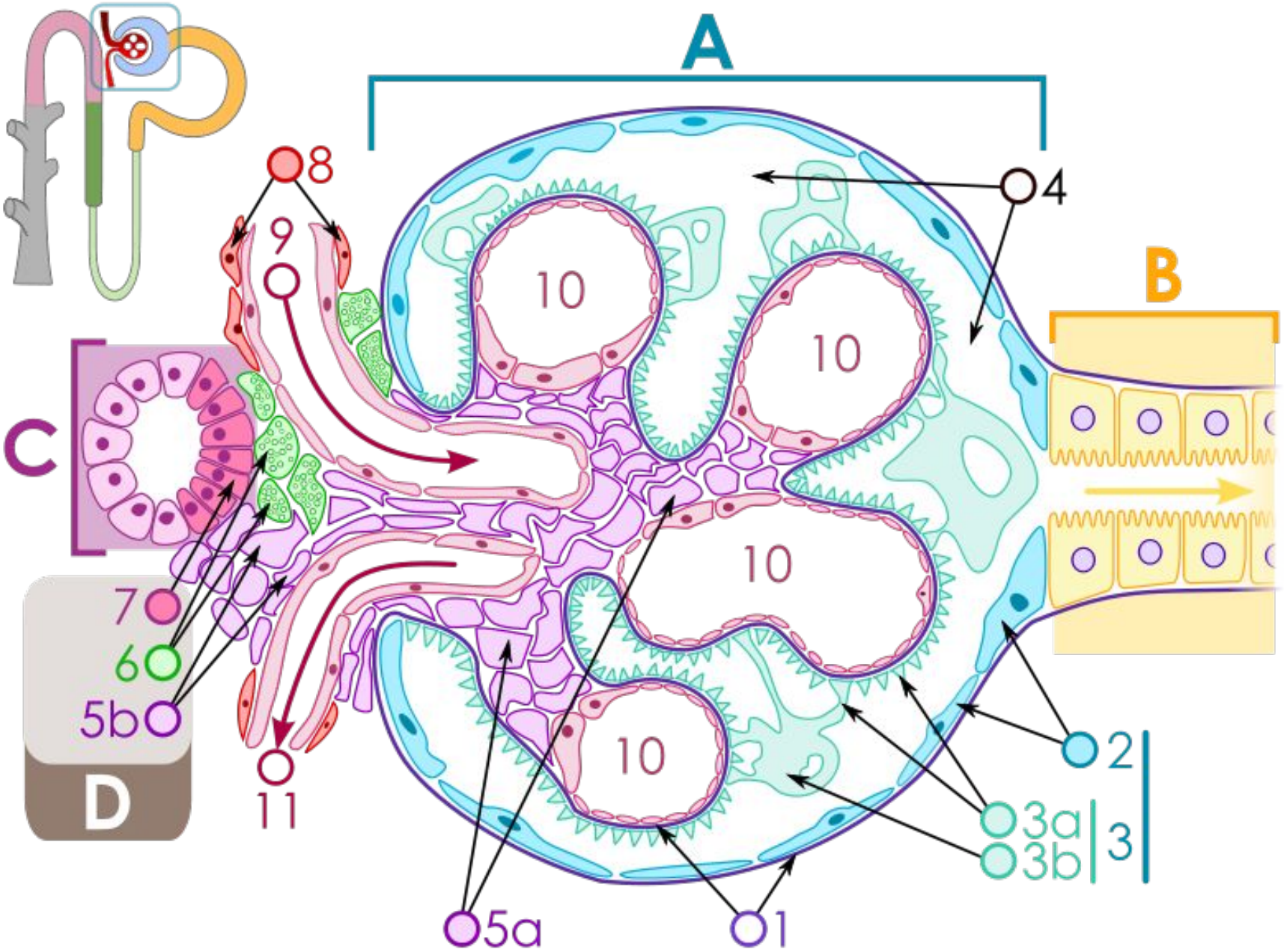
Гемодинамические механизмы:
изменение СКФ
перитубулярные силы

Нейрогуморальные механизмы:
РААС
САС
НУП
ПгЕ2

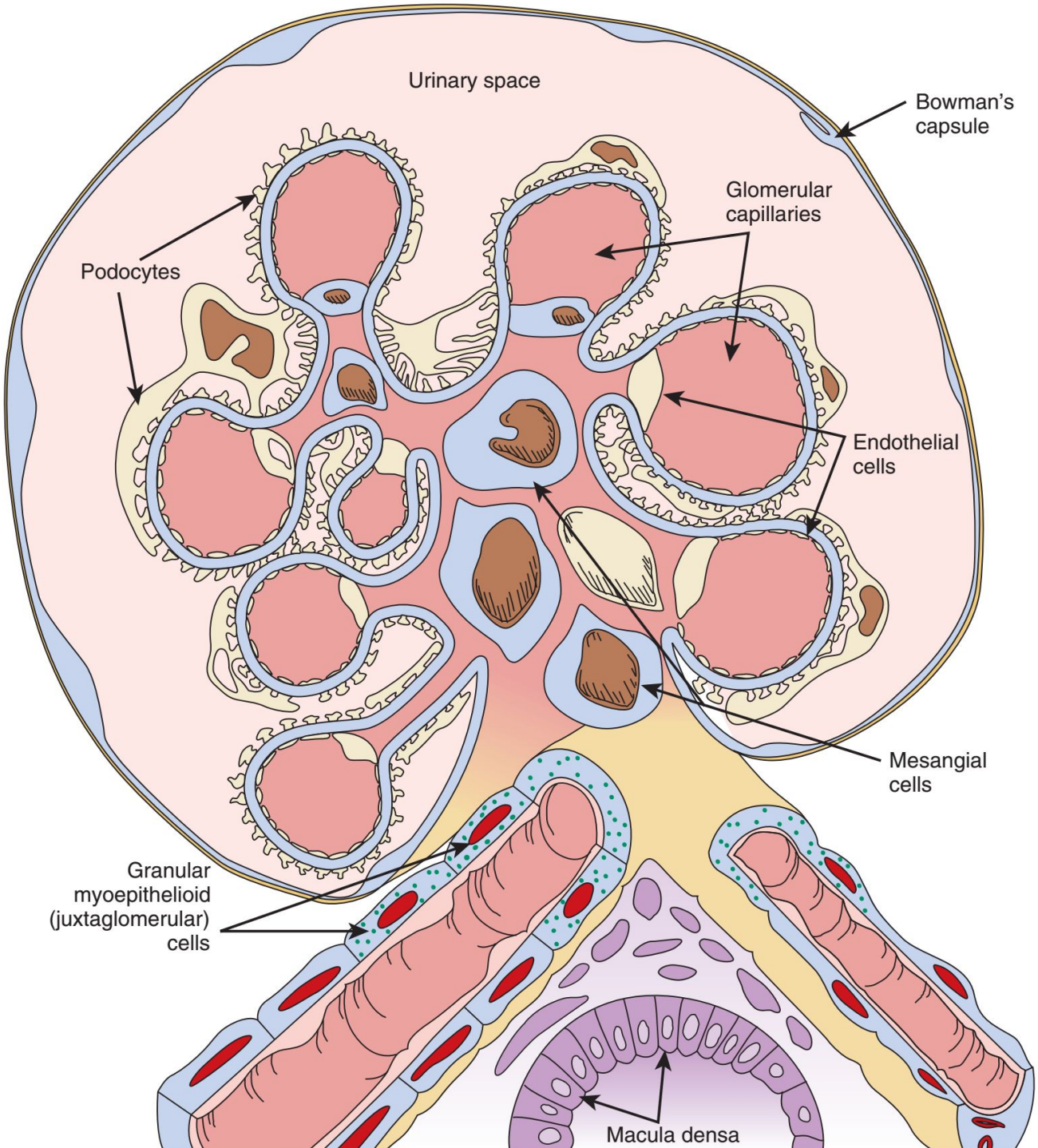
изменение Na плазмы и/или ОЦК

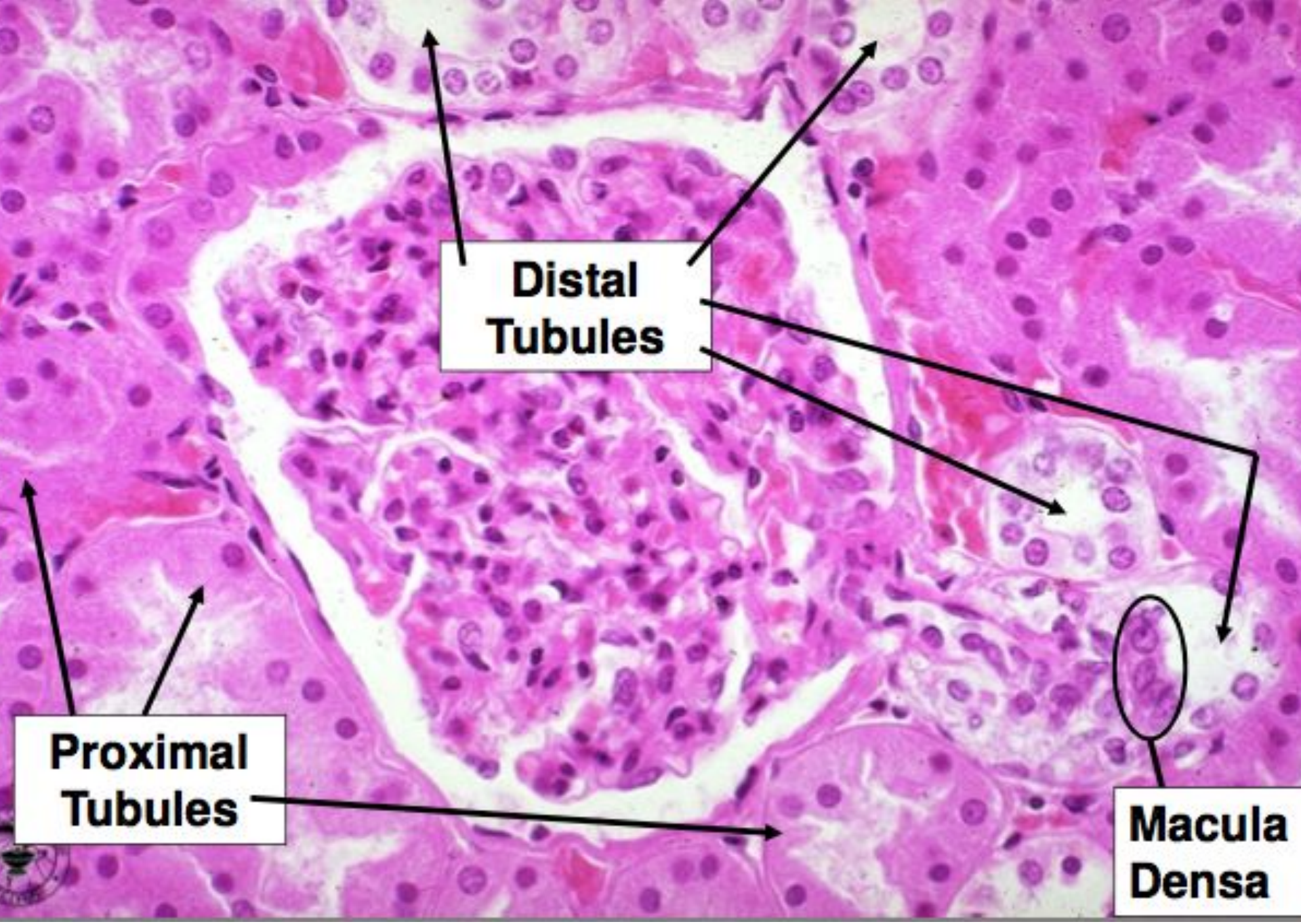
Ауторегуляция почечного кровотока

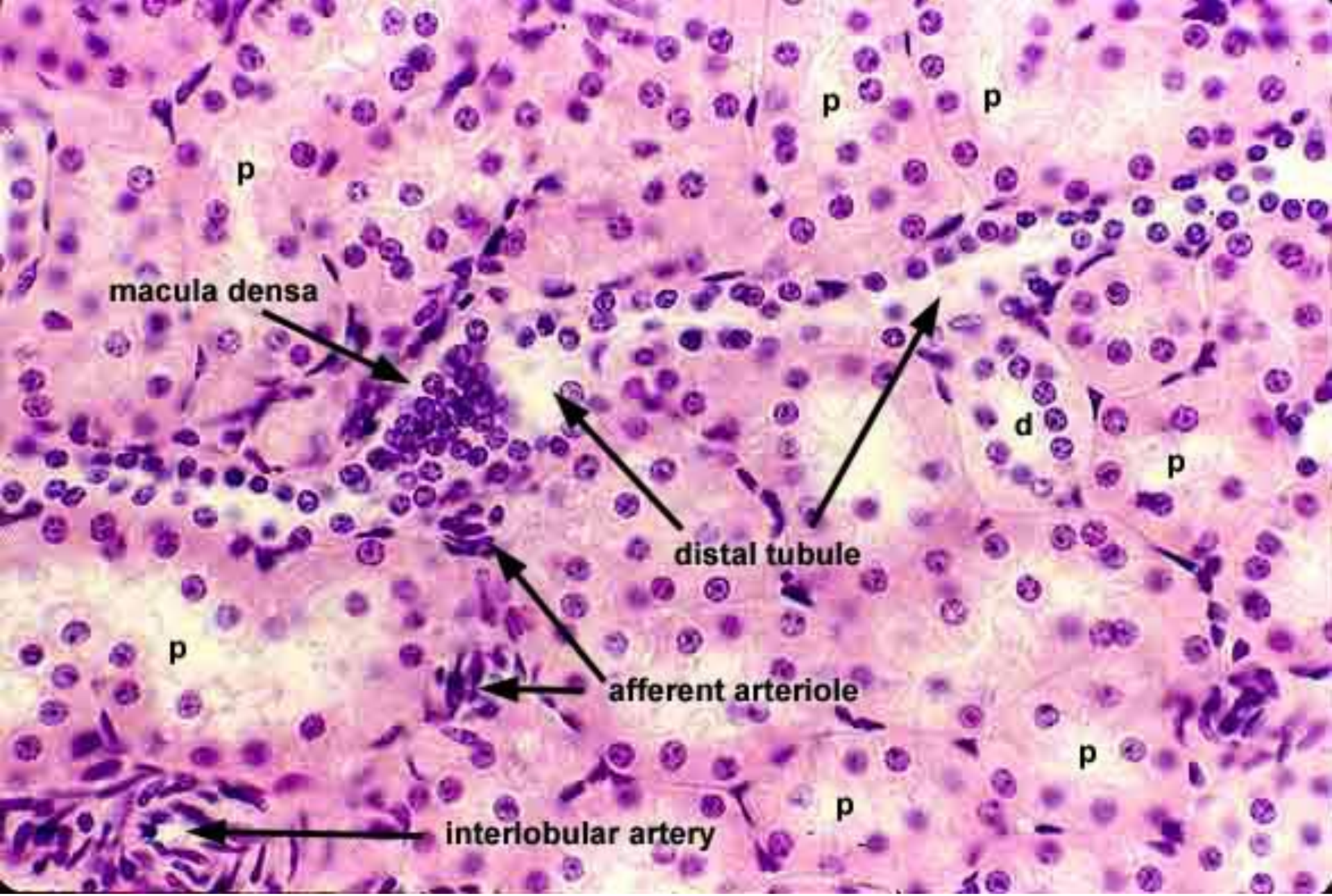


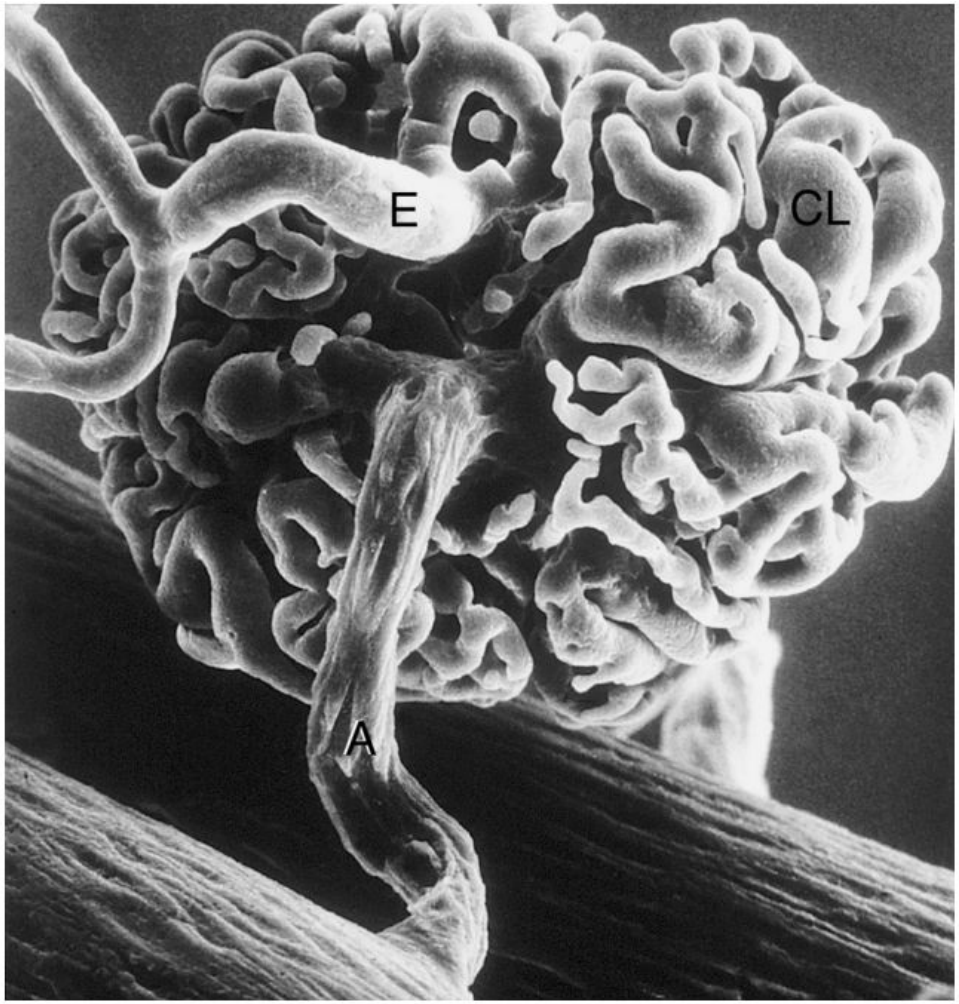


A — Почечное тельце B — Проксимальный каналец C — Дистальный извитой каналец D — Юкстагломерулярный аппарат 1. Базальная мембрана 2. Капсула Шумлянского-Боумена — париетальная пластинка 3. Капсула Шумлянского-Боумена — висцеральная пластинка 3a. Подии (ножки) подоцита 3b. Подоцит 4. Пространство Шумлянского-Боумена 5a. Мезангий — Интрагломерулярные клетки 5b. Мезангий — Экстрагломерулярные клетки 6. Гранулярные (юкстагломерулярные) клетки 7. Плотное пятно 8. Миоцит (гладкая мускулатура) 9. Приносящая артериола 10. Клубочковые капилляры 11. Выносящая артериола


Urinary space
Bowman's capsule
Glomerular capillaries
Podocytes
Endothelial cells
Mesangial cells
Granular myoepithelioid (juxtaglomerular) cells
Macula densa


Distal
Tubules
Proximal
Tubules
Macula
Densa


p
p
p
macula densa
d
p
distal tubule
p
afferent arteriole
p
p
interlobular artery



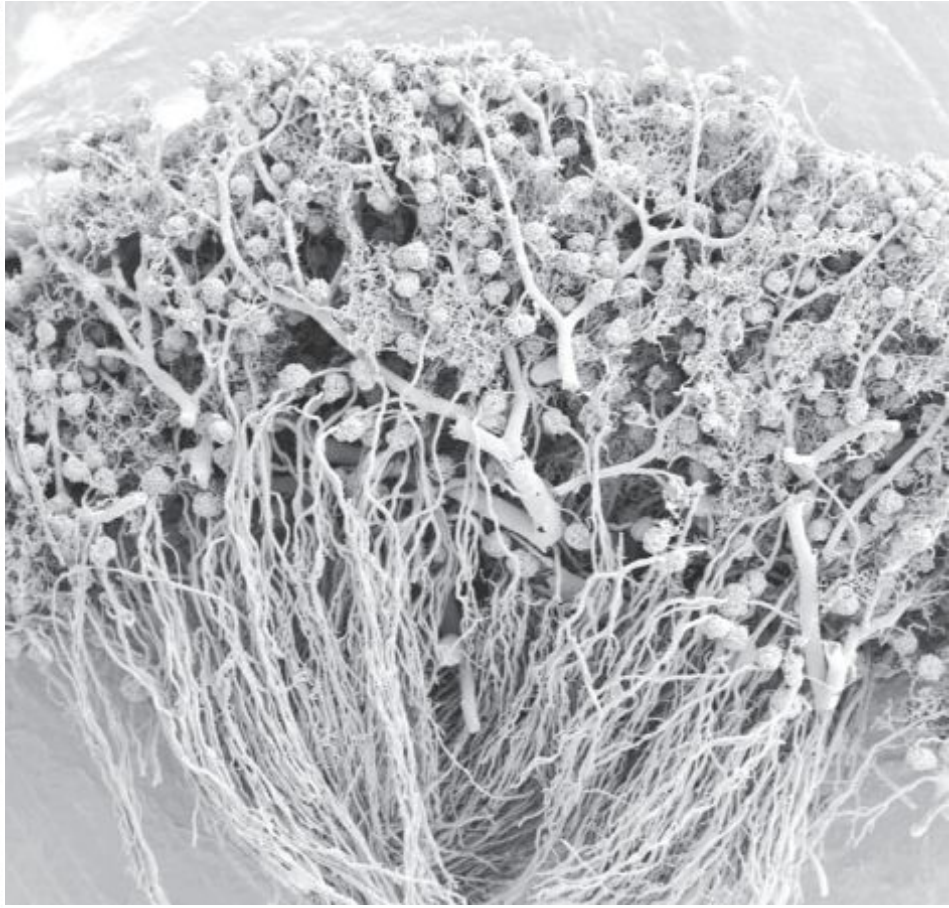
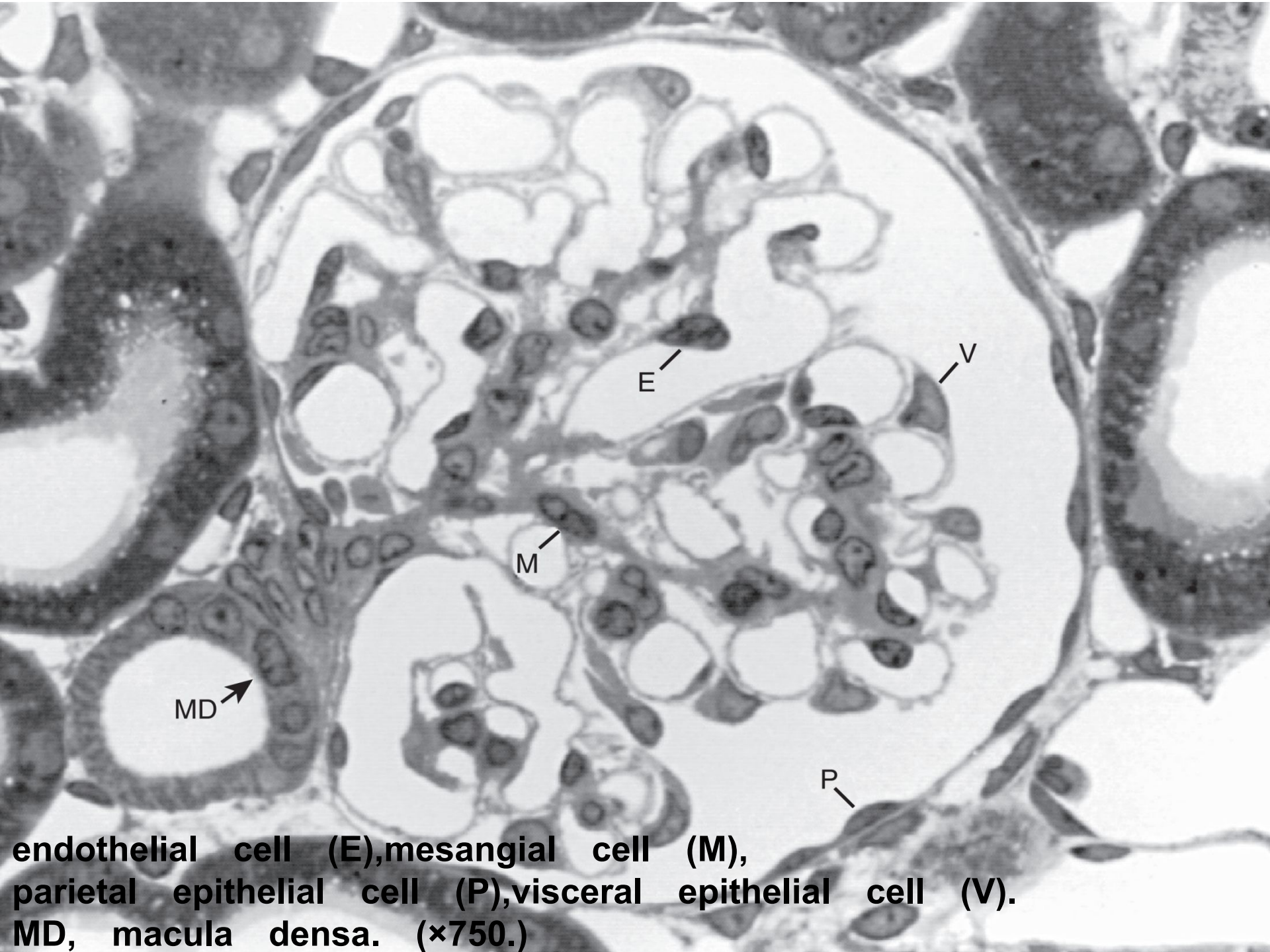
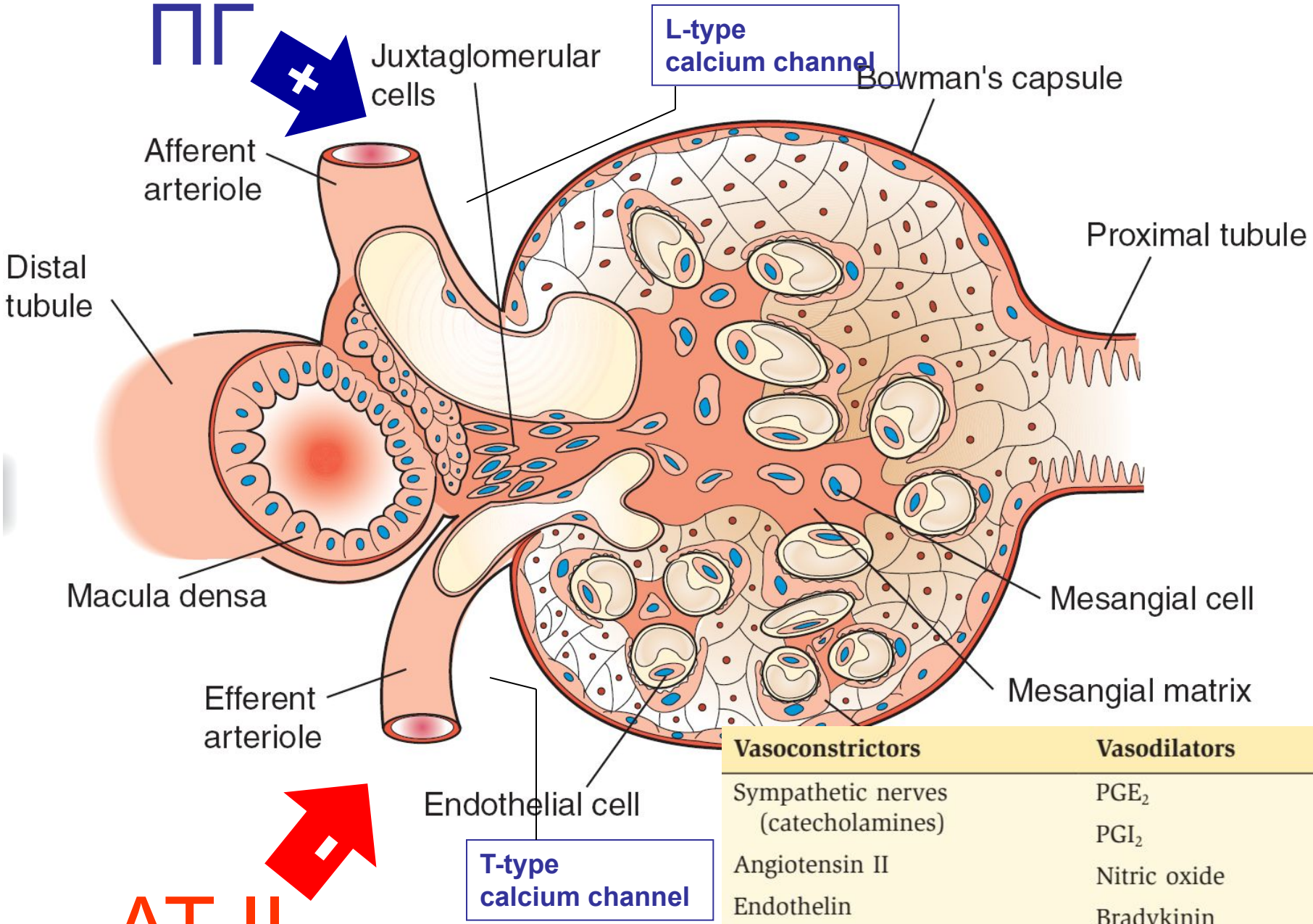


Figure 3.12 Scanning electron micrograph of a cast of a glomerulus showing the capillary loops (CL) and adjacent renal vessels. The afferent arteriole (A) is shown branching from an interlobular artery. The efferent arteriole (E) branches to form the peritubular capillary plexus *(upper left)*. (×300.) (Courtesy Waykin Nopanitaya, PhD.)



endothelial cell (E),mesangial cell (M), parietal epithelial cell (P),visceral epithelial cell (V). MD, macula densa. (×750.)



Vasoconstrictors	Vasodilators
Sympathetic nerves (catecholamines)	PGE_2
Angiotensin II	PGI_2
Endothelin	Nitric oxide
	Bradykinin
	Dopamine
	Atrial natriuretic peptide

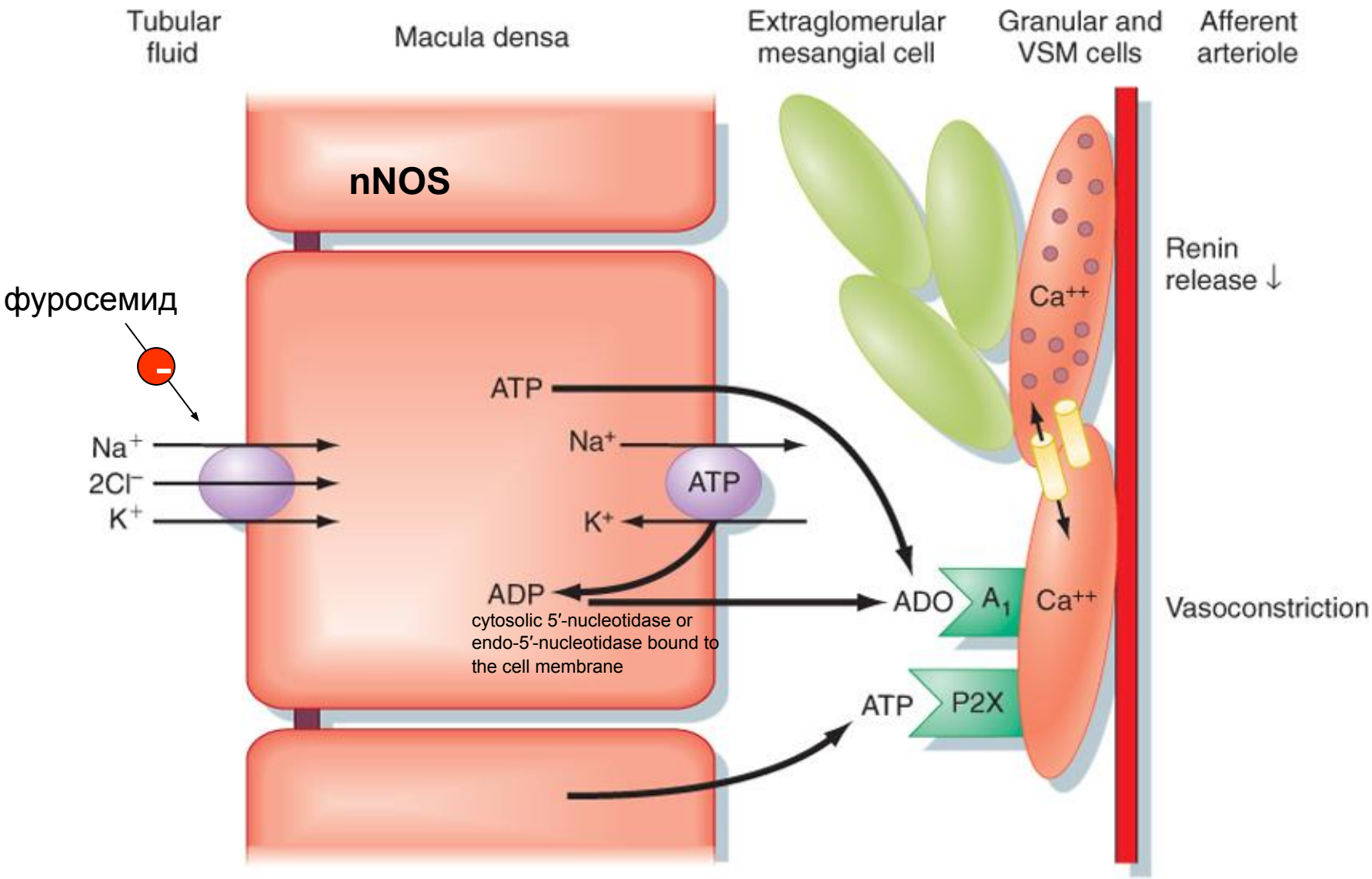
!

ПРАКТИЧЕСКИЕ МОМЕНТЫ

Нестероидные противовоспалительные препараты (НПВП) ингибируют образование простагландинов, что может препятствовать расширению приносящей артериолы и, таким образом, вести к снижению СКФ. Эти препараты не должны применяться у пациентов с нарушением функции почек, а также при гиповолемии, когда СКФ поддерживается за счет расширения приносящей артериолы.

У пациентов со **стенозом почечной артерии** высокое фильтрационное давление в клубочке поддерживается за счет повышенного тонуса выносящей артериолы. **Ингибиторы АПФ** противопоказаны таким пациентам, поскольку они препятствуют констрикции выносящих артериол (ингибируя образование ангиотензина-II), в результате чего резко снижается СКФ, что сопровождается быстрым ухудшением почечной функции.

Tubuloglomerular feedback



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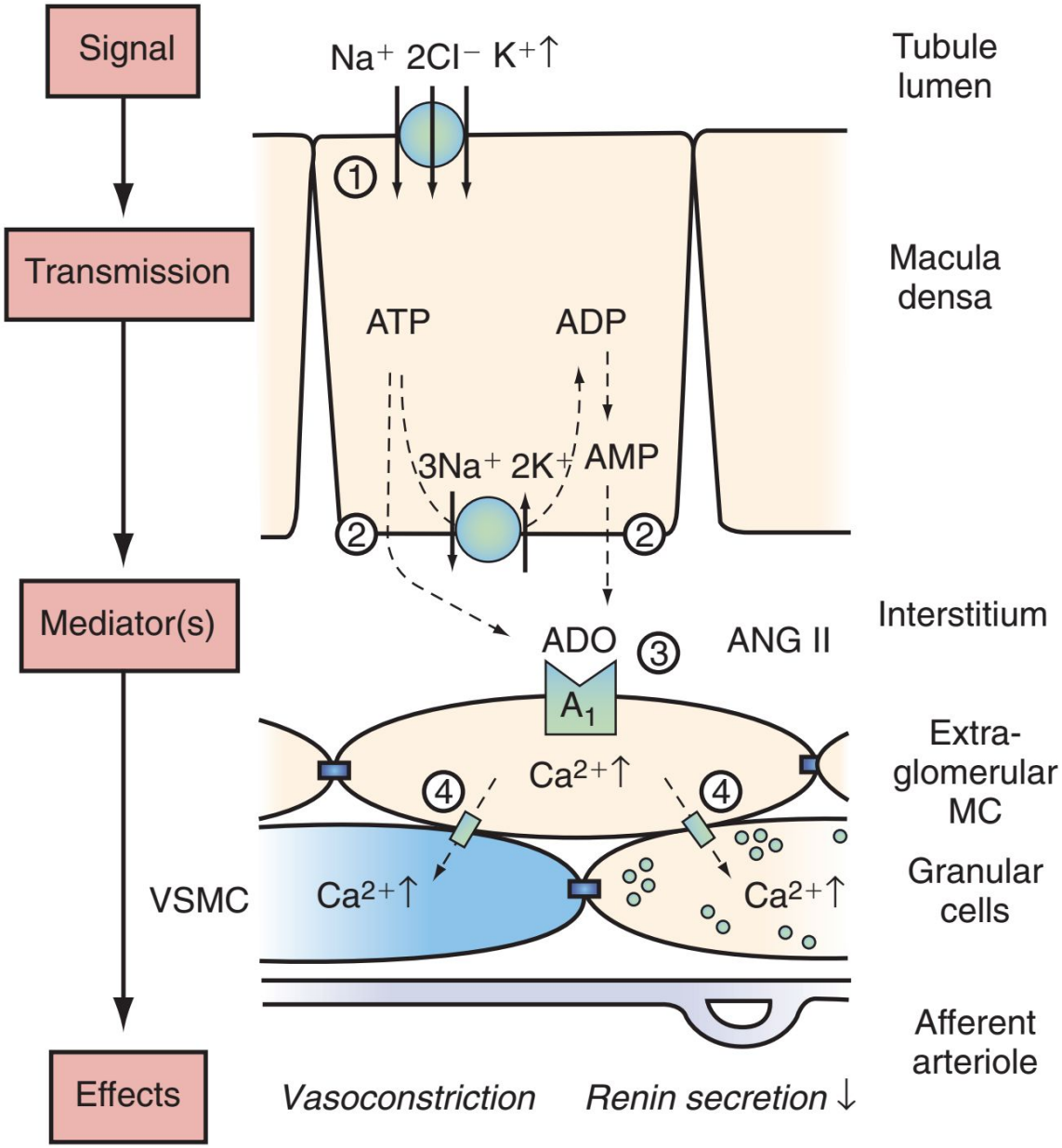


Figure 3.24 Proposed mechanism of tubuloglomerular feedback (TGF). The sequence of events *(numbers in circles)* are: (1) uptake of Na^+, Cl^-, and K^+ by the Na^+-K^+-$2Cl^-$ cotransporter on the luminal cell membrane of the macula densa cells; (2) intracellular or extracellular production of adenosine (ADO); (3) ADO activation of adenosine A_1 receptors, triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangial cells (MCs); and (4) coupling between extraglomerular MCs and granular cells (containing renin) and smooth muscle cells of the afferent arteriole (VSMCs) by gap junctions, allowing propagation of the increased $[Ca^{2+}]_i$ (intracellular calcium concentration) and resulting in afferent arteriolar vasoconstriction and inhibition of renin release. Local angiotensin II and neuronal nitric oxide synthase (nNOS) activity modulate the response. ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate. (From Vallon V: Tubuloglomerular feedback and the control of glomerular filtration rate. *News Physiol Sci* 18:169-174, 2003.)

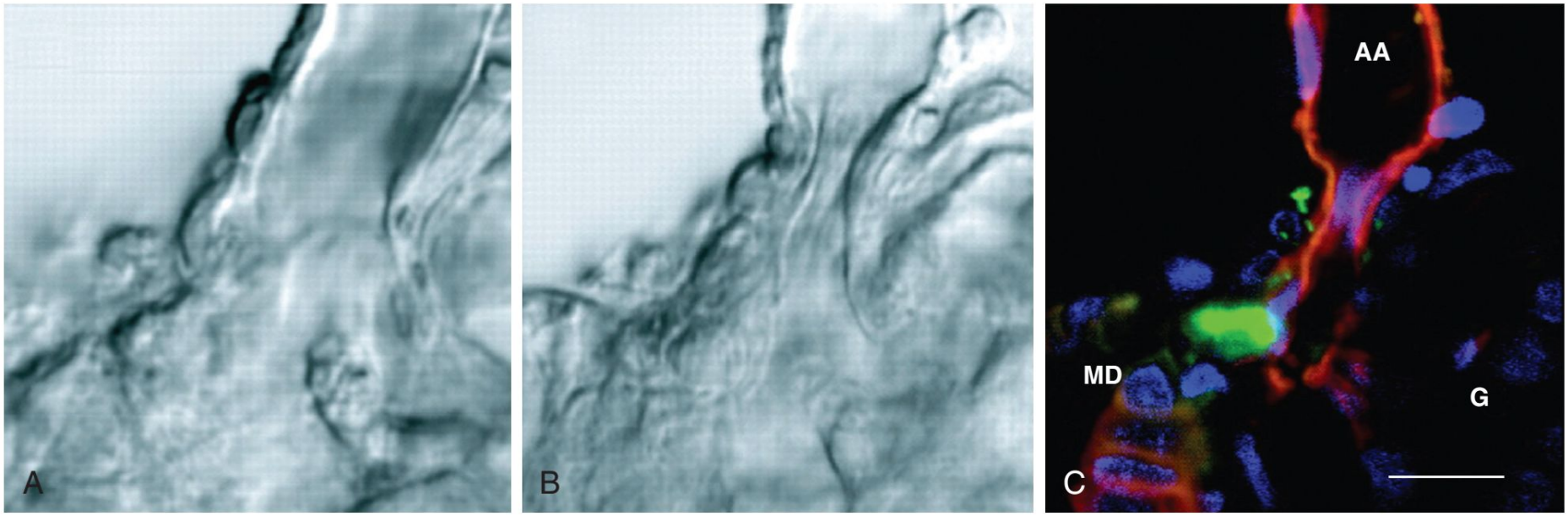
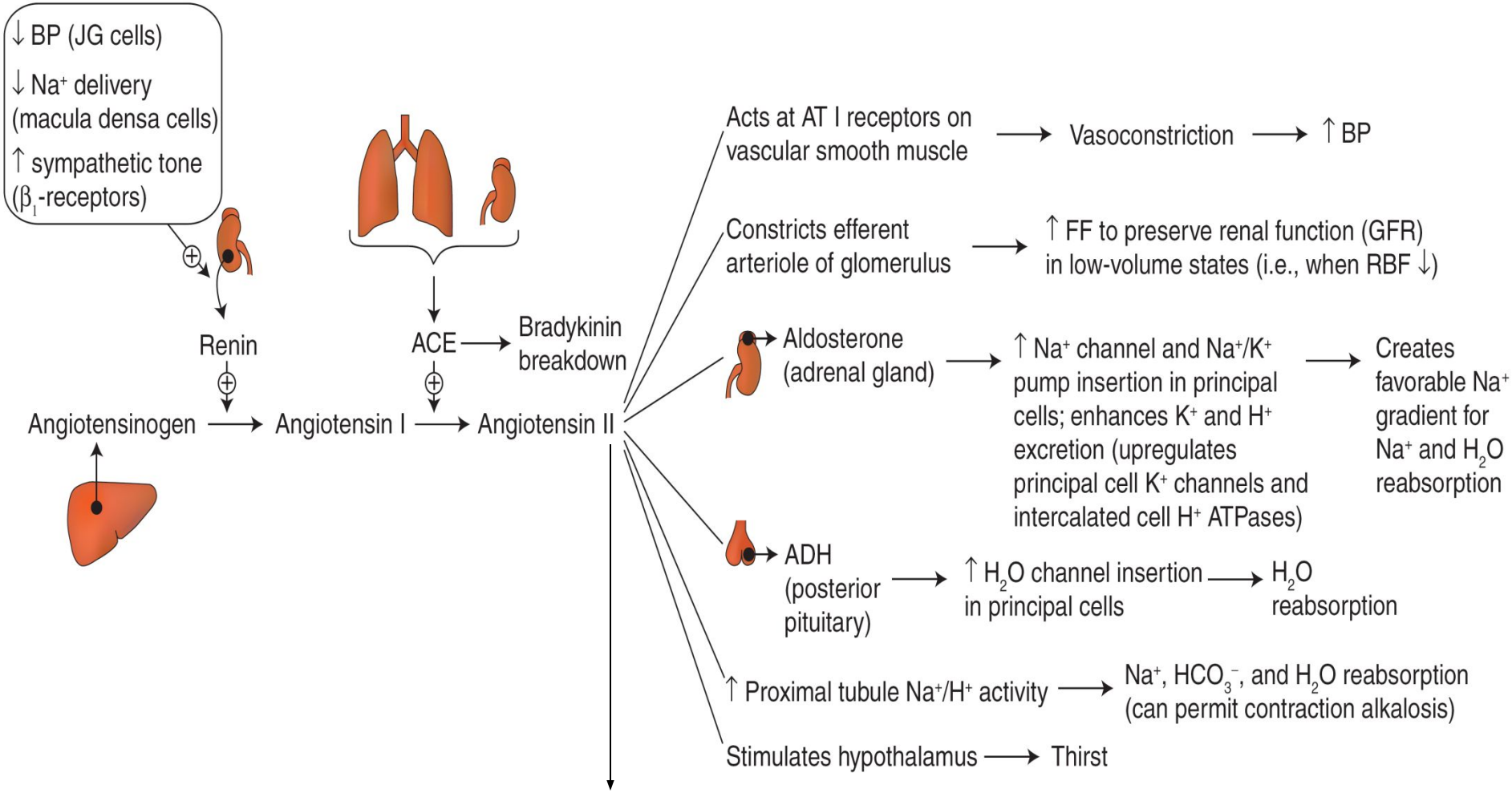
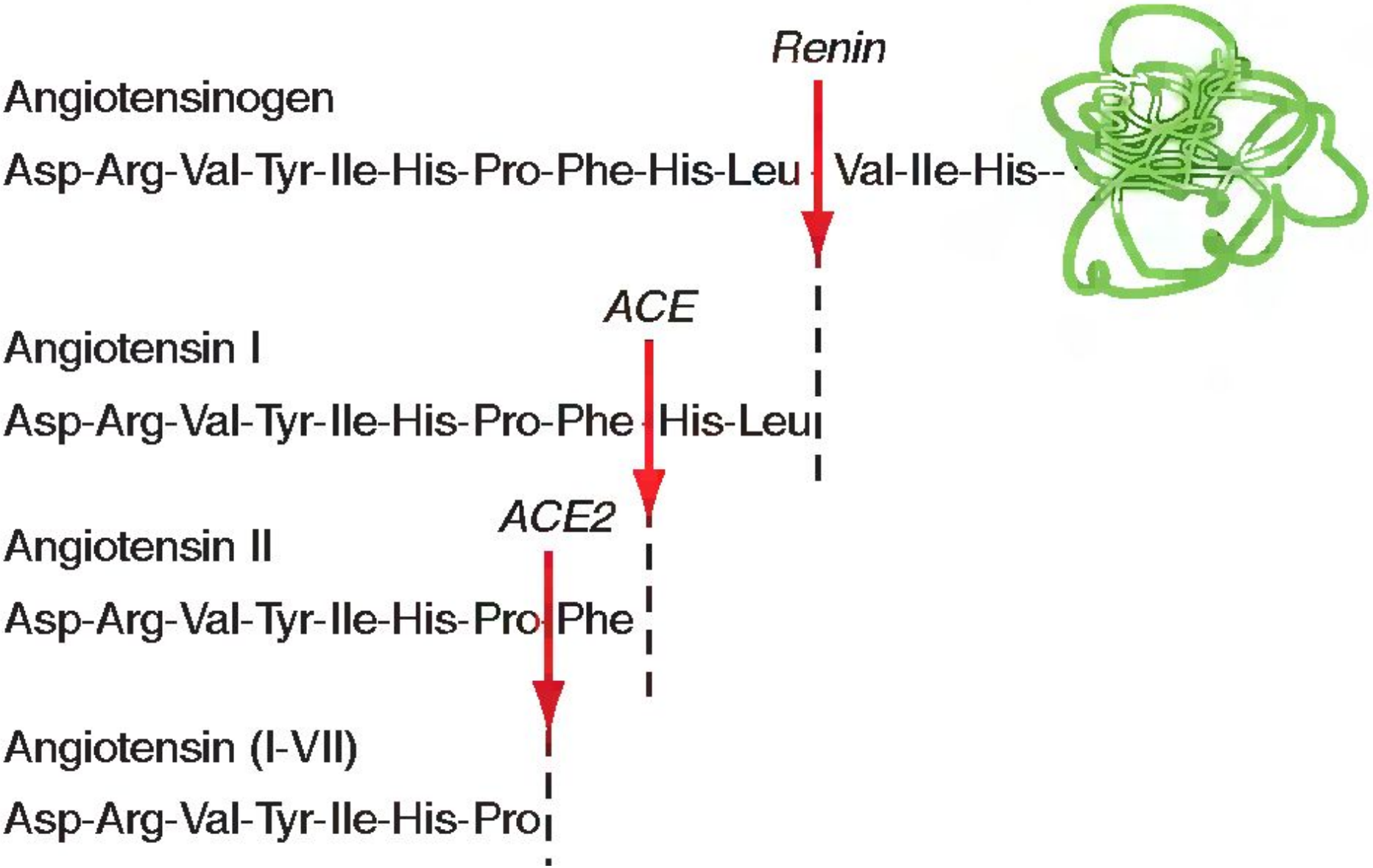


Figure 3.5 Constriction of the terminal afferent arteriole (AA), an intraglomerular precapillary sphincter, in response to elevations in distal tubular salt content. **A** and **B,** Transmitted light–differential interference contrast (DIC) images. **A,** Control, with NaCl concentration at the macula densa at 10 mM. **B,** NaCl concentration is increased to 60 mM, resulting in an almost complete closure of the AA. **C,** Fluorescence image of the same preparation as shown in **B**. Vascular endothelium and tubular epithelium are labeled with R18 *(red)*, renin granules with quinacrine *(green)*, cell nuclei with Hoechst 33342 *(blue)*. Note that renin-positive granular cells constitute the sphincter. MD, macula densa. Scale bar = 10 μm. (From Peti-Peterdi J: Multiphoton imaging of renal tissues in vitro. *Am J Physiol Renal Physiol* 288:F1079-F1083, 2005.)

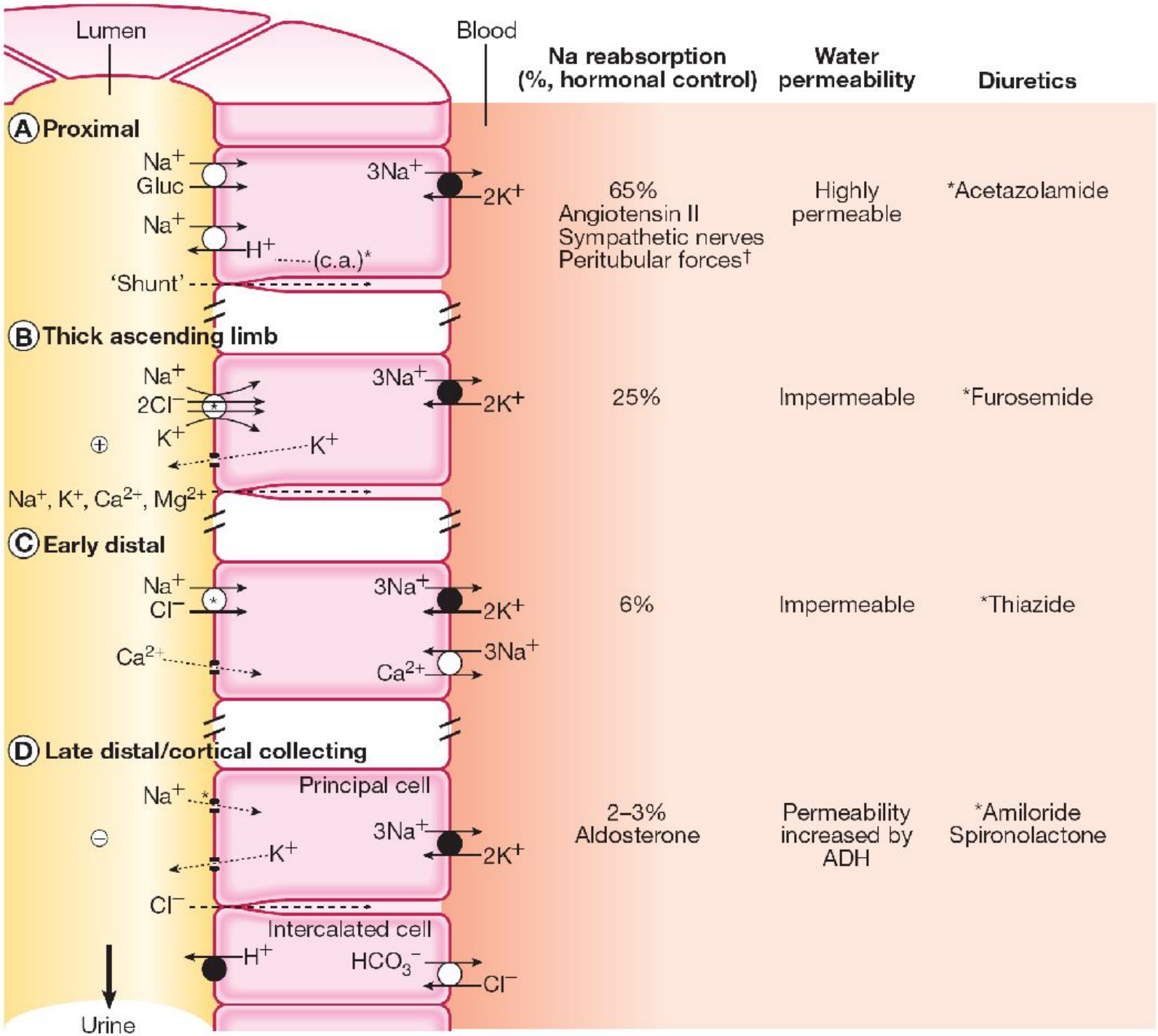
РААС



ИНСУЛИНОРЕЗИСТЕНТНОСТЬ

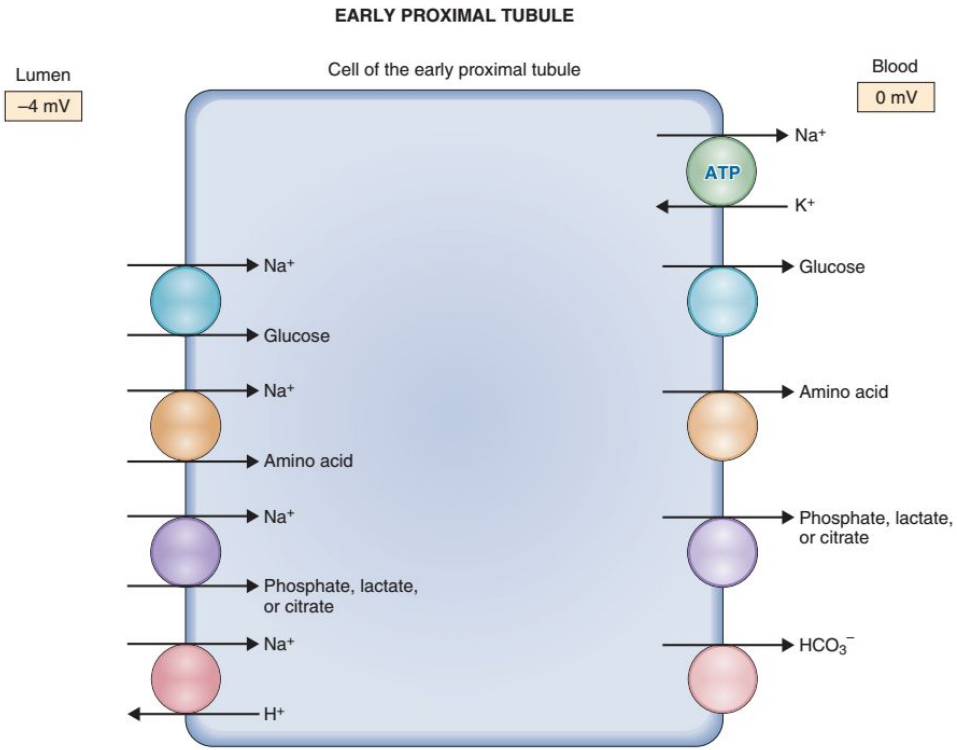

Renin
Angiotensinogen
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu Val-Ile-His--
ACE
Angiotensin I
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe His-Leu
ACE2
Angiotensin II
Asp-Arg-Val-Tyr-Ile-His-Pro Phe
Angiotensin (I-VII)
Asp-Arg-Val-Tyr-Ile-His-Pro

Реабсорбция


Lumen
Blood
Na reabsorption (%, hormonal control)
Water permeability
Diuretics
A Proximal
Na+
Gluc
Na+
H+
(c.a.)*
3Na+
2K+
65%
Angiotensin II
Sympathetic nerves
Peritubular forces†
Highly permeable
*Acetazolamide
'Shunt'
B Thick ascending limb
Na+
2Cl−
K+
K+
3Na+
2K+
25%
Impermeable
*Furosemide
Na+, K+, Ca2+, Mg2+
C Early distal
Na+
Cl−
Ca2+
3Na+
2K+
Ca2+
3Na+
6%
Impermeable
*Thiazide
D Late distal/cortical collecting
Principal cell
Na+
K+
3Na+
2K+
2–3%
Aldosterone
Permeability increased by ADH
*Amiloride
Spironolactone
Cl−
Intercalated cell
H+
HCO3−
Cl−
Urine

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

There is a **lumen-negative** potential difference across the cells of the early proximal tubule, which is created by Na^+-glucose and Na^+-amino acid cotransport. These transporters bring net positive charge into the cell and leave negative charge in the lumen. The other transporters are electroneutral (e.g., Na^+-H^+ exchange) and, therefore, do not contribute to the transepithelial potential difference.



Furthermore, this fluid has a **high Cl^- concentration**, although it may not be immediately evident why this is so. The Cl^- concentration is high because HCO_3^- has been preferentially reabsorbed in the early proximal tubule, leaving Cl^- behind in the tubular fluid. As water is reabsorbed isosmotically along with solute, the tubular fluid Cl^- concentration increases and becomes higher than the Cl^- concentration of the glomerular filtrate and of blood.

In contrast to the early proximal tubule, the late proximal tubule reabsorbs primarily NaCl (Fig. 6-21).

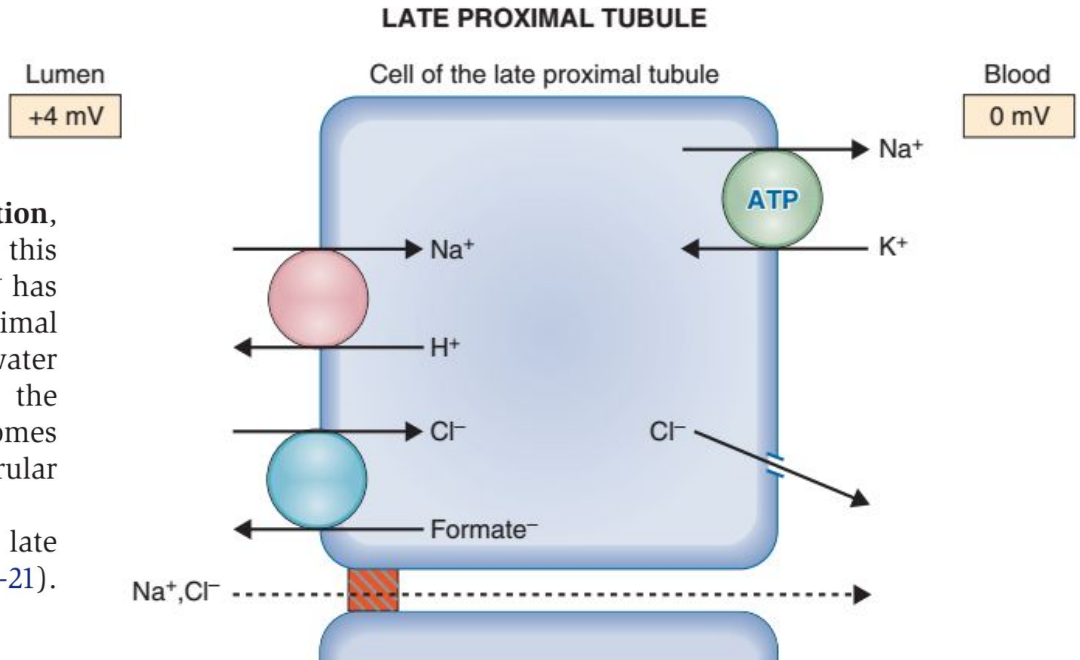


Таблица 1. Вещества, реабсорбируемые в проксимальном извитом канальце (ПИК)

Вещество	Примерный % реабсорбции в ПИК
Вода	65
Натрий	60
Калий / хлор / бикарбонат	80
Глюкоза	100
Аминокислоты не менее 7 видов транспортеров	100
Кальций	60
Фосфат	80
Мочевина	50

+ регулируется ПТГ

-

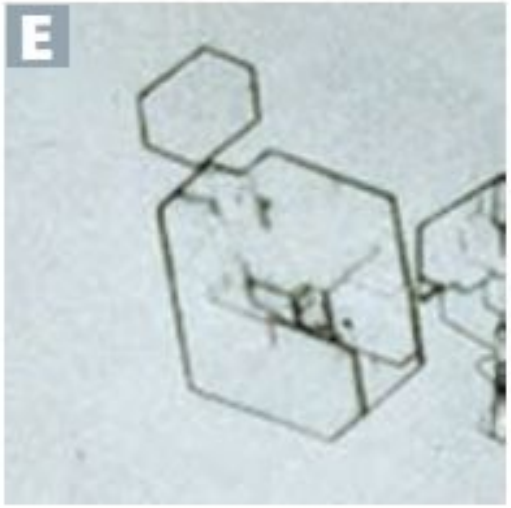
наследственный дефект всасывания цистина и 2-основных ак (аргинин, лизин, орнитин) – **цистинурия** (не путать с цистинозом), частота - 1:7000, образование камней.

наследственный дефект всасывания нейтральных ак в кишечнике и в канальцах – **болезнь Хартнупа и пеллагра-подобные симптомы**

Disease or Syndrome	Gene
Disorders Involving the Proximal Tubule	
Proximal renal tubular acidosis	Sodium bicarbonate cotransporter (*SLC4A4*, 4q21)
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (*SLC2A2*, 3q26.2)
Isolated renal glycosuria	Sodium glucose cotransporter (*SLC5A2*, 16p11.)
Cystinuria	
Type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1*, 2p16.3)
Non-type I	Amino acid transporter, light subunit (*SLC7A9*, 19q13.1)
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7*, 4q11.2)
Hartnup disorder	Neutral amino acid transporter (*SLC6A19*, 5p15.33)
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (*SLC34A3*, 9q34)
Renal hypouricemia	
Type 1	Urate-anion exchanger (*SLC22A12*, 11q13)
Type 2	Urate transporter, GLUT9 (*SLC2A9*, 4p16.1)
Dent disease	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)

Cystine (1%)	↓ pH	Radiopaque

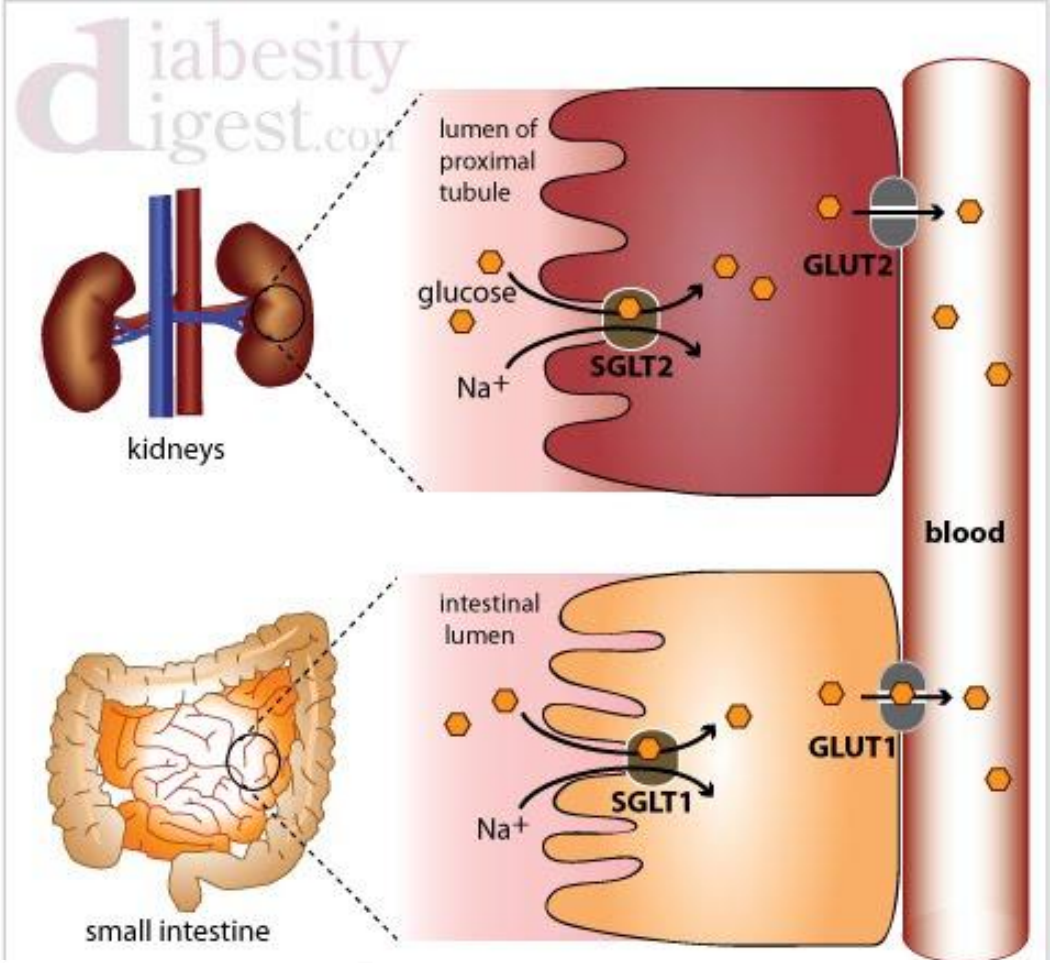
Hexagonal E



Mostly seen in children, 2° to cystinuria. Can form staghorn calculi. Sodium nitroprusside test ⊕.

Treatment: alkalinization of urine and hydration.

Disorders Involving the Loop of Henle		
Bartter syndrome		
Type 1	Sodium, potassium chloride cotransporter (*SLC12A1*, 15q21.1)	241200
Type 2	Potassium channel, ROMK (*KCNJ1*, 11q24)	601678
Type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.33))	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman syndrome	Sodium chloride cotransporter (*SLC12A3*, 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B*, *SCNN1G*, 16p12.1)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, a, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B*, *SCNN1G*, 16pp12.1)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (*AQP2*, 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (*SLC4A1*, 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (*SLC4A1*, 17q21.31)	602722
with neural deafness	Proton ATPase, β1 subunit (*ATP6V1B1*, 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (*ATP6V0A4*, 7q34)	602722

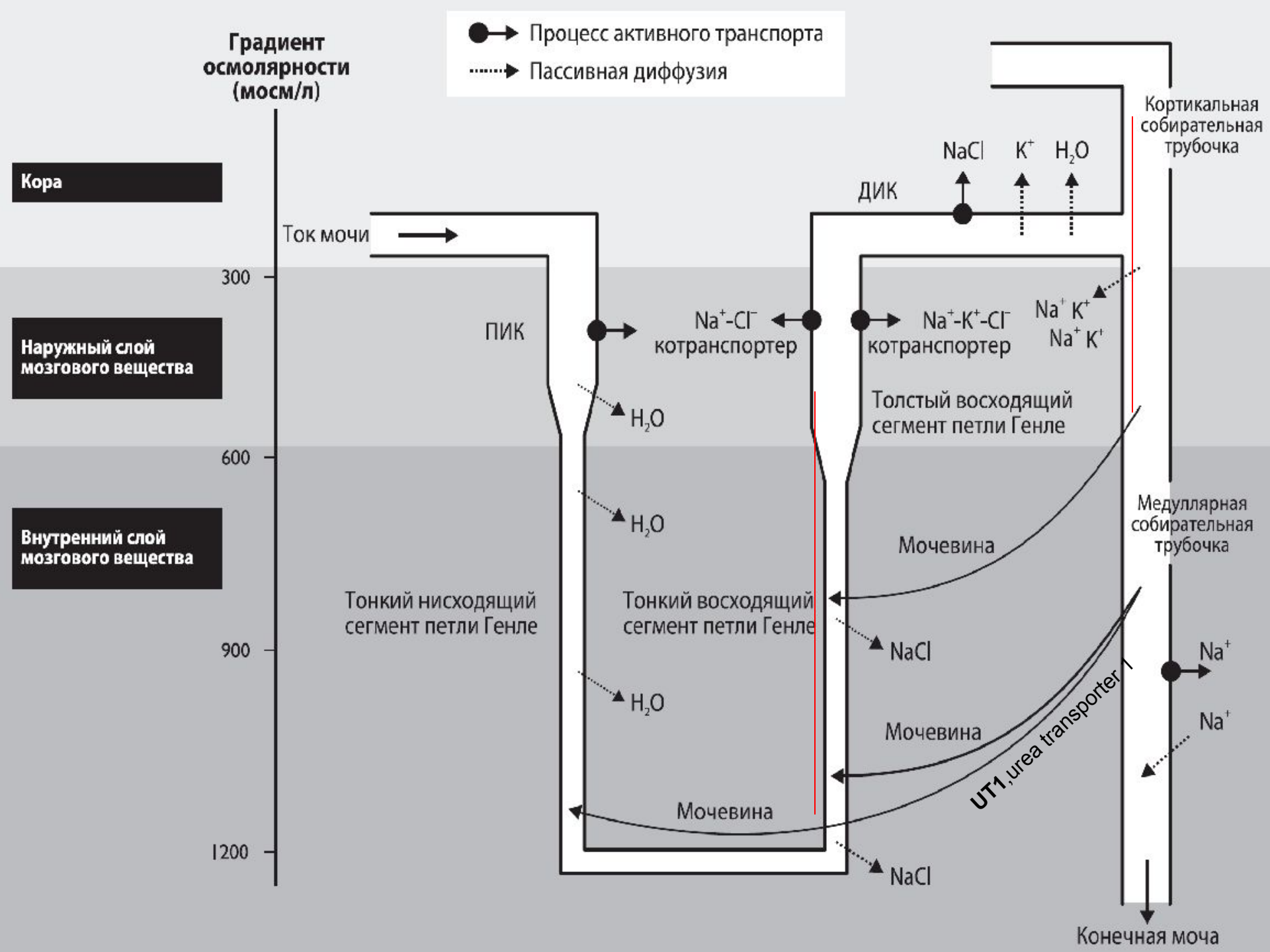


Type of SGLT	Major sites	Functions : Transport of
SGLT 1	Small intestine, Heart, Trachea, Kidney(S3)	Na, Glucose Galactose
SGLT 2	Kidney(S1, S2)	Na, Glucose
SGLT 3	Small intestine, Uterus Lung, Thyroid, Testis	Na
SGLT 4	Small intestine, Kidney, Liver, Stomach, Lung	Glucose, Mannose
SGLT 5	Kidney	Unknown
SGLT 6	Spinal cord, Kidney, Brain, Small intestine	Myoinositol, Glucose

Эмпаглифлозин
канаглифлозин
дапаглифлозин
ипраглифлозин и др.

Противоточная система

- **Противоточный множитель** (петля Генле), обеспечивающий увеличение осмотического градиента по мере продвижения к нижней части петли.
- **Противоточный обменник** (прямые сосуды), поддерживающий осмотический градиент. Выход воды из собирательных трубочек регулируется АДГ. Иначе осмотический градиент постепенно бы уменьшался из-за реабсорбции воды за счет осмоса.


Процесс активного транспорта
Пассивная диффузия
Градиент осмолярности (мосм/л)
Кора
Наружный слой мозгового вещества
Внутренний слой мозгового вещества
300
600
900
1200
Ток мочи
ПИК
ДИК
NaCl
K+
H2O
Кортикальная собирательная трубочка
Na+-Cl- котранспортер
Na+-K+-Cl- котранспортер
Na+ K+
Na+ K+
H2O
H2O
H2O
Толстый восходящий сегмент петли Генле
Мочевина
Медуллярная собирательная трубочка
Тонкий нисходящий сегмент петли Генле
Тонкий восходящий сегмент петли Генле
NaCl
Na+
Na+
Мочевина
UT1,urea transporter 1
Мочевина
NaCl
Конечная моча

Осмолярность мочи –

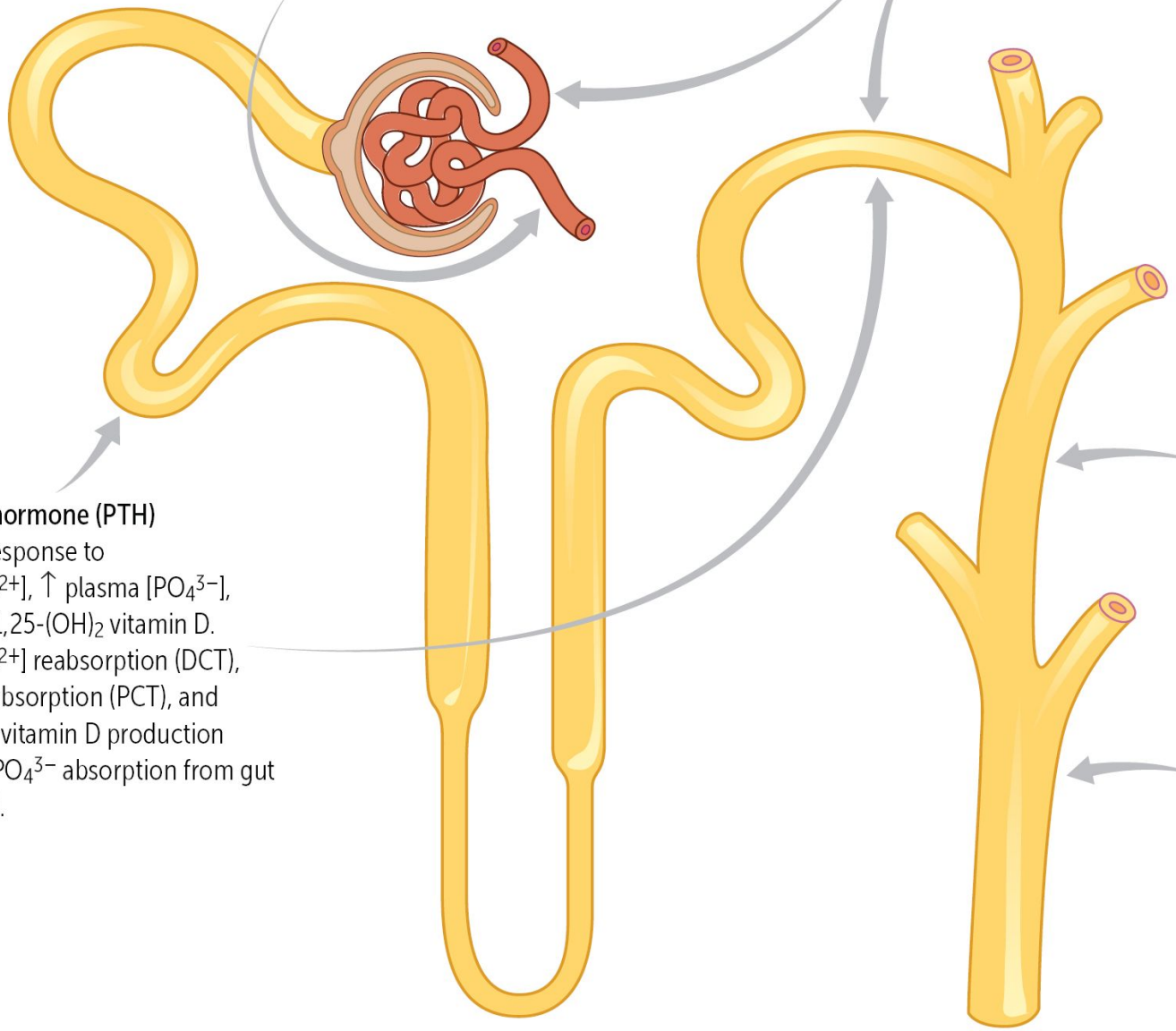
300 мОсм/л

Относительная плотность мочи –

1010 - 1030

Angiotensin II (AT II)
Synthesized in response to ↓ BP. Causes efferent arteriole constriction →↑ GFR and ↑ FF but with compensatory Na^+ reabsorption in proximal and distal nephron. Net effect: preservation of renal function in low-volume state (↑ FF) with simultaneous Na^+ reabsorption (both proximal and distal) to maintain circulating volume.

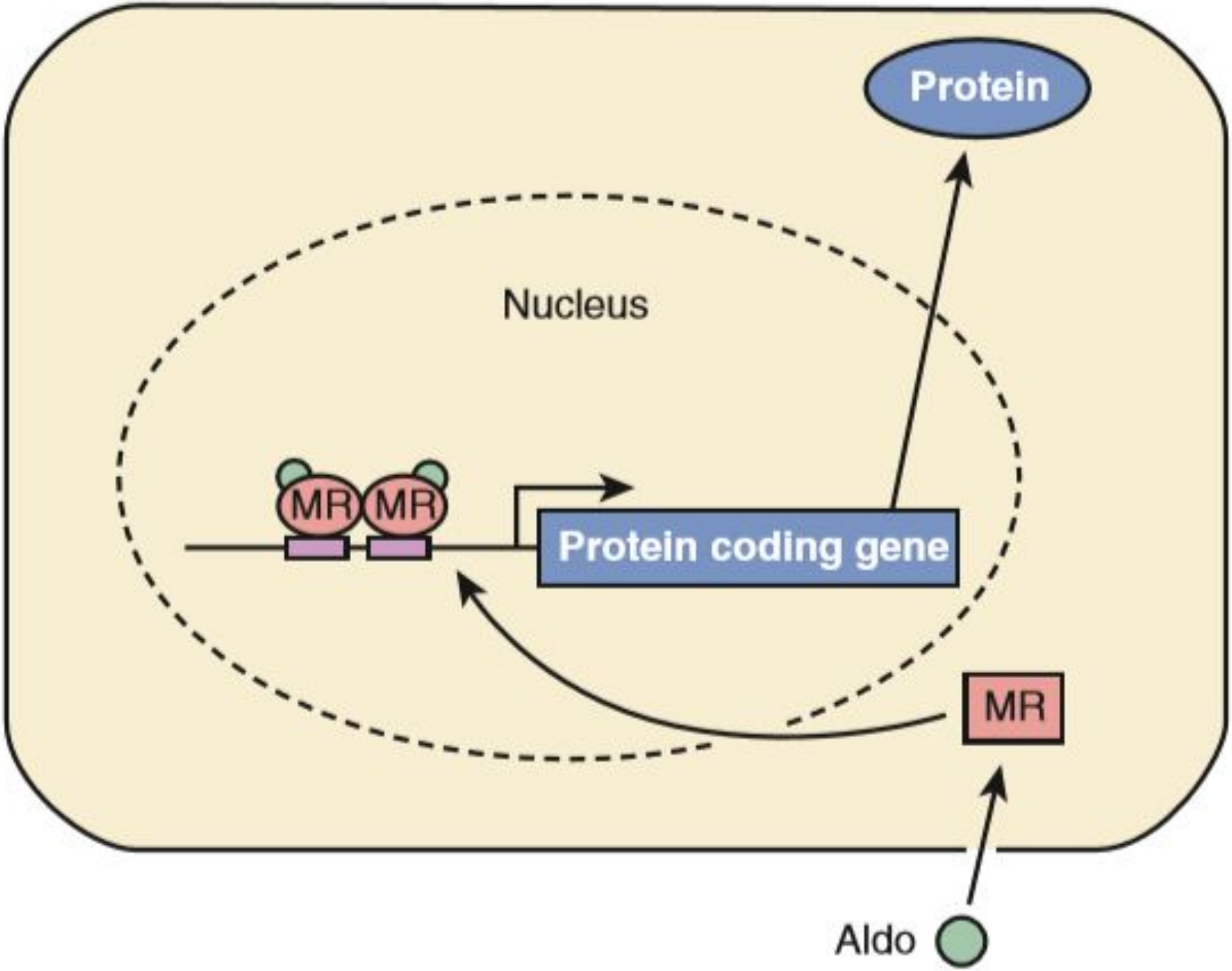
Atrial natriuretic peptide (ANP)
Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ Na^+ filtration **with no compensatory Na^+ reabsorption** in distal nephron. Net effect: Na^+ loss and volume loss.

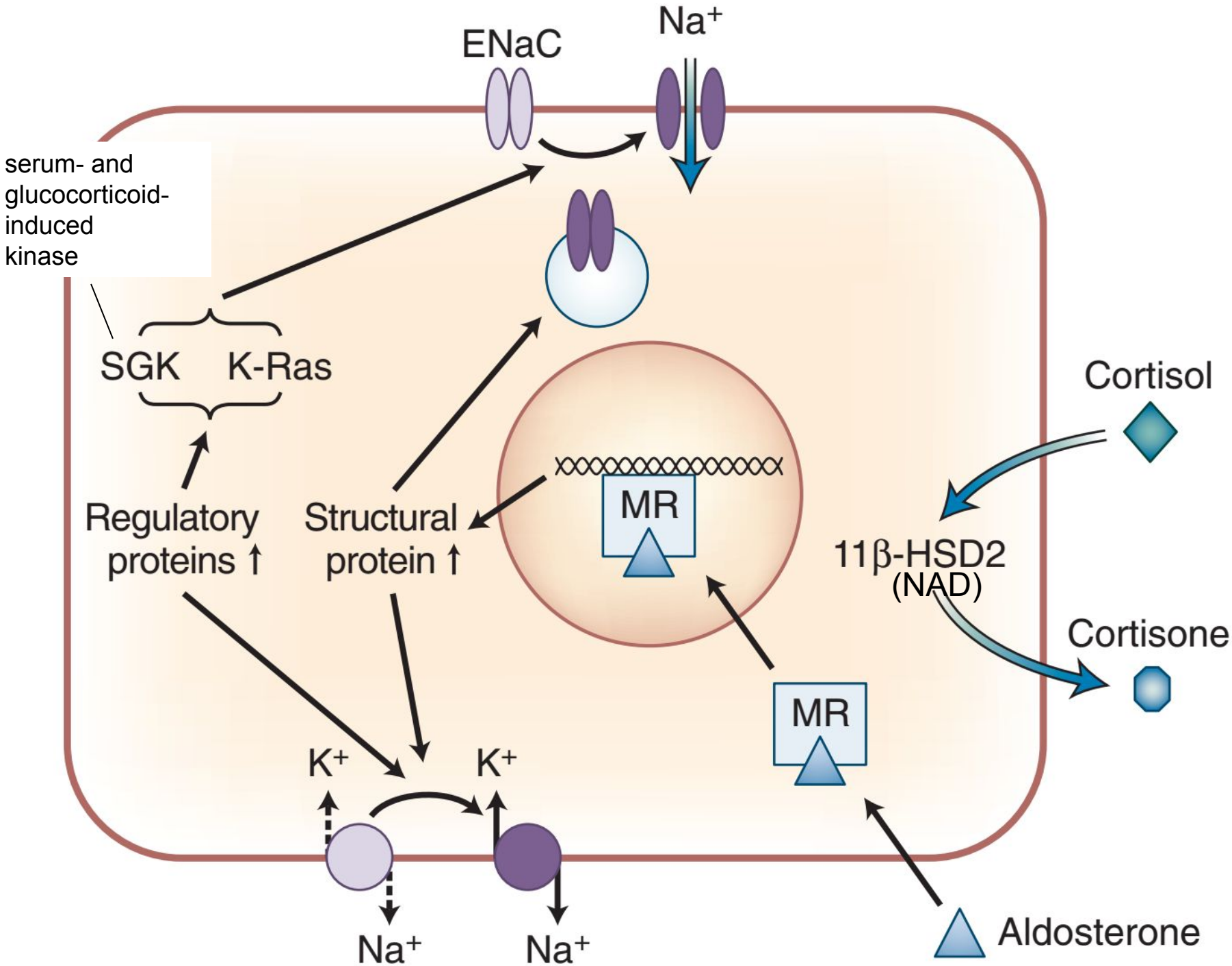


Parathyroid hormone (PTH)
Secreted in response to ↓ plasma [Ca^{2+}], ↑ plasma [PO_4^{3-}], or ↓ plasma 1,25-$(OH)_2$ vitamin D. Causes ↑ [Ca^{2+}] reabsorption (DCT), ↓ [PO_4^{3-}] reabsorption (PCT), and ↑ 1,25-$(OH)_2$ vitamin D production (↑ Ca^{2+} and PO_4^{3-} absorption from gut via vitamin D).

Aldosterone
Secreted in response to ↓ blood volume (via AT II) and ↑ plasma [K^+]; causes ↑ Na^+ reabsorption, ↑ K^+ secretion, ↑ H^+ secretion.

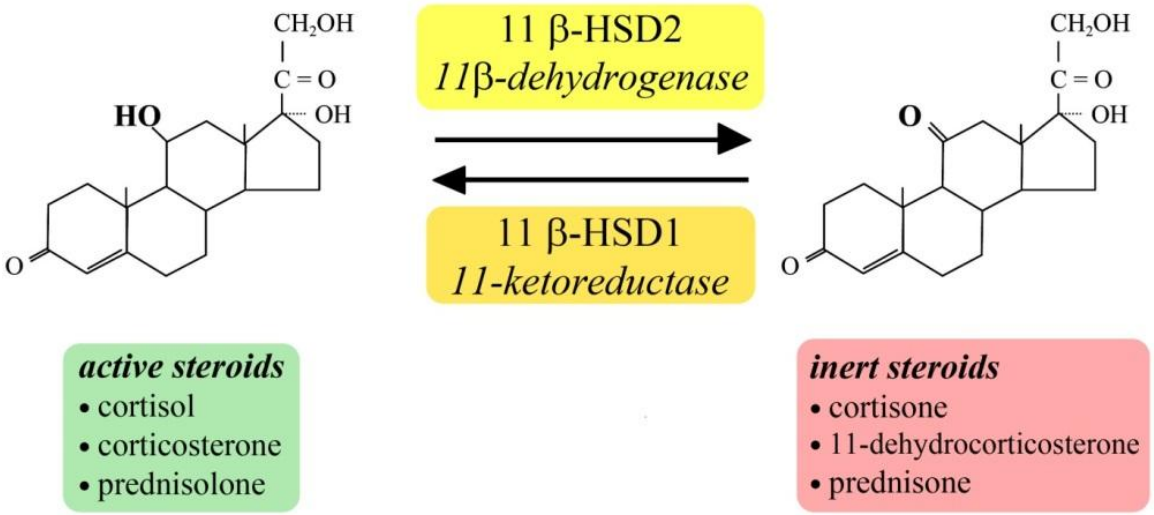
ADH (vasopressin)
Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of water channels and ↑ H_2O reabsorption.


Protein
Nucleus
MR
MR
Protein coding gene
MR
Aldo

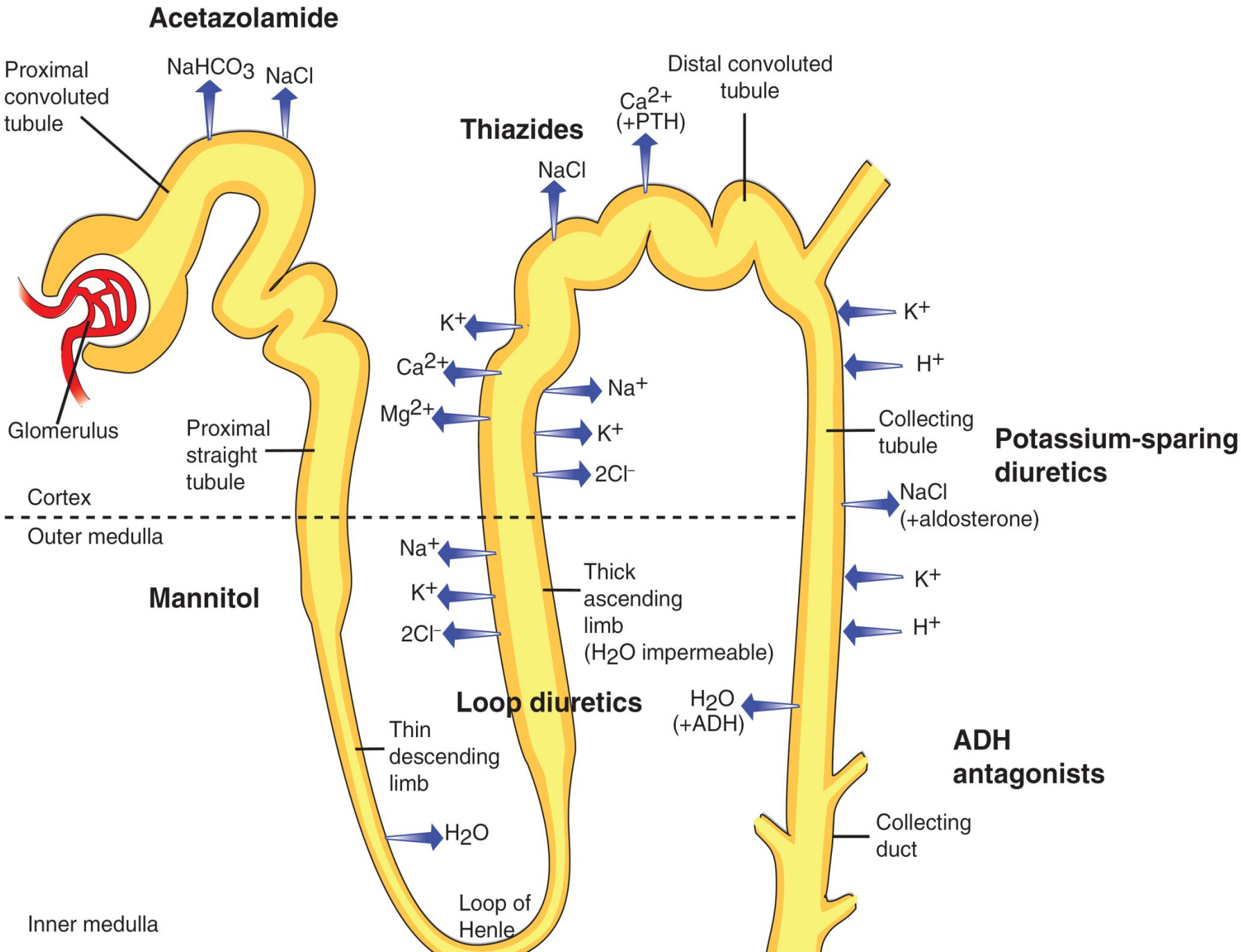

ENaC
Na+
serum- and glucocorticoid-induced kinase
SGK
K-Ras
Regulatory proteins ↑
Structural protein ↑
MR
Cortisol
11β-HSD2
(NAD)
Cortisone
MR
K+
K+
Na+
Na+
Aldosterone

- **Синдром кажущегося избытка минералокортикоидов (SAME)** мутация гена HSD11B2 (гипертензия и гипокалиемия)

- **Лакрица** (глицирризиновая кислота) – ингибитор 11β-гидроксистероид дегидрогеназы



Diuretics: site of action



РОЛЬ АНТИДИУРЕТИЧЕСКОГО ГОРМОНА И РЕНИН-АНГИОТЕНЗИНОВОЙ СИСТЕМЫ В РАЗЛИЧНЫХ ГЕМОДИНАМИЧЕСКИХ РЕАКЦИЯХ:

1000 мл 0,9% NaCl внутривенно — реакция на небольшое увеличение внутрисосудистого объема

Это объемная нагрузка изотоническим раствором. Первоначально внутрисосудистый объем увеличивается на 1000 мл, но происходит быстрое перераспределение жидкости во внеклеточных секторах и во внутрисосудистом русле остается около 250 мл, остальной объем наполняет интерстициальное пространство.

- Увеличение объема крови стимулирует кардиопульмональные рецепторы растяжения (правое предсердие).
- Задняя доля гипофиза — снижается секреция АДГ.
- Подавление жажды и активация диуреза.

1000 мл крови внутривенно — реакция на значимое увеличение внутрисосудистого объема

Весь объем остается во внутрисосудистом пространстве.

Быстрая реакция:

- Стимуляция барорецепторов артериального русла (каротидный и аортальный синусы) через языкоглоточный и блуждающий нервы.
- Рефлекторное снижение сердечного выброса и сосудистого тонуса.

Медленная реакция:

- Подавление ренин-ангиотензиновой системы.
- Снижение секреции альдостерона.

1000 мл 5% глюкозы (внутривенно) или воды (per os) — реакция на снижение осмолярности

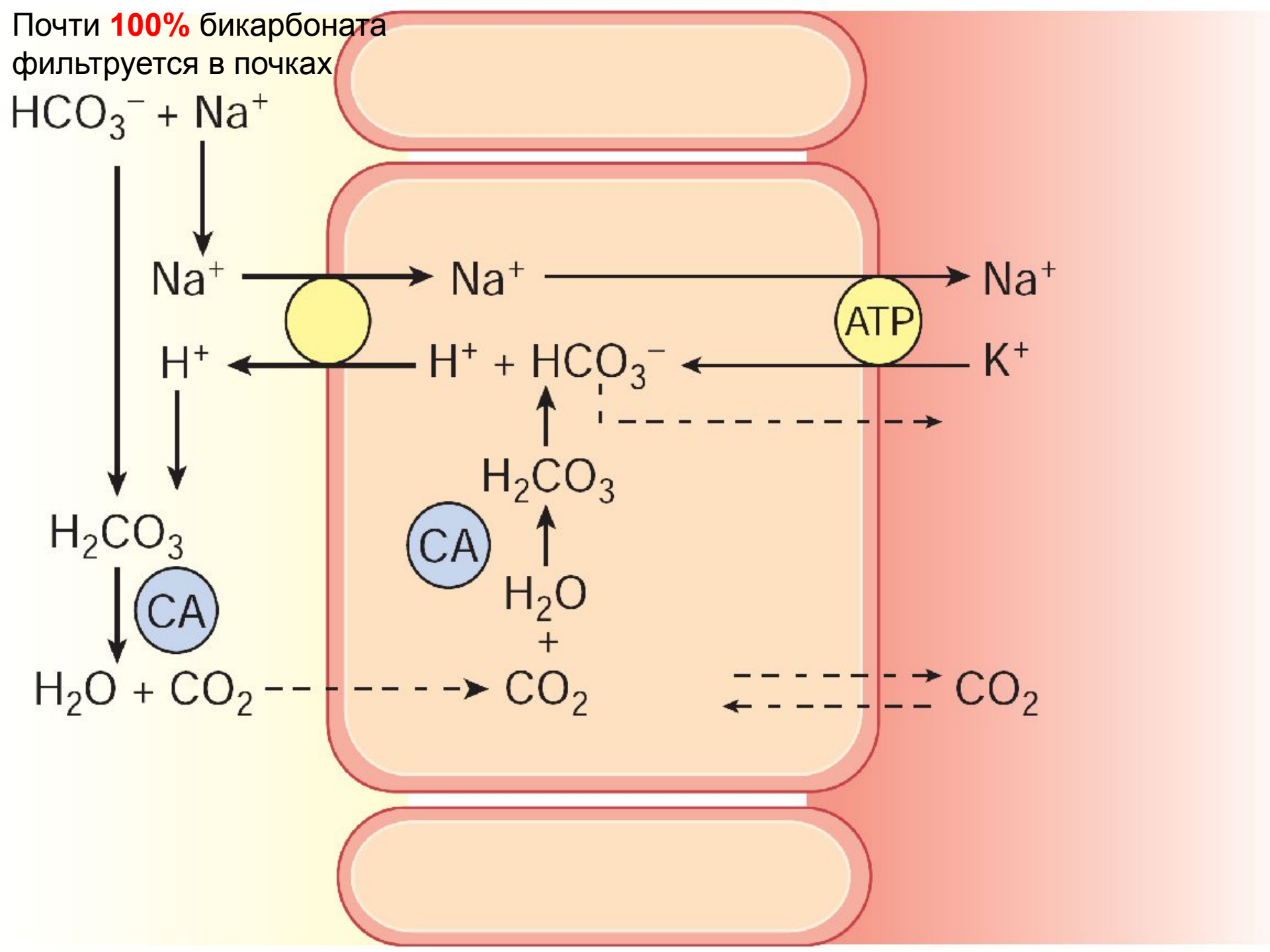
Объемная нагрузка небольшая, так как вода распределяется во всех жидкостных секторах организма и во внутрисосудистом русле остается одна двенадцатая часть (83 мл). Прием воды вызывает схожий эффект, так как она быстро абсорбируется из желудка. При этом происходит разведение плазмы и снижение осмолярности.

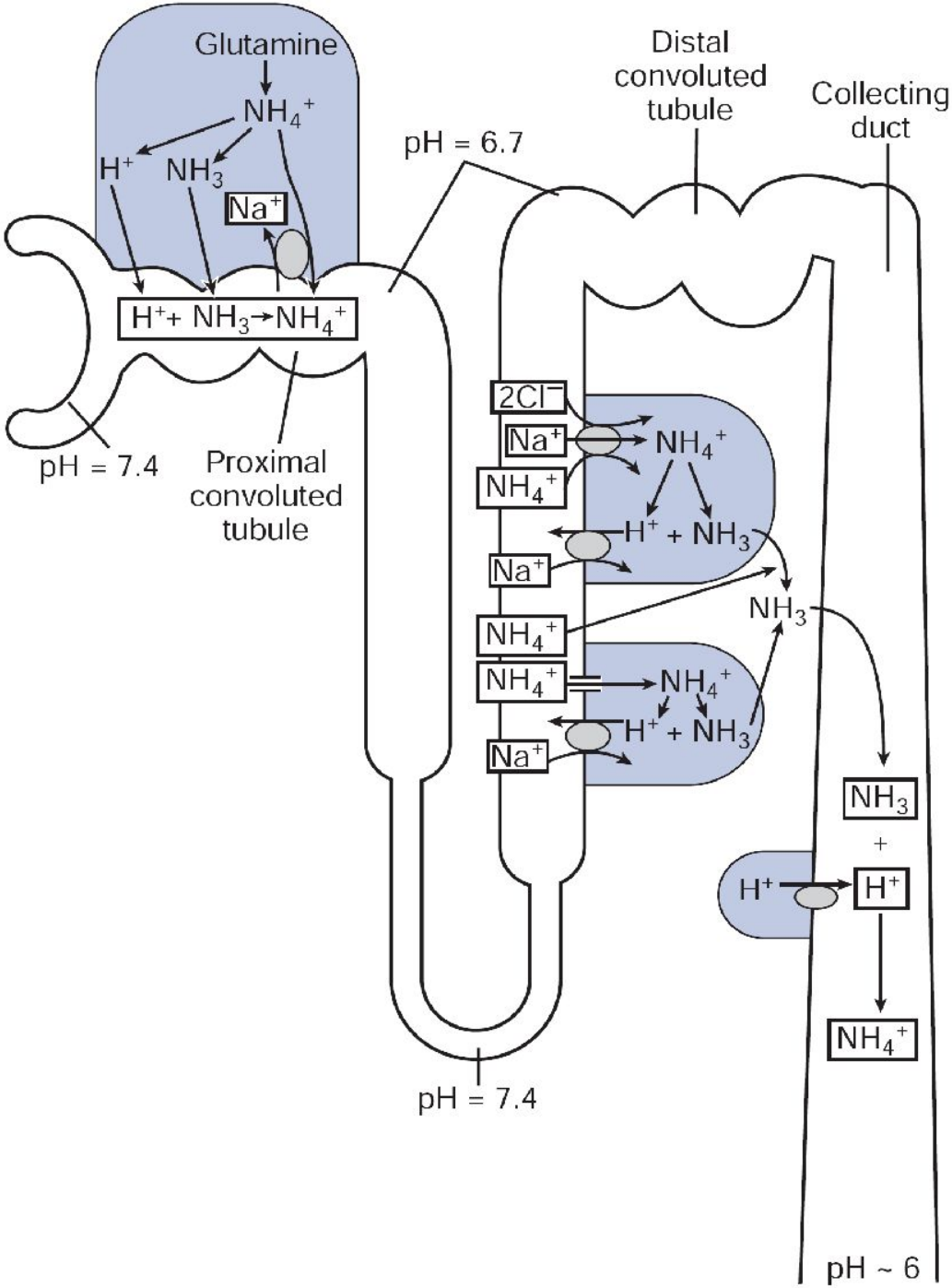
- Реакция опосредуется осморецепторами гипоталамуса.
- Снижение секреции альдостерона.

Почки и КЩС

- Реабсорбция бикарбоната (проксим.)
- Аммонигенез
- HPO_3
- ацидогенез (дист.)

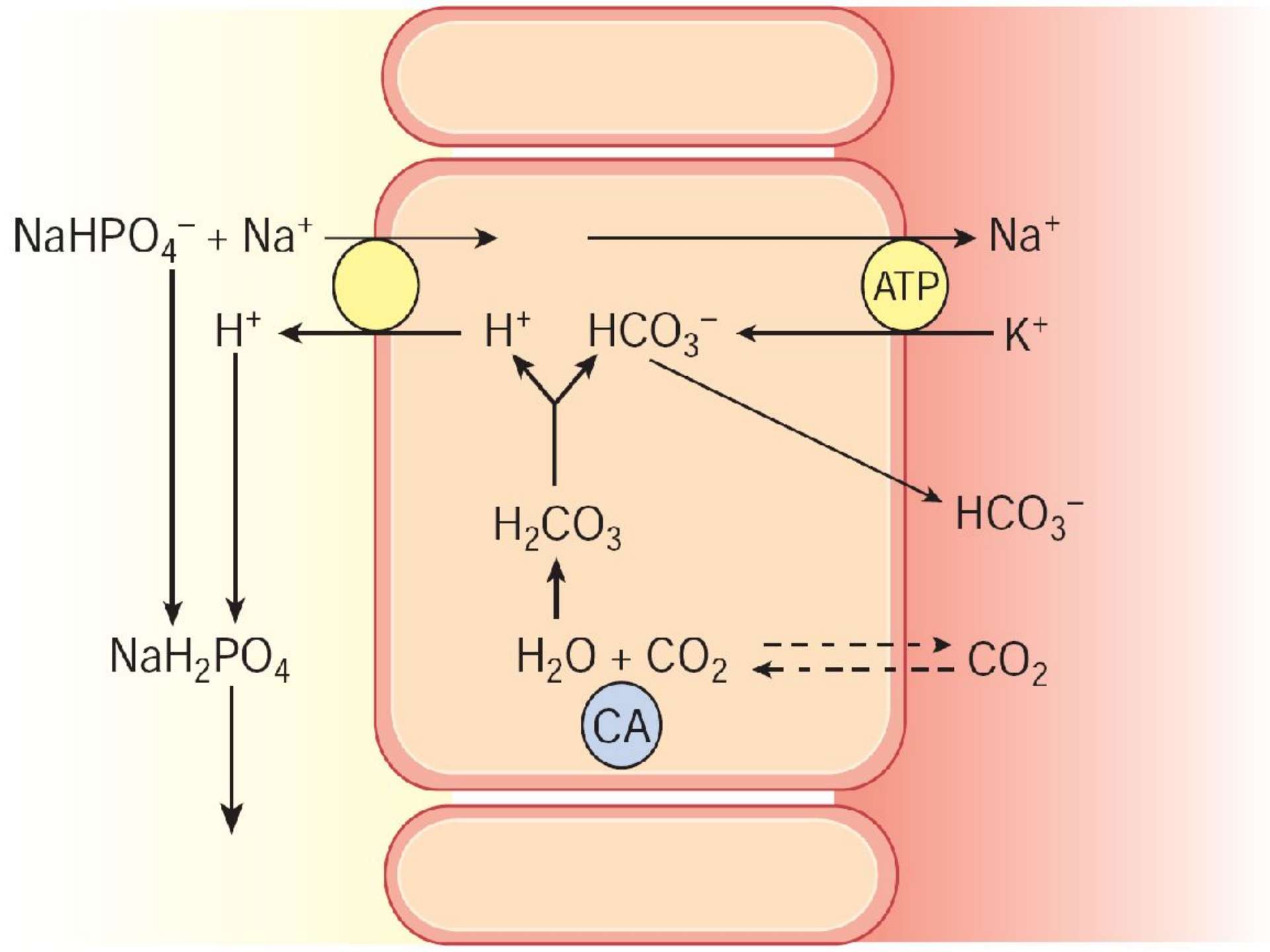
Почти **100%** бикарбоната фильтруется в почках





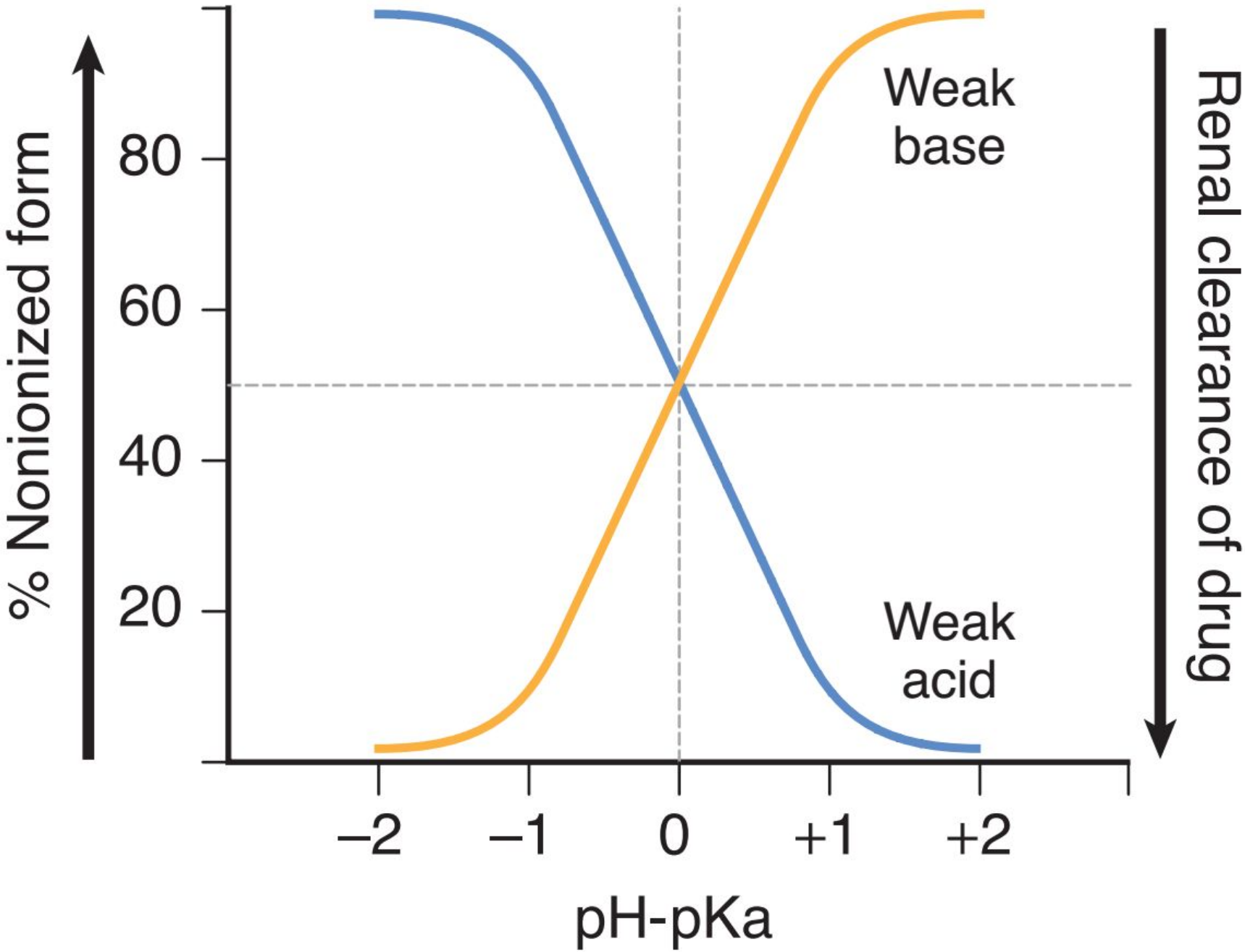
1. The synthesis of ammonium (NH_4^+) from the amino acid glutamine in the proximal tubule
2. The reabsorption and recycling of NH_4^+ within the medullary portion of the kidney
3. The buffering of H^+ ions by NH_3 in the collecting tubules[1,3]

Ammonia (NH3 + NH4) is chiefly produced in proximal tubule cells and is secreted into the tubular urine. NH4 is reabsorbed in the thick ascending limb and accumulates in the kidney medulla. NH3 diffuses into acidic collecting duct urine, where it is trapped as NH4.


$NaHPO_4^- + Na^+$
Na^+
ATP
H^+
H^+
HCO_3^-
K^+
HCO_3^-
H_2CO_3
NaH_2PO_4
$H_2O + CO_2$
CO_2
CA

Type 1 (distal, pH > 5.5)	Defect in ability of α intercalated cells to secrete H^+. Thus, new HCO_3^- is not generated → metabolic acidosis. Associated with **hypokalemia**, ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover). Causes—amphotericin B toxicity, analgesic nephropathy, multiple myeloma (light chains), and congenital anomalies (obstruction) of the urinary tract.
Type 2 (proximal, pH < 5.5)	Defect in proximal tubule HCO_3^- reabsorption results in ↑ excretion of HCO_3^- in urine and subsequent metabolic acidosis. Urine is acidified by α intercalated cells in collecting tubule. Associated with **hypokalemia**, ↑ risk for hypophosphatemic rickets. Causes—Fanconi syndrome (e.g., Wilson disease), chemicals toxic to proximal tubule (e.g., lead, aminoglycosides), and carbonic anhydrase inhibitors.
Type 4 (hyperkalemic, pH < 5.5)	Hypoaldosteronism, aldosterone resistance, or K^+-sparing diuretics. The resulting hyperkalemia impairs ammoniagenesis in the proximal tubule → ↓ buffering capacity and ↓ H^+ excretion into urine.

"ACID"azolamide causes ACIDosis.

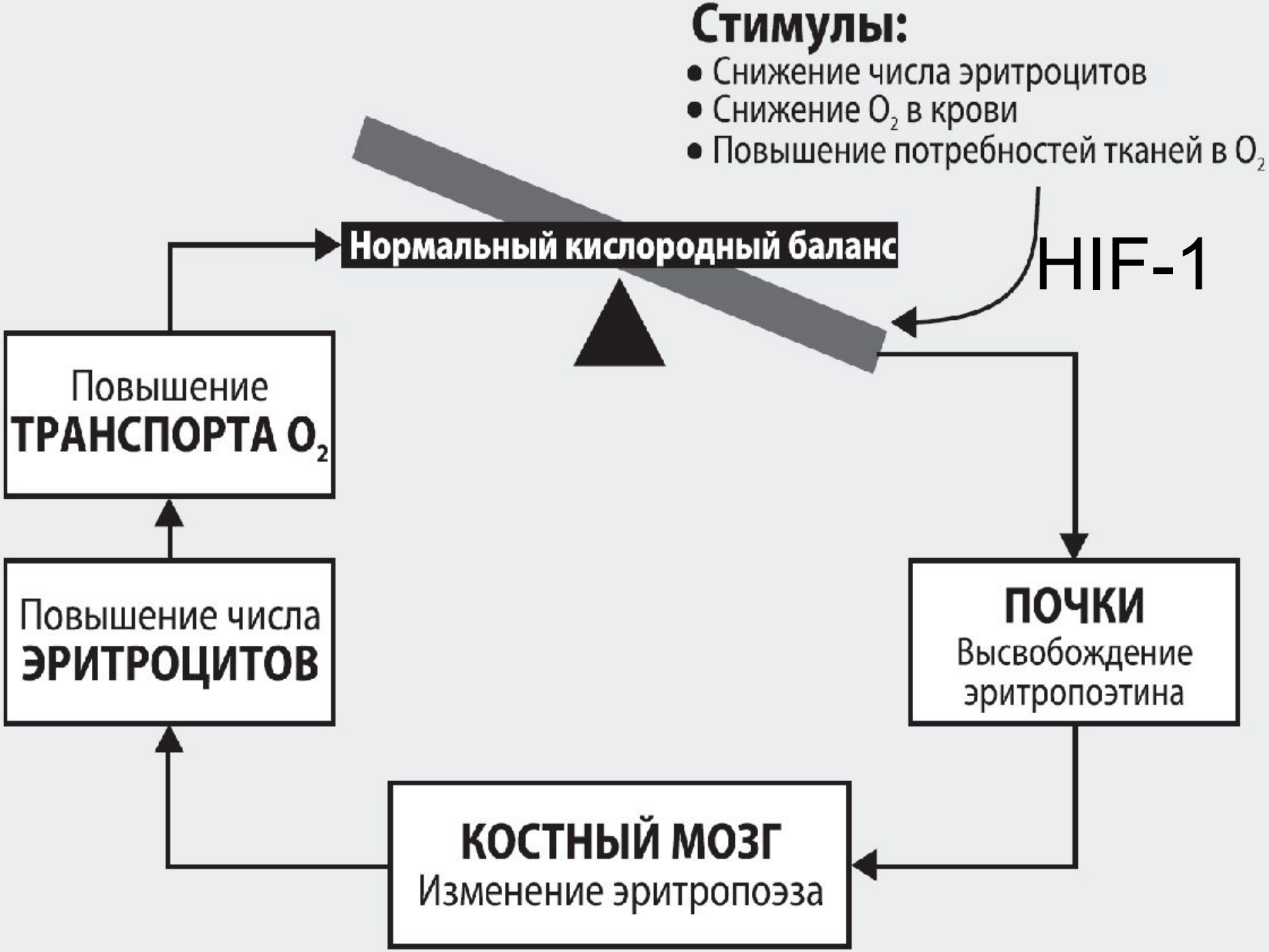

% Nonionized form
80
60
40
20
Weak
base
Weak
acid
Renal clearance of drug
–2
–1
0
+1
+2
pH-pKa

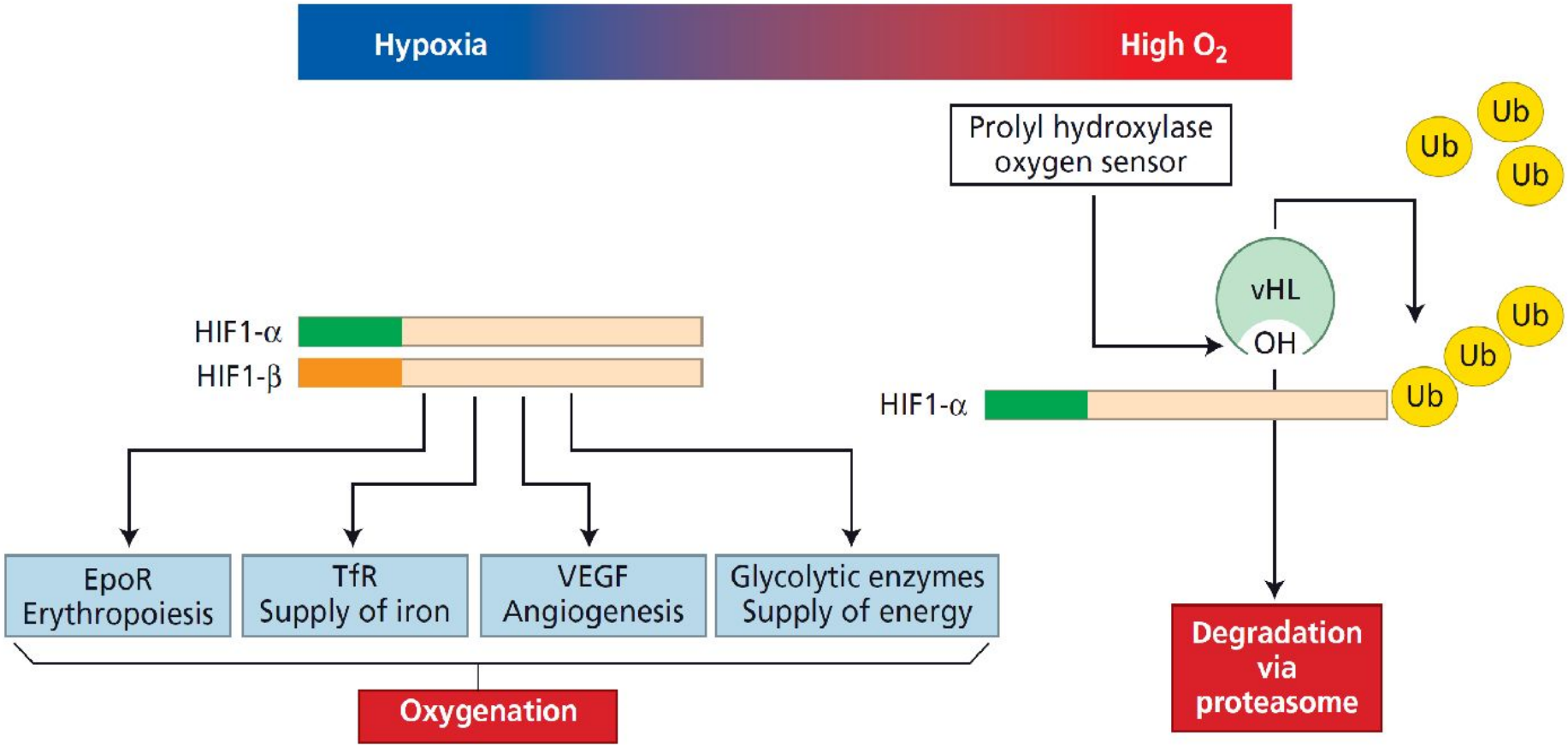
Case: A 70-year-old woman with a history of osteoarthritis comes to the emergency department because of shortness of breath, tinnitus, and decreased hearing. Her blood gas is initially alkalotic but changes to a pH of 7.28 with a pCO_2 of 23. Her serum bicarbonate is low, and the anion gap is increased.

1. What is the diagnosis?
2. What is the best initial therapy?
3. How does it work?

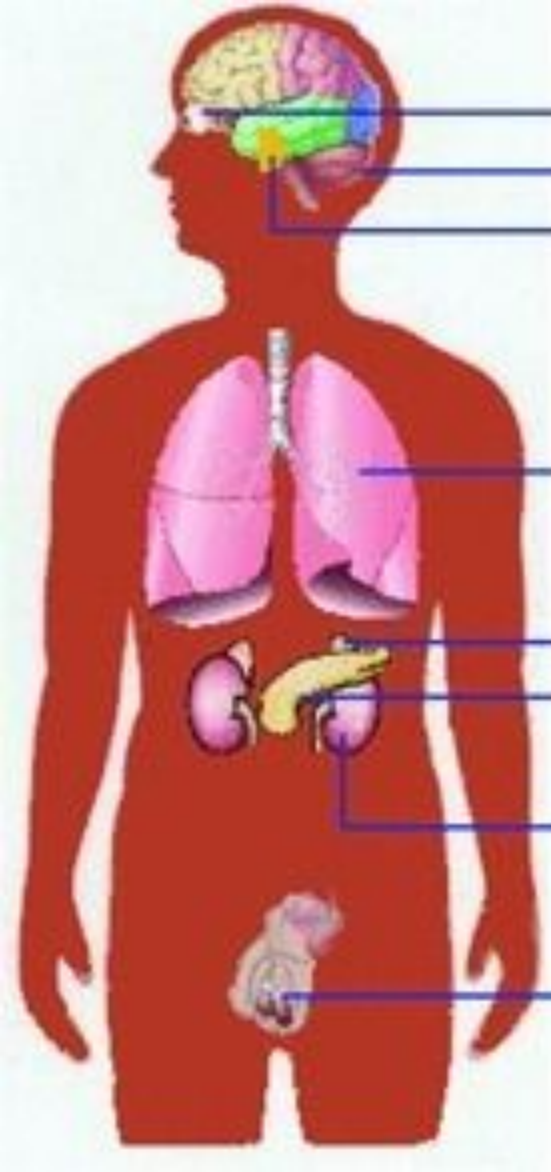
A. Toxicology

1. **Aspirin (salicylate) toxicity** presents with hyperventilation secondary to direct stimulation of the respiratory centers in the brain. In addition, aspirin toxicity can cause tinnitus, encephalopathy, and with severe toxicity pulmonary edema and hyperthermia. In early toxicity, there is respiratory alkalosis from direct stimulation of the brain stem. This is followed by metabolic acidosis, because aspirin poisons the mitochondria and you lose the aerobic metabolism of oxidative phosphorylation. Lactic acidosis accumulates from anaerobic glycolysis.
2. **Bicarbonate** is the best initial therapy for aspirin poisoning.
3. Bicarbonate will **alkalinize the urine**, resulting in increased excretion of aspirin at the kidney tubule.


Стимулы:
• Снижение числа эритроцитов
• Снижение O_2 в крови
• Повышение потребностей тканей в O_2
HIF-1
Нормальный кислородный баланс
Повышение ТРАНСПОРТА O_2
Повышение числа ЭРИТРОЦИТОВ
ПОЧКИ
Высвобождение эритропоэтина
КОСТНЫЙ МОЗГ
Изменение эритропоэза



The **juxta-tubular cells** of the kidney sense oxygen tension. Proline hydroxylase requires O2 to hydroxylate a key protein: hypoxia-inducible factor (HIF). This allows the ubiquitination of HIF-alpha by the von Hippel-Lindau factor (VHL) & ubiquitin ligase (UL), resulting in the degradation of HIF in the proteasome. When O2 is low, HIF activates the gene for EPO and other genes, increasing Hb and encouraging blood vessel formation.



Retinal haemangioomas (70%)

CNS haemangioblastomas (60-84%)

Endolymphatic sac tumours of the middle ear (14%)

Lung cysts (rare, <1%)

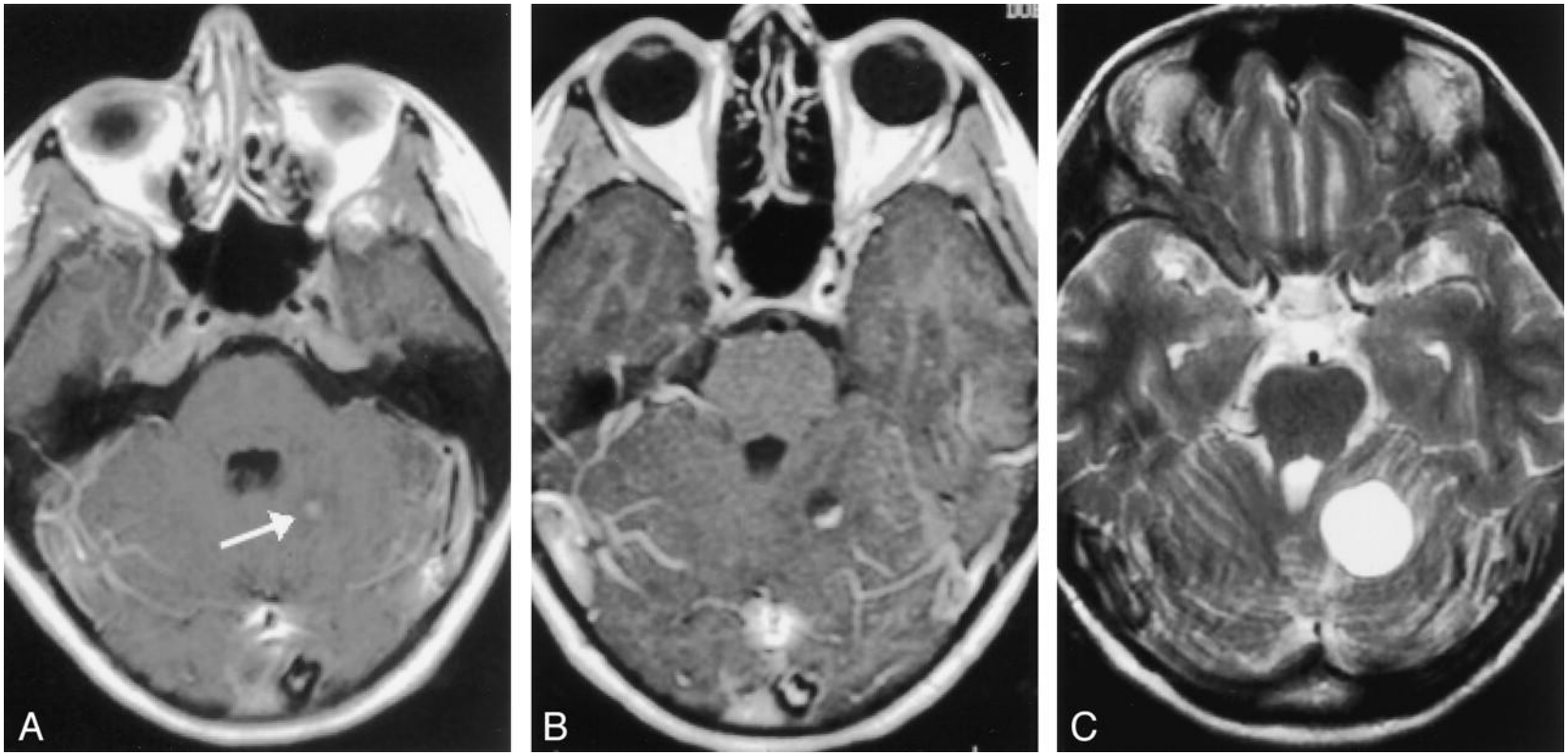
Pheochromocytomas (18%)

Pancreas: cysts (70%), serous cystadenomas (9%), neuroendocrine tumours (9%)

Kidney: cysts (66%), clear cell renal cell carcinomas (69%)

Epididymal (male, 54%) or broad ligament (female) papillary cystadenomas

Images in a third patient with a solid cerebellar tumor that progressed to enlarging cyst with the subsequent development of symptoms.A, Contrast-enhanced T1-weighted MR image obtained at presentation shows a tiny enhancing nodule in the left cerebellar hem...



Andrew Slater et al. AJNR Am J Neuroradiol 2003;24:1570-1574

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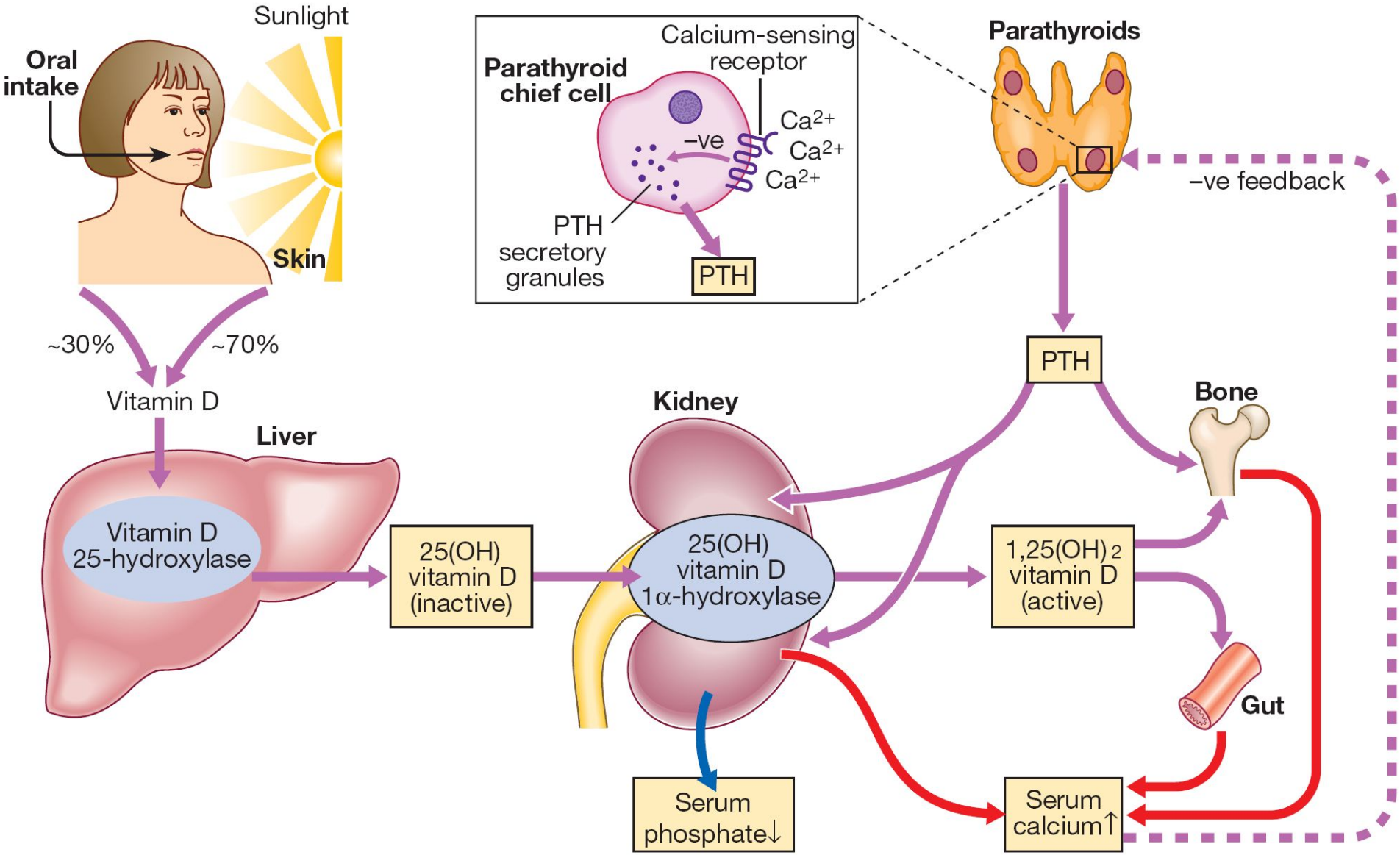
Одна из причин эритроцитоза

! Почечно-клеточный рак !



Vitamin D promotes bone mineralization by stimulating the release of **alkaline phosphatase** from osteoblasts. Alkaline phosphatase hydrolyzes pyrophosphate (removes the phosphate) and **other inhibitors** of calcium-phosphate crystallization