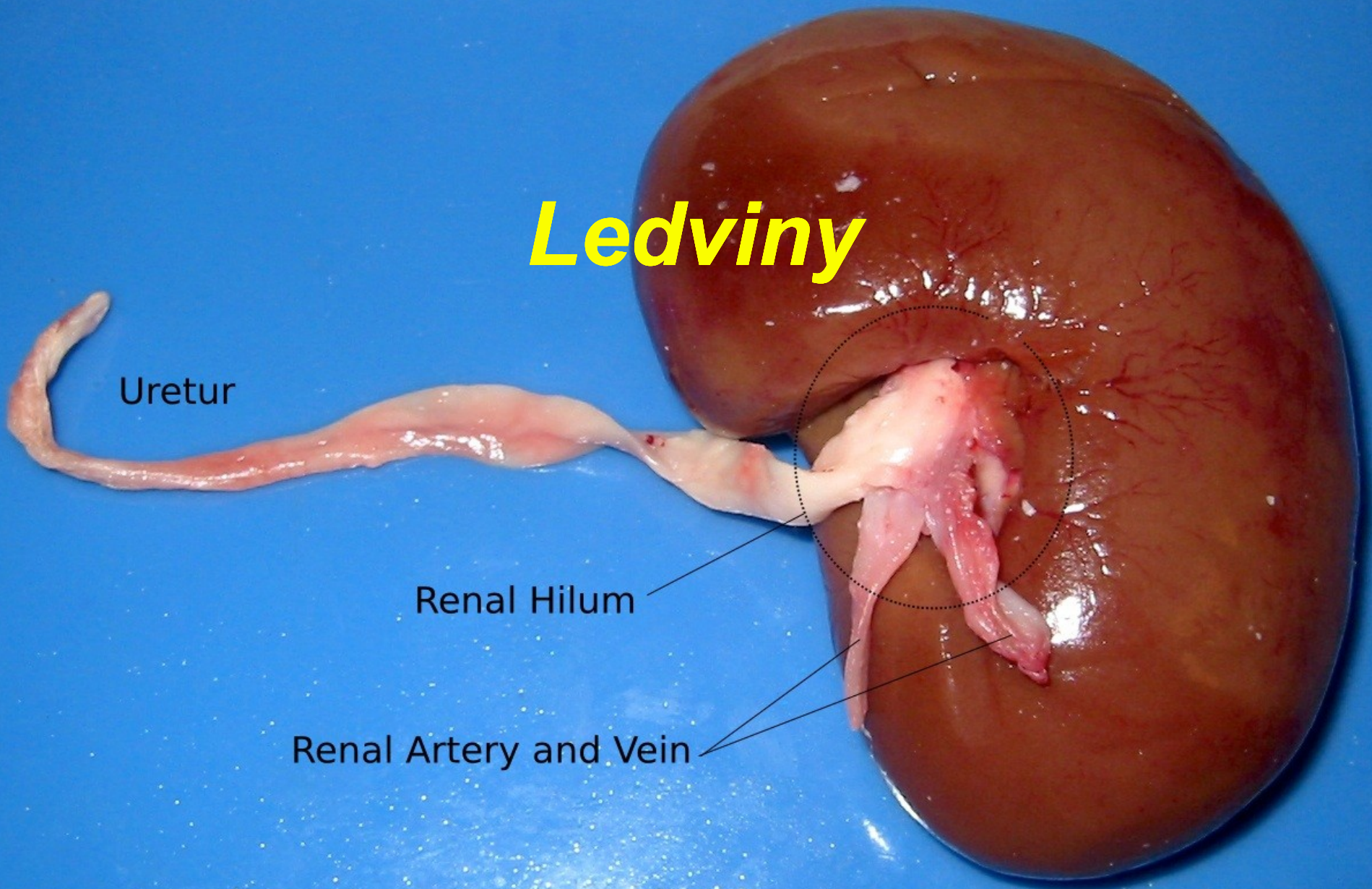


# *Ledviny*

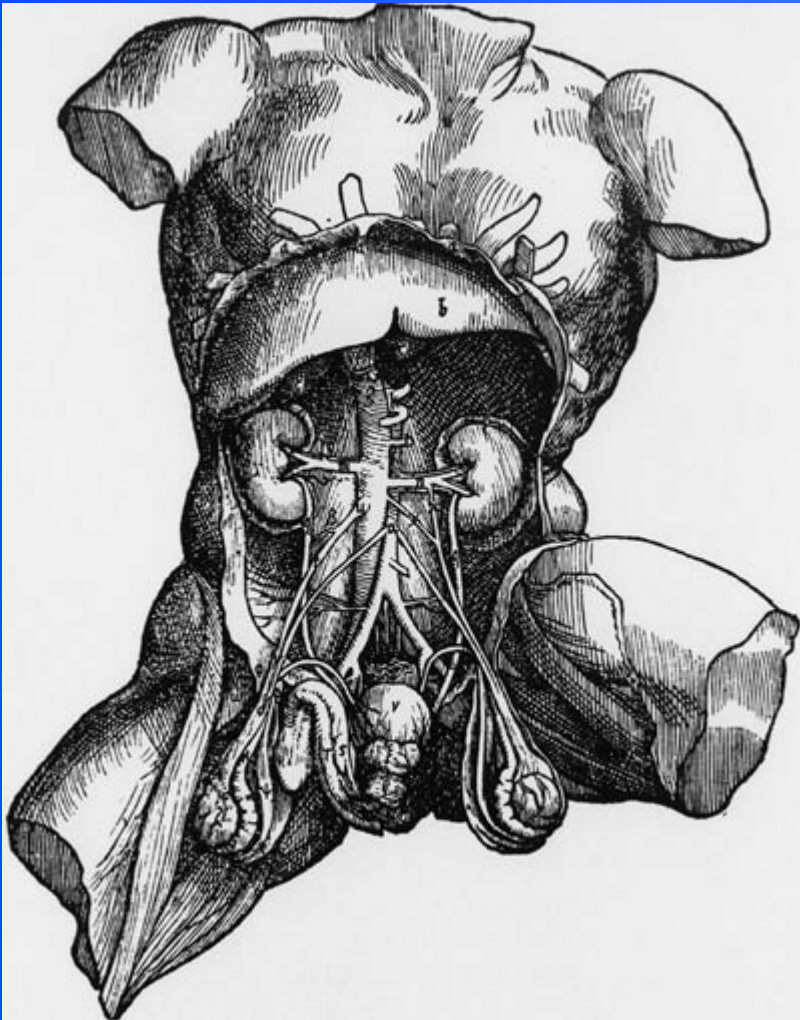
Uretur

Renal Hilum

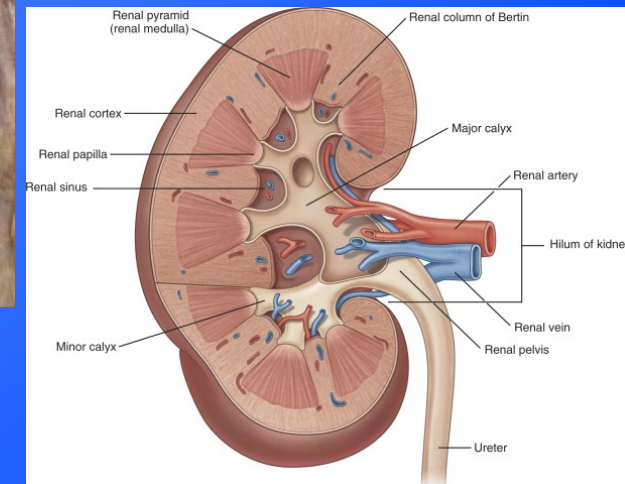
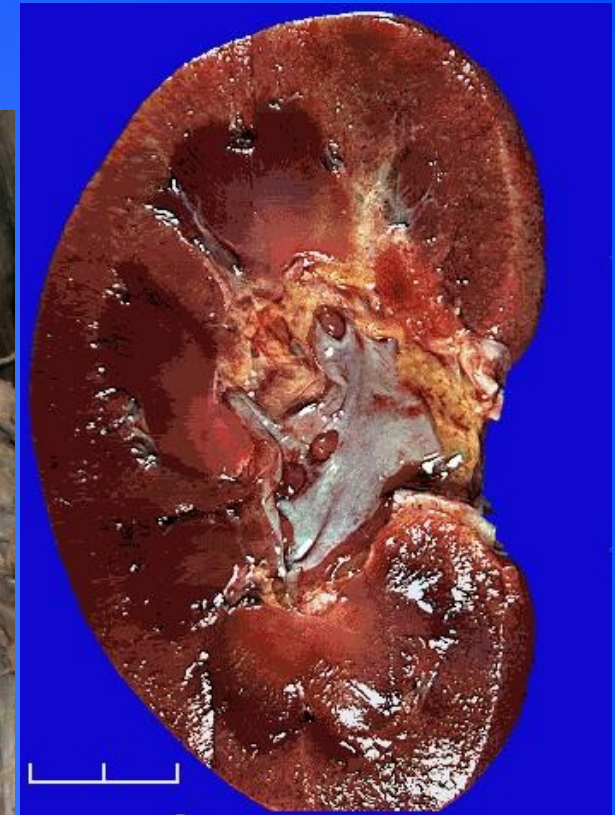
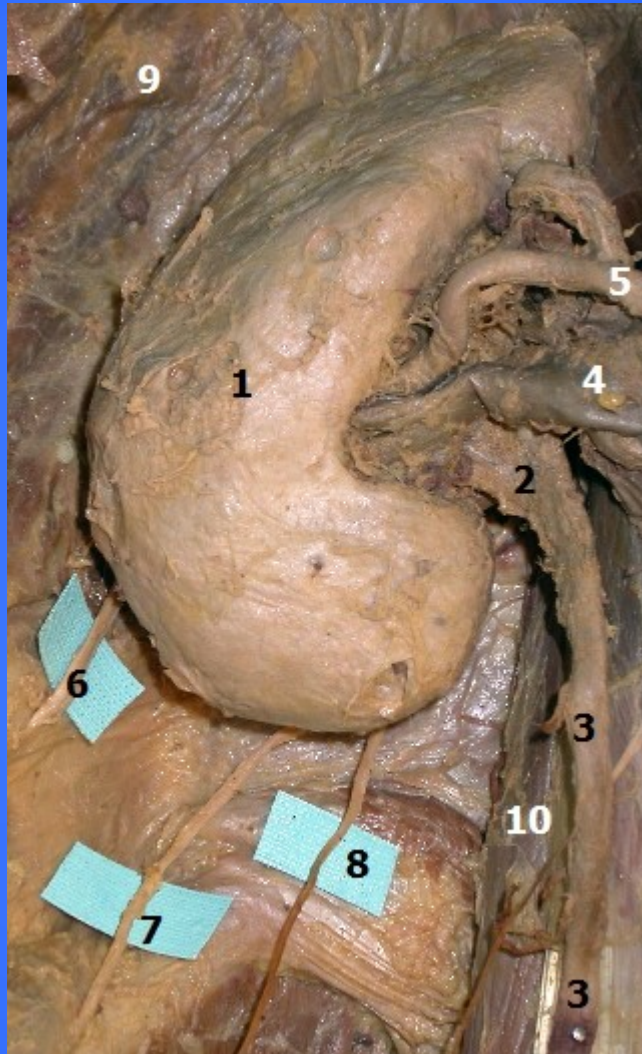
Renal Artery and Vein



# FUNKČNÍ ANATOMIE LEDVIN



Andreas Versalius' 1543 illustration of the male genitourinary tract. Although most anatomic details are correct, the left kidney is placed lower than the right kidney. (From Book 5 *De Humani Corporis Fabrica*.)



# ***FUNKCE LEDVIN***

- **Vyloučení dusíkatých látek** (močovina, kreatinin, močová kyselina, urobilinogen, xenobiotika)
- **Isoionie** (Na, K, Cl, Mg, Ca, H,  $\text{HCO}_3^-$ )
- **Isovolemie** (ECV, objem plazmy)
- **Isotonie** (homeostáza osmotického tlaku)
- **Isohydrie** (homeostáza ACB rovnováhy,  $\text{H}^+$  a  $\text{HCO}_3^-$ ) – pH 7,36 – 7,44
- **Regulace TK** (renin, kininy, prostaglandiny)
- **Metabolismus** (proteiny, peptidy, toxiny, glukoneogeneze)
- **Tvorba hormonů** (calcitriol, erythropoetin, renin)
- **Účinek hormonů** (ADH, aldosteron, adrenalin, parathormon atd.)

# Homeostatická funkce ledvin

- *Řízení objemu krve a krevního tlaku – filtrační tlak*
  - **Zvýšený objem krve:**
    - Srdeční výdej
    - Zvýšená glomerulární filtrace
    - Zvýšená sekrece atriálního natriuretického peptidu
    - Snížená sekrece ADH a reninu
  - **Snížený objem krve**
    - Aktivace systému renin-angiotenzin-aldosteron
    - ADH, retence vody
- **Udržování koncentrace iontů v plazmě**
  - $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$  = aldosteron
  - $\text{Ca}^{2+}$  a fosfáty = parathormon
- **Udržování acidobazické rovnováhy**
  - Změna výdeje bikarbonátových iontů a vodíkových iontů

# Endokrinní funkce ledvin

## - *Renin*

- Snížená perfuze ledvin, stimulace autonomním systémem, zvýšená koncentrace sodíku a chloru v distálním tubulu
- **Systém renin-angiotenzin-aldosteron**
  - Renin aktivuje angiotenzinogen (játra) na angiotenzin I
  - Angiotenzin I konvertován v plicích na angiotenzin II
  - Angiotenzin II:
    - Vasokonstriční efekt (vas eferens)
    - Stimulace produkce a sekrece aldosteronu
  - Aldosteron po vazbě na receptory v distálním tubulu zvyšuje resorpci sodíku

## - *Erythropoetin*

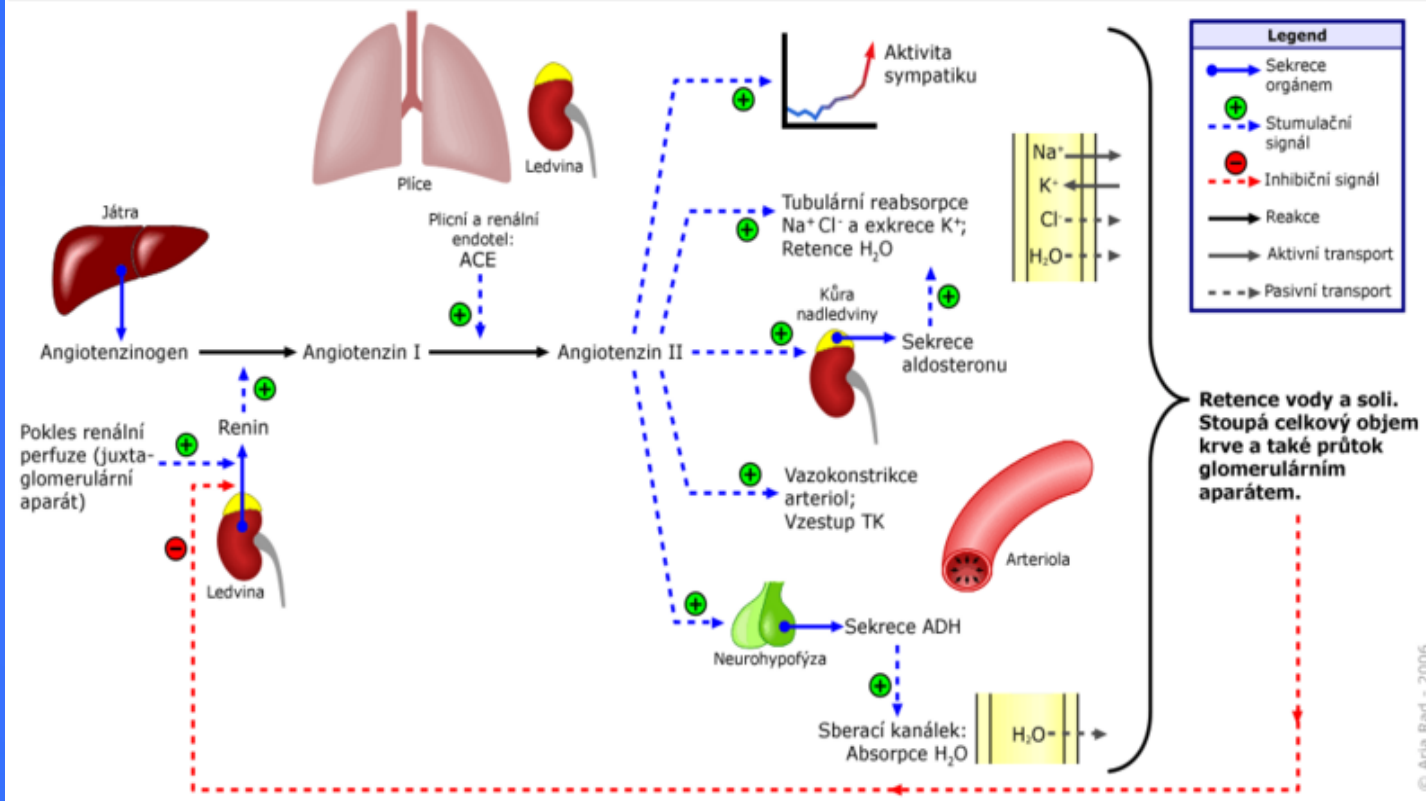
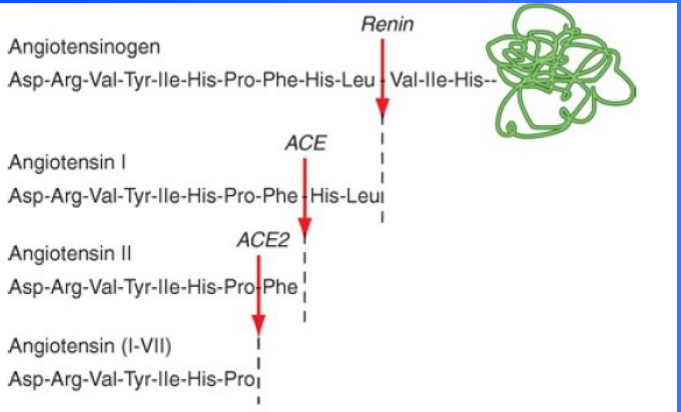
## - *Trombopoetin*

## - *Vitamín D*

- 1-hydroxyláza – konverze 25-hydroxycholekalCIFerolu na 1,25-dihydrocholekalCIFerol

## - *Parathormon* - odbourávání

# System renin-angiotenzin-aldosteron



# ERYTROPOETIN

*Glykoprotein, 39 000,  $\alpha$ 2-globulin.*

*Rekombinantní erythropoetin.*

*Malé množství v plazmě, moči, lymfě, fetální krvi.*

***Inaktivace:*** *játra*

***Vznik:*** *ledviny (85-90%) – endotelové buňky peritubulárních kapilár ledvinné kůry, játra (10-15%)*

***Stimulace vyplavení:*** *tkáňová hypoxie libovolného původu (ledviny), alkalóza, soli kobaltu, androgeny, katecholaminy ( $\beta$ -receptory)*

***Účinky:***

*Kmenová buňka citlivá na erythropoetin (erythropoetin responsive cell) – diferenciací do erytroidní řady:*

- zvýšení syntézy nukleových kyselin*
- zvýšení resorpce železa v erytroidních buňkách*
- stimulace uvolňování buněk z dřeně do oběhu*

***Aklimatizace*** – *adaptace na vysokou nadmořskou výšku*

# Osteoblasts – next cellular source of erythropoietin

*HIF signaling in cells of the osteoblastic lineage regulate EPO expression in bone under physiologic and pathophysiologic conditions.*

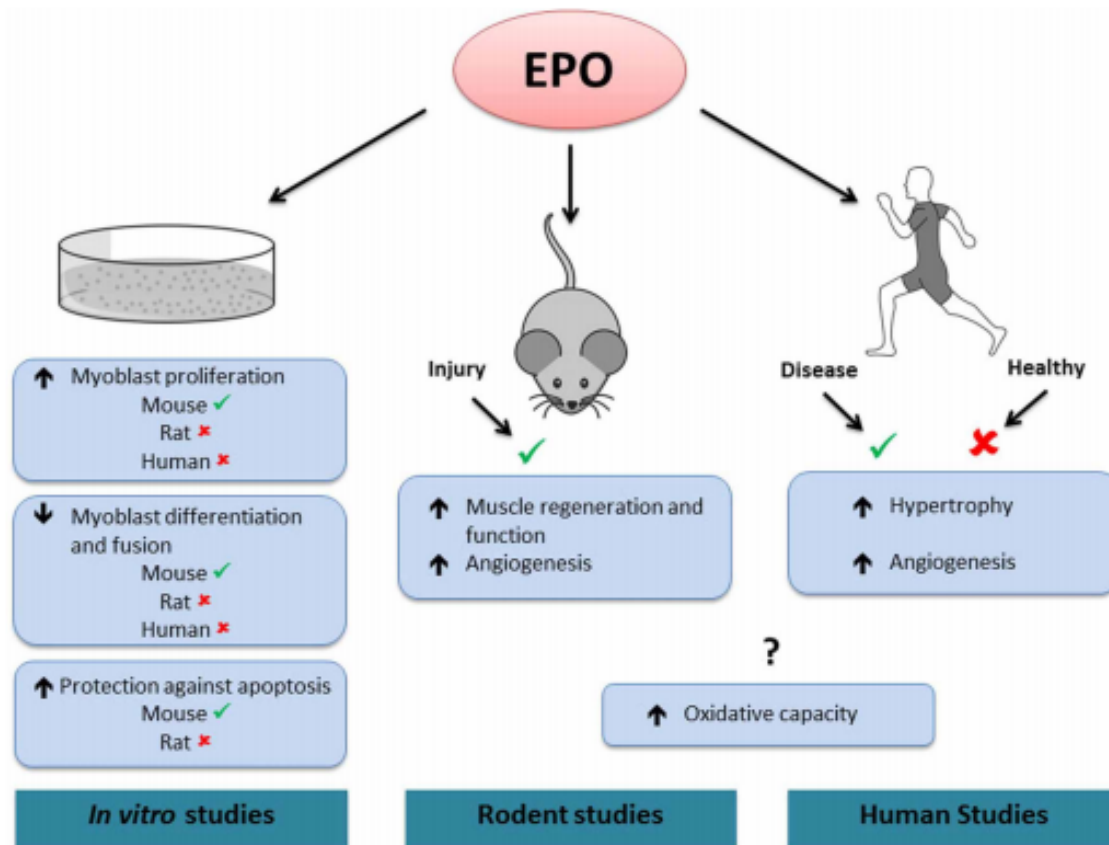
*In addition to regulating erythropoiesis, EPO has also been implicated in the regulation of bone formation and repair.*

Source	Model	Phenotype	Reference
Osteoblast (OSX-VHL)	Remodeling (mouse)	Increased trabecular bone volume associated with increased angiogenesis and erythropoiesis.	Rankin et al.
EPO (4500; 6,000 U/Kg)	Remodeling (mouse)	Increased bone volume in neonatal and adult mice associated with increased osteoblasts and erythropoiesis.	Shiozawa et al.
EPO (300 U/Kg)	Remodeling (mouse)	Modest decrease in bone volume.	Singbrant et al.
EPO (5000 U/Kg)	Repair (mouse)	Increased torsional stiffness, callus density, and mineralized bone.	Holstein et al.
EPO (40 ng)	Repair (mouse)	Increased cartilaginous callus formation and bone healing associated with increased angiogenesis.	Wan et al.
EPO (1000 U)	Repair (mouse)	Increased BMP-2 induced bone regeneration in a cranial defect model associated with enhanced angiogenesis.	Sun et al.
EPO (500 IU)	Repair (mouse)	Increased bone volume in an bridging calvarial defect model.	Nair et al.
EPO (500 IE/Kg)	Repair (mouse)	Increased bone volume and repair in an femoral segmental defect model associated with increased angiogenesis.	Holstein et al.
EPO (500 U/Kg)	Repair (mouse)	Increased callus formation in a closed femoral fracture model.	Garcia et al.
EPO (250 IU/Kg)	Repair (rabbit)	Increased bone fusion in a posterolateral spinal fusion model associated with enhanced angiogenesis.	Rolfing et al. (2011)
EPO (900 IU)	Repair (porcine)	Modest increase in bone formation in a calvarial defect model.	Rolfing et al. (2013)
EPO (900 IU)	Repair (porcine)	Increase in bone formation when combined with bone marrow concentrate in a osteochondral defect model.	Betsch et al.

EPO erythropoietin

**Wu C, Giaccia AJ, Rankin EB: Osteoblasts: a Novel Source of Erythropoietin. Current Osteoporosis Reports 2014, 12(4):428-432.**



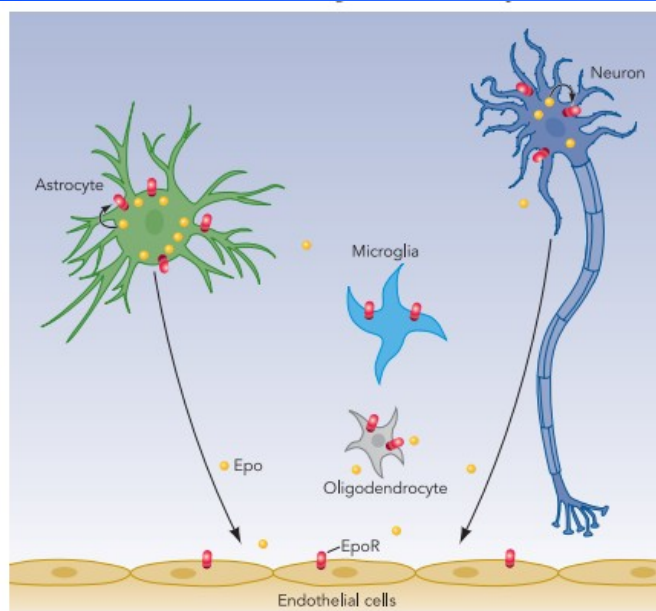


**FIGURE 2 | Effects of EPO in skeletal muscle.** ✓, activated by EPO. ✗, not activated by EPO. ?, contradictory results. *In vitro*, EPO treatment increases mouse, but not rat or human myoblast proliferation. EPO treatment decreases differentiation and fusion of mouse, but not rat or human myoblasts. EPO treatment protects against apoptosis in mouse but not in rat myoblasts. In rodents, EPO treatment increases muscle regeneration and angiogenesis following injury. In humans, EPO

treatment increases skeletal muscle hypertrophy and angiogenesis in diseased conditions (chronic renal failure and Friedreich ataxia, respectively), but has no effect in healthy muscle. In both rodent and human studies, EPO has been shown to increase or have no effect on muscle oxidative capacity. Note that it is presently unknown if the effects of EPO treatment observed in rodent and human skeletal muscle are direct or indirect.

*Lamon S, Russell AP: The role and regulation of erythropoietin (EPO) and its receptor in skeletal muscle: how much do we really know? Frontiers in Physiology 2013, 4.*

# EPO and brain



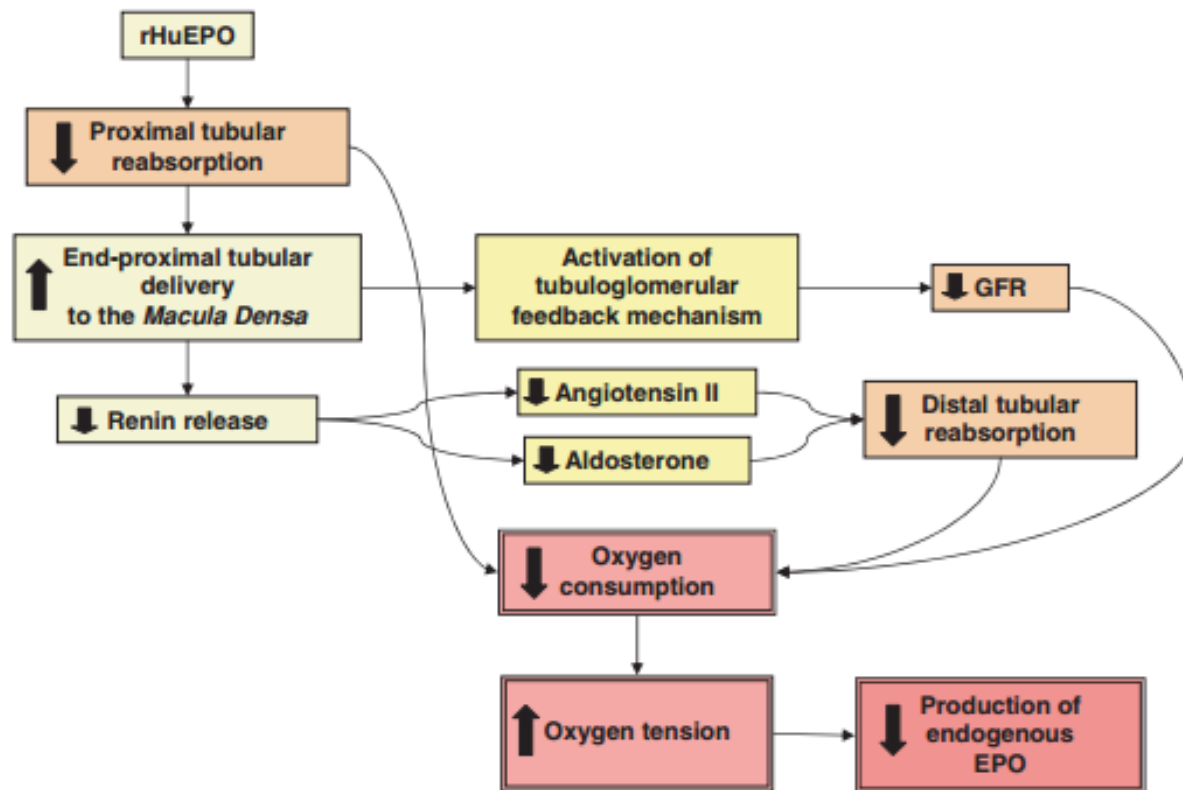
**FIGURE 1. Expression pattern of Epo/EpoR in the brain**  
Whereas Epo expression is restricted to astrocytes and neurons, EpoR is expressed on the surface of endothelial cells, microglia, astrocytes, oligodendrocytes, and neurons. Epo is thought to act in an autocrine as well as paracrine manner.

**Table 1. Functions of Epo**

Function	Description	Refs.
Neuroprotection	Infusion of soluble EpoR into the brain of gerbils, subjected to a mild form of ischemia, caused neuronal death in the hippocampus.	95
Neurotrophic factor	Regeneration of septal cholinergic neurons in adult rats, which had undergone fimbria-fornix transections. Promotion of the survival and differentiation of dopaminergic precursor neurons in vitro.	107 107
Neurogenesis	Hypoxia-induced Epo production acts directly on neuronal stem cells in the forebrain. Indirectly by inducing BDNF expression.	99 113
Anti-inflammation	Reduced production of inflammatory mediators leading to: Cerebral ischemia: smaller infarcts. Multiple sclerosis: protection. Optic neuritis: improved survival of retinal ganglion cells.	112 2, 96
Angiogenesis	Mitogenic action on: Human umbilical vein. Adrenal capillary endothelial cells. Brain capillary endothelial cells.	4 4 121
	Angiogenic action on: Rat aortic rings. Mouse endometrium. Chick embryo chorioallantonic membrane.	19 123 90
Vascular permeability	In vitro: BBB protection against VEGF-induced increase in vascular permeability	75

BDNF, brain-derived neurotrophic factor; BBB, blood-brain barrier; VEGF, vascular endothelial growth factor.

**Rabie T, Marti HH: Brain Protection by Erythropoietin: A Manifold Task. Physiology 2008, 23(5):263-274.**



**Figure 1. How high levels of circulating recombinant EPO may result in suppression of endogenous EPO synthesis secondary to a decrease in intrarenal oxygen consumption, by intrinsic renal effects**

(1) EPO decreases reabsorption of sodium and fluid in the proximal tubule, thereby directly reducing the major oxygen-consuming process in the kidney; (2) increase in end-proximal tubular delivery to the macula densa decreases renin release and subsequent angiotensin II- and aldosterone-dependent reabsorption in more distal nephron segments; (3) decreased proximal tubular reabsorption activates the tubuloglomerular feedback mechanism producing a fall in GFR and reduction of the filtered load; (4) the resulting increase in renal oxygen partial pressure in the environment of interstitial fibroblast-like cells down-regulates the hypoxia-inducible factor-2-dependent production of endogenous EPO.

*Lundby C, Olsen NV: Effects of recombinant human erythropoietin in normal humans. Journal of Physiology-London 2011, 589(6):1265-1271.*

# Trombopoetin

= *megakaryocyte growth and development factor (MGDF)*

*Glykoprotein, mára homologie s erythropoetinem (prvních 155 AMK)*

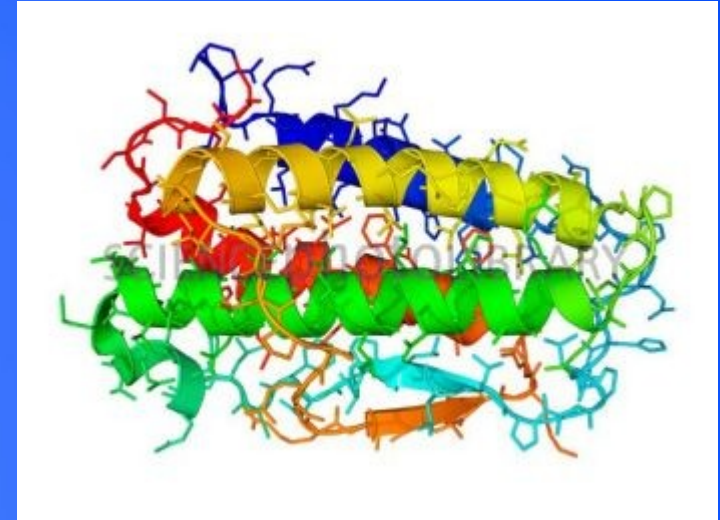
**Vznik:** *ledviny (buňky proximálního tubulu), játra (parenchym, sinusoidální endoteliální buňky), v menší míře další buňky*

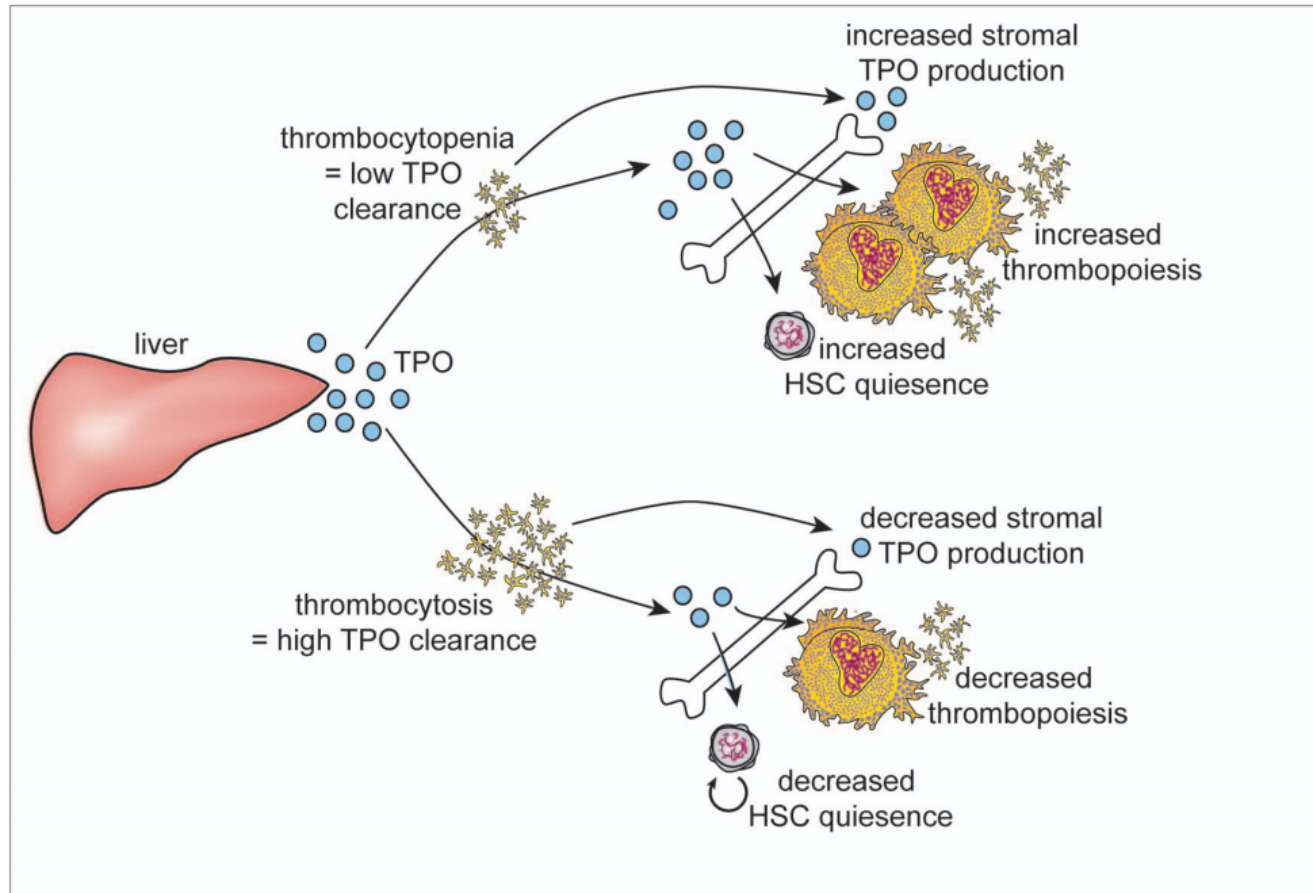
**Regulace:** *vazba trombopoetinu na receptory trombocytů (CD110) = snížená hladina trombopoetinu*

**Účinky:**

*Stimulace produkce a diferenciacie megakaryocytů (proliferace, maturace)*

**Možné terapeutické využití** – *problém s produkcí autoprotilátek proti trombopoetinu a následnou trombocytopenií po aplikaci rekombinantního trombopoetinu*





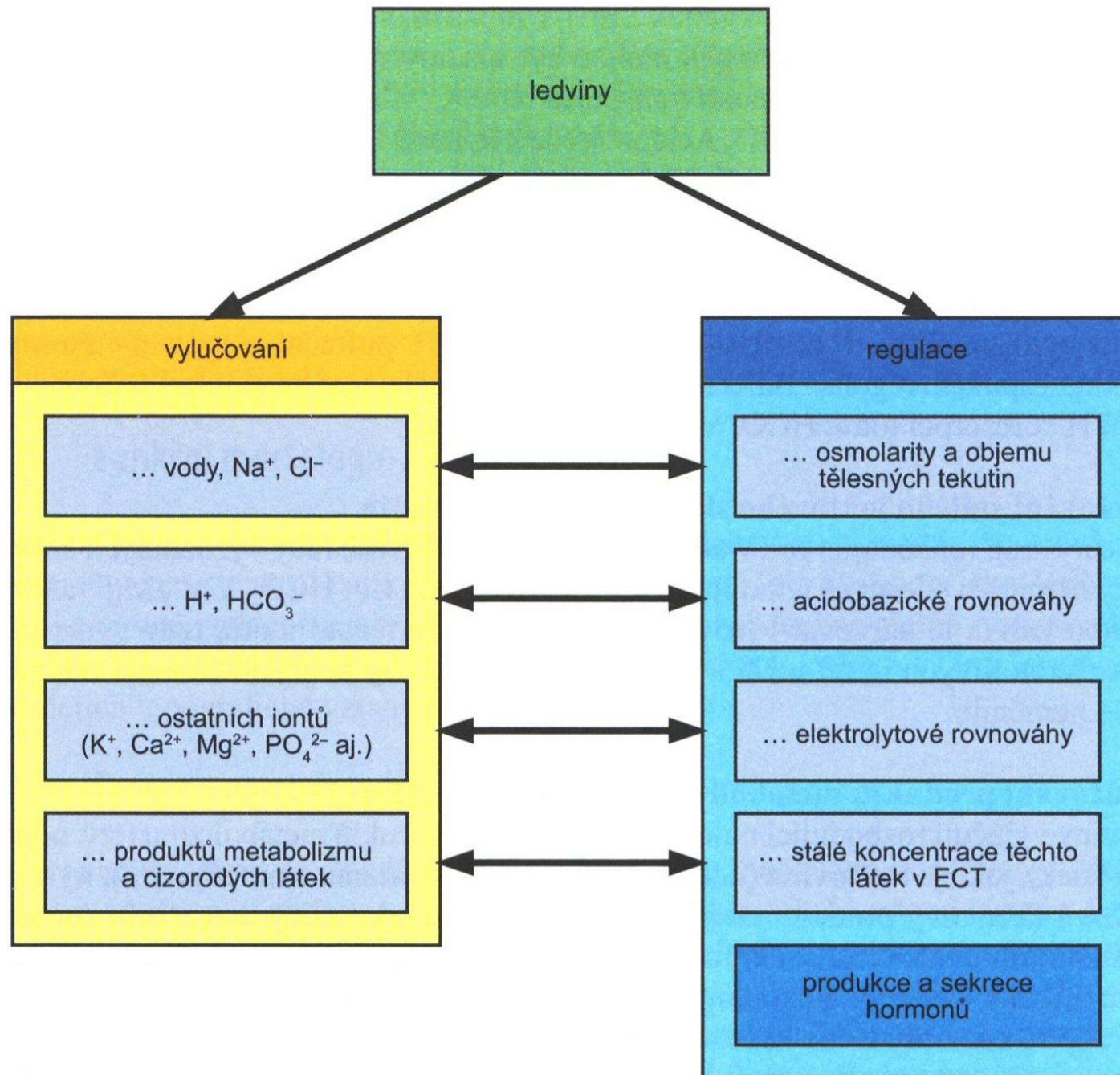
**Figure 1.** TPO levels are regulated by platelet mass. The liver constitutively produces TPO. Upon binding to Mpl receptors on platelets, TPO is internalized and removed from circulation. A smaller proportion of total TPO is produced by stromal cells in the bone marrow and their TPO mRNA production is sensitive to factors produced by platelets such as PF4 and thus also linked to platelet number. TPO then stimulates thrombopoiesis and HSC quiescence in the bone marrow. In the case of thrombocytosis, much TPO is removed from circulation, resulting in low levels of TPO signaling, while during thrombocytopenia, little TPO is cleared from circulation, resulting in high levels of TPO signaling. This feedback system allows thrombopoiesis to be regulated by the available platelet mass but also links HSC quiescence to platelet numbers.

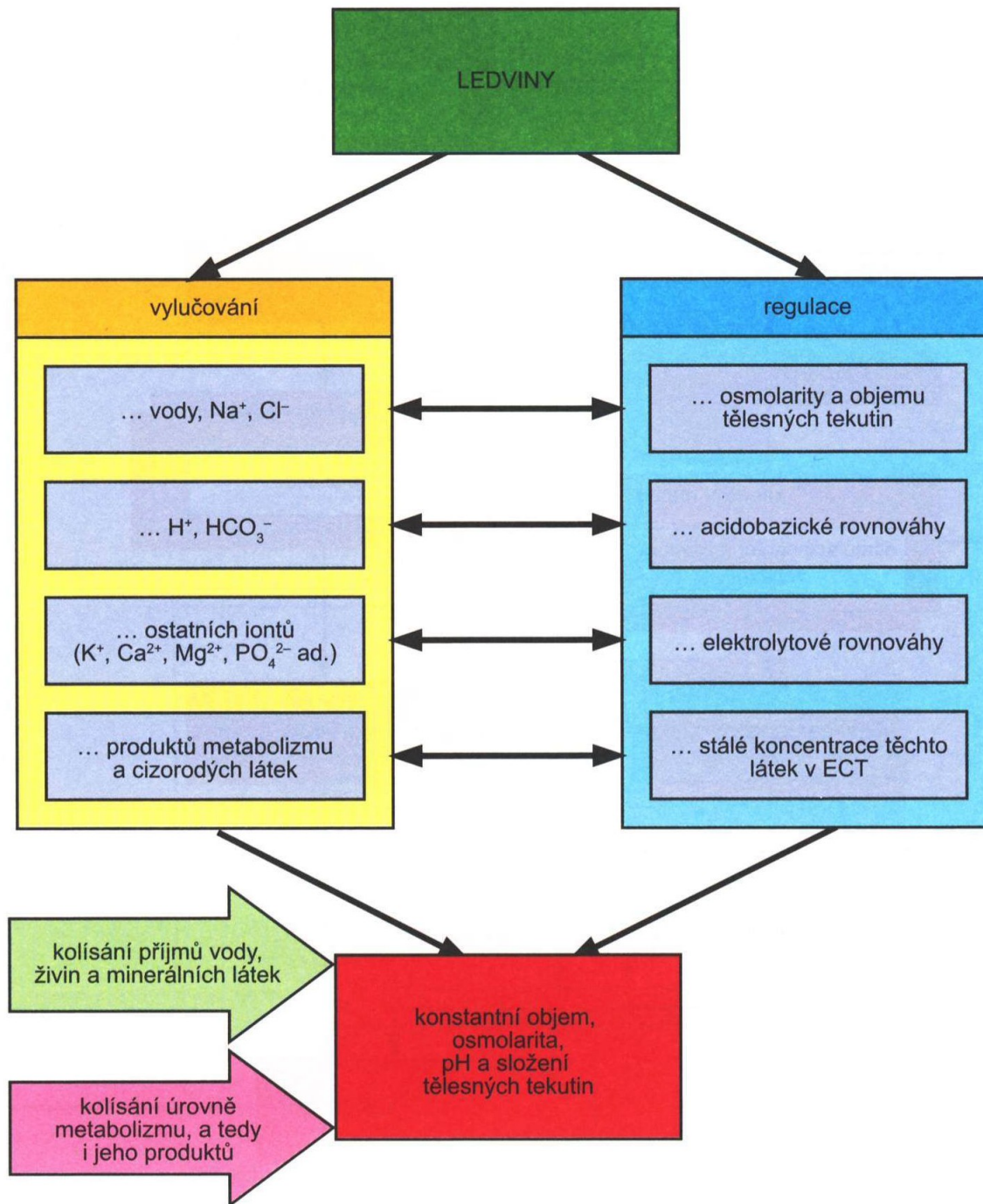
*de Graaf, C. A., Metcalf, D., 2011. Thrombopoietin and hematopoietic stem cells. Cell Cycle. 10, 1582-1589.*

# Metabolická funkce ledvin

- Glukoneogeneze, a to v závislosti na podmínkách (stresová reakce)
- Cca 10 – 20 % Glu při stresové odpovědi organismu
- Glukoneogeneze – kortikální části ledviny, zdrojem energie jsou zde MK
  - V postprandiální periodě paradoxní zvýšení glukoneogeneze
  - U jater je tomu naopak
  - Vazba mezi orgány? – reciproční provázanost mezi játry a ledvinami
- Utilizace glukózy – medulární část, anaerobní glykolýza
- Ledviny nejsou schopné glykogenolýzy – chybí enzymatická výbava + velmi malé zásoby glykogenu
- Produkce inzulinázy – odbourávání inzulinu



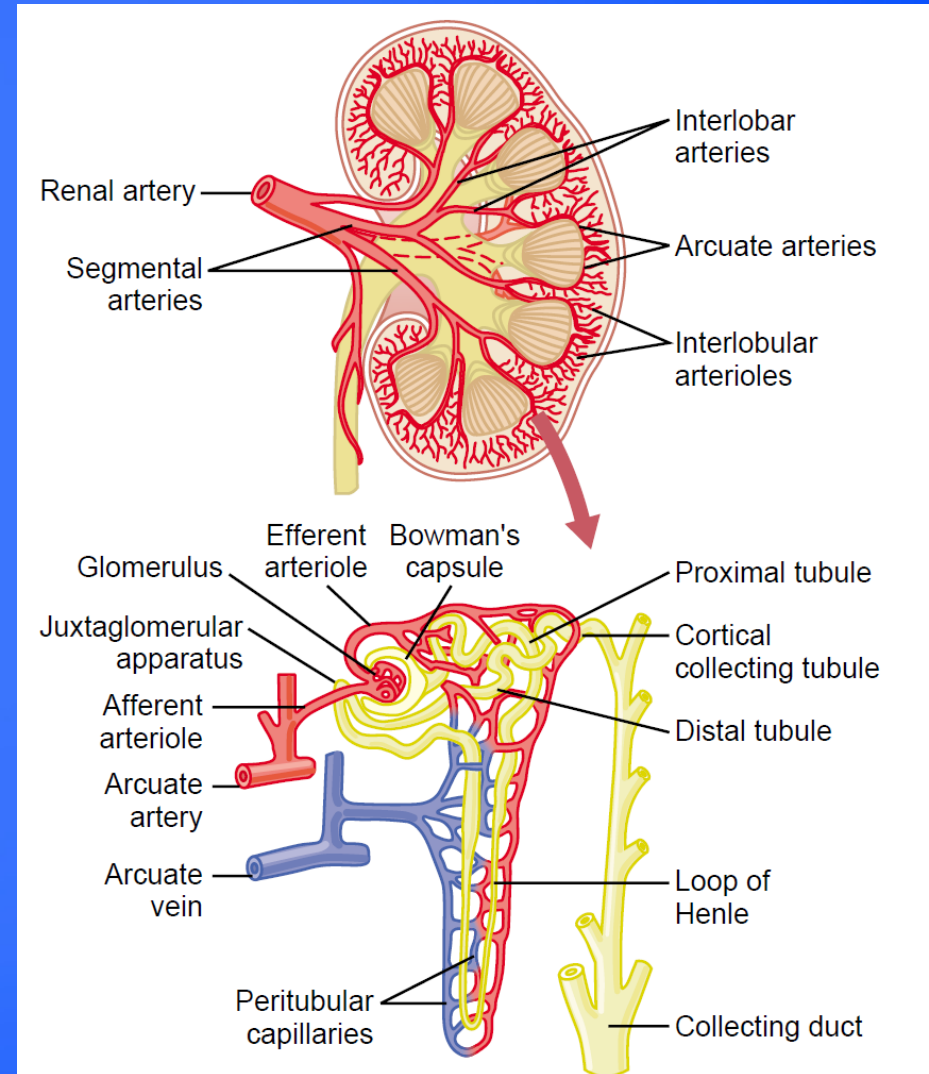




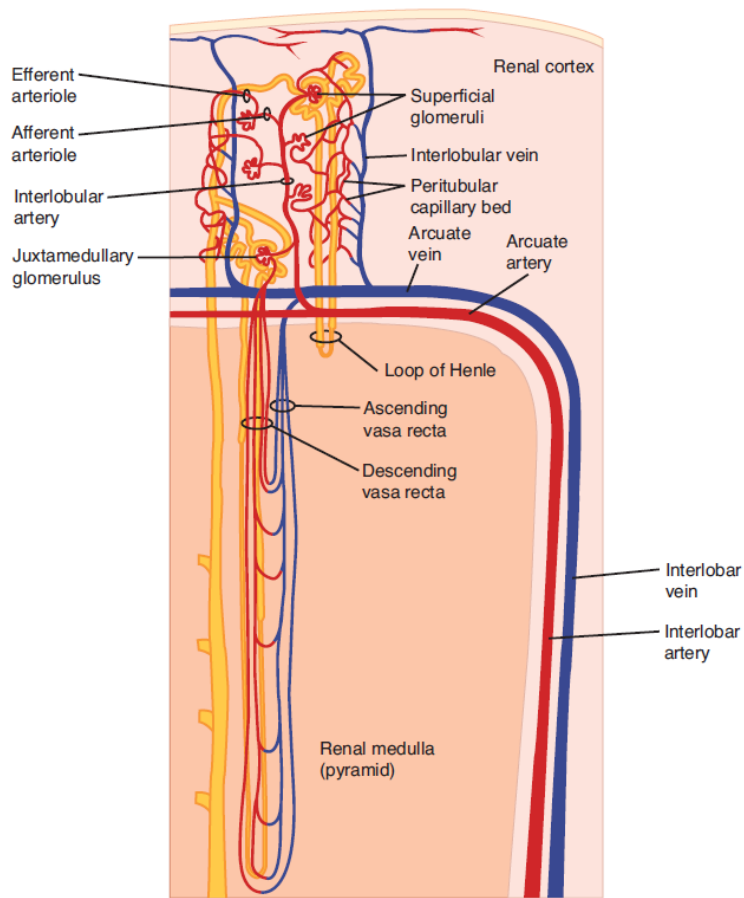


# Princip funkce ledvin

- ◆ **Glomerulární filtrace = primární moč (voda, nízkomolekulární látky krevní plazmy)**
- ◆ **Zpětný transport látek v tubulu a sběracím kanálku**
  - **Dle druhu látky (př. glukóza X močovina)**
  - **Dle potřeby vyloučení látky (regulace) = resorpce**
- ◆ **Exkrece = vyloučení zbytku filtrátu**
  - **Role sekrece**

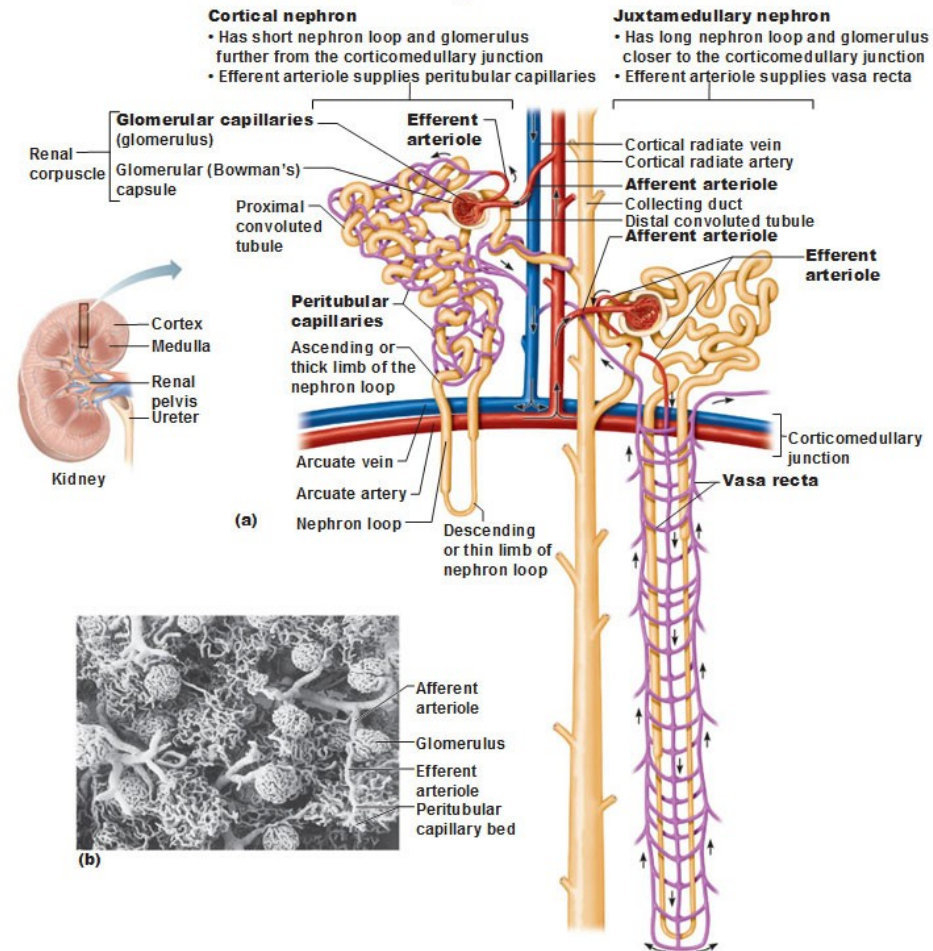


# Renální cirkulace a nefrony



## Korové x juxtamedulární nefrony

### Classes of Nephrons



**FIGURE 38-3 Renal circulation.** Interlobular arteries divide into arcuate arteries, which give off interlobular arteries in the cortex. The interlobular arteries provide an afferent arteriole to each glomerulus. The efferent arteriole from each glomerulus breaks up into capillaries that supply blood to the renal tubules. Venous blood enters interlobular veins, which in turn flow via arcuate veins to the interlobular veins. (Modified from Boron WF, Boulpaep EL: *Medical Physiology*. Saunders, 2003.)

**Dvojitá kapilární síť v sérii za sebou**

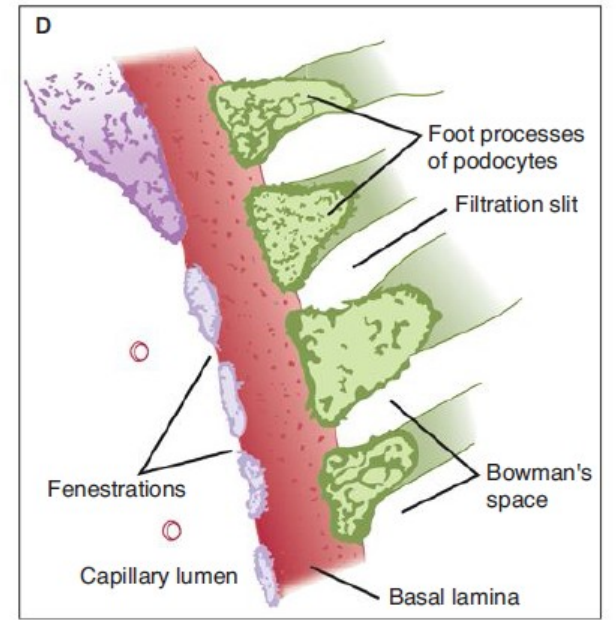
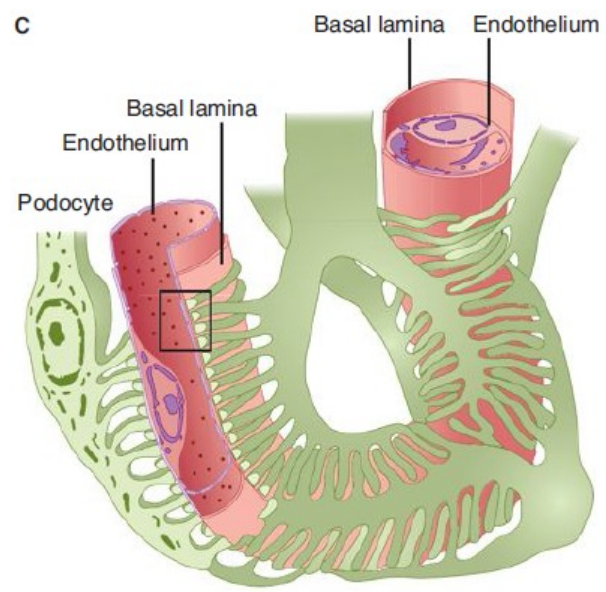
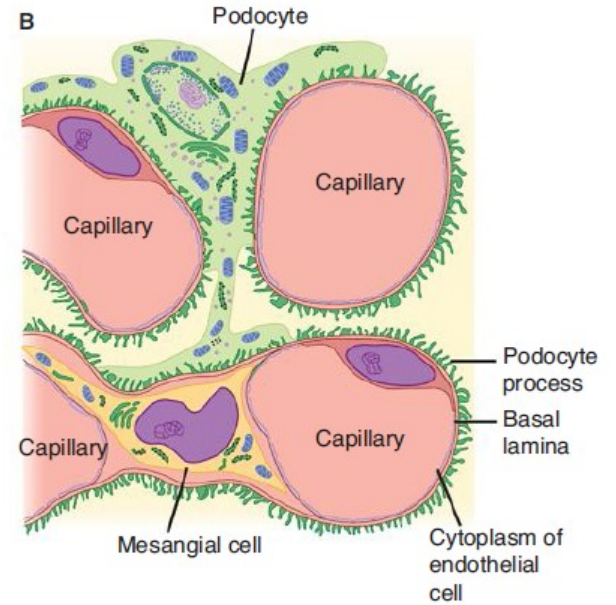
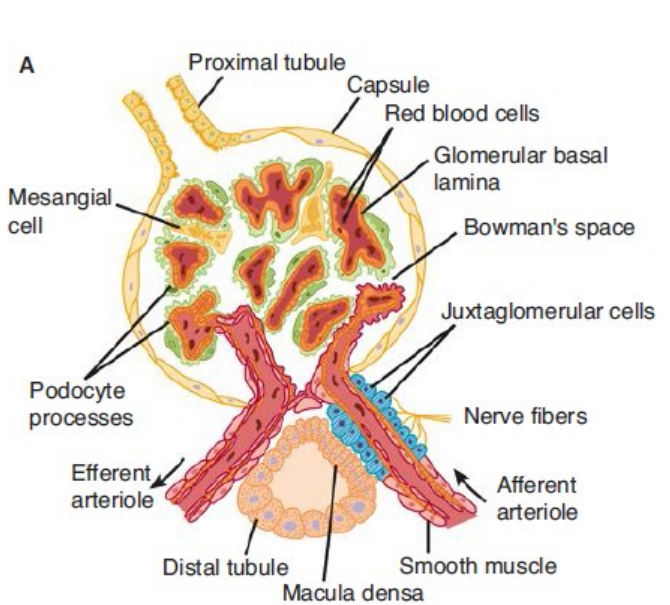
**Významný minutový průtok krve (1250 ml/min)**

**- 90 % kůra, 10 % dřeň**

**Tlak krve 60 mm Hg (glomerulární kapiláry) X 15 mm Hg (peritubulární kapilární síť)**

# Funkční histologie ledvin

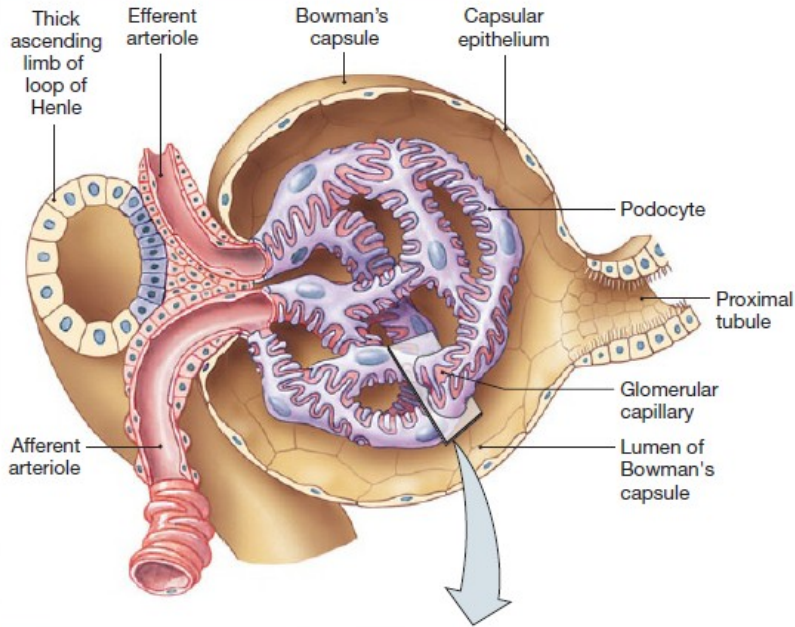
- Nefron
- Bowmanovo pouzdro
- Klubko kapilárních vlásečnic = glomerulus



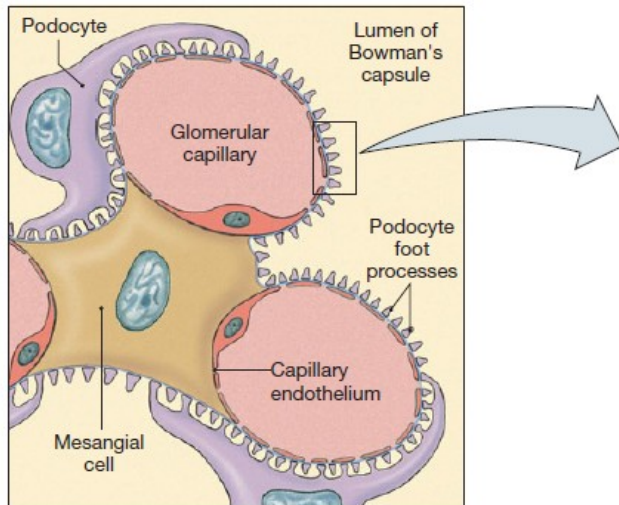
**FIGURE 38-2 Structural details of glomerulus.** A) Section through vascular pole, showing capillary loops. B) Relation of mesangial cells and podocytes to glomerular capillaries. C) Detail of the way podocytes form filtration slits on the basal lamina, and the relation of the lamina to the capillary endothelium. D) Enlargement of the rectangle in C to show the podocyte processes. The fuzzy material on their surfaces is glomerular polyanion.

## THE RENAL CORPUSCLE

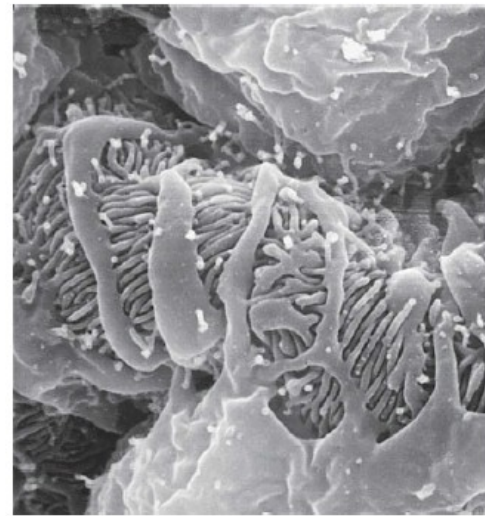
(a) The epithelium around glomerular capillaries is modified into podocytes.



(c) Podocyte foot processes surround each capillary, leaving slits through which filtration takes place. Mesangial cells between the capillaries contract to alter blood flow.



(b) Micrograph showing podocyte foot processes around glomerular capillary.



(d) The glomerular capillary endothelium, basal lamina, and Bowman's capsule epithelium create a three-layer filtration barrier. Filtered substances pass through endothelial pores and filtration slits.

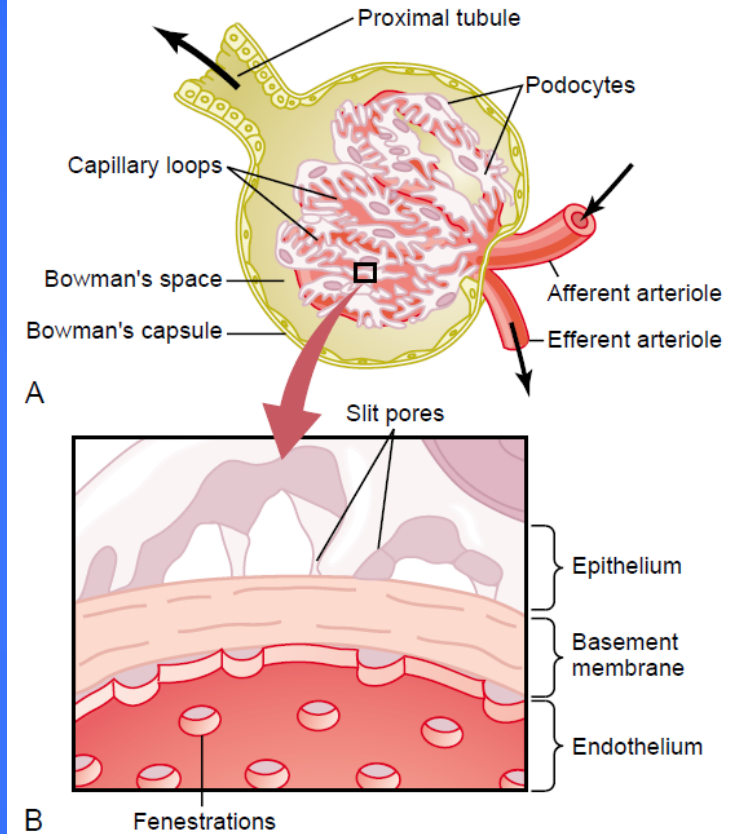
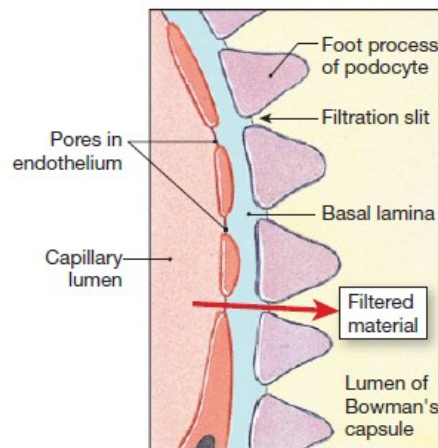
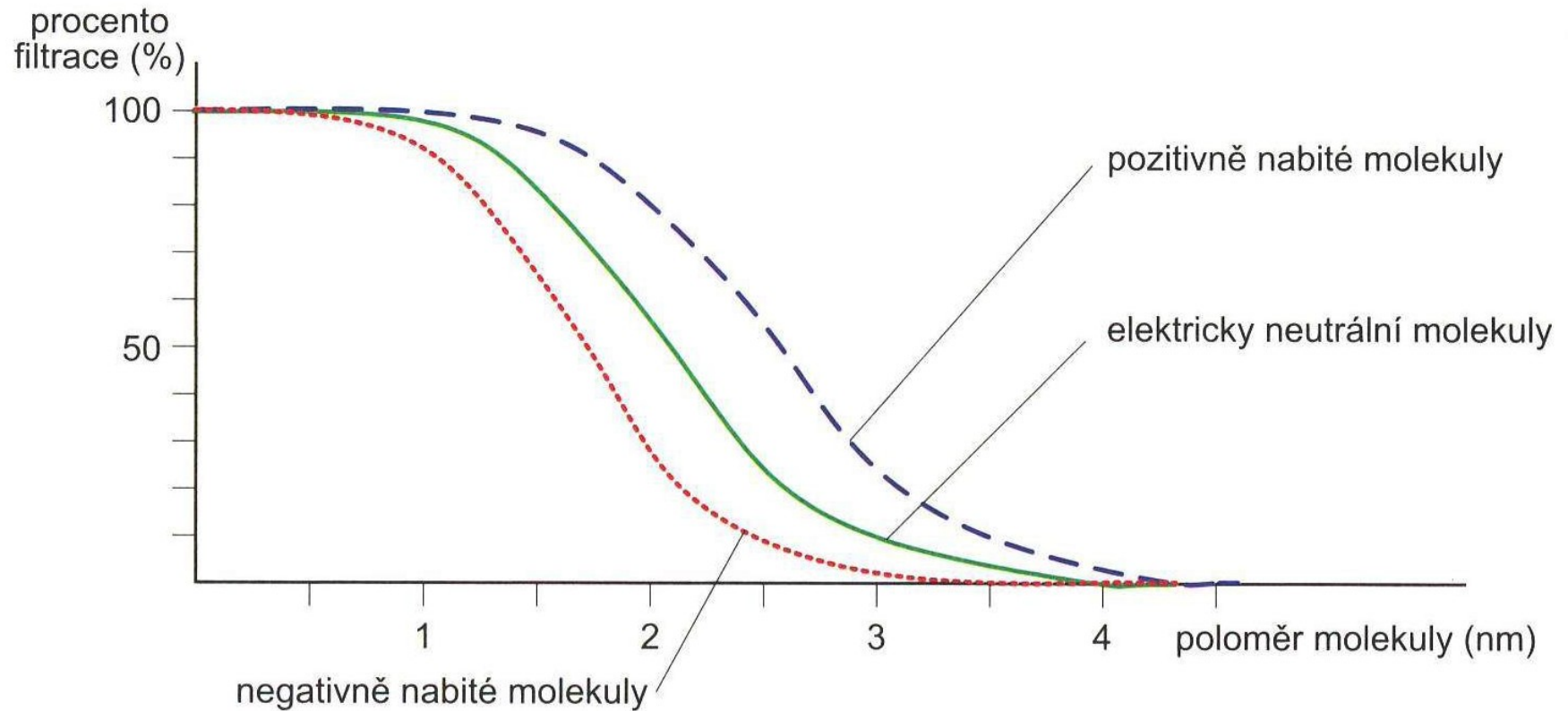


Figure 26-10

A, Basic ultrastructure of the glomerular capillaries. B, Cross section of the glomerular capillary membrane and its major components: capillary endothelium, basement membrane, and epithelium (podocytes).



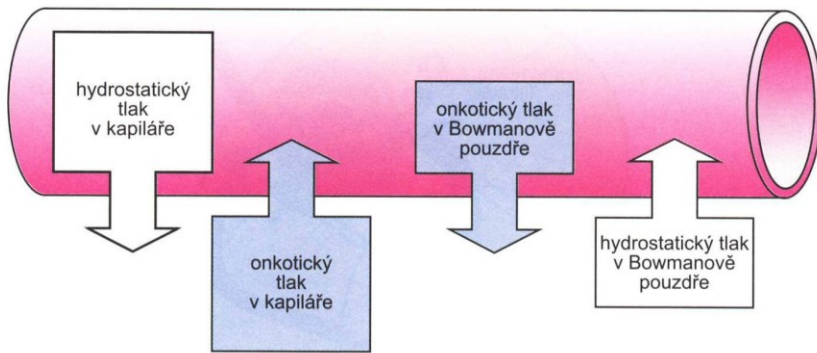
**Obr. 8.7** Vliv velikosti a elektrického náboje částic na jejich filtrabilitu v glomerulu; na obrázku je dobře vidět, že malé částice jsou volně filtrovány a velké naopak filtrační bariérou neprocházejí vůbec; částice o velikosti mezi 1,5 a 3,5 nm však procházejí v závislosti na svém náboji – zatímco kladně nabitě částice procházejí poměrně snadno, záporně nabitě částice procházejí jen velmi obtížně

### **Filterability of Substances by Glomerular Capillaries Based on Molecular Weight**

---

<b>Substance</b>	<b>Molecular Weight</b>	<b>Filterability</b>
Water	18	1.0
Sodium	23	1.0
Glucose	180	1.0
Inulin	5,500	1.0
Myoglobin	17,000	0.75
Albumin	69,000	0.005

---



Obr. 8.11 Starlingovy síly

## GLOMERULÁRNÍ FILTRAČNÍ TLAK

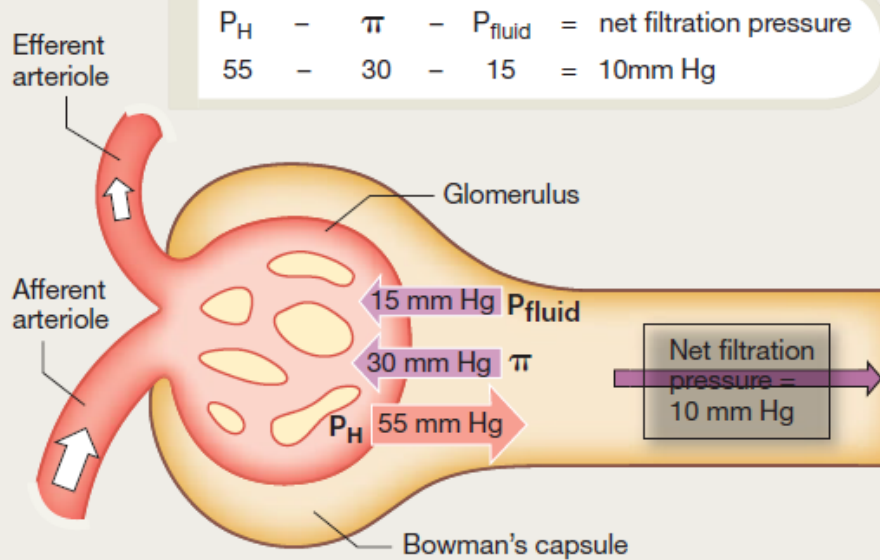
$$GFP = P_{GC} - P_{BC} + \pi_{BC} - \pi_{GC}$$

$P_{GC}$  je **hydrostatický tlak v glomerulárních kapilárách** a je totožný s tlakem krve v těchto kapilárách. Je prakticky hlavní silou podporující filtraci. Díky uspořádání krevního oběhu v ledvinách (viz kapitolu 8.2.2) a díky vysokému odporu ve *vas efferens* je tento tlak výrazně vyšší než v ostatních systémových kapilárách a představuje přibližně **60 mm Hg**.

$P_{BC}$  je **hydrostatický tlak v Bowmanově pouzdře**, který působí proti tlaku v kapilárách a tedy i proti filtraci. I tato hodnota je vyšší, než je tomu v případě hydrostatického tlaku v intersticiu okolo kapilár v ostatních částech systémového oběhu. Je to způsobeno skutečností, že do Bowmanova pouzdra je filtrován velký objem tekutiny a její odvod do tubulárního systému má omezenou kapacitu. Typicky představuje hydrostatický tlak v Bowmanově pouzdře **15 mm Hg**.

$\pi_{BC}$  je **onkotický tlak v Bowmanově pouzdře**, který podporuje filtraci. Protože tekutina, která je filtrována v ledvinových těliscích, obecně neobsahuje žádné proteiny, tedy i osmotický tlak, který proteiny vytvářejí v roztoku (tzv. onkotický tlak) musí být za normálních okolností prakticky nulový. Za patologických okolností ovšem tato hodnota nulová být vždy nemusí. Fyziologicky je ale onkotický tlak v pouzdře **0 mm Hg**.

$\pi_{GC}$  je **onkotický tlak plazmatických bílkovin v glomerulárních kapilárách**. Tento tlak brání filtraci, protože udržuje tekutinu v krevním oběhu. Protože v glomerulárních kapilárách dochází díky rozsáhlé filtraci k velkým ztrátám tekutin, hodnota onkotického tlaku v plazmě se během průtoku kapilárami zvyšuje z jinde obvyklých 25 mm Hg až na **29 mm Hg**.

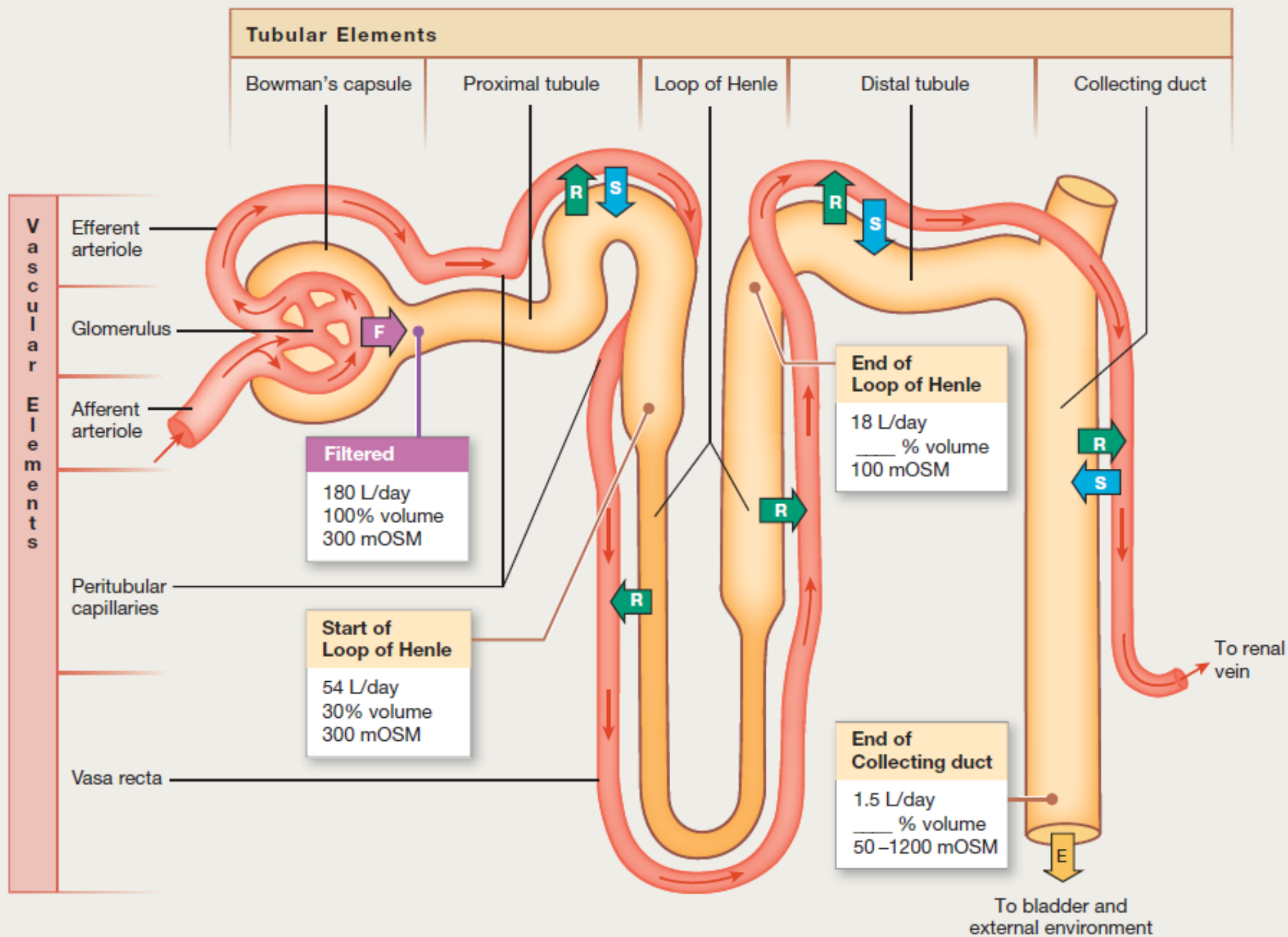


### KEY

$P_H$  = Hydrostatic pressure (blood pressure)

$\pi$  = Colloid osmotic pressure gradient due to proteins in plasma but not in Bowman's capsule

$P_{fluid}$  = Fluid pressure created by fluid in Bowman's capsule





# ŘÍZENÍ GLOMERULÁRNÍ FILTRACE

## ◆ Faktory ovlivňující GFP:

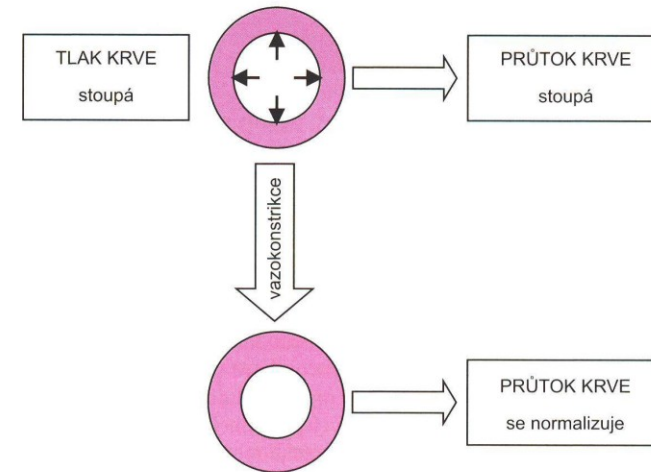
- Permeabilita glomerulárních kapilár
- Velikost kapilárního řečiště – mezangiální buňky = změna filtrační plochy
- Hydrostatický a osmotický tlak

## ◆ Lokální regulační mechanismy

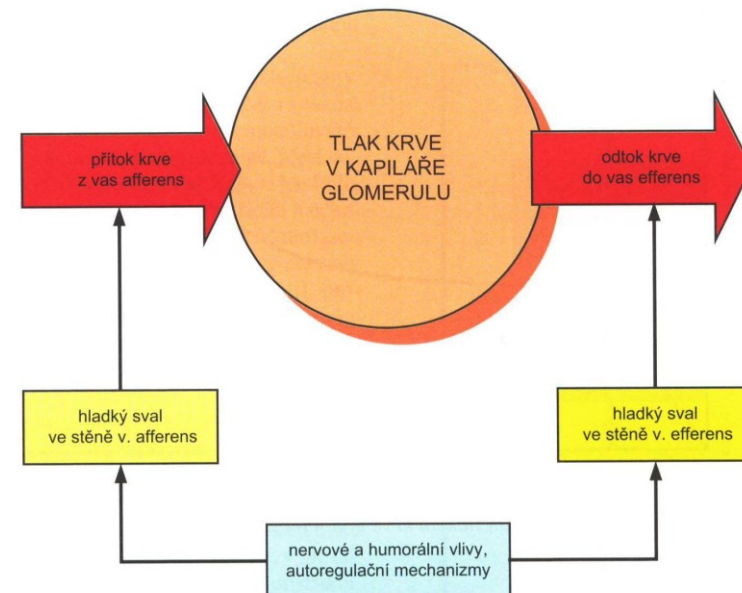
- Myogenní autoregulace
- Tubuloglomerulární zpětná vazba

$$Q = \Delta P / R$$

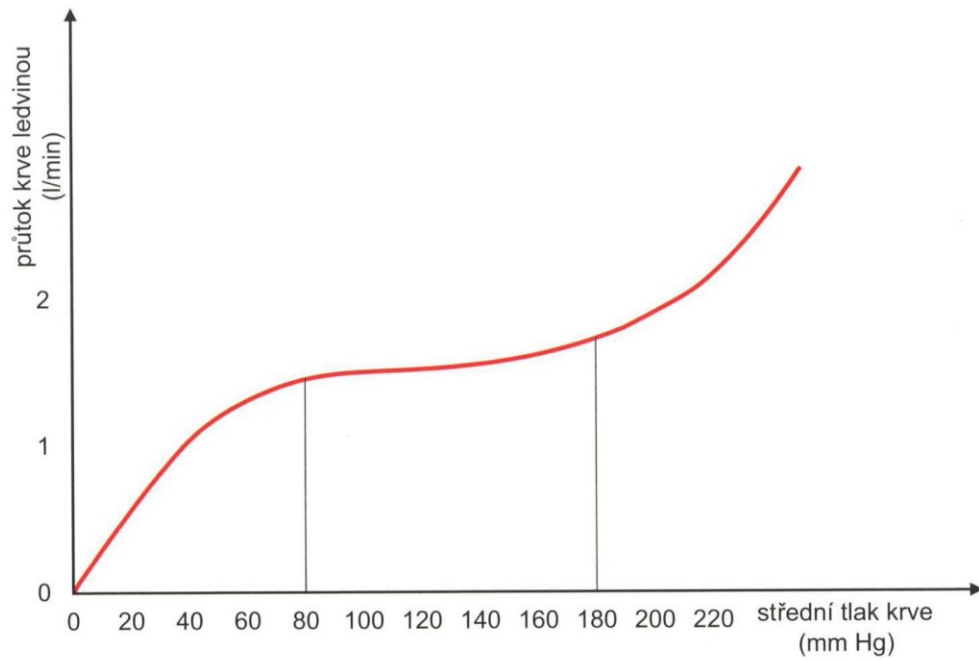
kde **Q** je **průtok krve** orgánem,  
 **$\Delta P$**  je pak **rozdíl tlaků** mezi arteriálním a venózním tlakem v daném orgánu (v případě ledvin je to tedy rozdíl tlaků mezi *a. renalis* a *v. renalis*),  
**R** je **periferní odpor**, který je v cévním řečišti orgánu kladen toku krve (v případě ledvin jsou hlavními rezistenčními cévami *vas afferens*, *vas efferens* a *arteria interlobularis* a ty fakticky určují periferní odpor v ledvině).



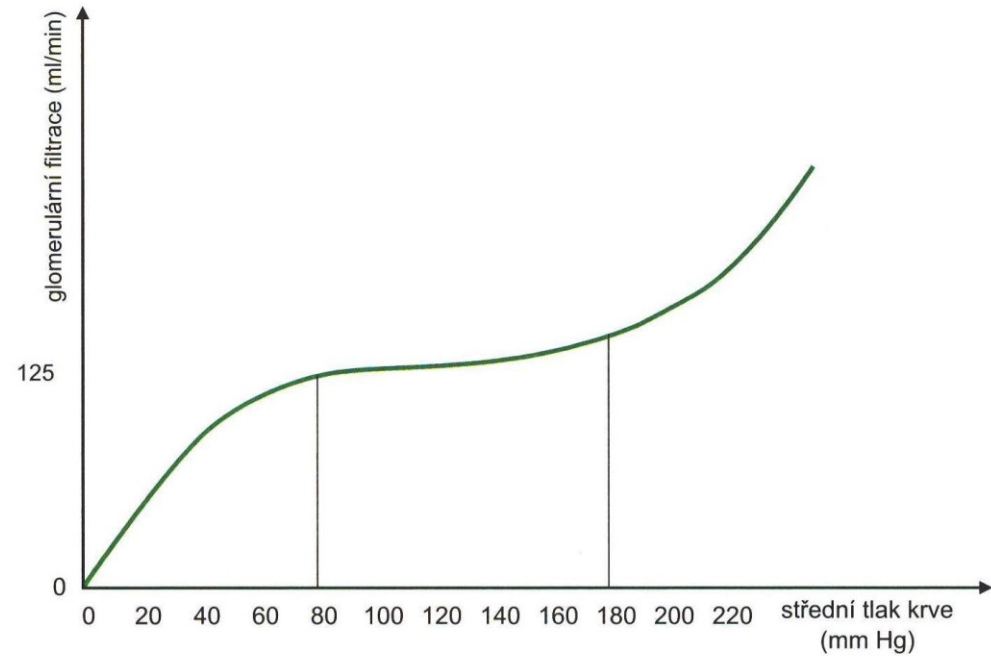
Obr. 8.12 Fungování myogenní autoregulace (podrobnosti viz text)



Obr. 8.13 Determinanty tlaku krve v glomerulární kapiláře



**Obr. 8.14** *Vztah mezi středním tlakem krve a průtokem krve ledvinou*



**Obr. 8.15** *Vztah mezi středním tlakem krve a glomerulární filtrací*

## Factors That Can Decrease the Glomerular Filtration Rate (GFR)

Physical Determinants*	Physiologic/Pathophysiologic Causes
$\downarrow K_f \rightarrow \downarrow \text{GFR}$	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow \text{GFR}$	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow \text{GFR}$	$\downarrow$ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow \text{GFR}$ $\downarrow A_P \rightarrow \downarrow P_G$	$\downarrow$ Arterial pressure (has only small effect due to autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	$\downarrow$ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	$\uparrow$ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

\* Opposite changes in the determinants usually increase GFR.

$K_f$ , glomerular filtration coefficient;  $P_B$ , Bowman's capsule hydrostatic pressure;  $\pi_G$ , glomerular capillary colloid osmotic pressure;  $P_G$ , glomerular capillary hydrostatic pressure;  $A_P$ , systemic arterial pressure;  $R_E$ , efferent arteriolar resistance;  $R_A$ , afferent arteriolar resistance.

## Hormones and Autacoids That Influence Glomerular Filtration Rate (GFR)

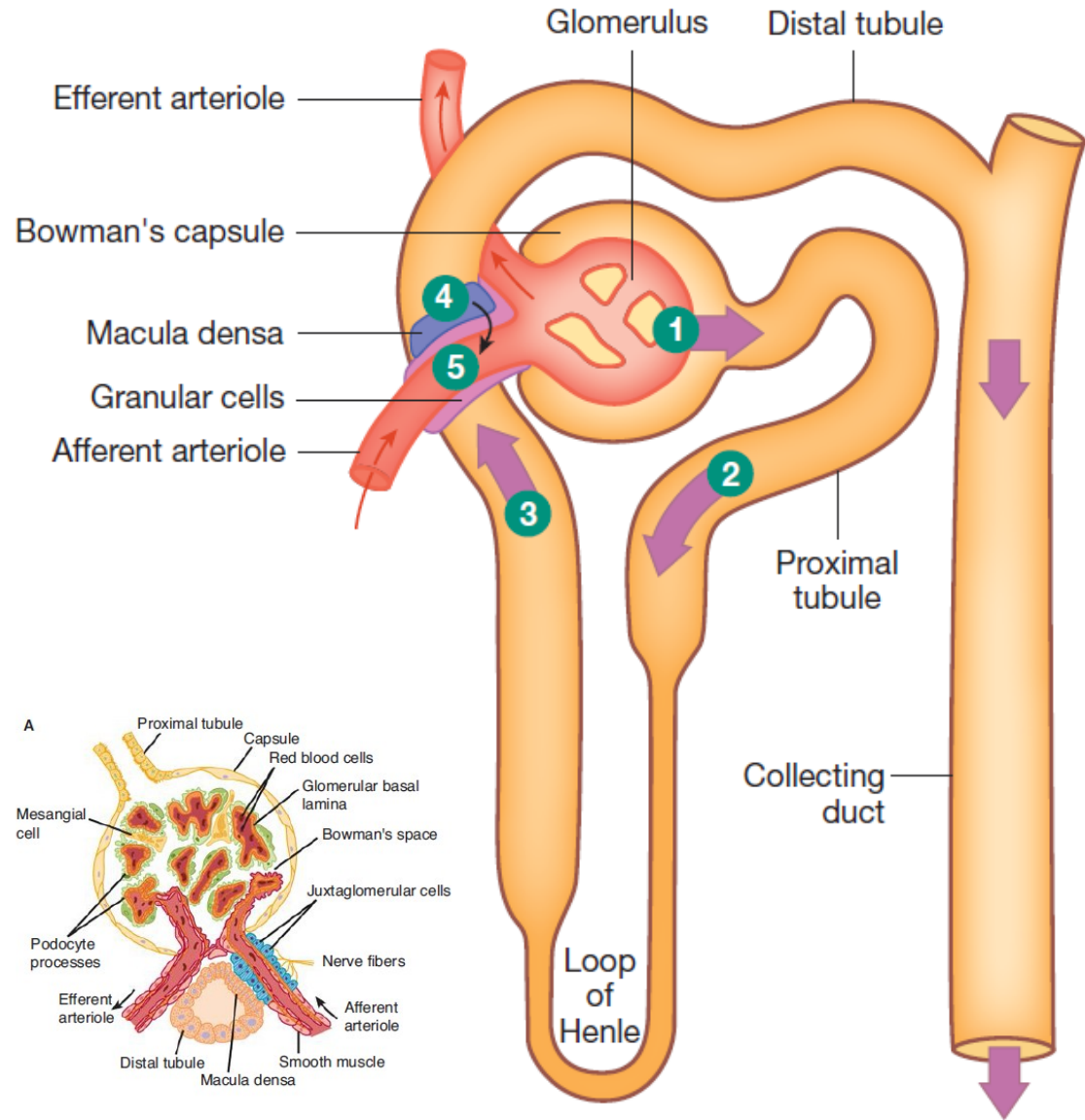
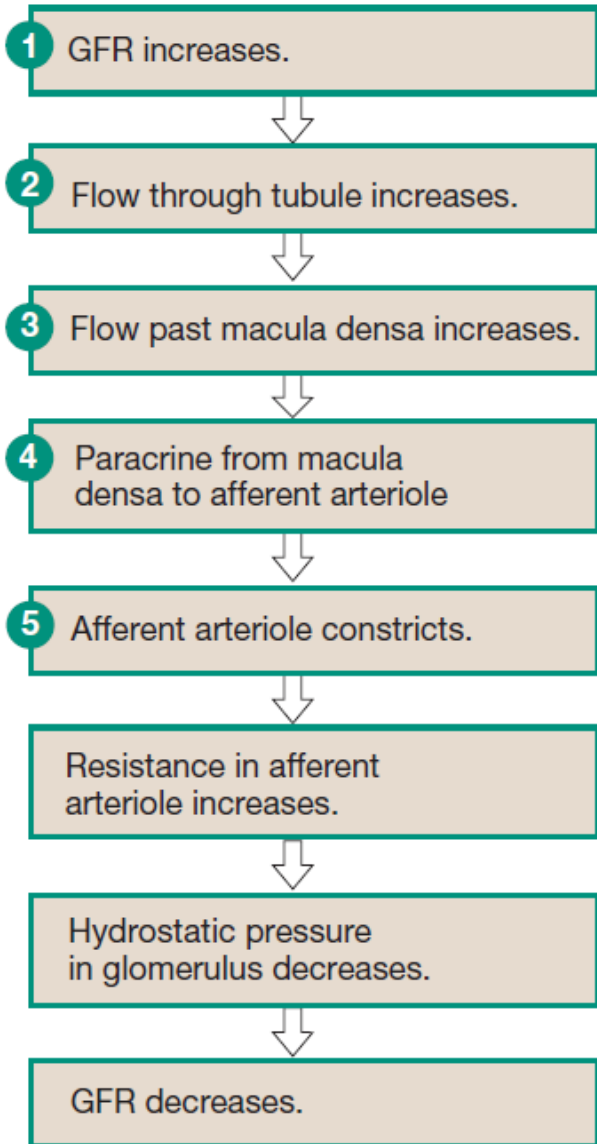
Hormone or Autacoid	Effect on GFR
Norepinephrine	$\downarrow$
Epinephrine	$\downarrow$
Endothelin	$\downarrow$
Angiotensin II	$\longleftrightarrow$ (prevents $\downarrow$ )
Endothelial-derived nitric oxide	$\uparrow$
Prostaglandins	$\uparrow$

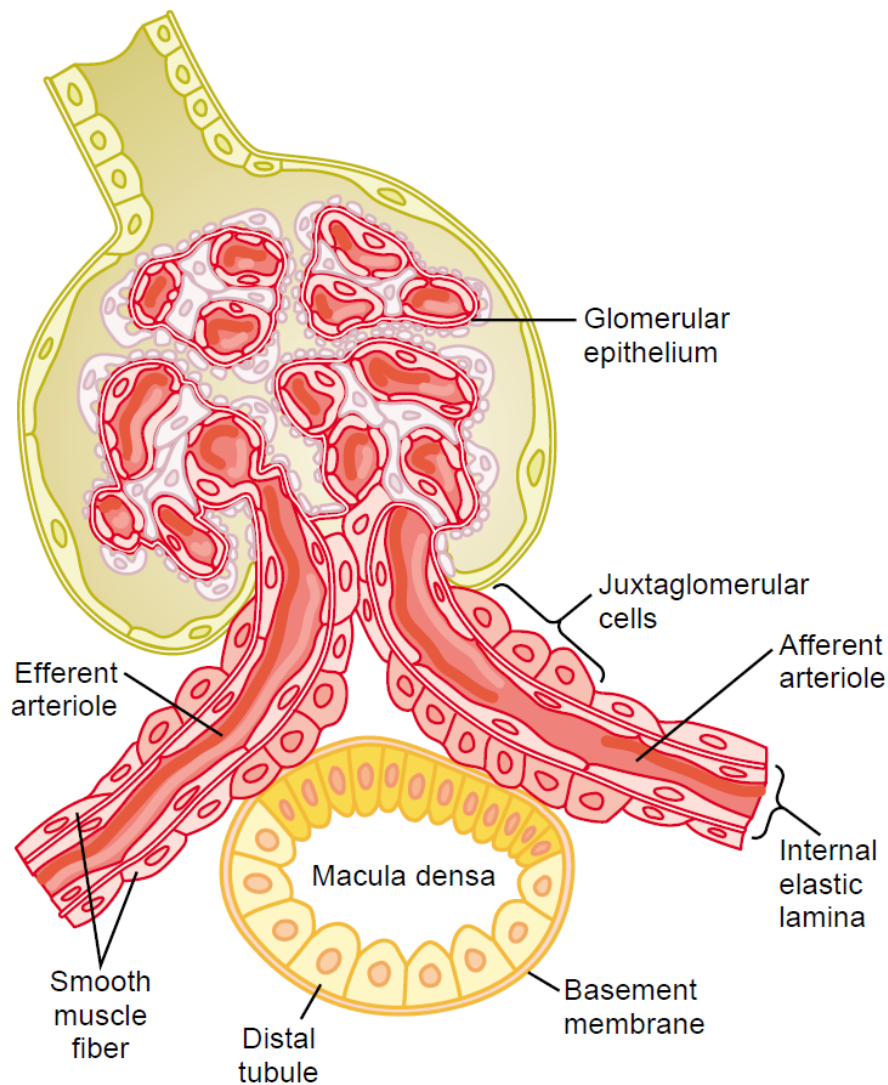
Changes in renal blood flow
Changes in glomerular capillary hydrostatic pressure
Changes in systemic blood pressure
Afferent or efferent arteriolar constriction
Changes in hydrostatic pressure in Bowman's capsule
Ureteral obstruction
Edema of kidney inside tight renal capsule
Changes in concentration of plasma proteins: dehydration, hypoproteinemia, etc (minor factors)
Changes in $K_f$
Changes in glomerular capillary permeability
Changes in effective filtration surface area

**TABLE 38-3** Agents causing contraction or relaxation of mesangial cells.

Contraction	Relaxation
Endothelins	ANP
Angiotensin II	Dopamine
Vasopressin	$\text{PGE}_2$
Norepinephrine	cAMP
Platelet-activating factor	
Platelet-derived growth factor	
Thromboxane $A_2$	
$\text{PGF}_2$	
Leukotrienes $C_4$ and $D_4$	
Histamine	

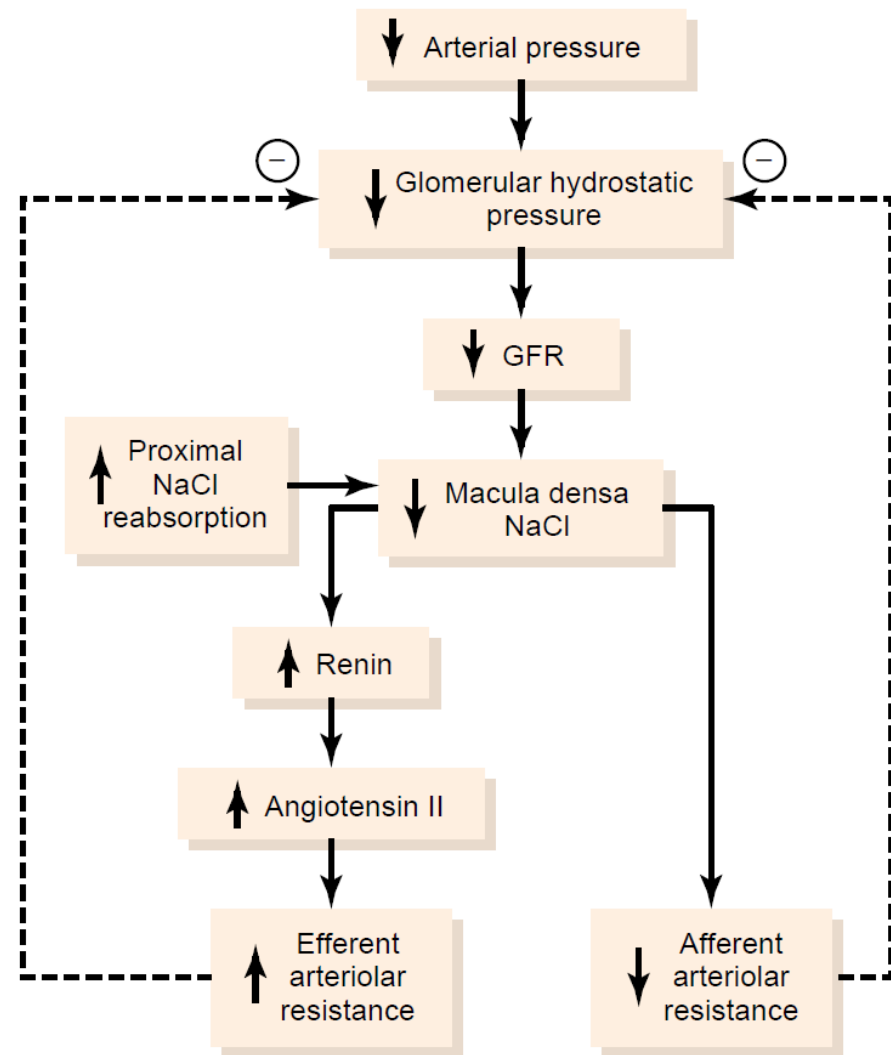
(c) Tubuloglomerular feedback helps GFR autoregulation.





**Figure 26-17**

Structure of the juxtaglomerular apparatus, demonstrating its possible feedback role in the control of nephron function.



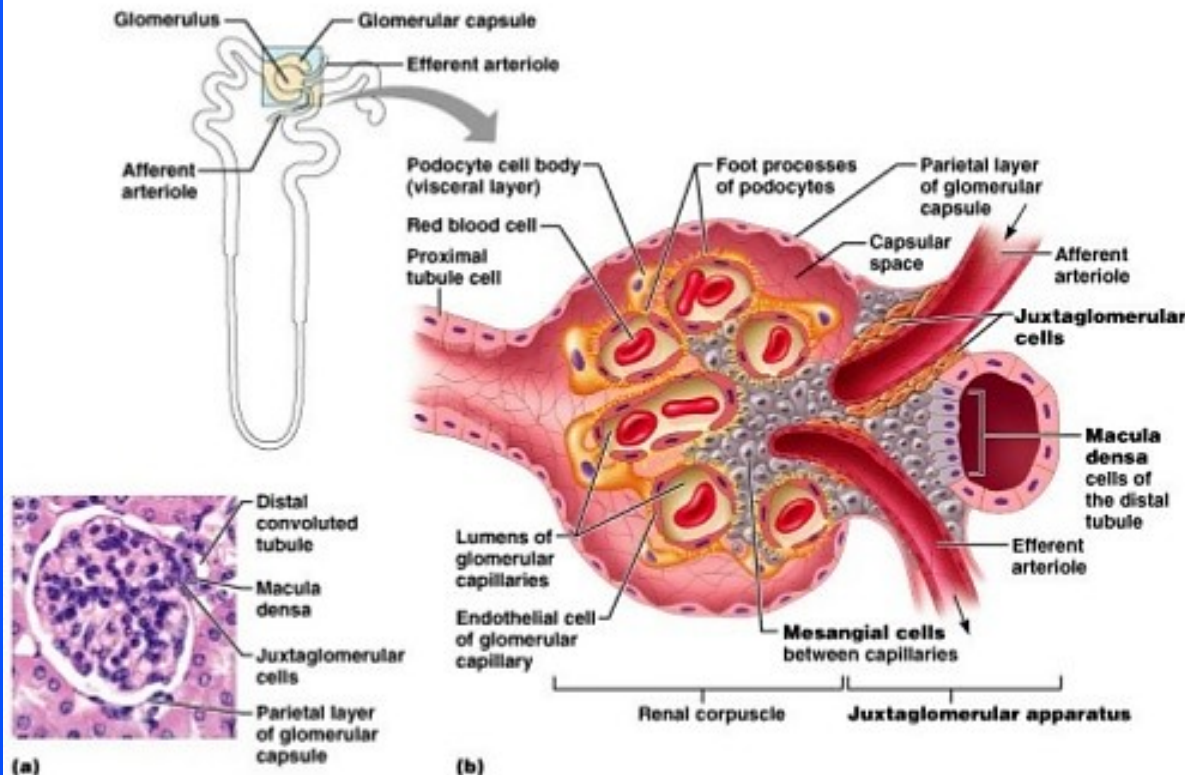
**Figure 26-18**

Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure.

# Juxtaglomerular apparatus

- Regulation of blood pressure
- Granule (jg cells) – modified muscle cells secreting renin in response to falling blood pressure in afferent arteriole
- Macula densa – chemoreceptors which secrete renin if solute concentration falls

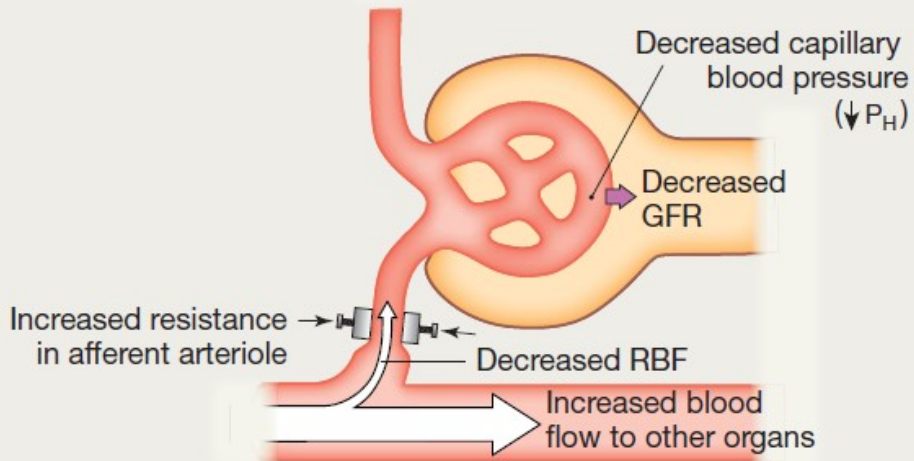
*Mezangiální buňky*  
*Buňky macula densa*  
*Granulární buňky*



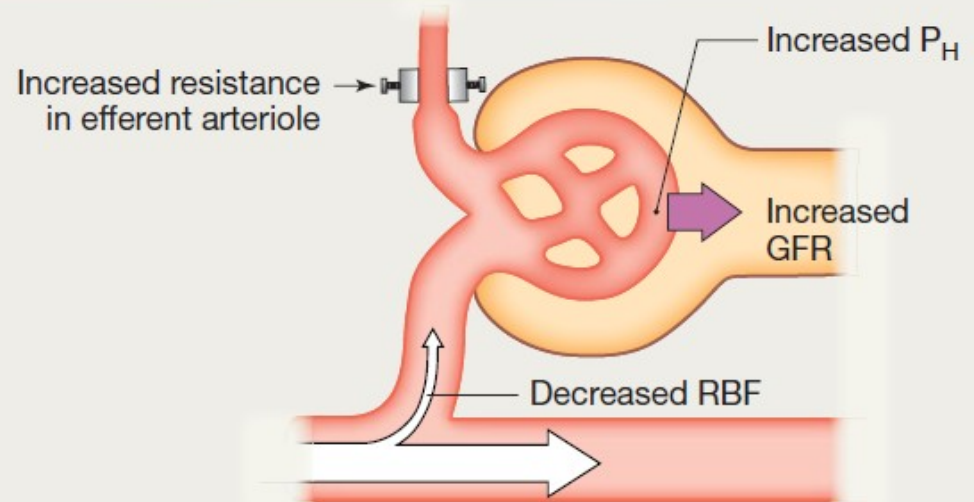
## Renin-angiotensin mechanism:

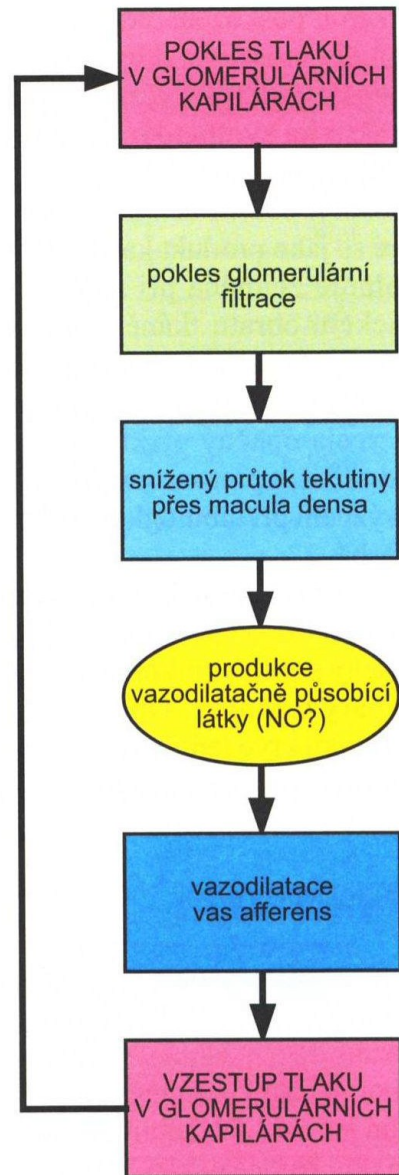
Sequence of reactions resulting in aldosterone secretion from adrenal cortex: increases sodium resorption from distal convoluted tubules: water follows, blood volume increases and blood pressure increases

(d) Vasoconstriction of the afferent arteriole increases resistance and decreases renal blood flow, capillary blood pressure ( $P_H$ ), and GFR.

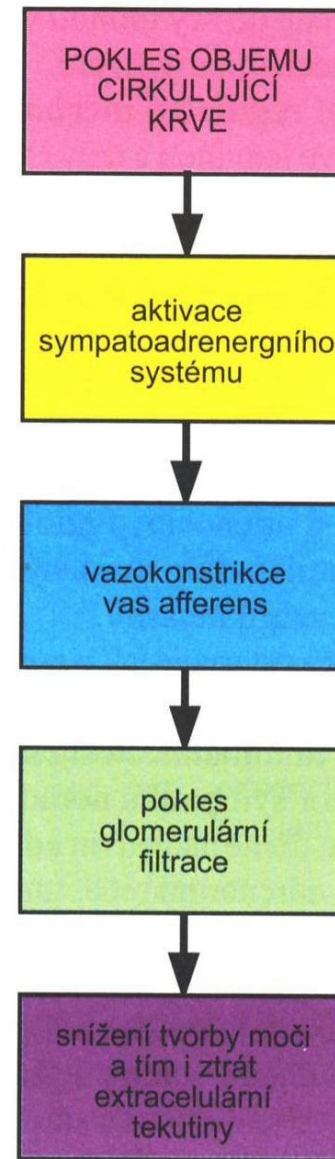


(e) Increased resistance of efferent arteriole decreases renal blood flow but increases  $P_H$  and GFR.





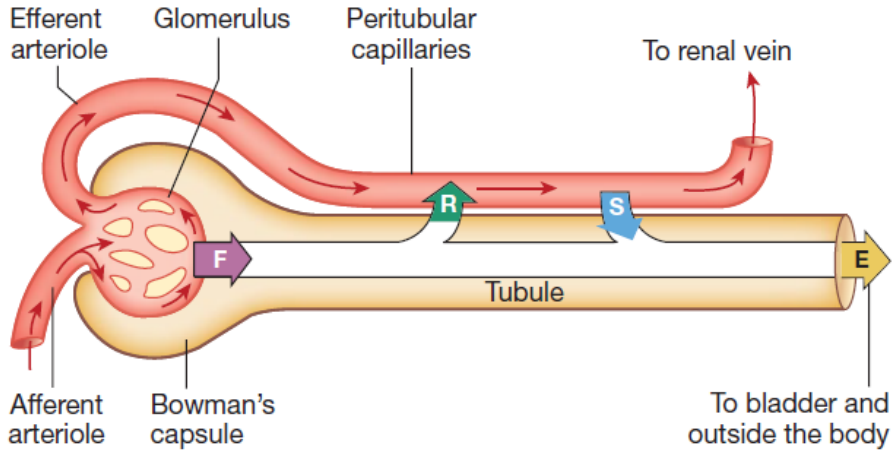
**Obr. 8.16** Schéma fungování tubuloglomerulární zpětné vazby



**Obr. 8.17** Účast ledvin v reakci na pokles cirkulující krve



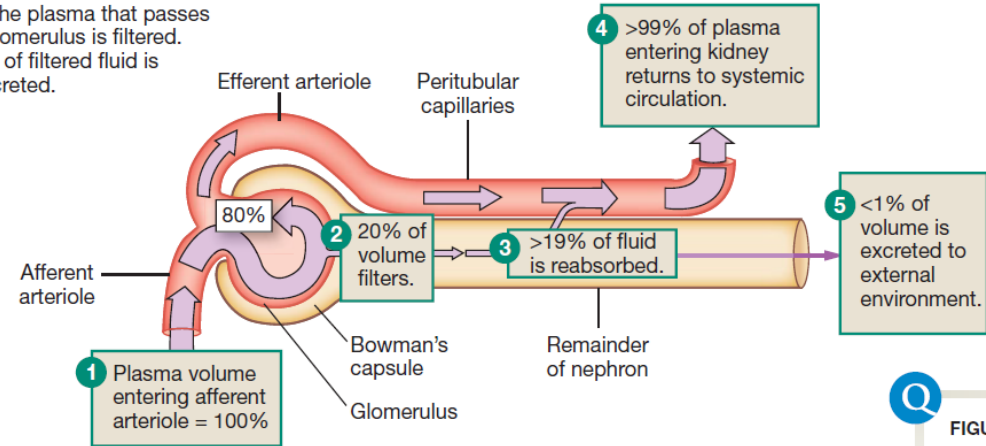
The urinary excretion of a substance depends on its filtration, reabsorption, and secretion.



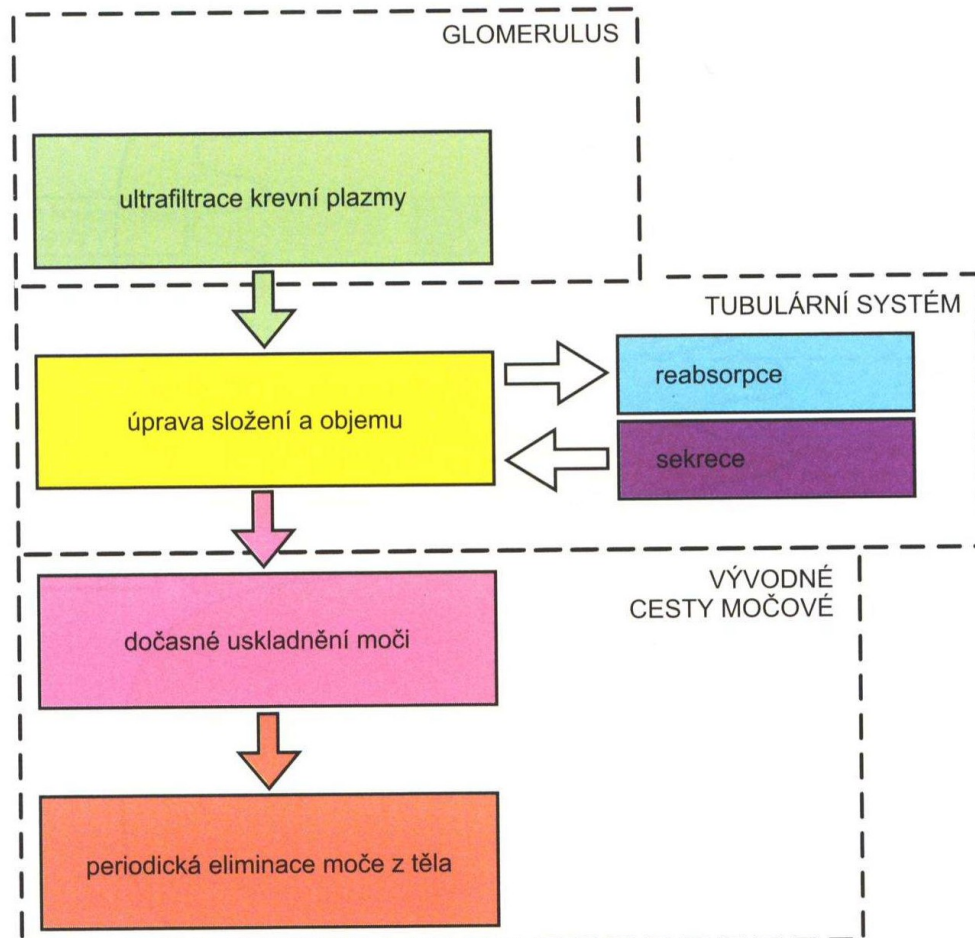
$$\text{Amount filtered (F)} - \text{amount reabsorbed (R)} + \text{amount secreted (S)} = \text{amount of solute excreted (E)}$$

### THE FILTRATION FRACTION

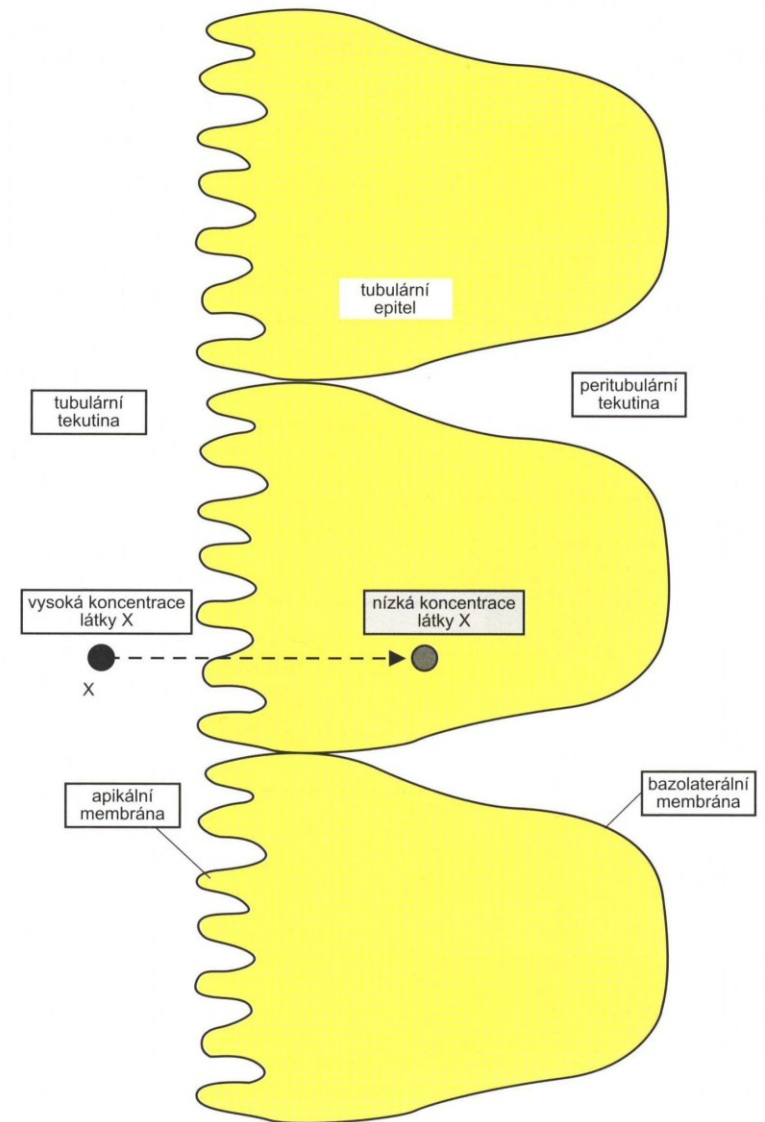
Only 20% of the plasma that passes through the glomerulus is filtered. Less than 1% of filtered fluid is eventually excreted.



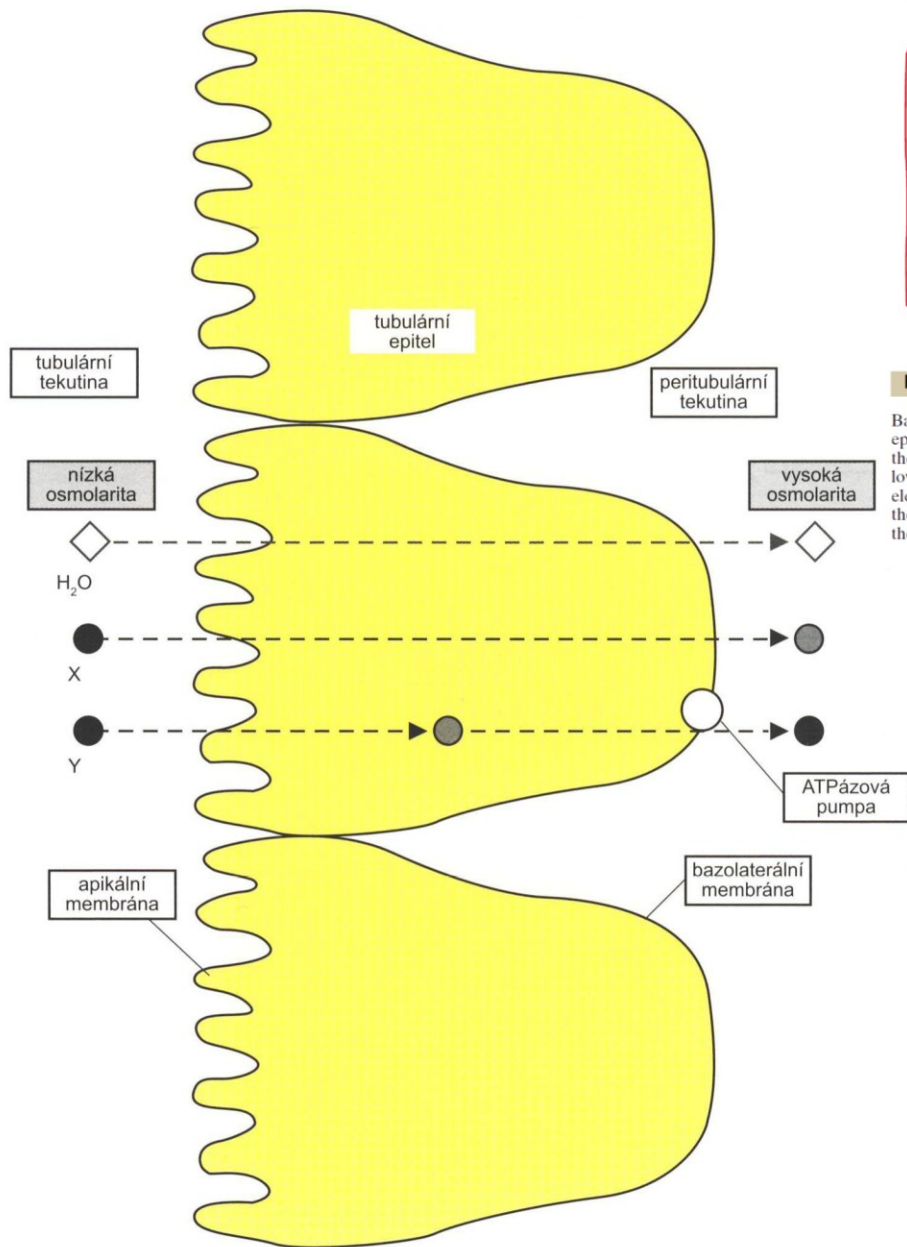
# TUBULÁRNÍ FUNKCE



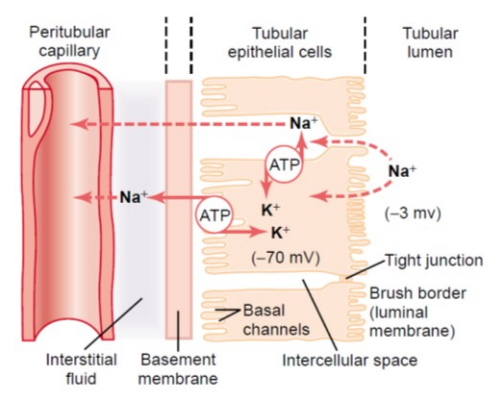
**Obr. 8.18** Jednotlivé procesy v průběhu tvorby, úpravy a vylučování moči



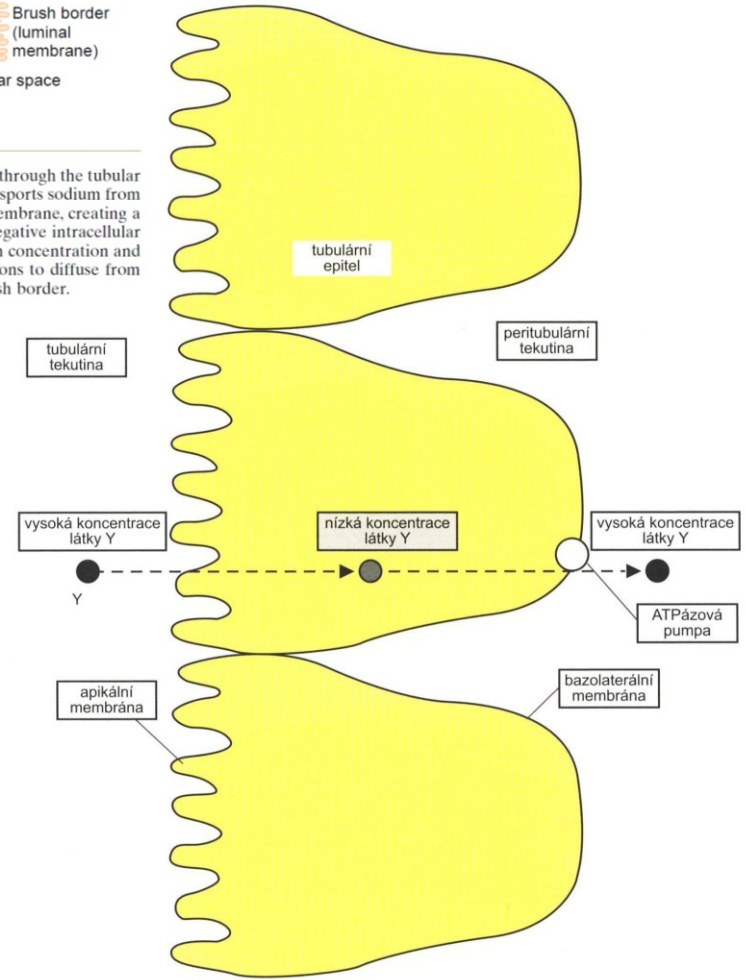
**Obr. 8.19** Pasivní transport: tento typ transportu se odehrává ve směru koncentračního gradientu a nespotřebává žádnou energii



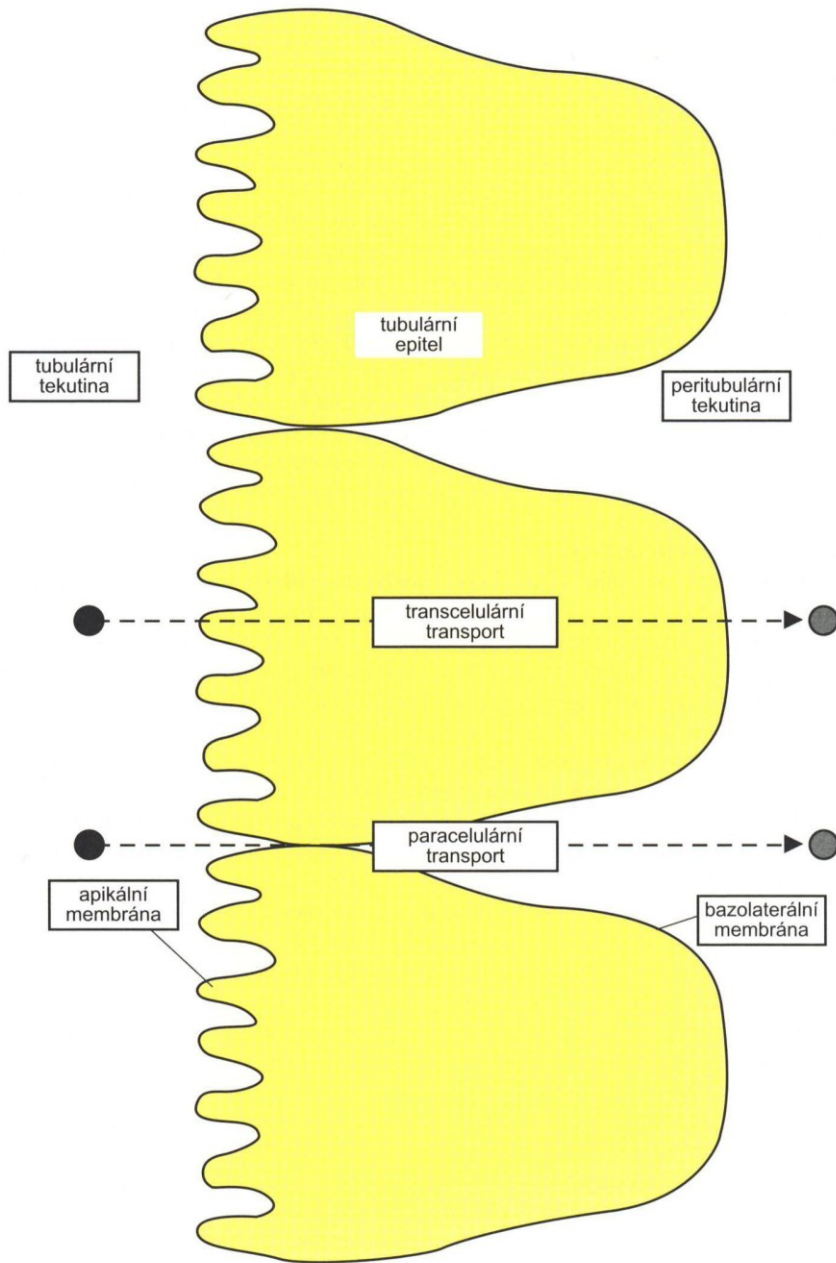
**Obr. 8.21** Transport vody přes tubulární buňky: voda difunduje pasivně ve směru osmotického gradientu vytvořeného transportem solutů



**Figure 27-2**  
Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. The low intracellular sodium concentration and the negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.



**Obr. 8.20** Aktivní transport: probíhá proti elektrochemickému gradientu a je energeticky náročný; na obrázku je látka Y transportována aktivně přes bazolaterální membránu; sekundární aktivní transport: na apikální membráně transportní bílkovina využívá koncentračního gradientu vytvořeného primárně aktivním transportem realizovaným jinou transportní bílkovinou na bazolaterální membráně



Obr. 8.22 Transport transcelulární a paracelulární

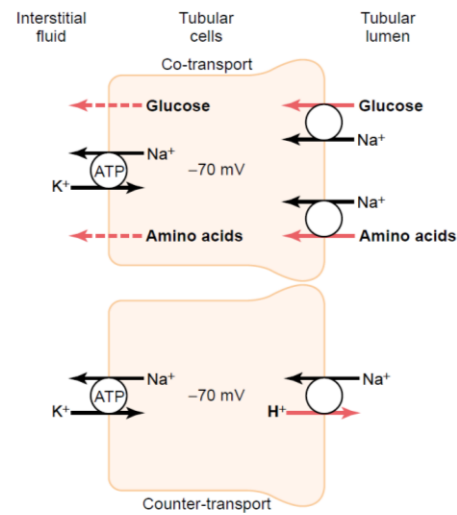
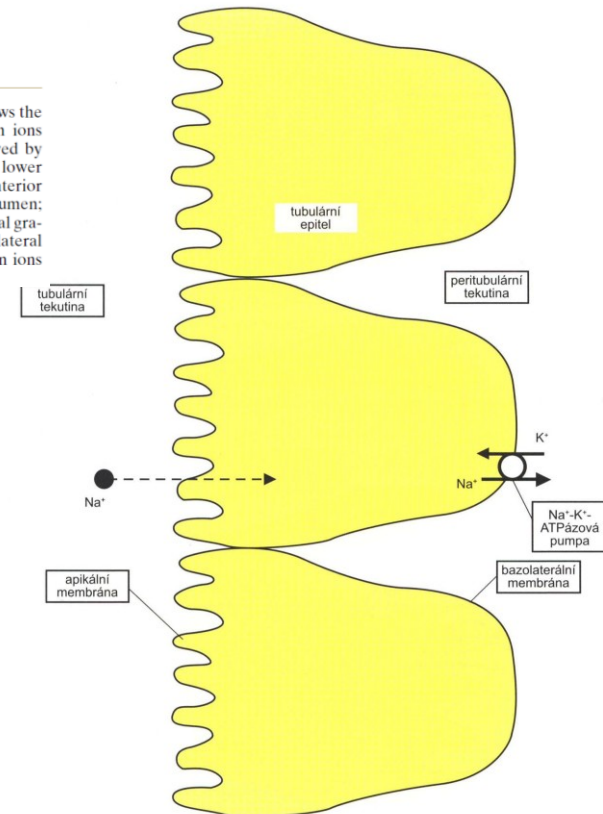


Figure 27-3

Mechanisms of secondary active transport. The upper cell shows the *co-transport* of glucose and amino acids along with sodium ions through the apical side of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The lower cell shows the *counter-transport* of hydrogen ions from the interior of the cell across the apical membrane and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump on the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen.



Obr. 8.23 Podstata sekundárně aktivního transportu v ledvinných tubulech

**TABLE 38–5 Renal handling of various plasma constituents in a normal adult human on an average diet.**

Substance	Per 24 Hours				Percentage Reabsorbed
	Filtered	Reabsorbed	Secreted	Excreted	
Na <sup>+</sup> (mEq)	26,000	25,850		150	99.4
K <sup>+</sup> (mEq)	600	560 <sup>a</sup>	502	90	93.3
Cl <sup>-</sup> (mEq)	18,000	17,850		150	99.2
HCO <sub>3</sub> <sup>-</sup> (mEq)	4,900	4,900		0	100
Urea (mmol)	870	460 <sup>b</sup>		410	53
Creatinine (mmol)	12	1 <sup>c</sup>	1 <sup>c</sup>	12	
Uric acid (mmol)	50	49	4	5	98
Glucose (mmol)	800	800		0	100
Total solute (mOsm)	54,000	53,400	100	700	98.9
Water (mL)	180,000	179,000		1000	99.4

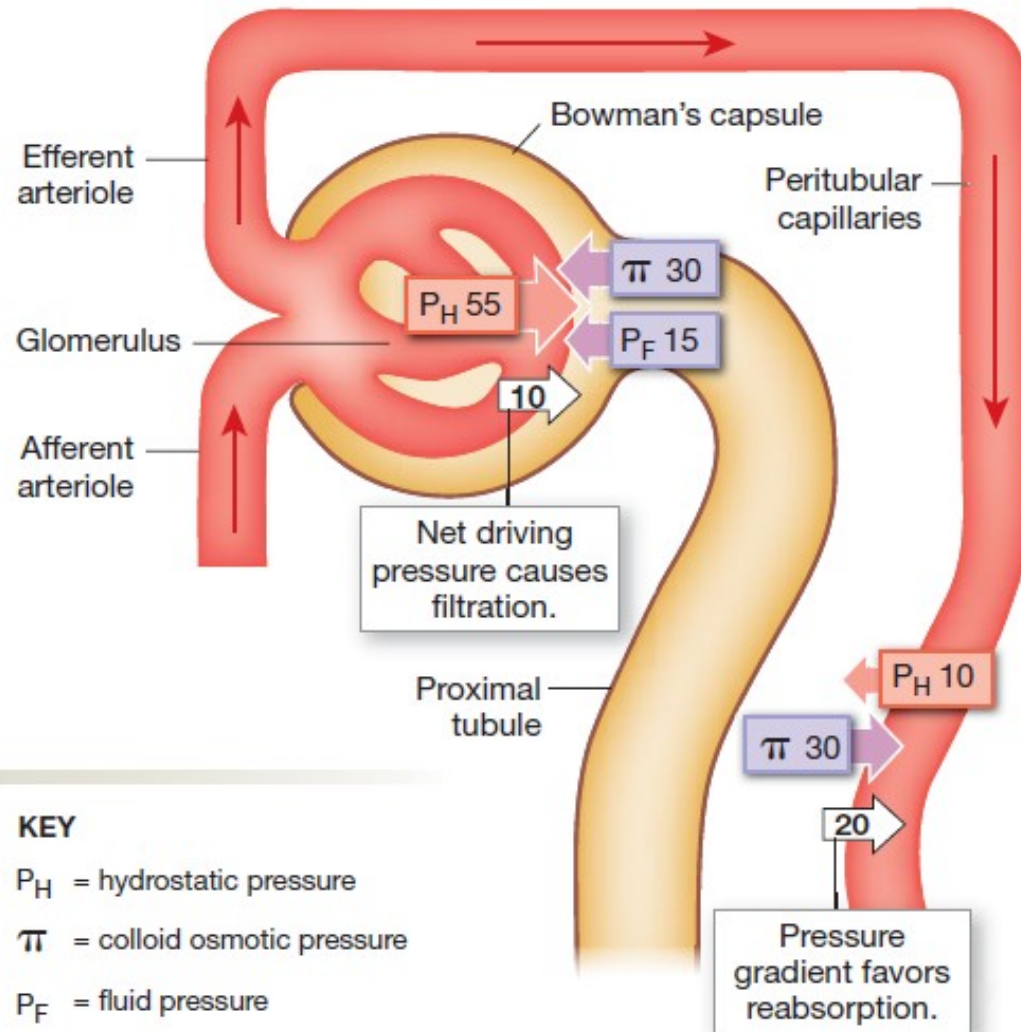
<sup>a</sup>K<sup>+</sup> is both reabsorbed and secreted.

<sup>b</sup>Urea moves into as well as out of some portions of the nephron.

<sup>c</sup>Variable secretion and probable reabsorption of creatinine in humans.

## REABSORPTION IN PERITUBULAR CAPILLARIES

Lower hydrostatic pressure in peritubular capillaries results in net reabsorption of interstitial fluid.



### KEY

$P_H$  = hydrostatic pressure

$\pi$  = colloid osmotic pressure

$P_F$  = fluid pressure

All numbers are mm Hg

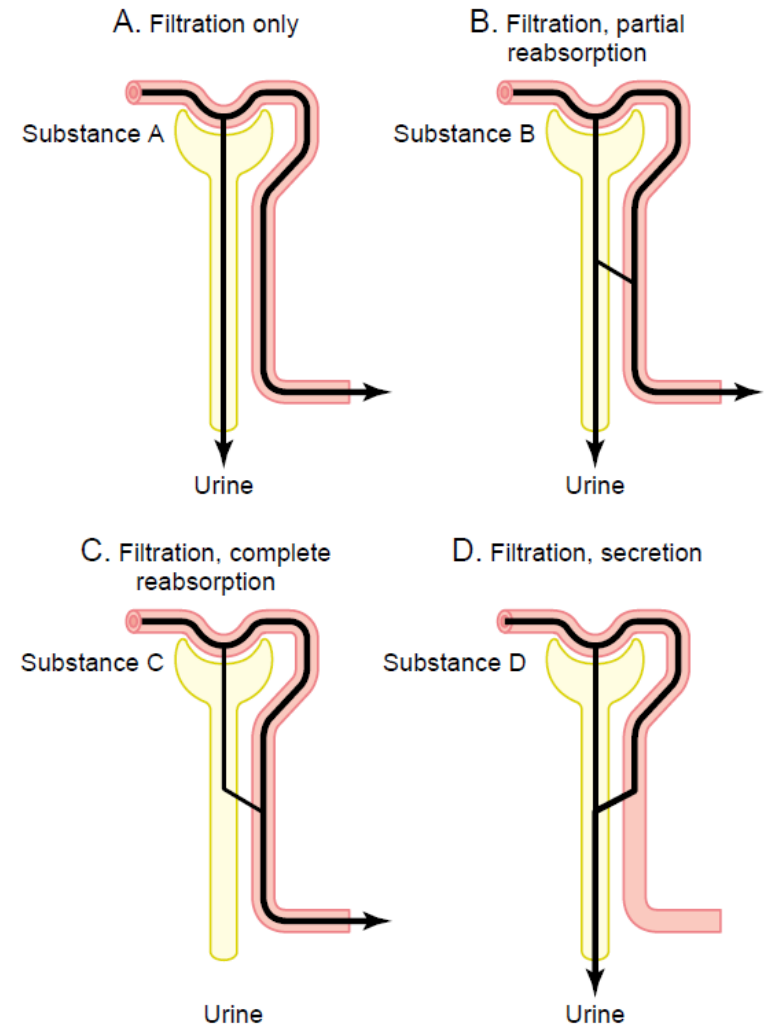


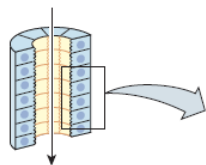
Figure 26-9

Renal handling of four hypothetical substances. *A*, The substance is freely filtered but not reabsorbed. *B*, The substance is freely filtered, but part of the filtered load is reabsorbed back in the blood. *C*, The substance is freely filtered but is not excreted in the urine because all the filtered substance is reabsorbed from the tubules into the blood. *D*, The substance is freely filtered and is not reabsorbed but is secreted from the peritubular capillary blood into the renal tubules.

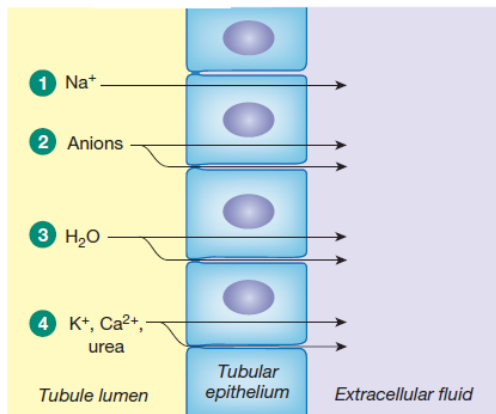
# REABSORPTION

## (a) Principles governing the tubular reabsorption of solutes

Some solutes and water move into and then out of epithelial cells (transcellular or epithelial transport); other solutes move through junctions between epithelial cells (the paracellular pathway). Membrane transporters are not shown in this illustration.



Filtrate is similar to interstitial fluid.



1 Na<sup>+</sup> is reabsorbed by active transport.

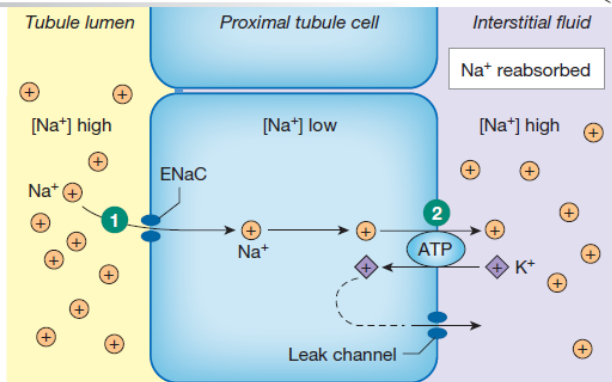
2 Electrochemical gradient drives anion reabsorption.

3 Water moves by osmosis, following solute reabsorption. Concentrations of other solutes increase as fluid volume in lumen decreases.

4 Permeable solutes are reabsorbed by diffusion through membrane transporters or by the paracellular pathway.

## (b) Sodium reabsorption in the proximal tubule: active transport

This figure shows the epithelial Na<sup>+</sup> channel, ENaC.

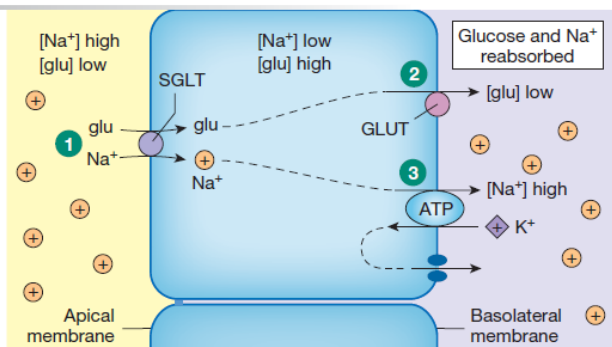


1 Na<sup>+</sup> enters cell through various membrane proteins, moving down its electrochemical gradient.

2 Na<sup>+</sup> is pumped out the basolateral side of cell by the Na<sup>+</sup>-K<sup>+</sup>-ATPase.

## (c) Sodium-linked reabsorption: indirect (secondary) active transport

This figure shows glucose, but amino acids, other organic metabolites, and some ions such as phosphate are also absorbed by Na<sup>+</sup>-dependent cotransport.



1 Na<sup>+</sup> moving down its electrochemical gradient uses the SGLT protein to pull glucose into the cell against its concentration gradient.

2 Glucose diffuses out the basolateral side of the cell using the GLUT protein.

3 Na<sup>+</sup> is pumped out by Na<sup>+</sup>-K<sup>+</sup>-ATPase.

## Substance

## Transport Maximum

Glucose	375 mg/min
Phosphate	0.10 mM/min
Sulfate	0.06 mM/min
Amino acids	1.5 mM/min
Urate	15 mg/min
Lactate	75 mg/min
Plasma protein	30 mg/min

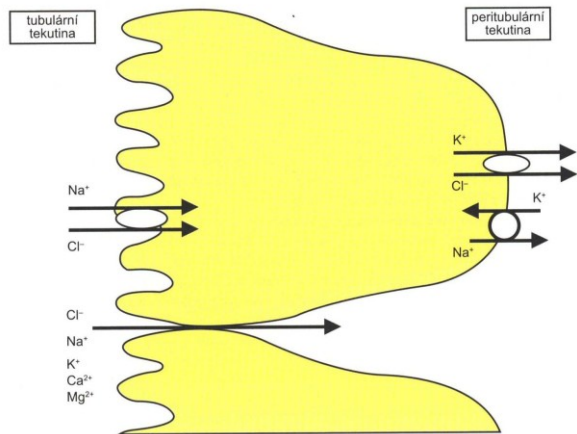
**Transport Maximums for Substances That Are Actively Secreted.** Substances that are *actively secreted* also exhibit transport maximums as follows:

## Substance

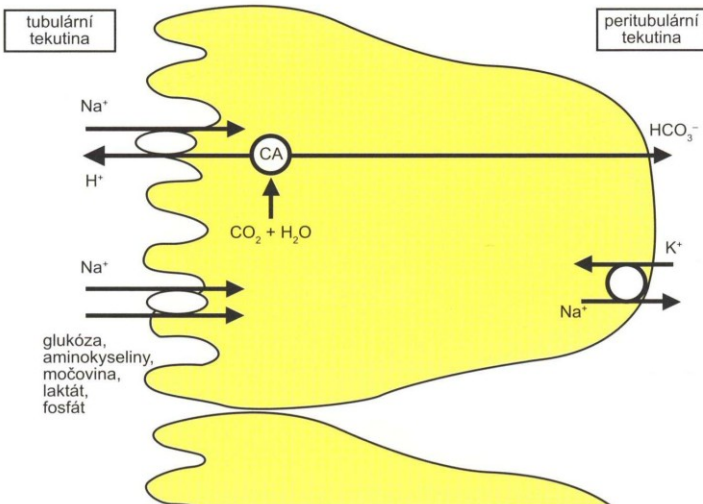
## Transport Maximum

Creatinine	16 mg/min
Para-aminohippuric acid	80 mg/min

# DĚJE V PROXIMÁLNÍM TUBULU



Obr. 8.27 Hlavní transportní mechanismy realizované v druhé polovině proximálního tubulu



Obr. 8.24 Hlavní transportní mechanismy realizované v první polovině proximálního tubulu

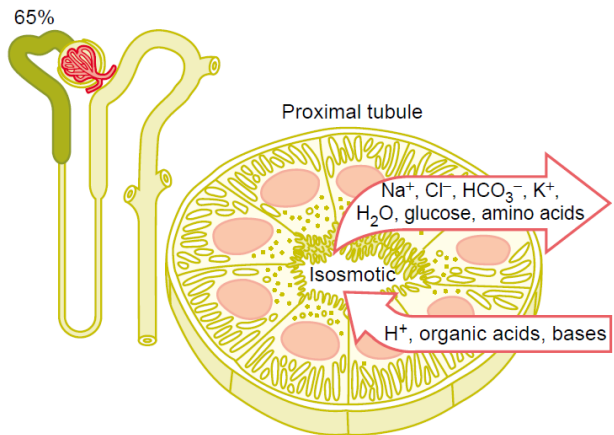
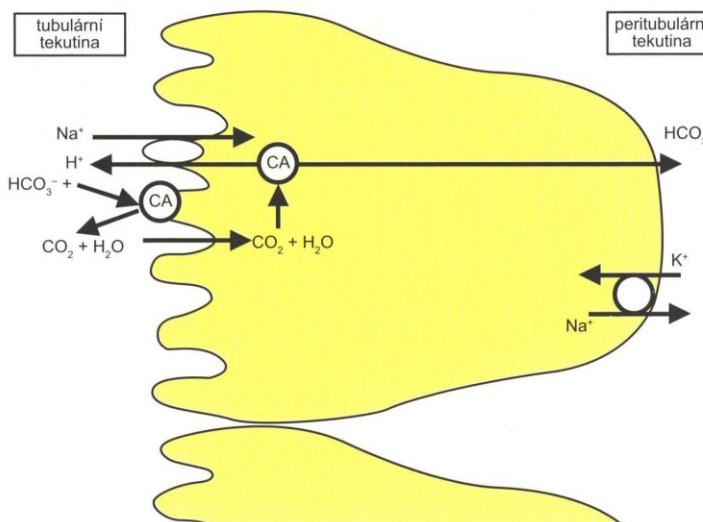


Figure 27-6

Cellular ultrastructure and primary transport characteristics of the proximal tubule. The proximal tubules reabsorb about 65 per cent of the filtered sodium, chloride, bicarbonate, and potassium and essentially all the filtered glucose and amino acids. The proximal tubules also secrete organic acids, bases, and hydrogen ions into the tubular lumen.



Obr. 8.25 Podstata resorpce bikarbonátových iontů

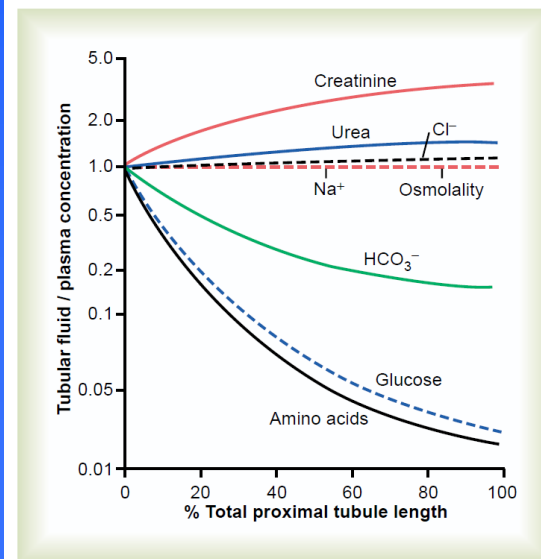
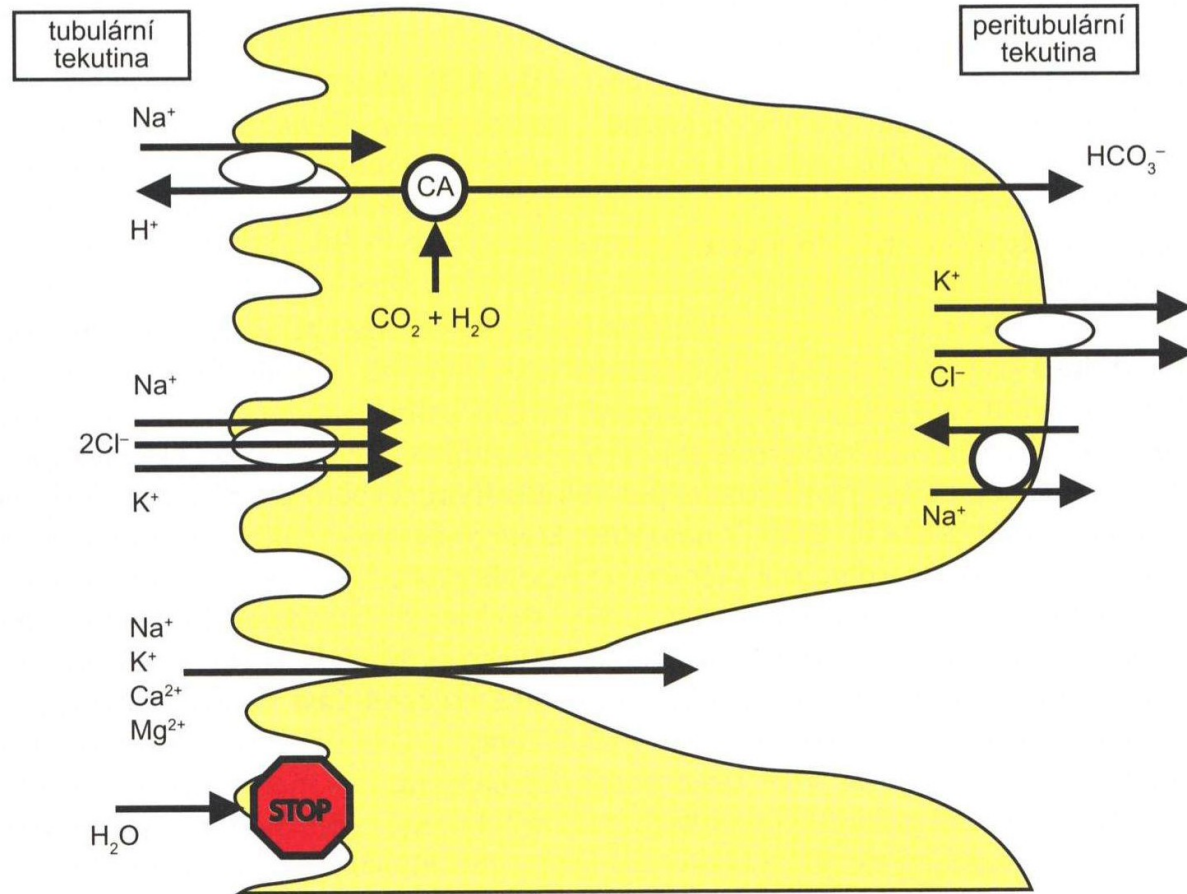


Figure 27-7

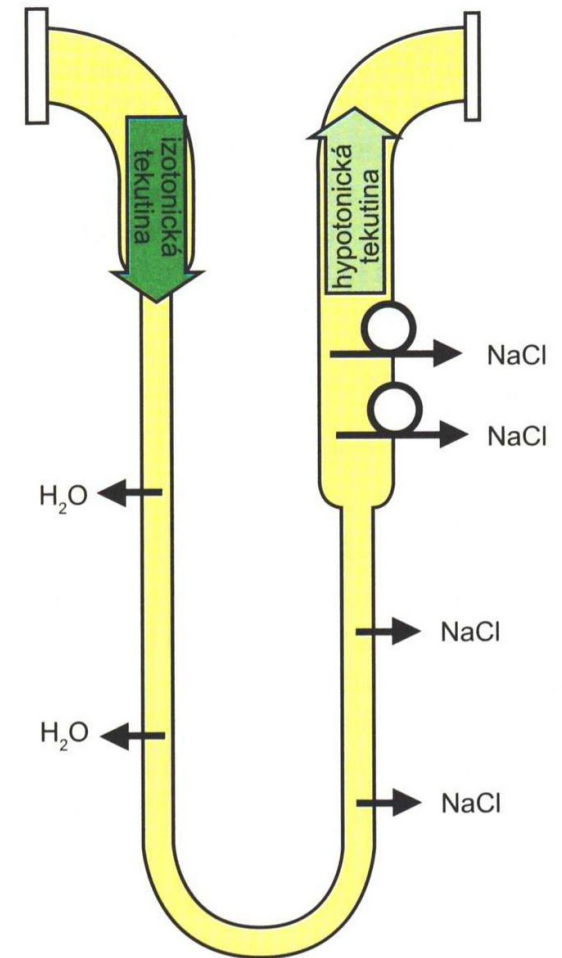
Changes in concentrations of different substances in tubular fluid along the proximal convoluted tubule relative to the concentrations of these substances in the plasma and in the glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules.



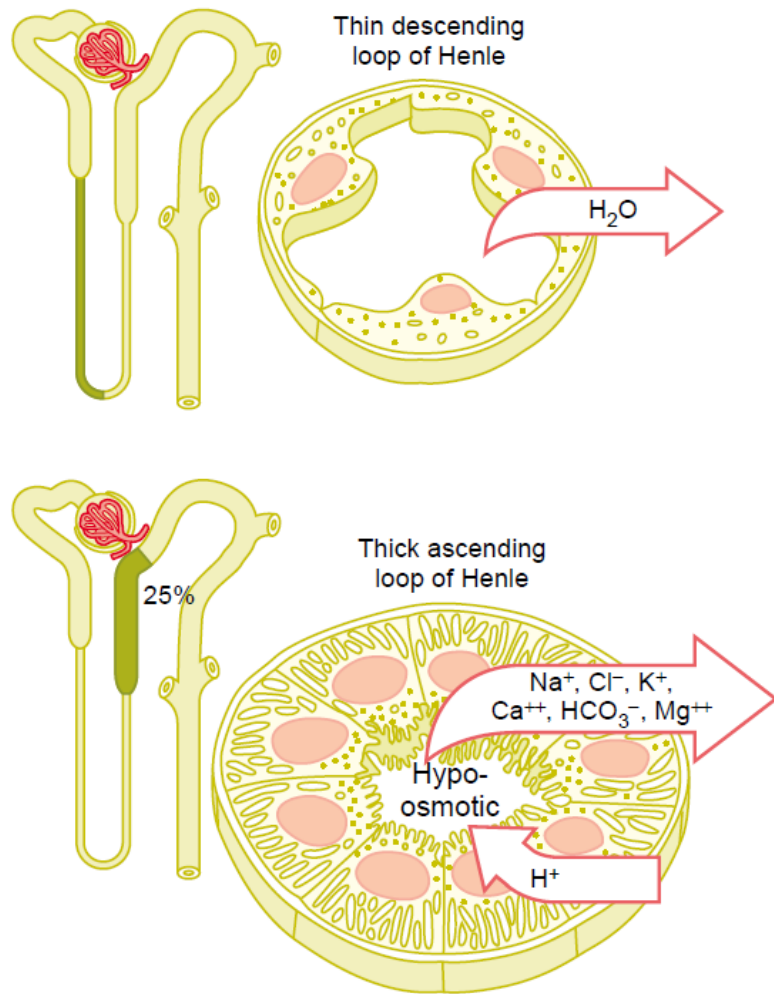
# DĚJE V HENLEOVĚ KLIČCE



**Obr. 8.28** Hlavní transportní mechanismy realizované v Henleově kličce (konkrétně v tlustém segmentu vzestupného raménka Henleovy kličky)

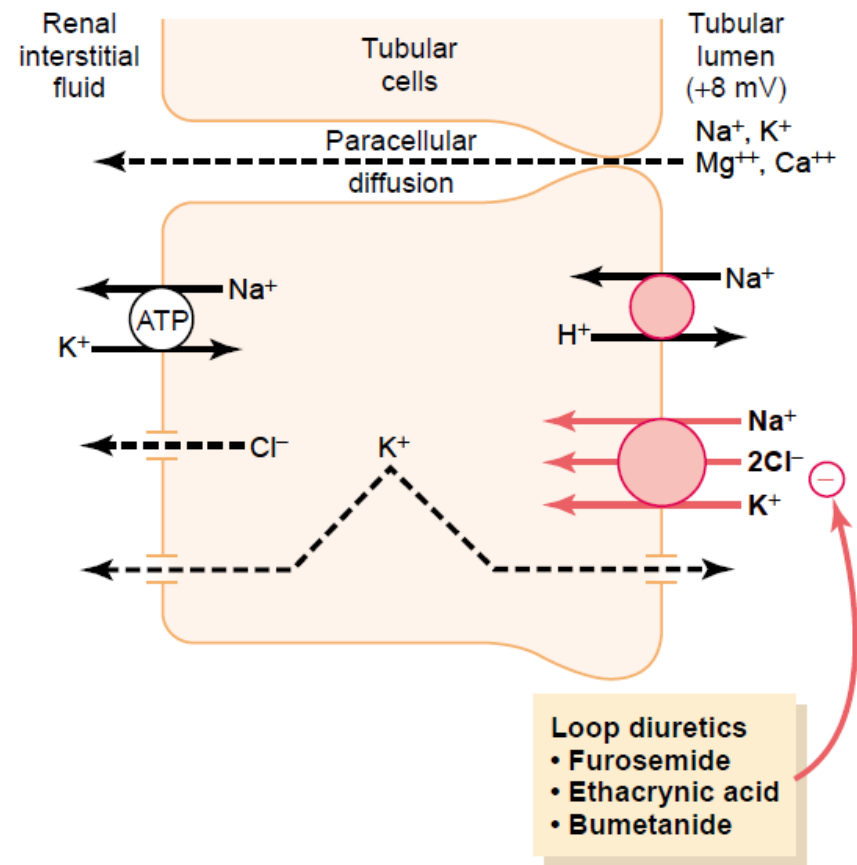


**Obr. 8.29** Osmolarita tubulární tekutiny přitékající do Henleovy kličky z proximálního tubulu a odtékající z Henleovy kličky do distálního tubulu



**Figure 27-8**

Cellular ultrastructure and transport characteristics of the thin descending loop of Henle (*top*) and the thick ascending segment of the loop of Henle (*bottom*). The descending part of the thin segment of the loop of Henle is highly permeable to water and moderately permeable to most solutes but has few mitochondria and little or no active reabsorption. The thick ascending limb of the loop of Henle reabsorbs about 25 per cent of the filtered loads of sodium, chloride, and potassium, as well as large amounts of calcium, bicarbonate, and magnesium. This segment also secretes hydrogen ions into the tubular lumen.



**Figure 27-9**

Mechanisms of sodium, chloride, and potassium transport in the thick ascending loop of Henle. The sodium-potassium ATPase pump in the basolateral cell membrane maintains a low intracellular sodium concentration and a negative electrical potential in the cell. The 1-sodium, 2-chloride, 1-potassium co-transporter in the luminal membrane transports these three ions from the tubular lumen into the cells, using the potential energy released by diffusion of sodium down an electrochemical gradient into the cells. Sodium is also transported into the tubular cell by sodium-hydrogen counter-transport. The positive charge (+8 mV) of the tubular lumen relative to the interstitial fluid forces cations such as  $Mg^{++}$  and  $Ca^{++}$  to diffuse from the lumen to the interstitial fluid via the paracellular pathway.

# DĚJE V DISTÁLNÍM TUBULU A SBĚRACÍM KANÁLKU

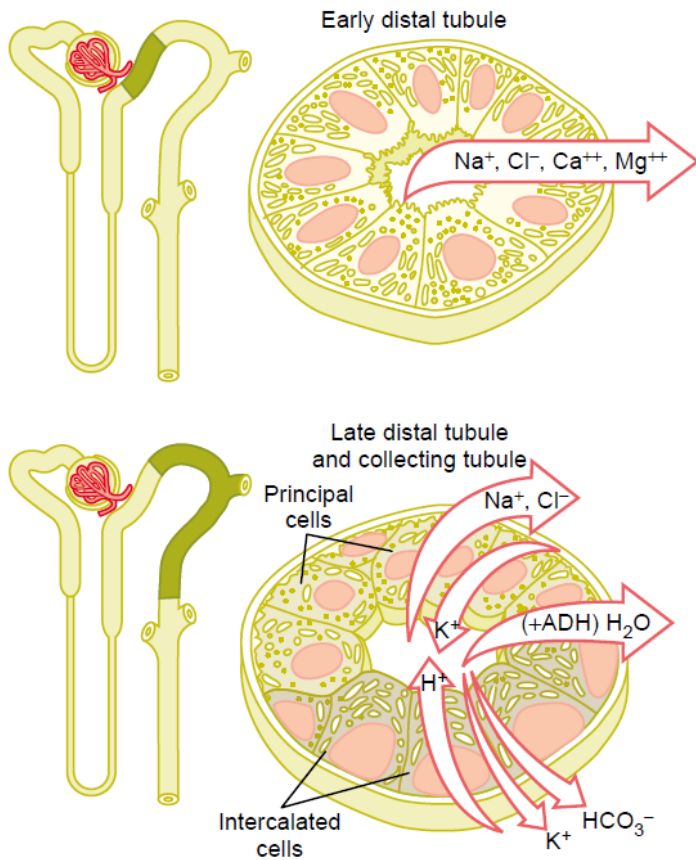


Figure 27-11

Cellular ultrastructure and transport characteristics of the early distal tubule and the late distal tubule and collecting tubule. The early distal tubule has many of the same characteristics as the thick ascending loop of Henle and reabsorbs sodium, chloride, calcium, and magnesium but is virtually impermeable to water and urea. The late distal tubules and cortical collecting tubules are composed of two distinct cell types, the *principal cells* and the *intercalated cells*. The principal cells reabsorb sodium from the lumen and secrete potassium ions into the lumen. The intercalated cells reabsorb potassium and bicarbonate ions from the lumen and secrete hydrogen ions into the lumen. The reabsorption of water from this tubular segment is controlled by the concentration of *antidiuretic hormone*.

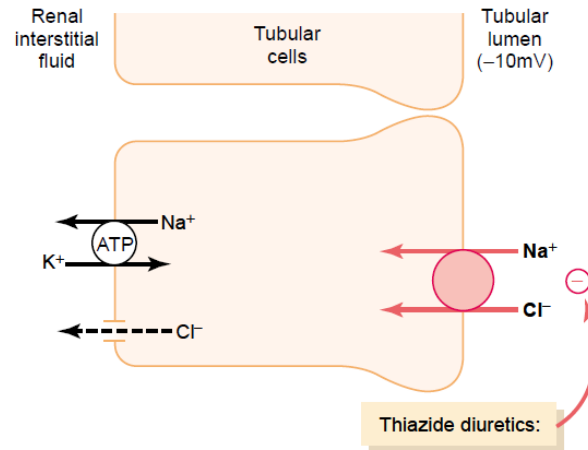


Figure 27-10

Mechanism of sodium chloride transport in the early distal tubule. Sodium and chloride are transported from the tubular lumen into the cell by a co-transporter that is inhibited by thiazide diuretics. Sodium is pumped out of the cell by sodium-potassium ATPase and chloride diffuses into the interstitial fluid via chloride channels.

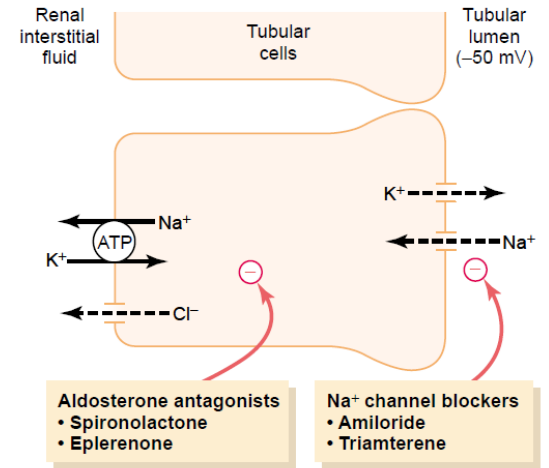
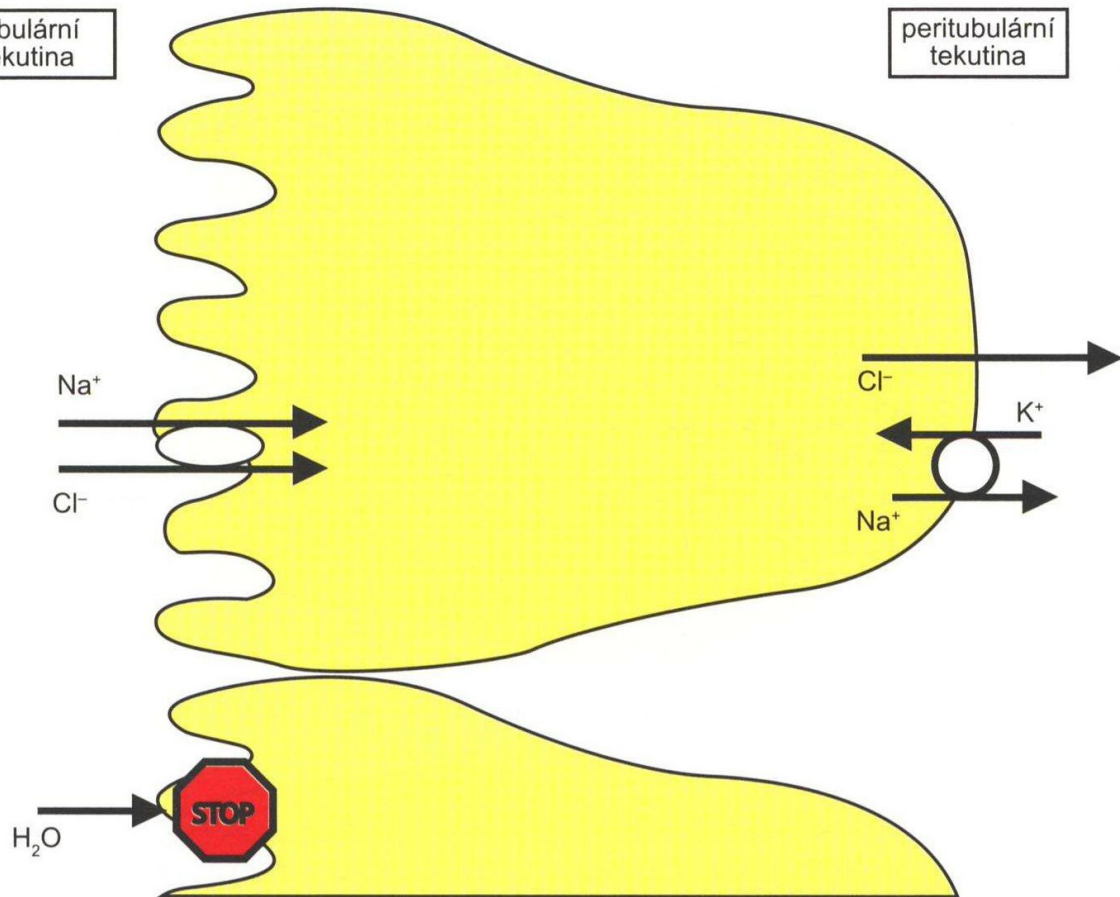


Figure 27-12

Mechanism of sodium chloride reabsorption and potassium secretion in the late distal tubules and cortical collecting tubules. Sodium enters the cell through special channels and is transported out of the cell by the sodium-potassium ATPase pump. Aldosterone antagonists compete with aldosterone for binding sites in the cell and therefore inhibit the effects of aldosterone to stimulate sodium reabsorption and potassium secretion. Sodium channel blockers directly inhibit the entry of sodium into the sodium channels.

tubulární tekutina

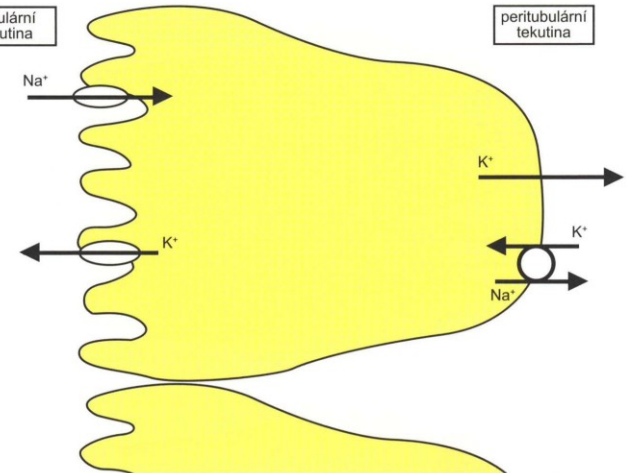
peritubulární tekutina



**Obr. 8.30** Hlavní transportní mechanismy realizované v první polovině distálního tubulu

tubulární tekutina

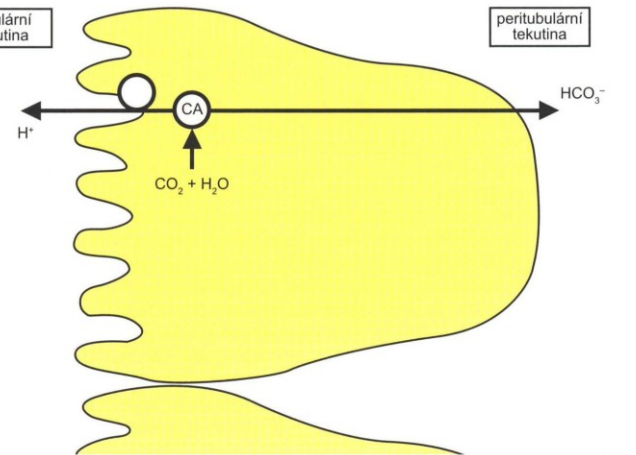
peritubulární tekutina



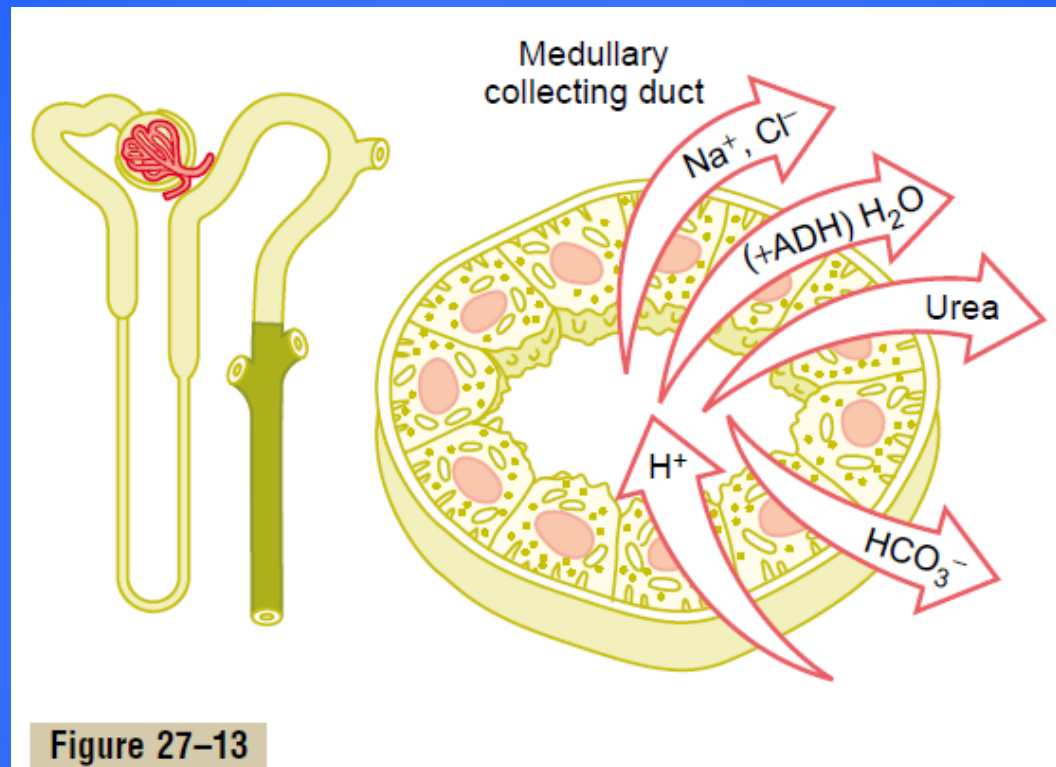
**Obr. 8.31** Hlavní transportní mechanismy realizované v druhé polovině distálního tubulu a ve sběracím kanálku; funkce hlavních buněk

tubulární tekutina

peritubulární tekutina



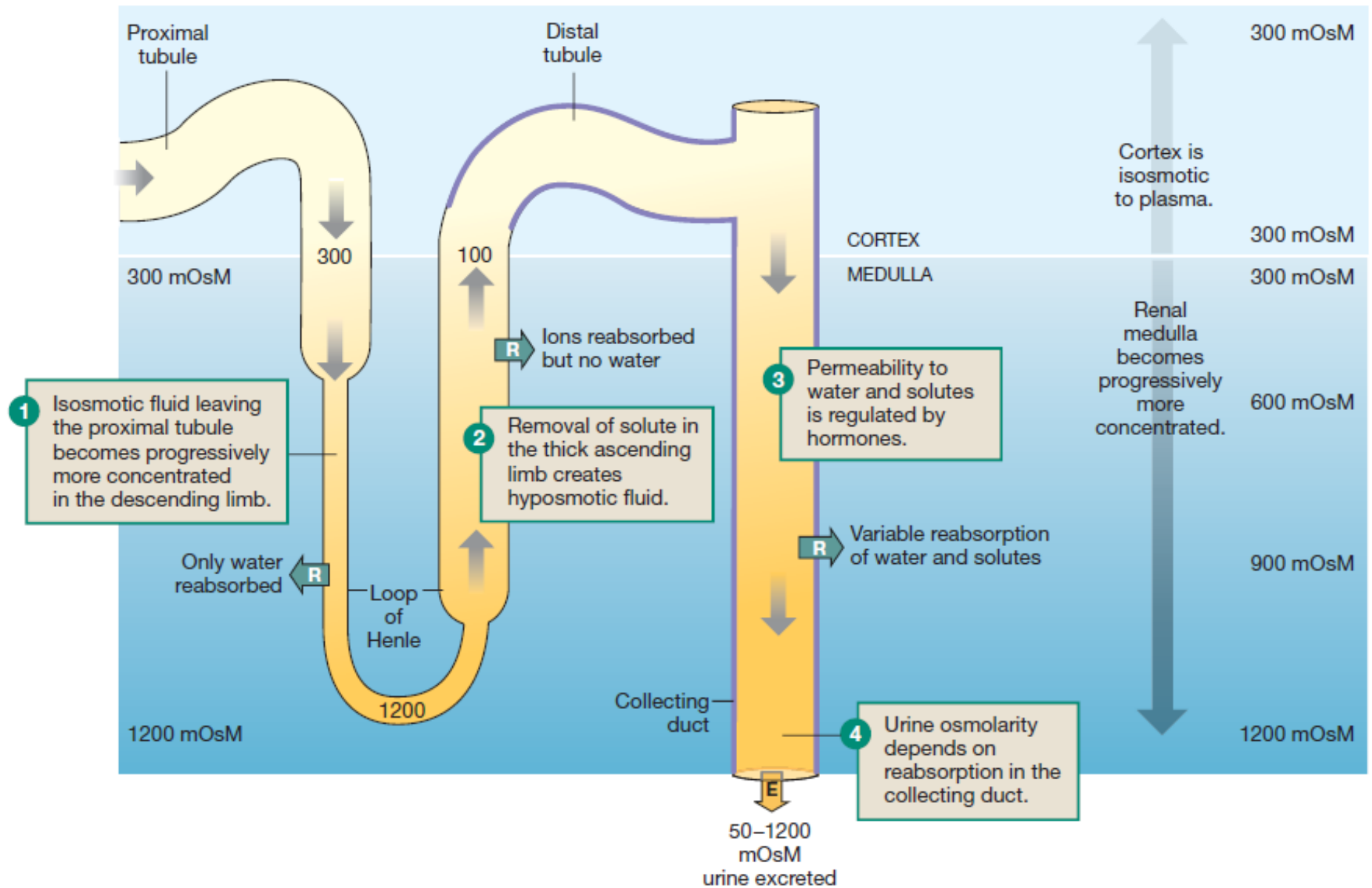
**Obr. 8.32** Hlavní transportní mechanismy realizované v druhé polovině distálního tubulu a ve sběracím kanálku; funkce vmezeřených buněk



**Figure 27-13**

Cellular ultrastructure and transport characteristics of the medullary collecting duct. The medullary collecting ducts actively reabsorb sodium and secrete hydrogen ions and are permeable to urea, which is reabsorbed in these tubular segments. The reabsorption of water in medullary collecting ducts is controlled by the concentration of antidiuretic hormone.

# OSMOLARITY CHANGES THROUGH THE NEPHRON



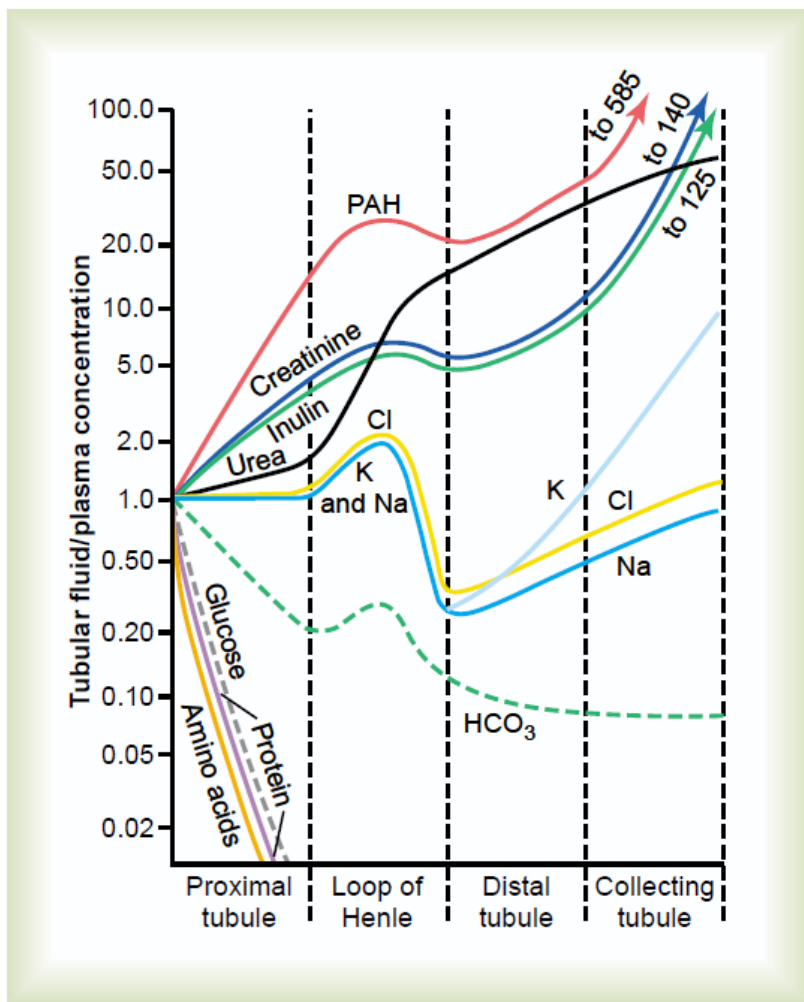


Figure 27-14

Changes in average concentrations of different substances at different points in the tubular system relative to the concentration of that substance in the plasma and in the glomerular filtrate. A value of 1.0 indicates that the concentration of the substance in the tubular fluid is the same as the concentration of that substance in the plasma. Values below 1.0 indicate that the substance is reabsorbed more avidly than water, whereas values above 1.0 indicate that the substance is reabsorbed to a lesser extent than water or is secreted into the tubules.

#### D. Resorpce, sekrece a frakční vylučování

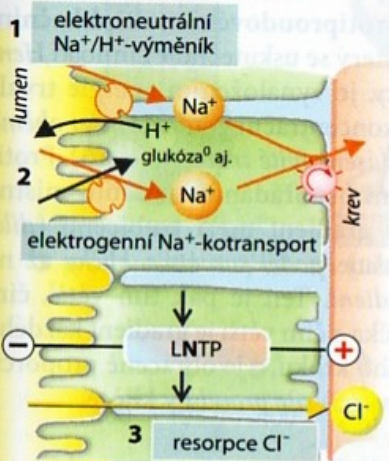
látky	koncentrace v plazmě (P) [mmol/l]	frakční resorpce (FR) [%]			frakční vylučování (FE) [% filtrovaného množství]	vlivy
		% v proximálním tubulu (TF/P)	% v Henleově klíče (TF/P)	celkové %		
H <sub>2</sub> O	---	65 %	10 %	93–99,5 %	0,5%–7%	ADH: ↓
Na <sup>+</sup>	153	65 % (1,0)	25 % (0,4)	95%–99,5 %	0,5%–5%	aldosteron: ↓ ADH: ↓ ANP: ↑
K <sup>+</sup>	4,6	65 % (1,0)	10%–20%	mj. sekrece	2%–150 %	aldosteron: ↑
Ca <sup>2+</sup>	volné: 1,6	60 % (1,1)	30 %	95%–99%	1%–5%	PTH: ↓ acidóza: ↑
Mg <sup>2+</sup>	volné: 0,6	15 % (2,5)	okolo 70 %	80%–95%	5%–20%	P stoupá: ↑
Cl <sup>-</sup>	112	55 % (1,3)	okolo 20 %	95%–99,5 %	0,5%–5%	---
HCO <sub>3</sub> <sup>-</sup>	24	93 % (0,2)		98%–99%	1%–2%	alkalóza: ↑
fosfáty	2,2	65 % (1,0)	15%	80%–97%	3%–20%	P stoupá: ↑↑ PTH: ↑↑ Ca <sup>2+</sup> klesá: ↑↑ acidóza: ↑↑
glukóza	5	96 % (0,1)	4%	≈ 100%	≈ 0%	P silně stoupá: ↑
močovina	5	50 % (1,4)	sekrece	okolo 60 %	okolo 40 %	diuréza: ↑
kreatinin	0,1	0 % (2,9)	0%	0%	100 %	---
PAH (i. v.)	C <sub>test</sub>	sekrece	sekrece	sekrece	≈ 500 %	P silně stoupá: ↓

P = koncentrace v plazmě  
TF = koncentrace v tubulární tekutině

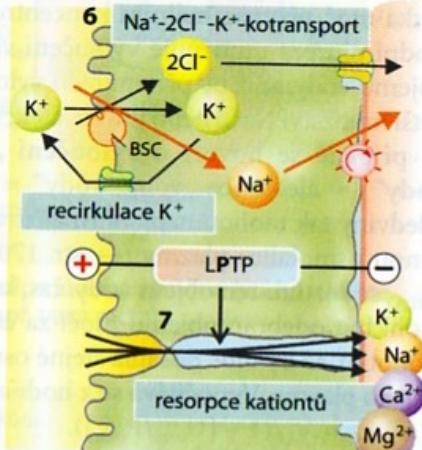
↑ zvyšuje FE  
↓ snižuje FE

## B. Resorpce Na<sup>+</sup> a Cl<sup>-</sup>

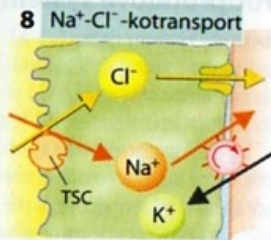
začátek proximálního tubulu



tlustý segment vzestupného raménka Henleovy kličky



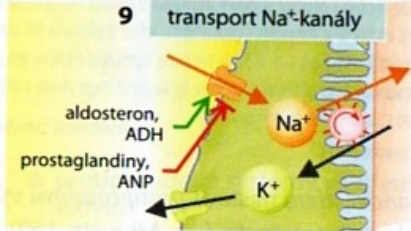
pars convoluta distálního tubulu



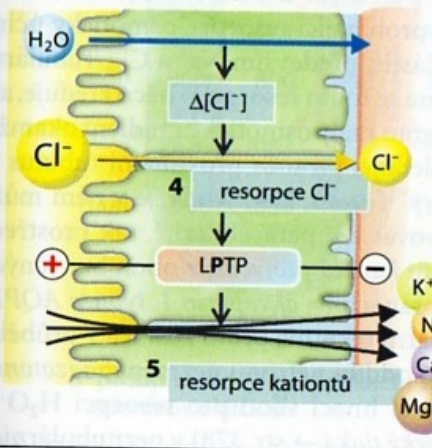
Na<sup>+</sup>

filtrát: 100 %  
pozdní prox. tubulus: 35 %  
začátek dist. tubulu: 10 %  
definitivní moč: 0,5-5 %

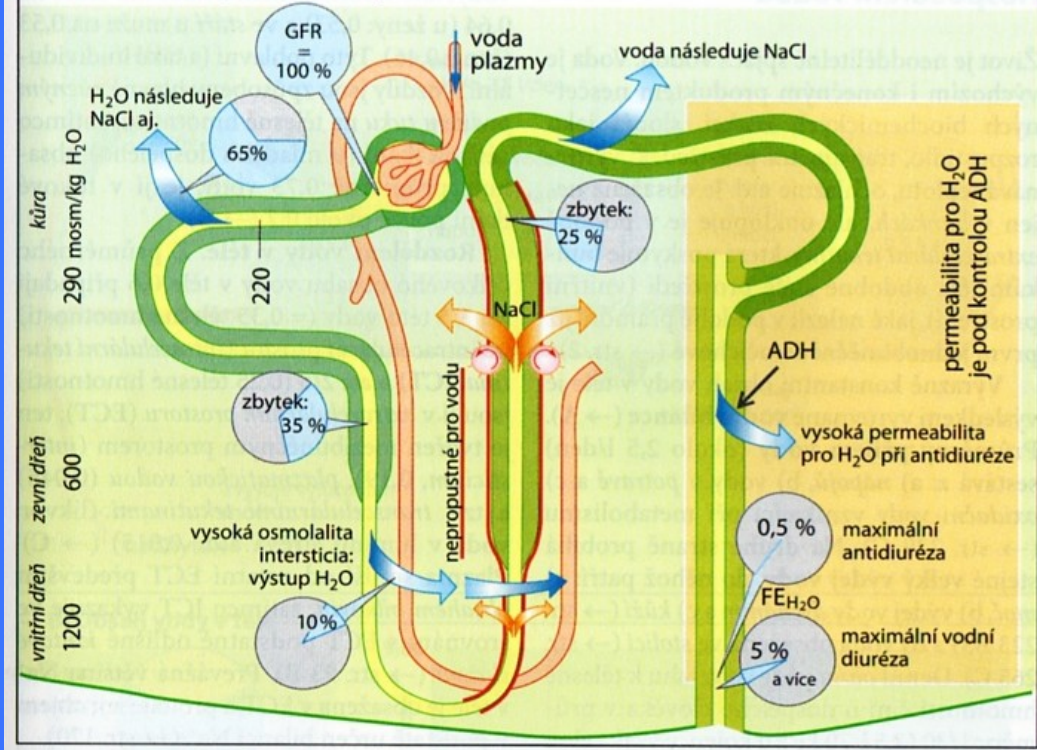
sběrací kanálek (hlavní buňky)



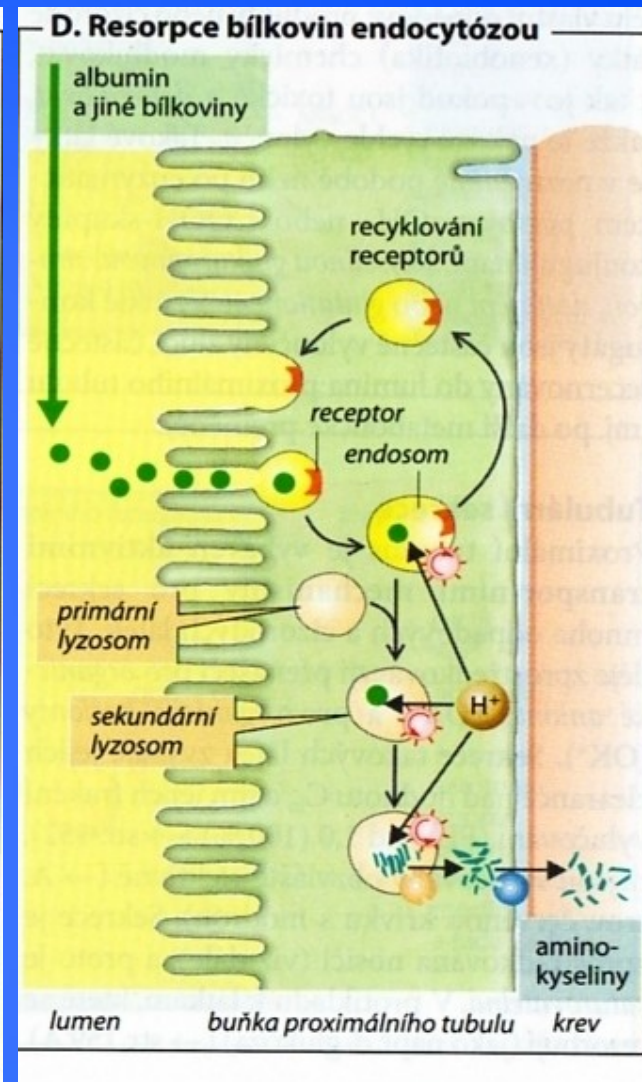
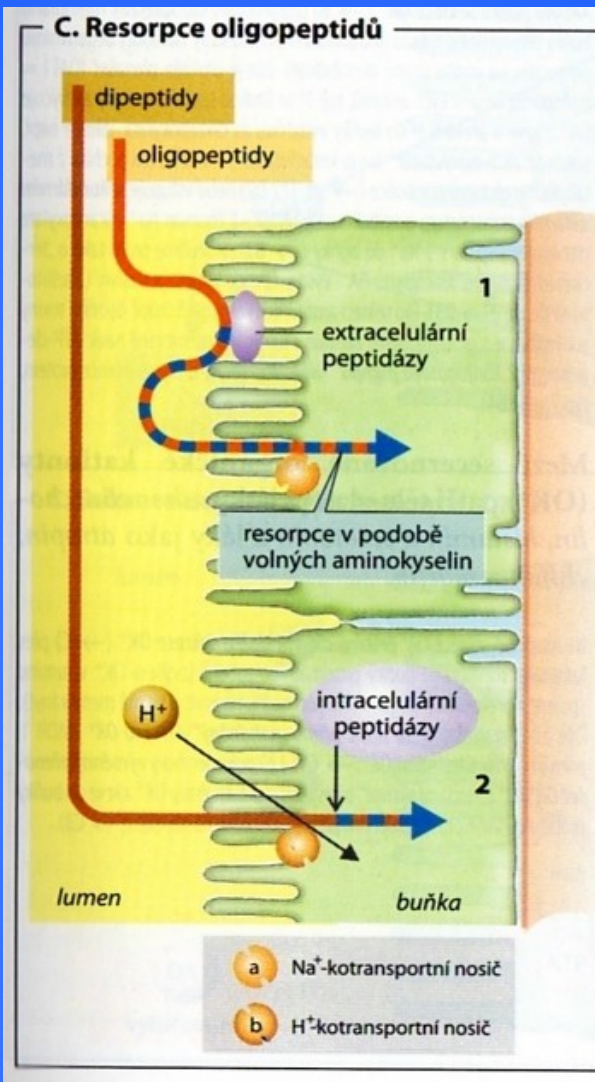
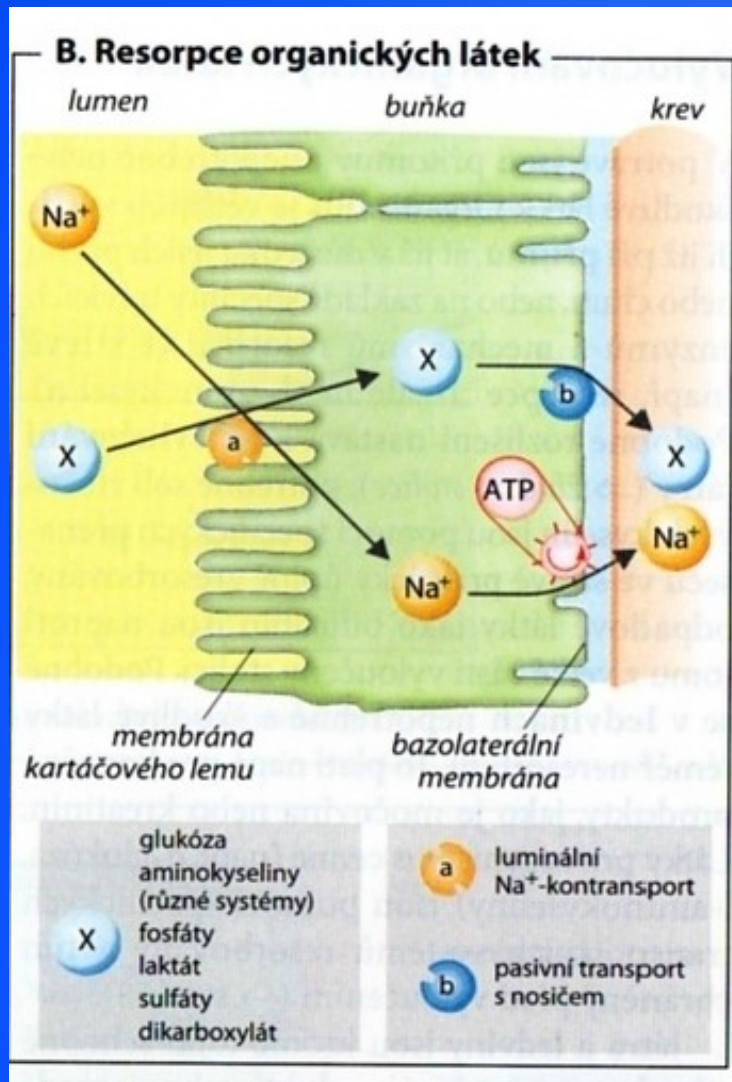
střední a pozdní segment proximálního tubulu



## B. Resorpce a vylučování vody







**Organické látky** – sekundární aktivní transport (kotransport), glukóza – SLGT2/1 – pozn. saturovatelnost!

**Oligopeptidy** – glutathion, angiotenzin II, atd. – enzymy (gama-glutamyltransferáza, aminopeptidázy, endopeptidáza – volné AMK)

**Nehydrolyzovatelné volné dipeptidy** – intaktní molekuly, kotransportní nosič pepT2, který je poháněn  $\text{H}^+$  gradientem

**Proteiny** – albumin, lysozym, mikroglobuliny – receptorově zprostředkovaná endocytóza, ! Saturována již za fyziologických podmínek

# SEKRECE ORGANICKÝCH IONTŮ

## DETOXIKACE XENOBIOTIK!

- NEZMĚNĚNÁ PODOBA
- ENZYMATICKÉ PŘIPOJENÍ –OH NEBO –COOH
- KONJUGACE (kys. glukuronová, sírová, acetát, glutathion)
- Konjugáty jsou vyloučeny močí
- Proximální tubulus!

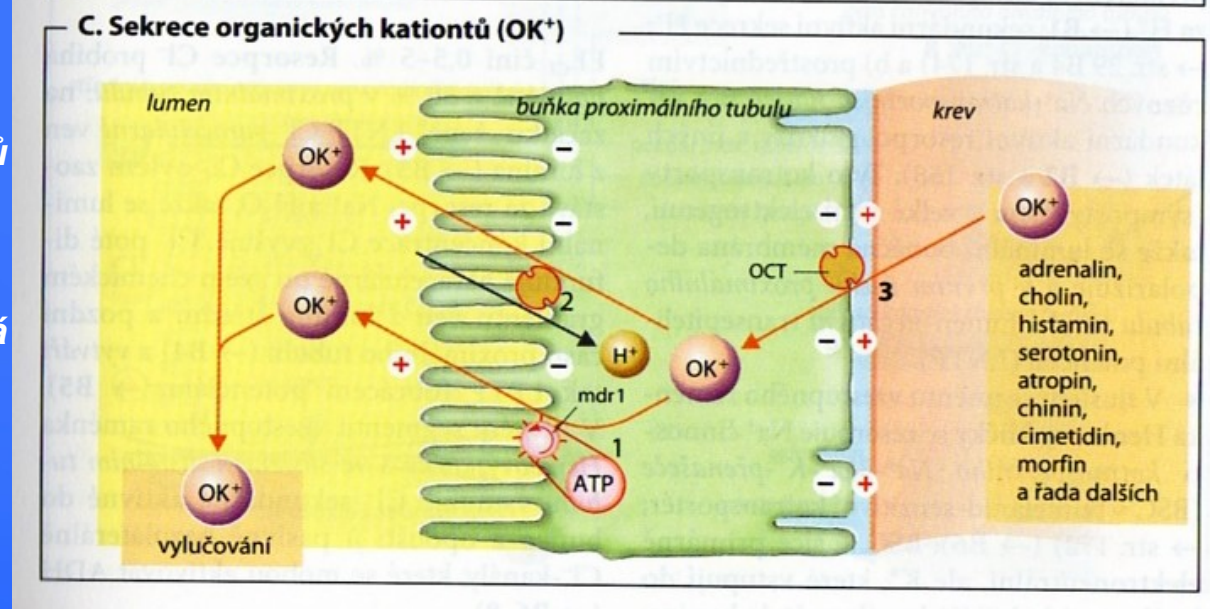
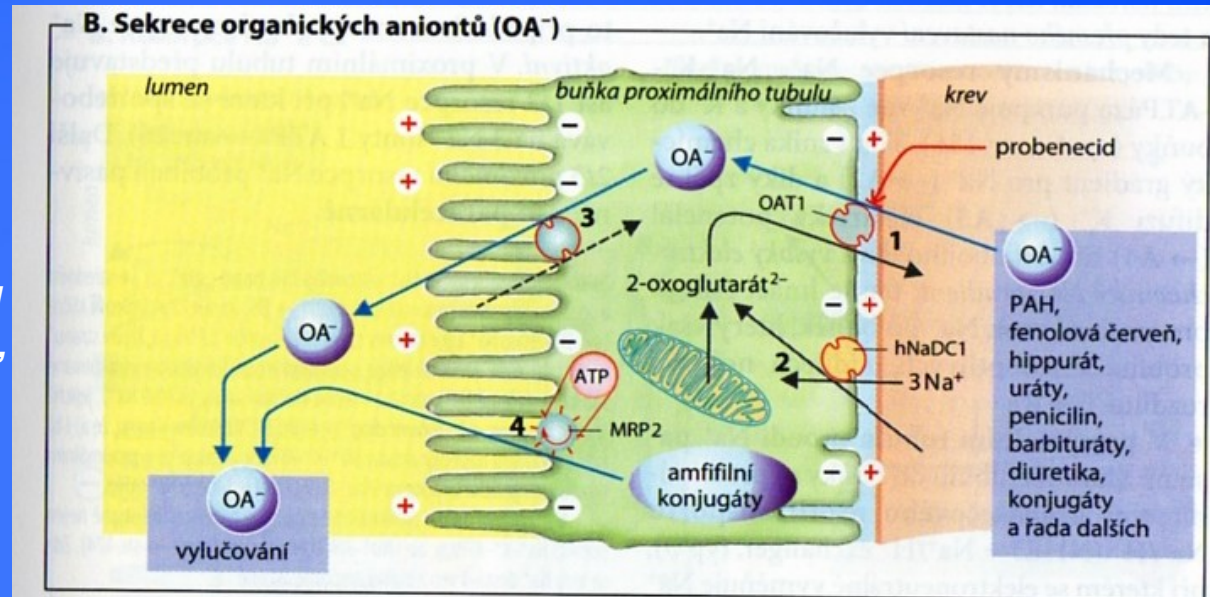
- Aktivní transportní mechanismy
- Přenašeče pro organické anionty (OA<sup>-</sup>)
- Přenašeče pro organické kationty (OK<sup>+</sup>)
- Saturovatelnost!

### Anionty

- OAT1 = transportér organických aniontů – VÝMĚNOU ZA DIKARBOXYLÁTY
- hNaDC-1 = sekundární aktivní transport
- Výstup OA<sup>-</sup> je pasivní
- MRP-1 – ATP-dependentní konjugátová pumpa

### Kationty

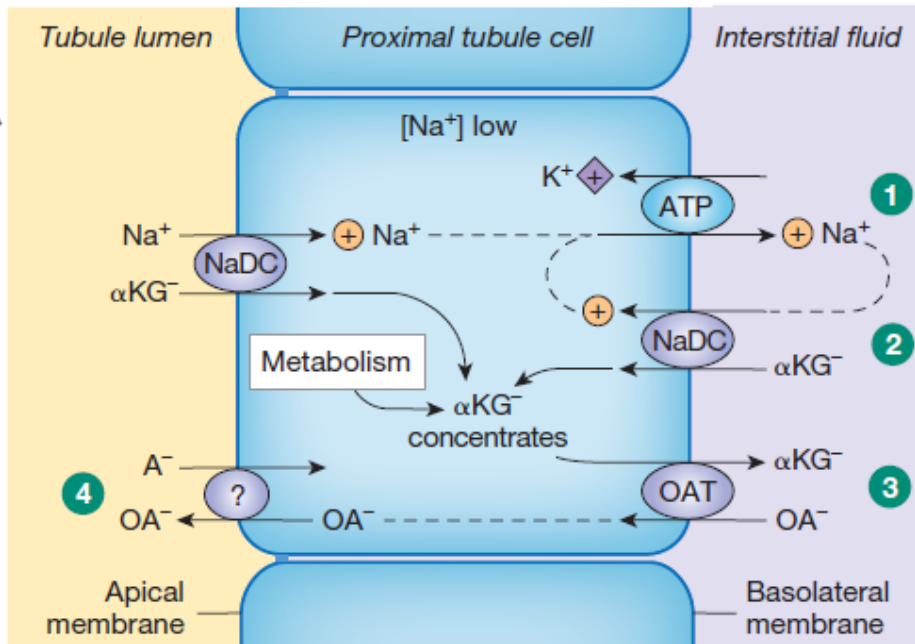
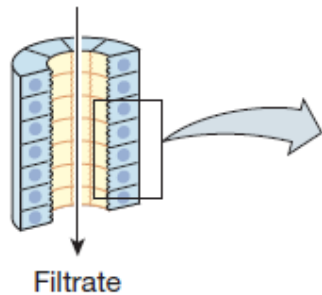
- Nosič pro OK<sup>+</sup> poháněný ATP = MDR-1
- Výměnný přenašeč OK<sup>+</sup>/H<sup>+</sup>
- Polyspecifický přenašeč OCT



# SEKRECE ORGANICKÝCH IONTŮ

## ORGANIC ANION SECRETION

Proximal tubule secretion of organic anions by the organic anion transporter (OAT) is an example of tertiary active transport.



4 Organic anions enter the lumen by facilitated diffusion.

1 Direct active transport. The  $\text{Na}^+-\text{K}^+-\text{ATPase}$  keeps intracellular  $[\text{Na}^+]$  low.

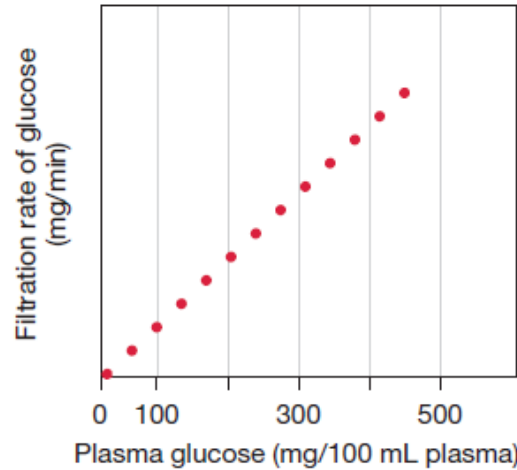
2 Secondary indirect active transport. The  $\text{Na}^+$ -dicarboxylate cotransporter ( $\text{NaDC}$ ) concentrates a dicarboxylate inside the cell using energy stored in the  $[\text{Na}^+]$  gradient.

3 Tertiary indirect active transport. The basolateral organic anion transporter ( $\text{OAT}$ ) concentrates organic anions ( $\text{OA}^-$ ) inside the cell, using the energy stored in the dicarboxylate gradient.

# RESORPCE GLUKÓZY

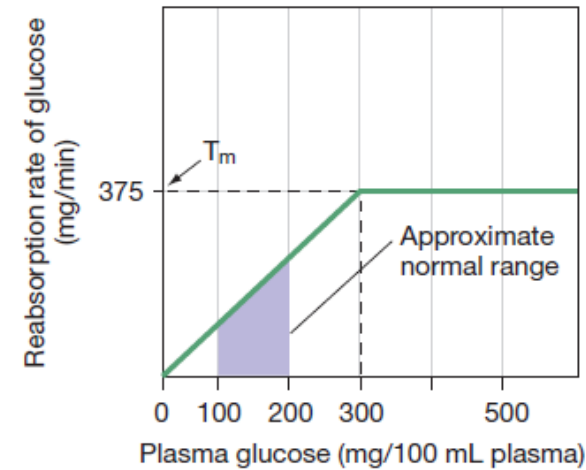
## GLUCOSE HANDLING BY THE NEPHRON

### (a) Filtration



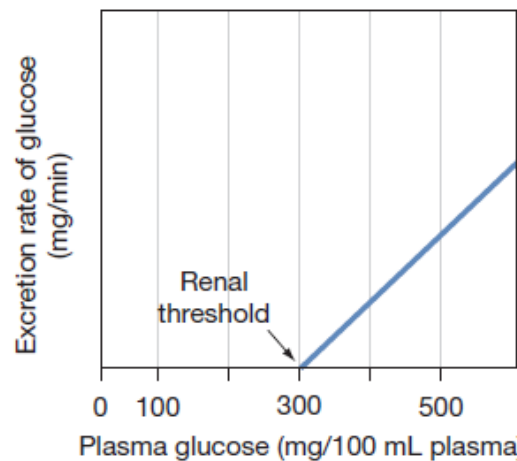
Filtration of glucose is proportional to the plasma concentration. Filtration does not saturate.

### (b) Reabsorption



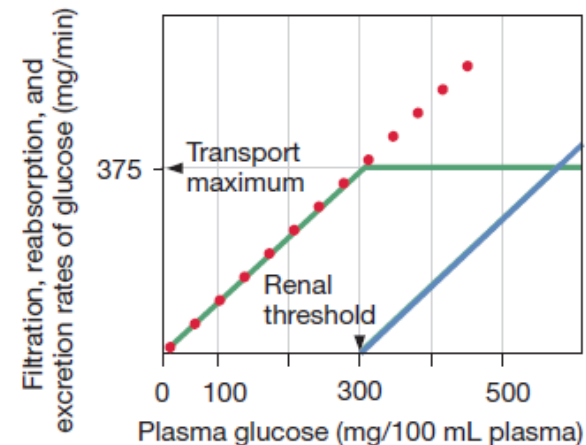
Reabsorption of glucose is proportional to plasma concentration until the transport maximum (T<sub>m</sub>) is reached.

### (c) Excretion = Filtration - Reabsorption



Glucose excretion is zero until the renal threshold is reached.

### (d) Composite graph shows the relationship between filtration, reabsorption, and excretion of glucose.



# DIURÉZA A DIURETIKA

## VODNÍ DIURÉZA

- *Pokles osmolality plazmy/zvětšení objemu krve = snížení hladiny ADH = vylučování volné vody*

## OSMOTICKÁ DIURÉZA

- *GF s větším množstvím neresorbovatelných látek*
- *Př. manitol*
- *Osmotické poutání vody*
- *Ta je spolu s nimi vyloučena*
- *Další příklad – hyperglykemie a glykosurie*

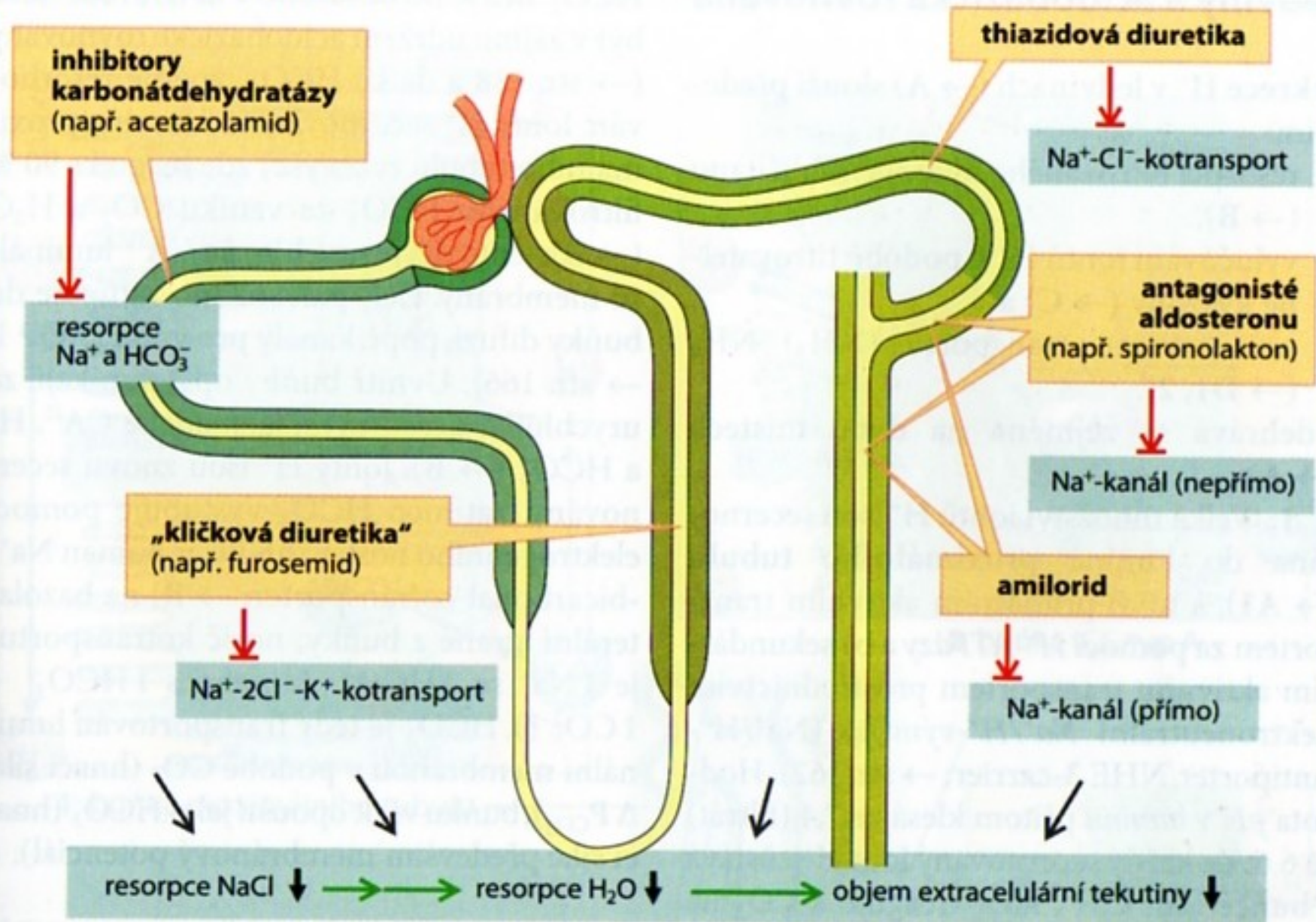
## TLAKOVÁ DIURÉZA

- *Při zvýšeném průtoku krve*
- *Nejčastěji důsledek hypertenze*

**TABLE 38–10** Mechanism of action of various diuretics.

Agent	Mechanism of Action
Water	Inhibits vasopressin secretion.
Ethanol	Inhibits vasopressin secretion.
Antagonists of V <sub>2</sub> vasopressin receptors such as astolvaptan	Inhibit action of vasopressin on collecting duct.
Large quantities of osmotically active substances such as mannitol and glucose	Produce osmotic diuresis.
Xanthines such as caffeine and theophylline	Decrease tubular reabsorption of Na <sup>+</sup> and increase GFR.
Acidifying salts such as CaCl <sub>2</sub> and NH <sub>4</sub> Cl	Supply acid load; H <sup>+</sup> is buffered, but an anion is excreted with Na <sup>+</sup> when the ability of the kidneys to replace Na <sup>+</sup> with H <sup>+</sup> is exceeded.
Carbonic anhydrase inhibitors such as acetazolamide (Diamox)	Decrease H <sup>+</sup> secretion, with resultant increase in Na <sup>+</sup> and K <sup>+</sup> excretion.
Metolazone (Zaroxolyn), thiazides such as chlorothiazide (Diuril)	Inhibit the Na–Cl cotransporter in the early portion of the distal tubule.
Loop diuretics such as furosemide (Lasix), ethacrynic acid (Edecrin), and bumetanide	Inhibit the Na–K–2Cl cotransporter in the medullary thick ascending limb of the loop of Henle
K <sup>+</sup> -retaining natriuretics such as spironolactone (Aldactone), triamterene (Dyrenium), and amiloride (Midamor)	Inhibit Na <sup>+</sup> –K <sup>+</sup> “exchange” in the collecting ducts by inhibiting the action of aldosterone (spironolactone) or by inhibiting the ENaCs (amiloride).

# A. Místa účinku diuretik



# RESORPCE VODY A KONCENTROVÁNÍ MOČI

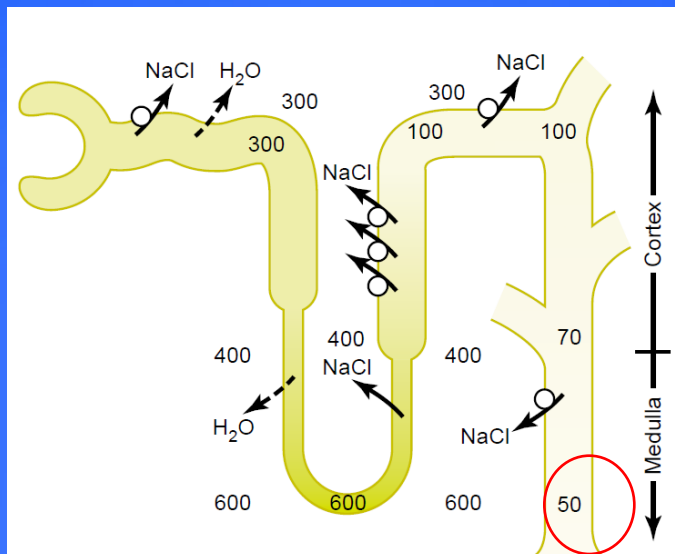


Figure 28-2

Formation of a dilute urine when antidiuretic hormone (ADH) levels are very low. Note that in the ascending loop of Henle, the tubular fluid becomes very dilute. In the distal tubules and collecting tubules, the tubular fluid is further diluted by the reabsorption of sodium chloride and the failure to reabsorb water when ADH levels are very low. The failure to reabsorb water and continued reabsorption of solutes lead to a large volume of dilute urine. (Numerical values are in milliosmoles per liter.)

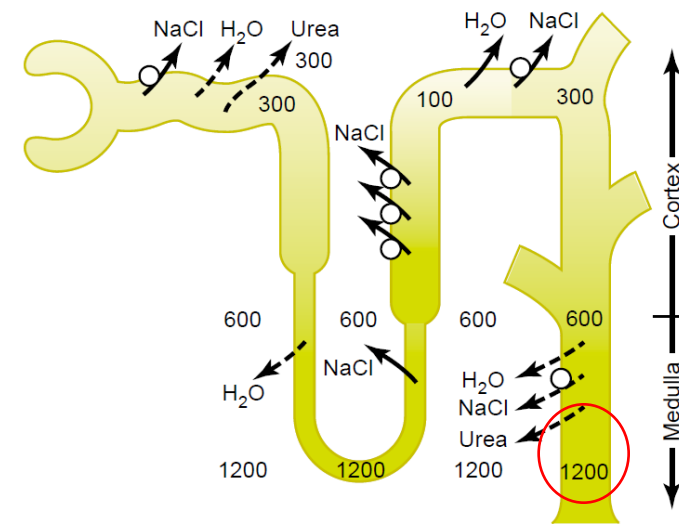


Figure 28-4

Formation of a concentrated urine when antidiuretic hormone (ADH) levels are high. Note that the fluid leaving the loop of Henle is dilute but becomes concentrated as water is absorbed from the distal tubules and collecting tubules. With high ADH levels, the osmolarity of the urine is about the same as the osmolarity of the renal medullary interstitial fluid in the papilla, which is about 1200 mOsm/L. (Numerical values are in milliosmoles per liter.)

- Osmolalita definitivní moči kolísá v závislosti na příjmu a vylučování vody

- Vodní diuréza umožňuje vyloučení velkého množství vody bez ztrát NaCl nebo dalších látek

- Předpokladem je důsledné oddělení resorpce vody a solutů v určitém segmentu tubulárního systému

## - Henleova klička

- V tlustém segmentu resorbovány soluty a žádná voda = zředění tubulární tekutiny = tvorba hypotonické moči

- V důsledku resorpce solutů je dřeň HYPERTONICKÁ = VZNIK OSMOTICKÉHO GRADIENTU

- Ten umožňuje v přítomnosti ADH extenzivní resorpci vody = vznik hyperosmotické moči

Co je nutné pro normální funkci zředování a zahuštění moči nutné?

- Tvorba hypertonické dřeně s rostoucím gradientem osmolarity = protiproudový multiplikační systém

- Řízená produkce ADH

- Koloběh močoviny ve dřeni

- Protiproudová výměna ve dřeni = Henleova klička X vasa recta

## Summary of Tubule Characteristics—Urine Concentration

	Active NaCl Transport	Permeability		
		<i>H<sub>2</sub>O</i>	<i>NaCl</i>	<i>Urea</i>
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

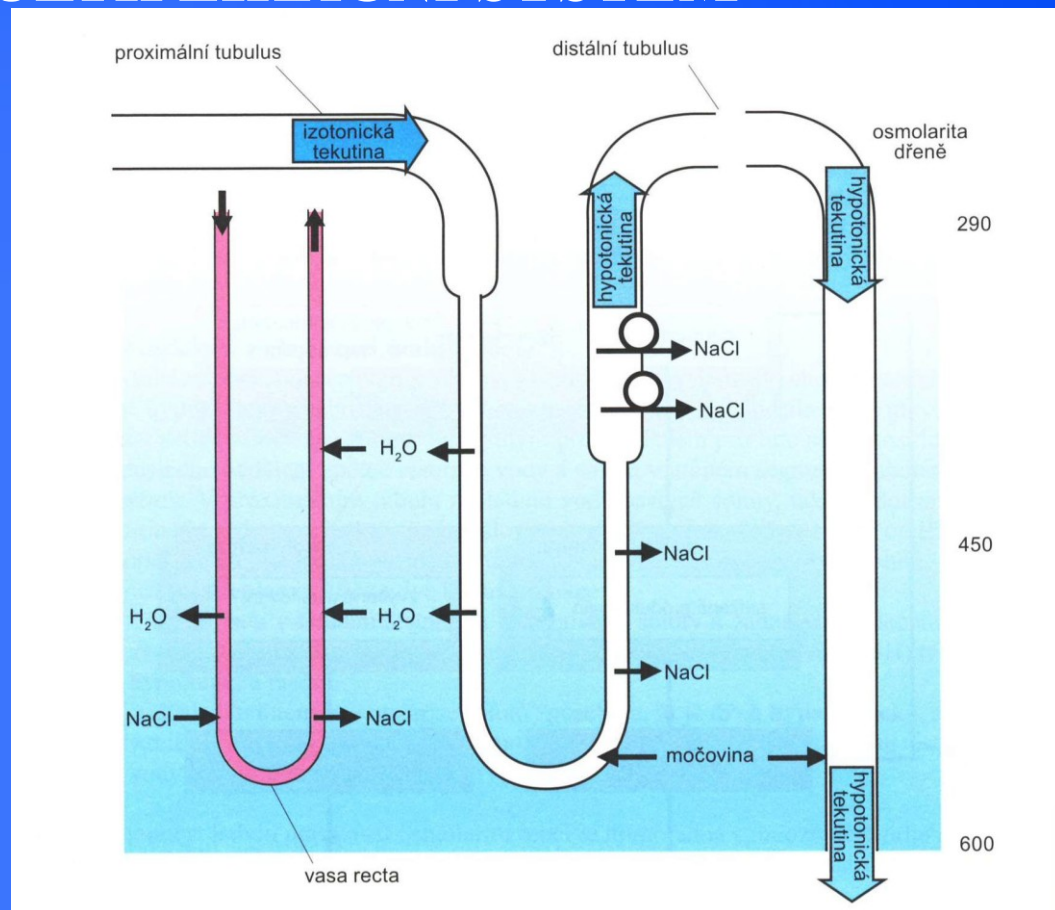
0, minimal level of active transport or permeability; +, moderate level of active transport or permeability; ++, high level of active transport or permeability; +ADH, permeability to water or urea is increased by ADH.



# PROTIPROUDOVÝ MULTIPLIKAČNÍ SYSTÉM

## TVORBA HYPOTONICKÉ MOČI

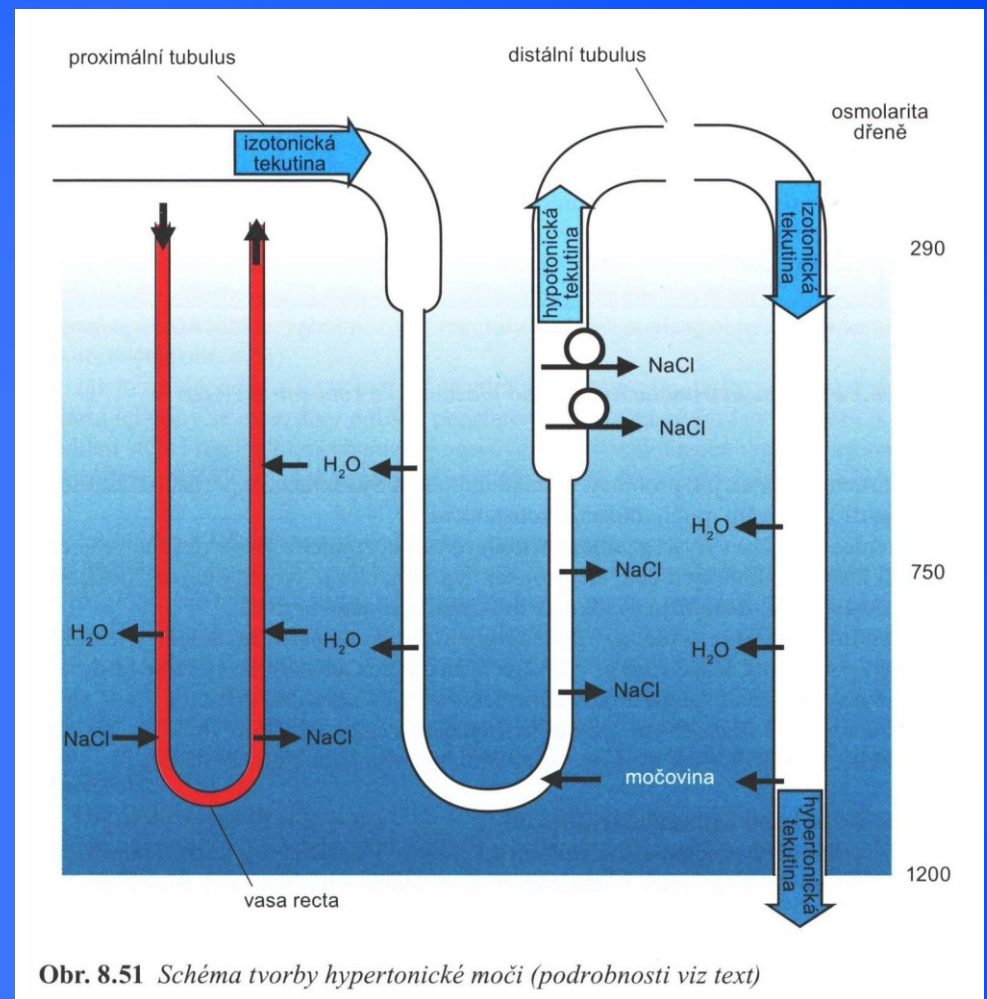
- **Sestupné raménko HK volně propustné pro vodu**
- **Ta se resorbuje ve směru osmotického gradientu = tubulární tekutina má na vrcholu klíčky stejnou osmolaritu jako okolní hypertonická dřeň**
- **Obsahuje však více Na<sup>+</sup> a Cl<sup>-</sup> a méně močoviny = osmolarita v tubulární tekutině je dána hlavně koncentrací NaCl, osmolarita dřeně pak koncentrací močoviny**
- **Tenký segment vzestupného raménka je nepropustný pro vodu, ale propustný pro NaCl a močovinu = PASIVNĚ DIFUNDUJÍ VE SMĚRU KONCENTRAČNÍHO GRADIENTU**
- **Objem proudící tubulární tekutiny ani její osmolarita se tak nemění – MĚNÍ SE VŠAK SLOŽENÍ, ABY ODPOVÍDALO SLOŽENÍ INTERSTICIA DŘENĚ LEDVIN**
- **Tlustý segment vzestupného raménka nepropustný pro vodu, ale je zde aktivní resorpce řady solutů = ředění tubulární tekutiny až k výrazné hypotonicitě**
- **V distálním tubulu a sběracím kanálku se dále resorbují soluty, ale v nepřítomnosti ADH je tato část nepropustná pro vodu**
- **Tubulární tekutina se dále ředí až do výrazné hypotonicity**
- **V konečném úseku sběracího kanálku vstupuje do moči malé množství močoviny = snížení hypertonicity dřeně v její hlubší části**



1. **Henleova klíčka vytváří gradient osmolarity hypertonické dřeně, ta je ale tvořena jen NaCl a minimálně močovinou – nedosahuje takové úrovně**
2. **Snížená produkce ADH = voda se neresorbuje v závěrečných úsecích tubulárního systému**
3. **Močovina přechází z dřeně do tubulárního systému = snížení maximální hypertonicity**

## TVORBA HYPERTONICKÉ MOČI

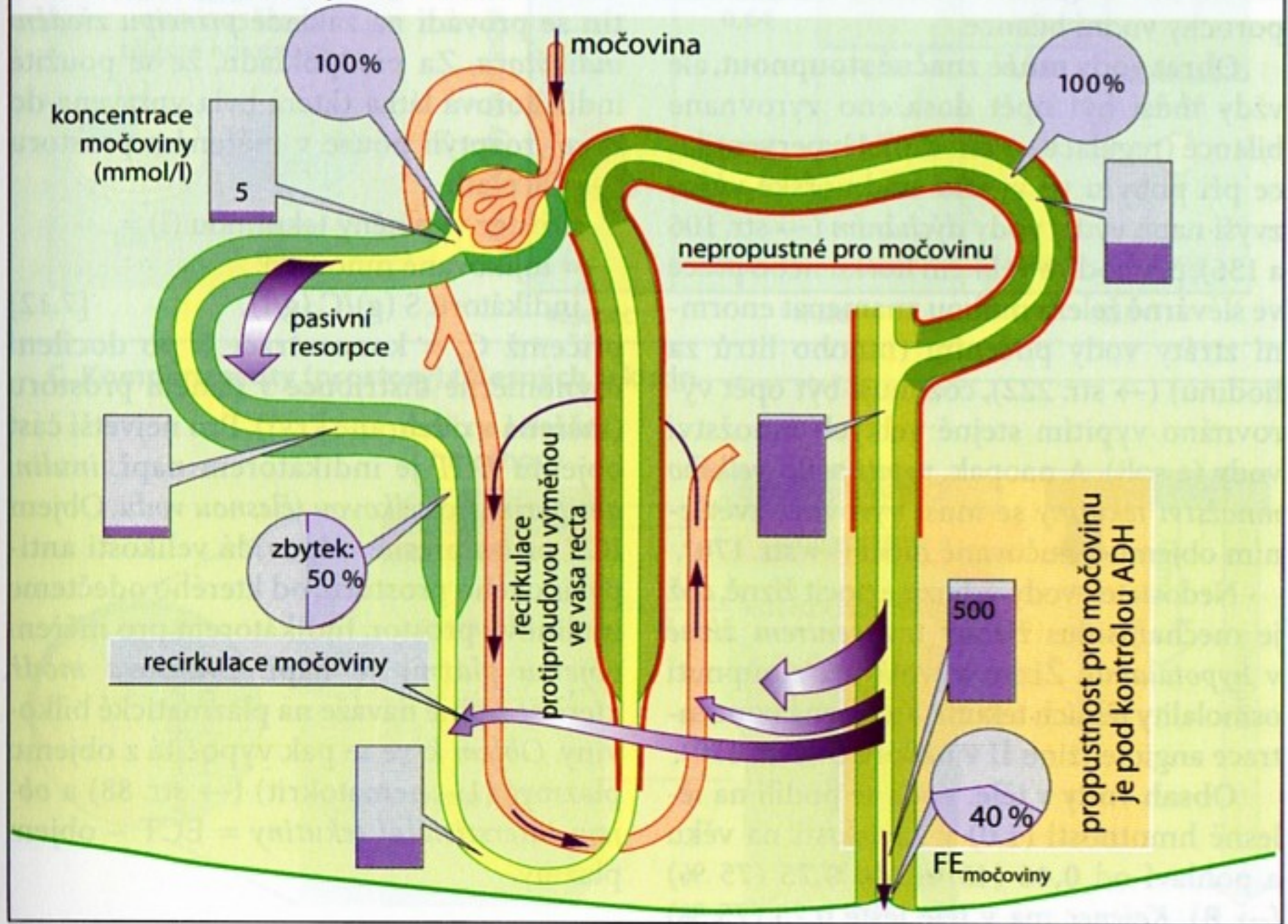
- **TLUSTÝ SEGMENT VZESTUPNÉHO RAMÉNKA NEPROPUSTNÝ PRO VODU, ALE JE ZDE AKTIVNÍ RESORPCE ŘADY SOLUTŮ = ŘEDĚNÍ TUBULÁRNÍ TEKUTINY ALE TAKÉ K TVORBĚ VÝRAZNĚ HYPERTONICKÉ DŘENĚ**
- VLÁSENKOVITÉ USPOŘÁDÁNÍ OBOU RAMÉNEK HENLEOVY KLIČKY A SBĚRACÍHO KANÁLKU
- ANALOGICKÉ PARALELNÍ USPOŘÁDÁNÍ KAPILÁR VASA RECTA
- Tento protiproudový multiplikační systém umožňuje kumulaci NaCl a močoviny ve dření
- Pokud je v plasmě přítomen ADH, následuje resorpce vody ze sběracího kanálku a tubulární tekutina se stává hyperosmotickou úměrně osmolaritě dřeně
- Díky zvýšené propustnosti koncové části sběracího kanálku pro močovinu (díky ADH) se část močoviny vrací do dřeně = zvyšování osmolarity
- Resorpce vody vyrovnává osmolaritu dřeně
- Výsledkem je hypertonická moč

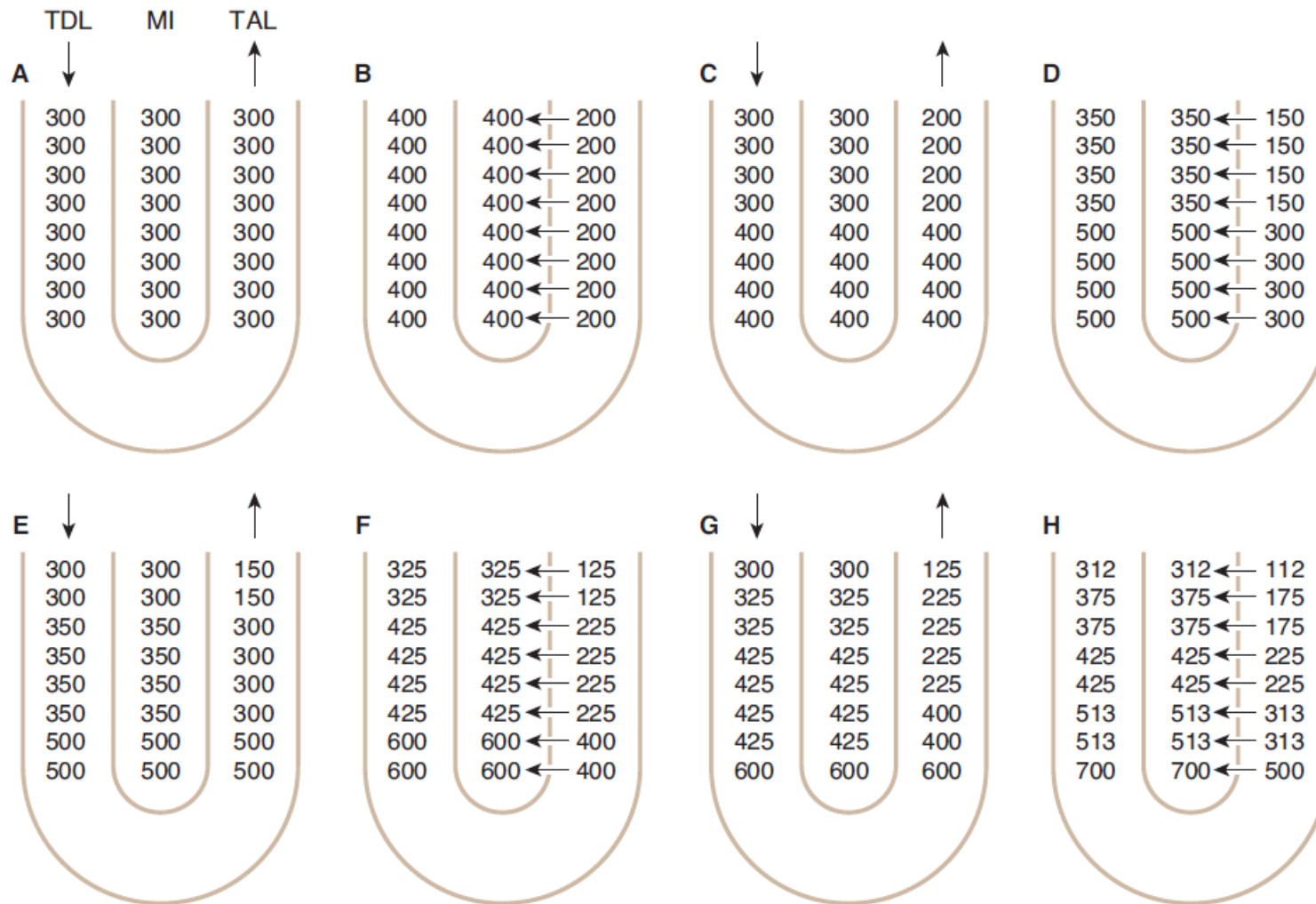


Obr. 8.51 Schéma tvorby hypertonické moči (podrobnosti viz text)

1. Henleova klička vytváří gradient osmolarity hypertonické dřeně, ta je ale tvořena nejen NaCl, ale také močovinou = dosahuje maximální úrovně
2. Zvýšená produkce ADH = voda se resorbuje v závěrečných úsecích tubulárního systému a vyrovnává osmolaritu dřeně
3. Močovina obíhá ve dření ledvin zpět ze sběracího kanálku do vrcholu vlásenky Henleovy kličky = zvyšuje hyperosmolaritu v hloubi dřeně

### C. Chování močoviny v ledvinách



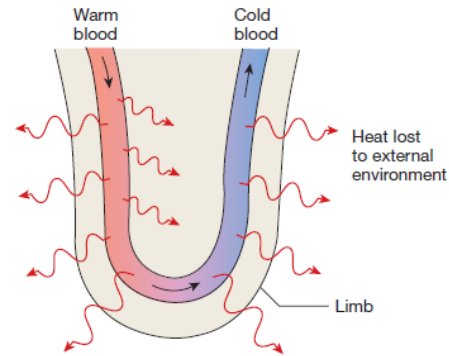


**FIGURE 38–16** Operation of the loop of Henle as a countercurrent multiplier producing a gradient of hyperosmolarity in the medullary interstitium (MI). TDL, thin descending limb; TAL, thick ascending limb. The process of generation of the gradient is illustrated as occurring in hypothetical steps, starting at A, where osmolality in both limbs and the interstitium is 300 mOsm/kg of water. The pumps in the thick ascending limb move  $\text{Na}^+$  and  $\text{Cl}^-$  into the interstitium, increasing its osmolality to 400 mOsm/kg, and this equilibrates with the fluid in the thin descending limb. However, isotonic fluid continues to flow into the thin descending limb and hypotonic fluid out of the thick ascending limb. Continued operation of the pumps makes the fluid leaving the thick ascending limb even more hypotonic, while hypertonicity accumulates at the apex of the loop. (Modified and reproduced with permission from Johnson LR [editor]: *Essential Medical Physiology*, Raven Press, 1992.)

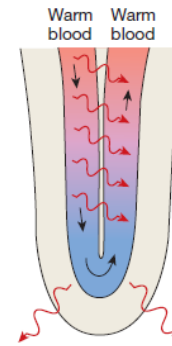
## COUNTERCURRENT MECHANISMS

### A countercurrent heat exchanger

(a) If blood vessels are not close to each other, heat is dissipated to the external environment.



(b) Countercurrent heat exchanger allows warm blood entering the limb to transfer heat directly to blood flowing back into the body.

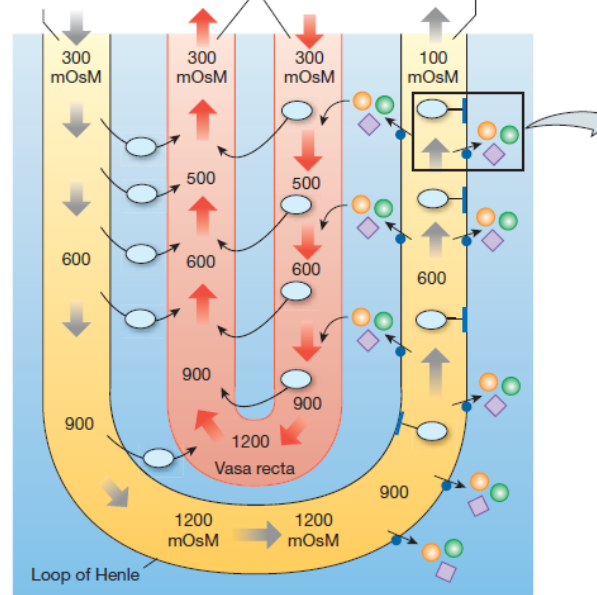


### (c) Countercurrent exchange in the vasa recta

Filtrate entering the descending limb becomes progressively more concentrated as it loses water.

Blood in the vasa recta removes water leaving the loop of Henle.

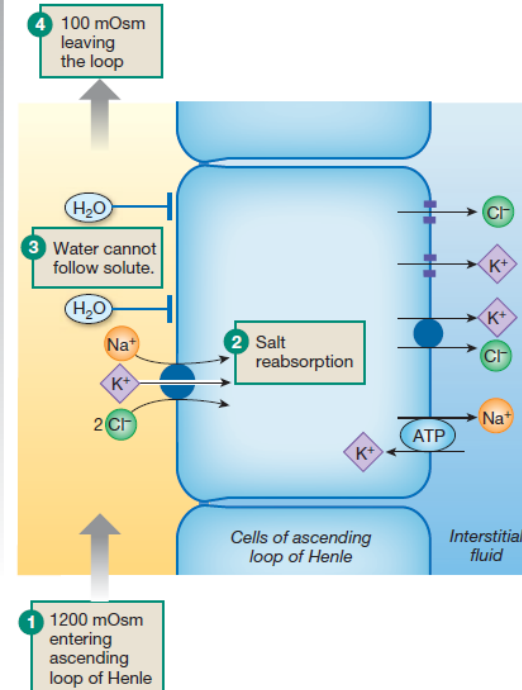
The ascending limb pumps out  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$ , and filtrate becomes hyposmotic.



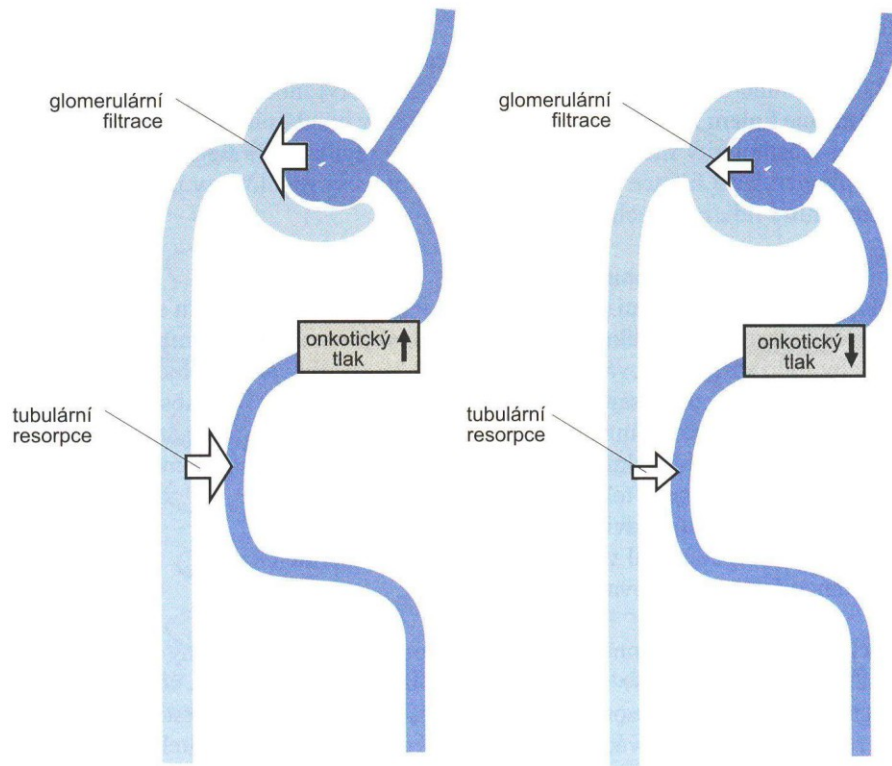
#### KEY

$\text{H}_2\text{O}$  =  $\text{K}^+$  =   
 $\text{Cl}^-$  =  $\text{Na}^+$  =

(d) The apical surface of the ascending limb is not permeable to water. Active reabsorption of ions in this region creates a dilute filtrate in the lumen.



# ŘÍZENÍ TUBULÁRNÍCH PROCESŮ



**Obr. 8.33** Schéma glomerulotubulární rovnováhy: vztah glomerulární filtrace, onkotického tlaku v peritubulárních kapilárách a tubulární resorpce

## Factors That Can Influence Peritubular Capillary Reabsorption

$\uparrow P_c \rightarrow \downarrow$  Reabsorption

- $\downarrow R_A \rightarrow \uparrow P_c$
- $\downarrow R_E \rightarrow \uparrow P_c$
- $\uparrow$  Arterial Pressure  $\rightarrow \uparrow P_c$

$\uparrow \pi_c \rightarrow \uparrow$  Reabsorption

- $\uparrow \pi_A \rightarrow \uparrow \pi_c$
- $\uparrow FF \rightarrow \uparrow \pi_c$

$\uparrow K_f \rightarrow \uparrow$  Reabsorption

$P_c$ , peritubular capillary hydrostatic pressure;  $R_A$  and  $R_E$ , afferent and efferent arteriolar resistances, respectively;  $\pi_c$ , peritubular capillary colloid osmotic pressure;  $\pi_A$ , arterial plasma colloid osmotic pressure; FF, filtration fraction;  $K_f$ , peritubular capillary filtration coefficient.

# CENTRÁLNÍ ŘÍZENÍ TUBULÁRNÍCH PROCESŮ

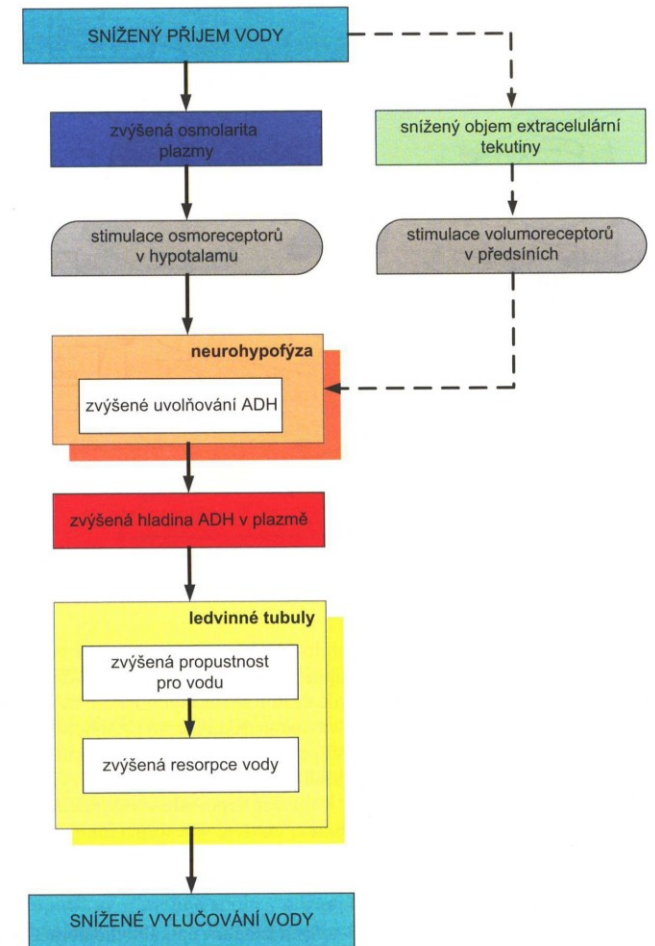
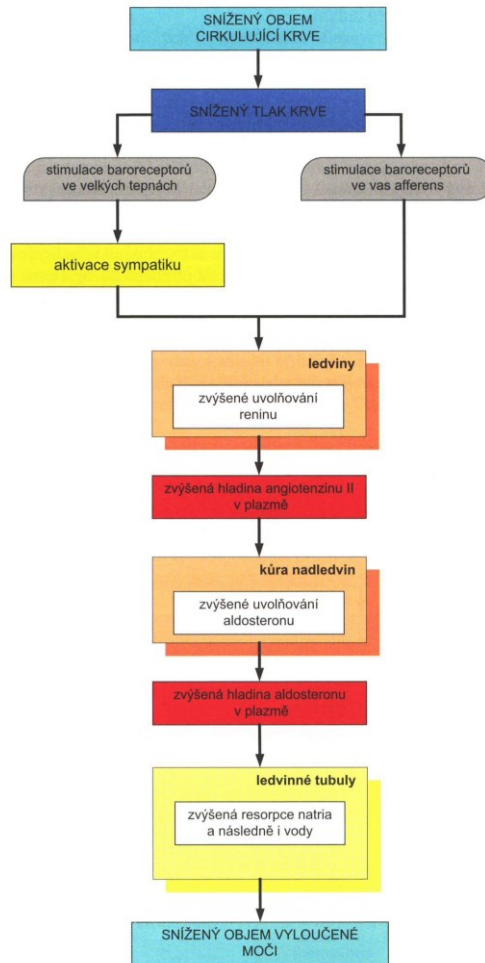
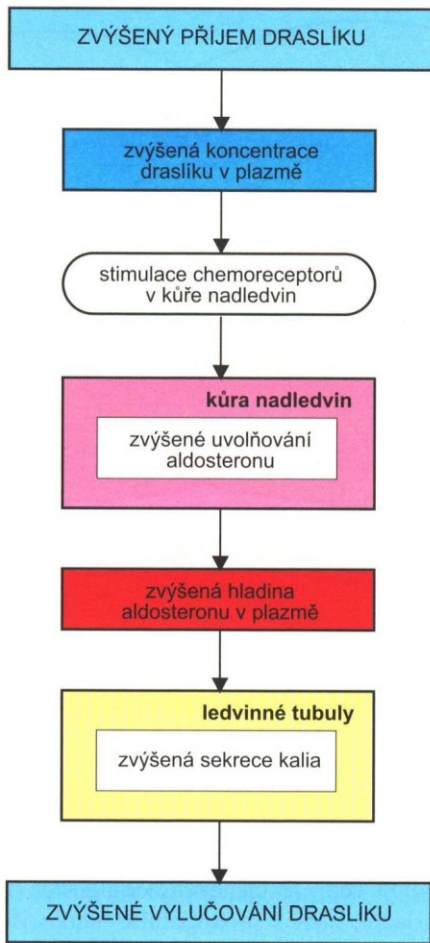
- ◆ Sympatikus (stimulace resorpce Na<sup>+</sup>)
- ◆ ADH
- ◆ Aldosteron
- ◆ Angiotenzin II
- ◆ ANP
- ◆ Dopamin
- ◆ Parathormon (zpětná resorpce Ca<sup>2+</sup>)

Hormone	Stimulus for Secretion	Time Course	Mechanism of Action	Actions on Kidneys
PTH	↓ plasma [Ca <sup>2+</sup> ]	Fast	Basolateral receptor Adenylate cyclase cAMP → urine	↓ phosphate reabsorption (proximal tubule) ↑ Ca <sup>2+</sup> reabsorption (distal tubule) Stimulates 1α-hydroxylase (proximal tubule)
ADH	↑ plasma osmolarity ↓ blood volume	Fast	Basolateral V <sub>2</sub> receptor Adenylate cyclase cAMP (Note: V <sub>1</sub> receptors are on blood vessels; mechanism is Ca <sup>2+</sup> -IP <sub>3</sub> )	↑ H <sub>2</sub> O permeability (late distal tubule and collecting duct principal cells)
Aldosterone	↓ blood volume (via renin-angiotensin II) ↑ plasma [K <sup>+</sup> ]	Slow	New protein synthesis	↑ Na <sup>+</sup> reabsorption (ENaC, distal tubule principal cells) ↑ K <sup>+</sup> secretion (distal tubule principal cells) ↑ H <sup>+</sup> secretion (distal tubule α-intercalated cells)
ANP	↑ atrial pressure	Fast	Guanylate cyclase cGMP	↑ GFR ↓ Na <sup>+</sup> reabsorption
Angiotensin II	↓ blood volume (via renin)	Fast		↑ Na <sup>+</sup> -H <sup>+</sup> exchange and HCO <sub>3</sub> <sup>-</sup> reabsorption (proximal tubule)

ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GFR = glomerular filtration rate; PTH = parathyroid hormone; ENaC = epithelial Na<sup>+</sup> channel.

## Hormones That Regulate Tubular Reabsorption

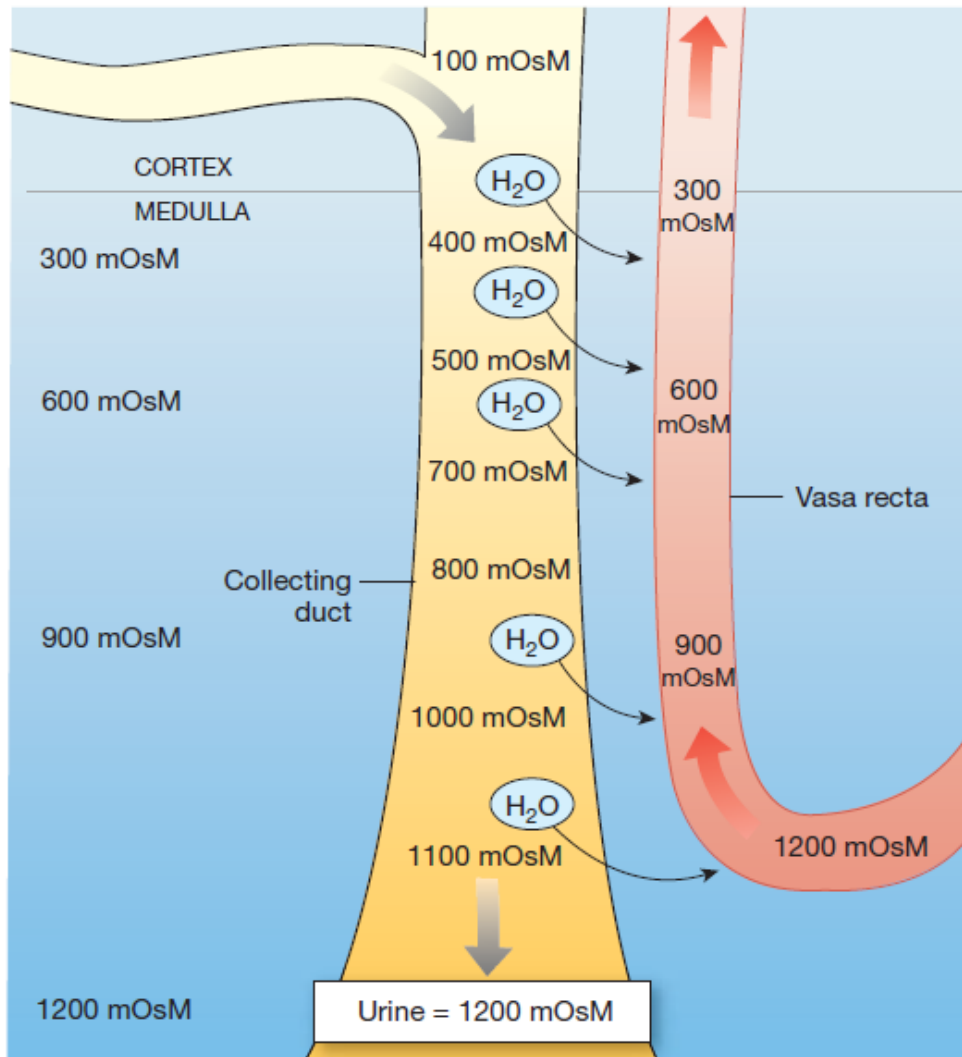
Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑ NaCl, H <sub>2</sub> O reabsorption, ↑ K <sup>+</sup> secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H <sub>2</sub> O reabsorption, ↑ H <sup>+</sup> secretion
Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑ H <sub>2</sub> O reabsorption
Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
Parathyroid hormone	Proximal tubule, thick ascending loop of Henle/distal tubule	↓ PO <sub>4</sub> <sup>3-</sup> reabsorption, ↑ Ca <sup>2+</sup> reabsorption



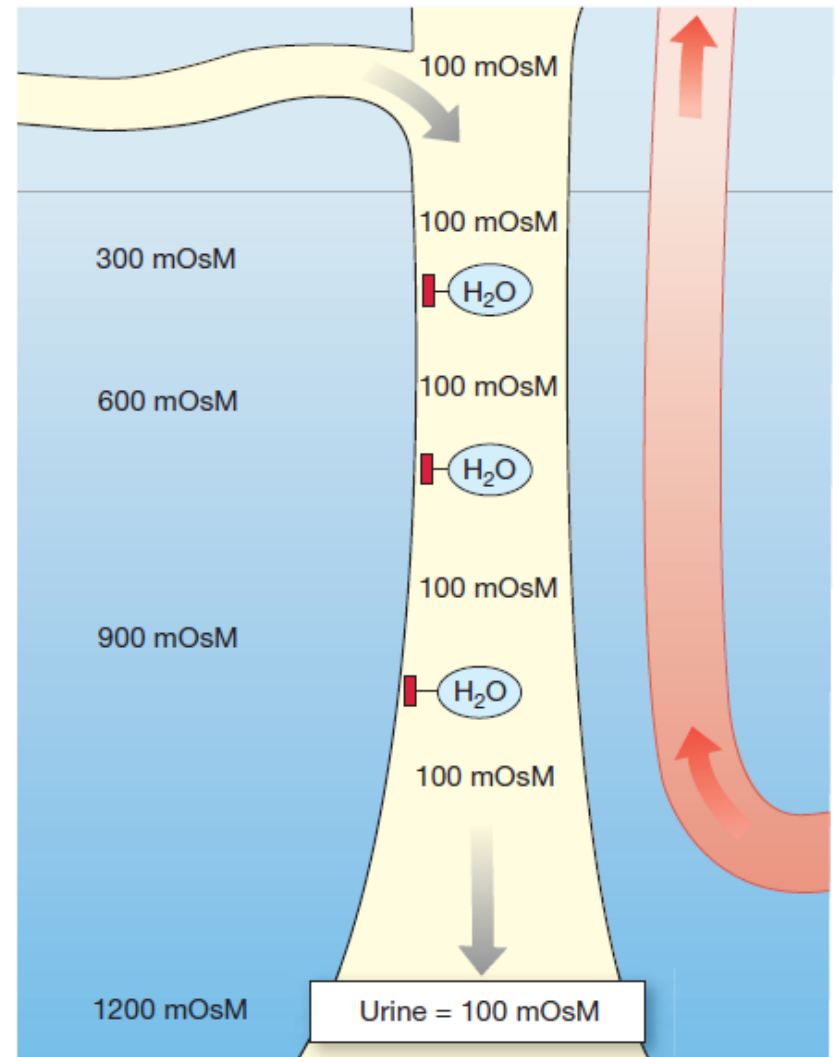


**Vasopressin makes the collecting duct permeable to water.**

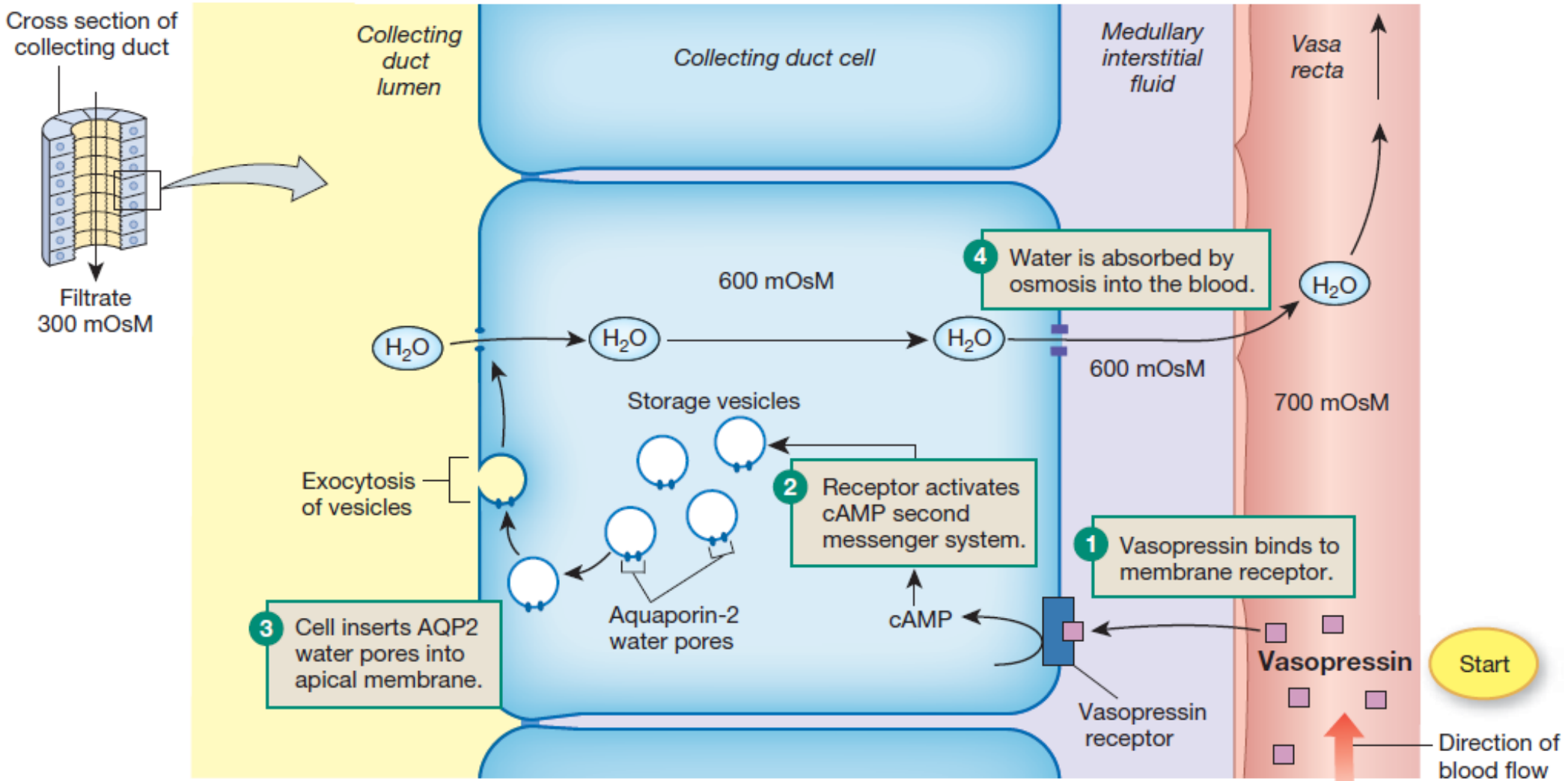
**(a)** With maximal vasopressin, the collecting duct is freely permeable to water. Water leaves by osmosis and is carried away by the vasa recta capillaries. Urine is concentrated.



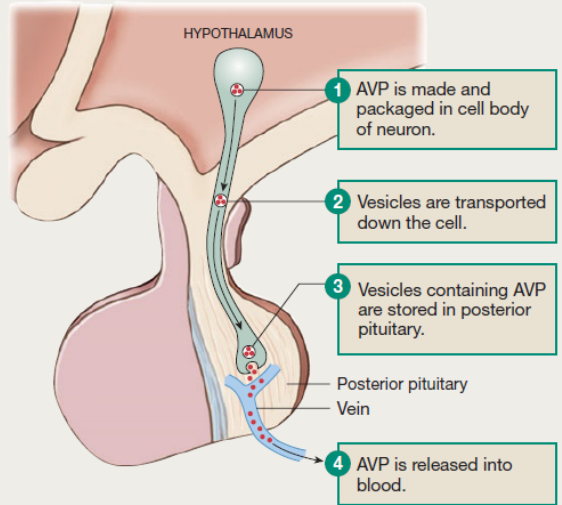
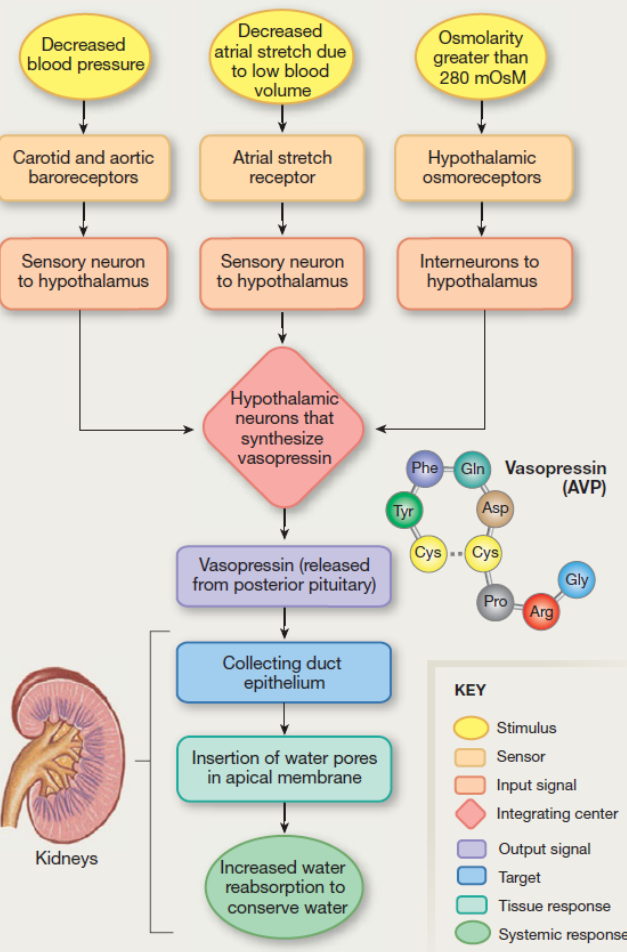
**(b)** In the absence of vasopressin, the collecting duct is impermeable to water and the urine is dilute.



(c) Vasopressin causes insertion of water pores into the apical membrane.

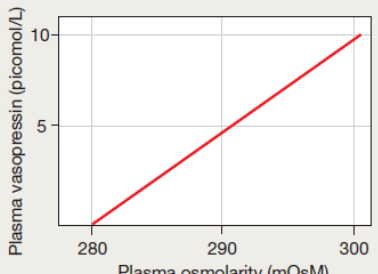


**(a) Control of vasopressin secretion**



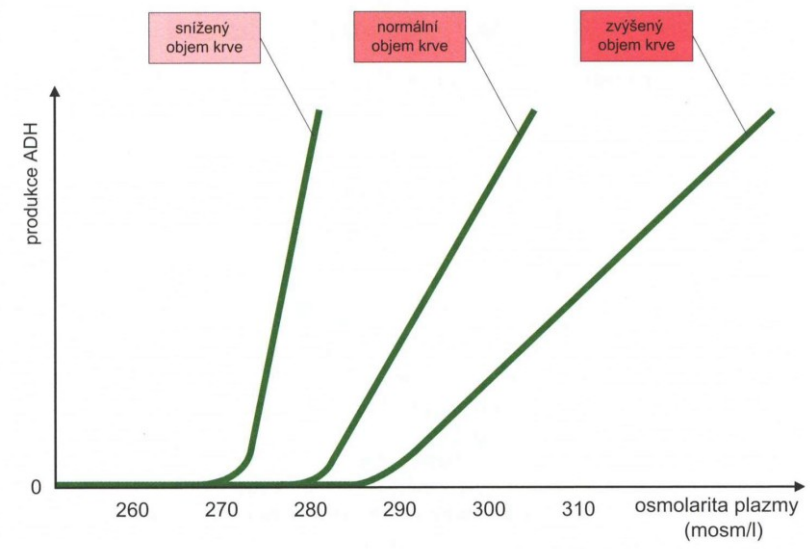
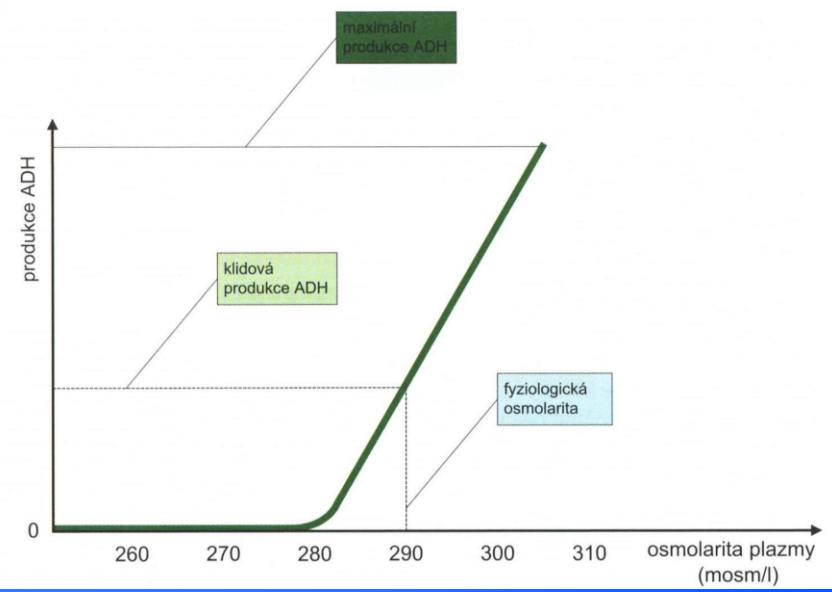
ARGININE VASOPRESSIN (AVP), Antidiuretic hormone (ADH)	
Origin	Hypothalamic neurons. Released from posterior pituitary
Chemical nature	9-amino acid peptide
Transport in the circulation	Dissolved in plasma
Half-life	15 min
Factors affecting release	↑ Osmolarity (hypothalamic osmoreceptors) ↓ Blood pressure or volume (carotid, aortic, atrial receptors)
Target cells or tissues	Renal collecting duct
Receptor/second messenger	V2 receptor/cAMP
Tissue action	Increases renal water reabsorption
Action at cellular-molecular level	Inserts AQP water pores in apical membrane

**(b) The effect of plasma osmolarity on vasopressin secretion**



**FIGURE QUESTIONS**

1. What is the threshold osmolarity for vasopressin release?
2. What signal in the AVP neuron triggers exocytosis of AVP-containing vesicles?



**Obr. 8.48** Moduluující vliv objemu krve na produkci antidiuretického hormonu

## Regulation of ADH Secretion

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### Increase ADH

↑ Plasma osmolarity  
↓ Blood volume  
↓ Blood pressure

Nausea  
Hypoxia

### Drugs:

Morphine  
Nicotine  
Cyclophosphamide

### Decrease ADH

↓ Plasma osmolarity  
↑ Blood volume  
↑ Blood pressure

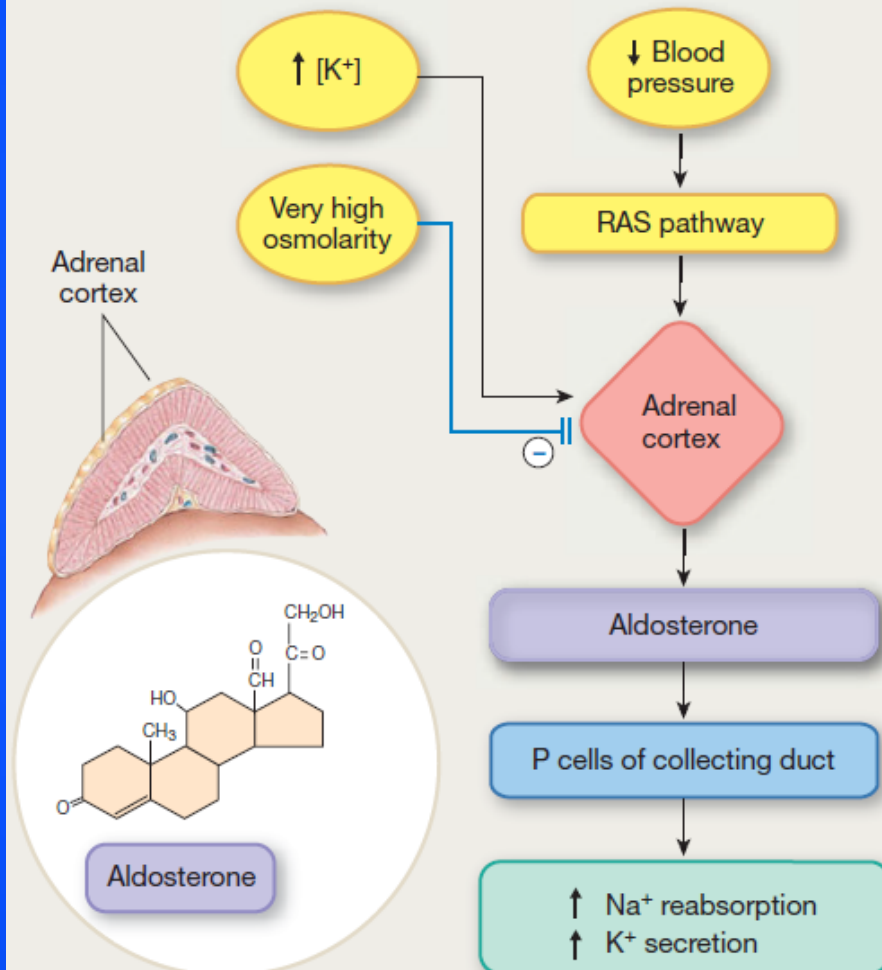
### Drugs:

Alcohol  
Clonidine (antihypertensive drug)  
Haloperidol (dopamine blocker)

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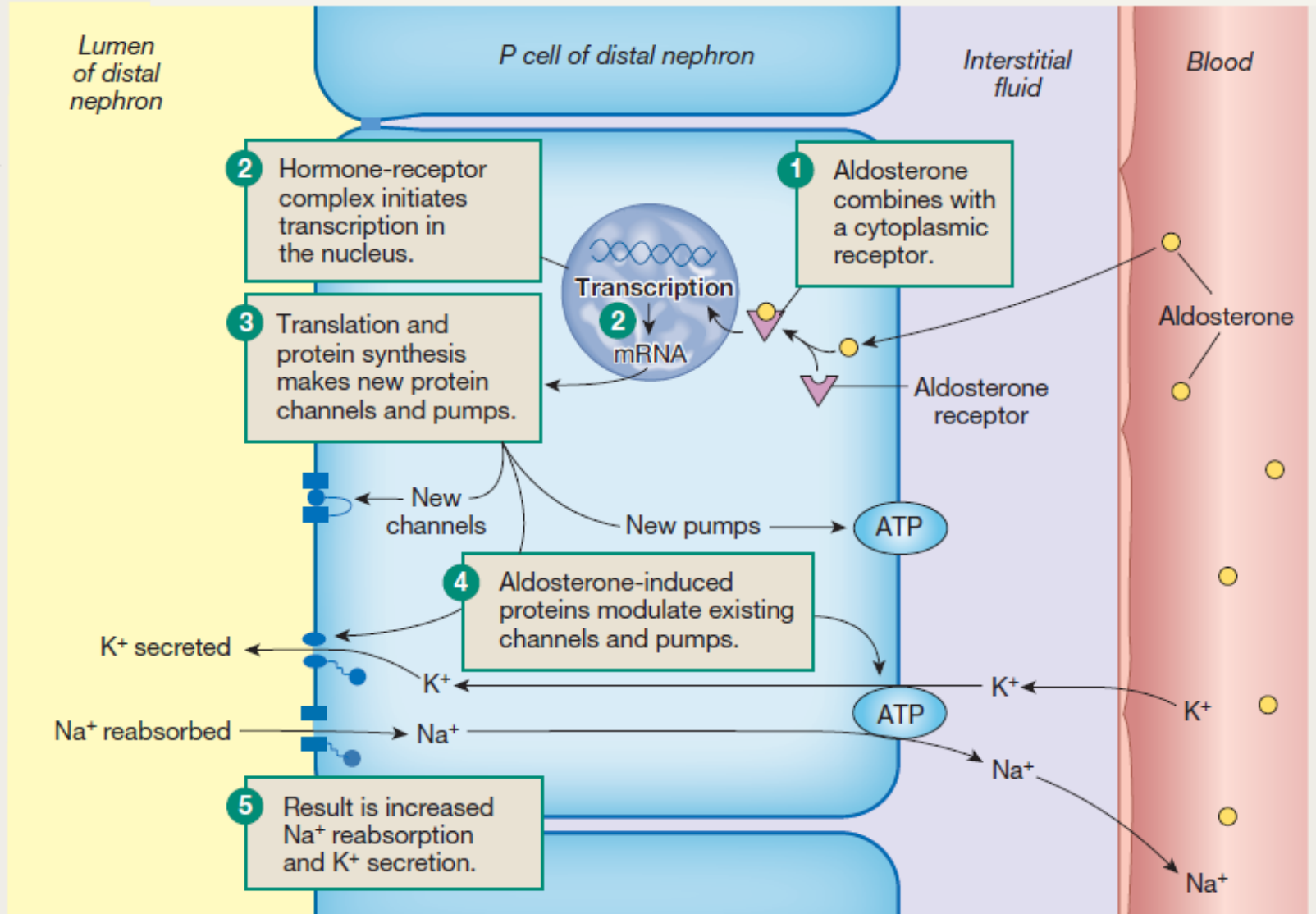
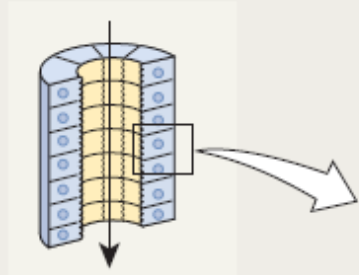
# Aldosterone

(a) The primary action of aldosterone is renal sodium reabsorption.



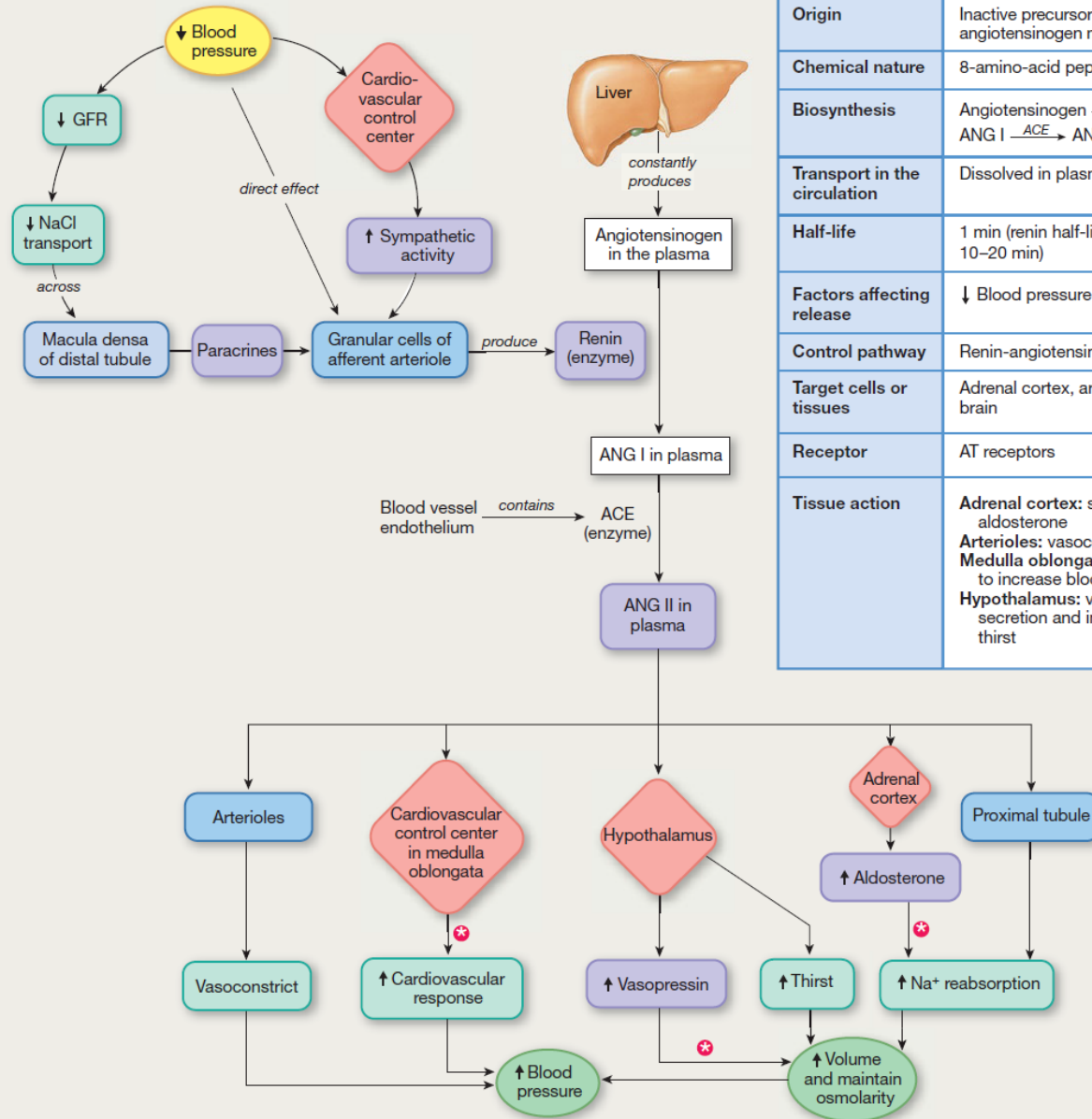
ALDOSTERONE	
Origin	Adrenal cortex
Chemical nature	Steroid
Biosynthesis	Made on demand
Transport in the circulation	50–70% bound to plasma protein
Half-life	15 min
Factors affecting release	$\downarrow$ Blood pressure (via renin) $\uparrow K^+$ (hyperkalemia) Natriuretic peptides inhibit release
Target cells or tissues	Renal collecting duct—principal cells
Receptor	Cytosolic mineralocorticoid (MR) receptor
Tissue action	Increases $Na^+$ reabsorption and $K^+$ secretion
Action at cellular-molecular level	Synthesis of new ion channels (ENaC and ROMK) and pumps ( $Na^+-K^+-ATPase$ ); increased activity of existing channels and pumps.

(b) Aldosterone acts on principal cells.



# The Renin-angiotensin System (RAS)

This map outlines the control of aldosterone secretion as well as the blood pressure-raising effects of ANG II. The pathway begins when decreased blood pressure stimulates renin secretion.

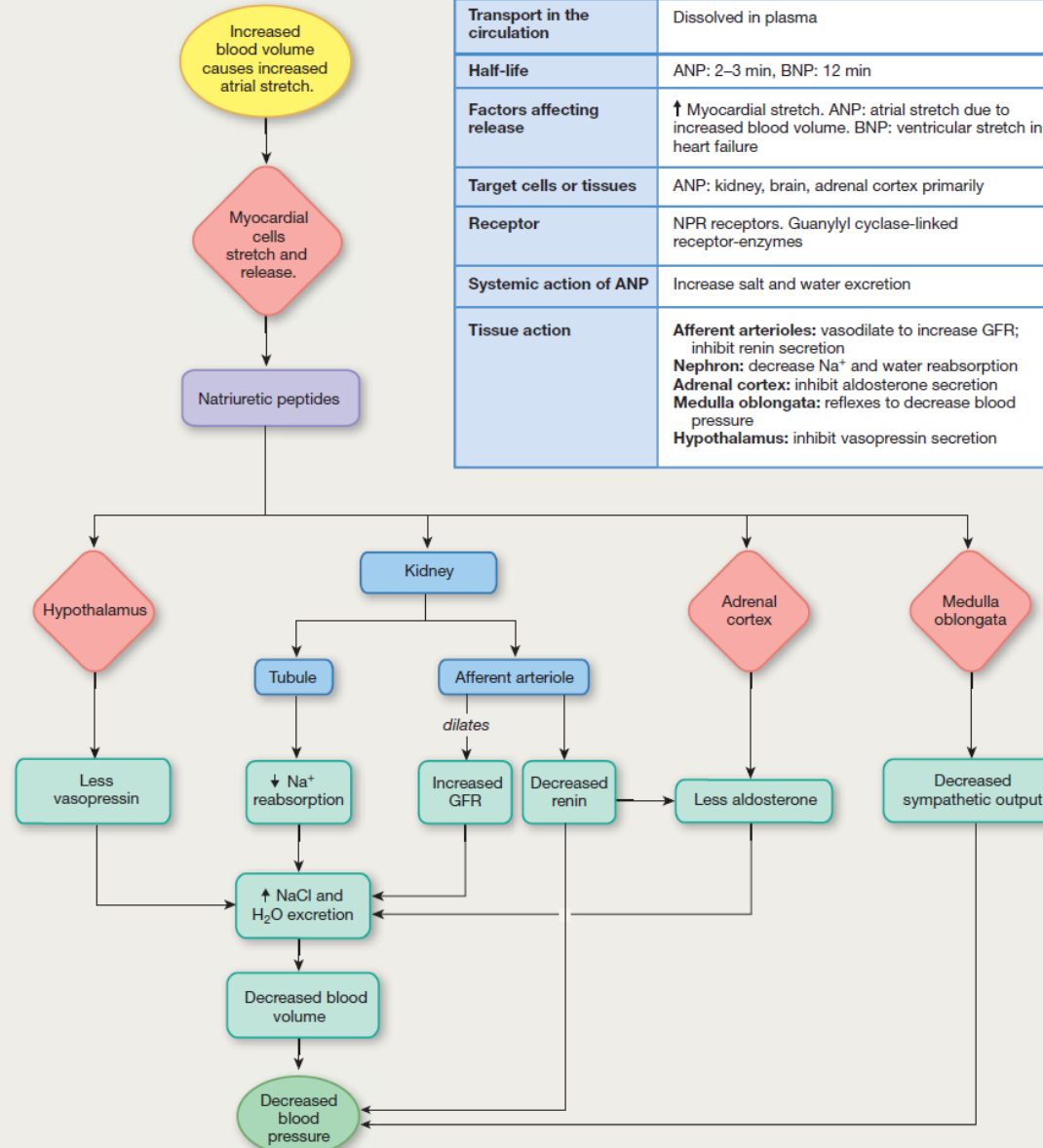


ANGIOTENSIN (ANG II)	
Origin	Inactive precursor protein angiotensinogen made by liver
Chemical nature	8-amino-acid peptide
Biosynthesis	Angiotensinogen $\xrightarrow{\text{renin}}$ ANG I $\xrightarrow{\text{ACE}}$ ANG II
Transport in the circulation	Dissolved in plasma
Half-life	1 min (renin half-life: 10–20 min)
Factors affecting release	↓ Blood pressure (via renin)
Control pathway	Renin-angiotensin system
Target cells or tissues	Adrenal cortex, arterioles, brain
Receptor	AT receptors
Tissue action	<b>Adrenal cortex:</b> secrete aldosterone <b>Arterioles:</b> vasoconstrict <b>Medulla oblongata:</b> reflexes to increase blood pressure <b>Hypothalamus:</b> vasopressin secretion and increased thirst

# Natriuretic Peptides

Atrial natriuretic peptide (ANP) promotes salt and water excretion. Brain natriuretic peptide (BNP) is a clinical marker for heart failure.

NATRIURETIC PEPTIDES (ANP, BNP)	
Origin	Myocardial cells
Chemical nature	Peptides. ANP: 28 amino acids, BNP: 32 amino acids
Biosynthesis	Typical peptide. Stored in secretory cells
Transport in the circulation	Dissolved in plasma
Half-life	ANP: 2–3 min, BNP: 12 min
Factors affecting release	↑ Myocardial stretch. ANP: atrial stretch due to increased blood volume. BNP: ventricular stretch in heart failure
Target cells or tissues	ANP: kidney, brain, adrenal cortex primarily
Receptor	NPR receptors. Guanylyl cyclase-linked receptor-enzymes
Systemic action of ANP	Increase salt and water excretion
Tissue action	<b>Afferent arterioles:</b> vasodilate to increase GFR; inhibit renin secretion <b>Nephron:</b> decrease Na <sup>+</sup> and water reabsorption <b>Adrenal cortex:</b> inhibit aldosterone secretion <b>Medulla oblongata:</b> reflexes to decrease blood pressure <b>Hypothalamus:</b> inhibit vasopressin secretion





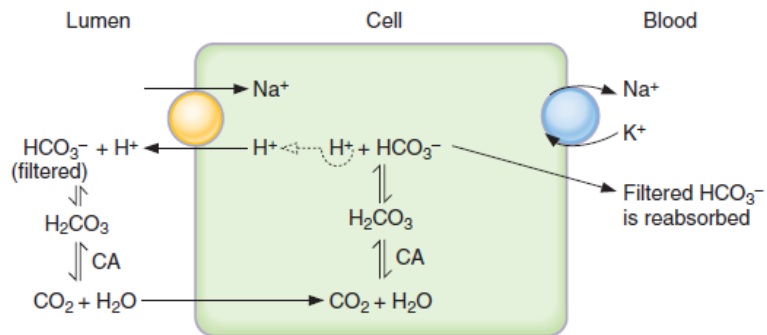


FIGURE 5-19 Mechanism for reabsorption of filtered  $\text{HCO}_3^-$  in the proximal tubule. CA = carbonic anhydrase.

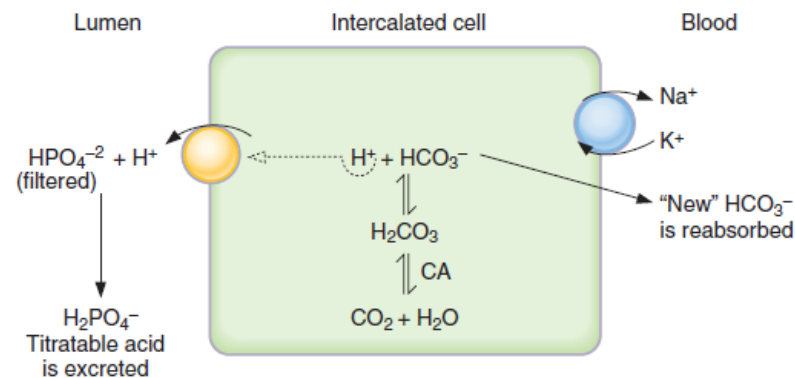


FIGURE 5-20 Mechanism for excretion of  $\text{H}^+$  as titratable acid. CA = carbonic anhydrase.

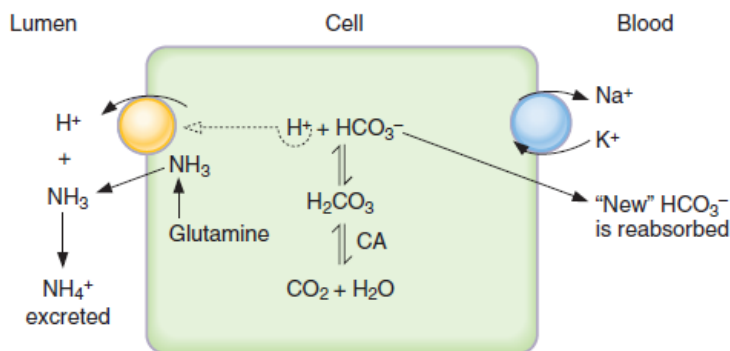
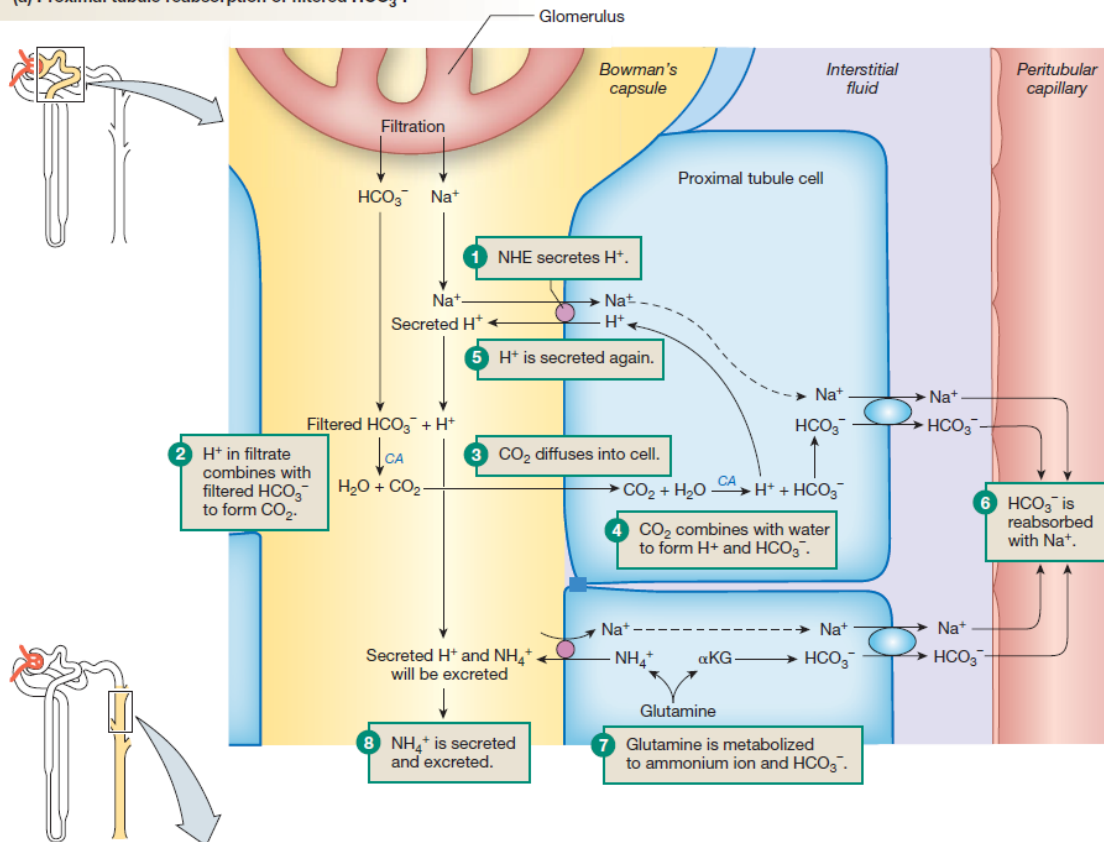


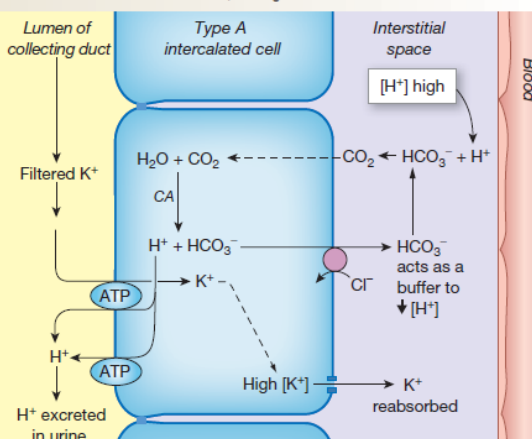
FIGURE 5-21 Mechanism for excretion of  $\text{H}^+$  as  $\text{NH}_4^+$ . CA = carbonic anhydrase.

RENAL MECHANISMS FOR ACID-BASE BALANCE

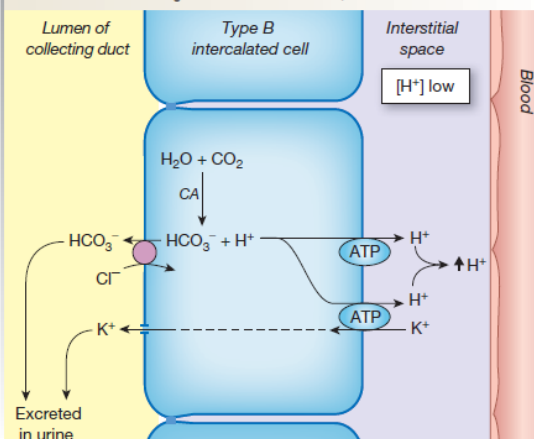
(a) Proximal tubule reabsorption of filtered  $\text{HCO}_3^-$ .



(b) Acidosis. Type A intercalated cells in collecting duct function in acidosis.  $\text{H}^+$  is excreted;  $\text{HCO}_3^-$  and  $\text{K}^+$  are reabsorbed.

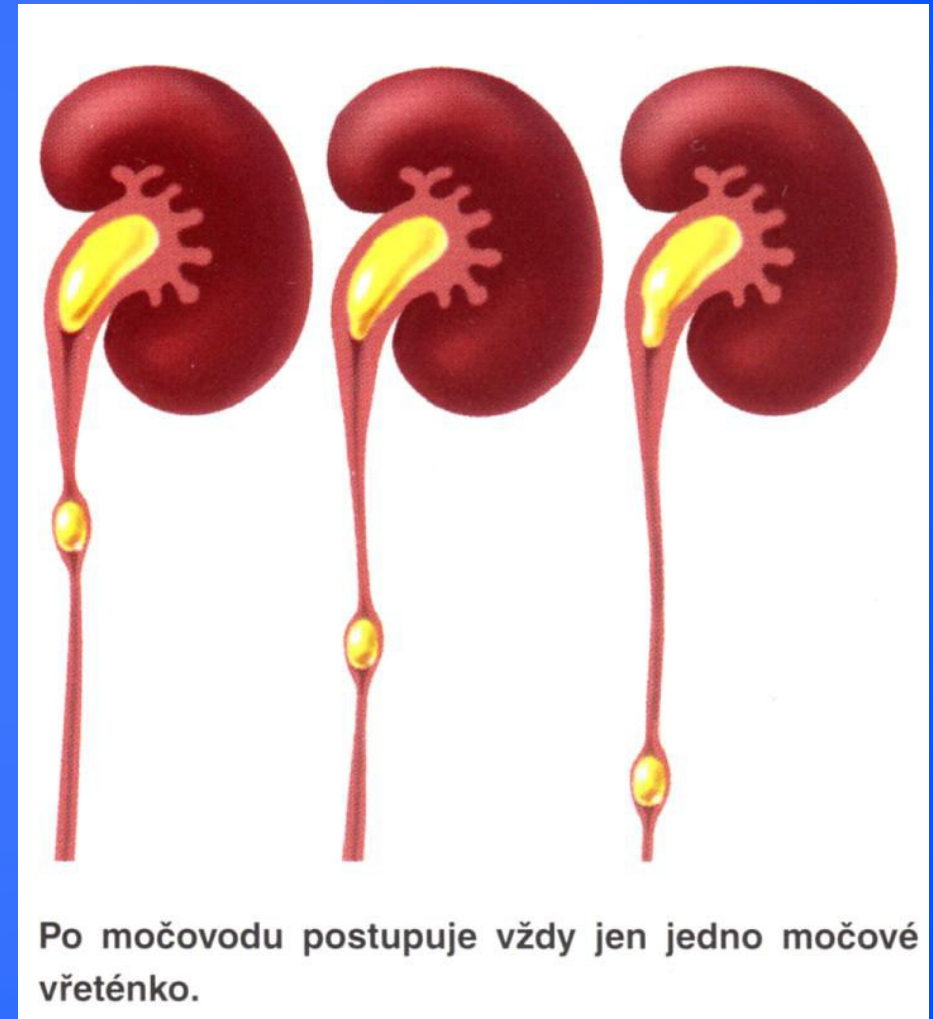
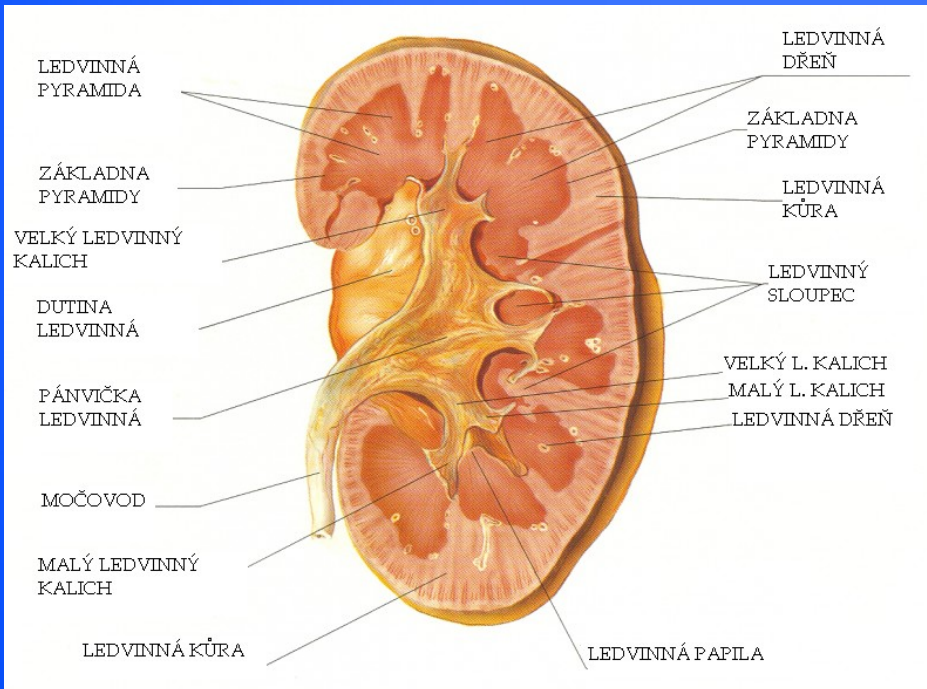


(c) Alkalosis. Type B intercalated cells in collecting duct function in alkalosis.  $\text{HCO}_3^-$  and  $\text{K}^+$  are excreted;  $\text{H}^+$  is reabsorbed.

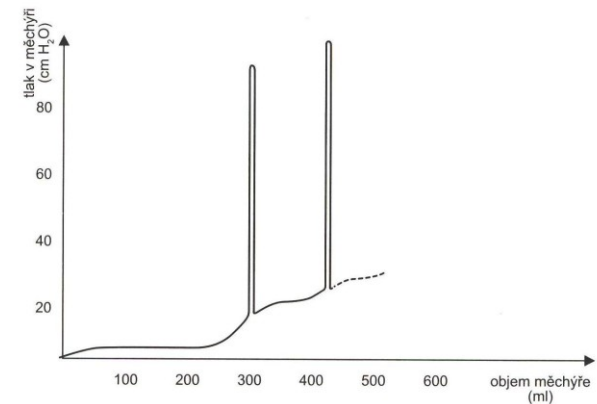


## FUNKCE HORNÍCH CEST MOČOVÝCH

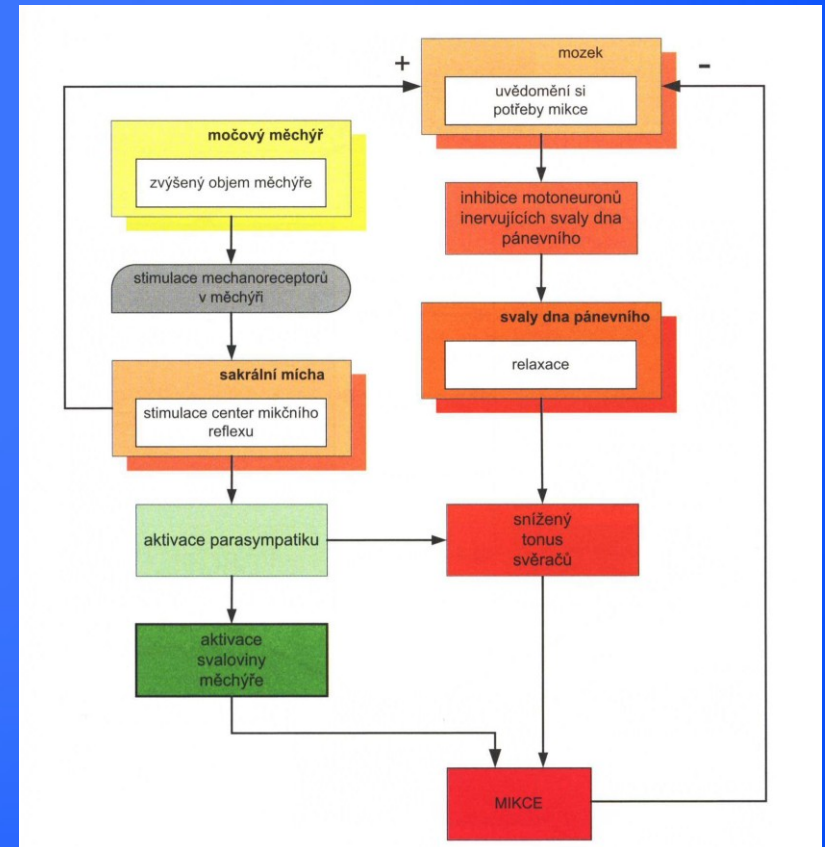
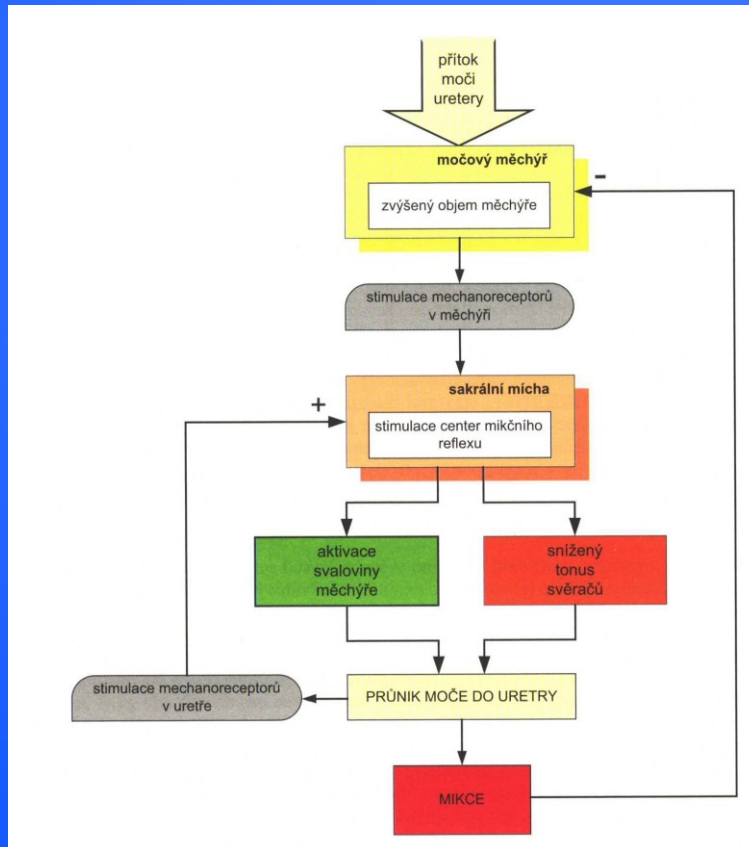
- Ledvinné kalichy – systola X diastola
- Pánvička ledvinná – rezervoár (5 ml), roztažitelnost
- Uretery
  - Nervová pletěň, hladká svalovina
  - Pacemakerové neurony v subrenálním segmentu
  - Peristalticky postupující kontrakce
  - Močové vřeténko



- **Fyziologická kapacita MM – 10 – 300 ml**
- **Po překročení stoupá tlak v močovém měchýři = první kontrakce m. detrusor = pocit nucení na močení**
- **Dále zkracující se intervaly kontrakcí**
- **Dosažení kritického intravezikálního tlaku = pocit imperativního nucení, který nelze potlačit vůlí**
- **Vyprázdnění močového měchýře = mikce, mikční reflex**
- **Stimulace mechanoreceptorů ve stěně MM**



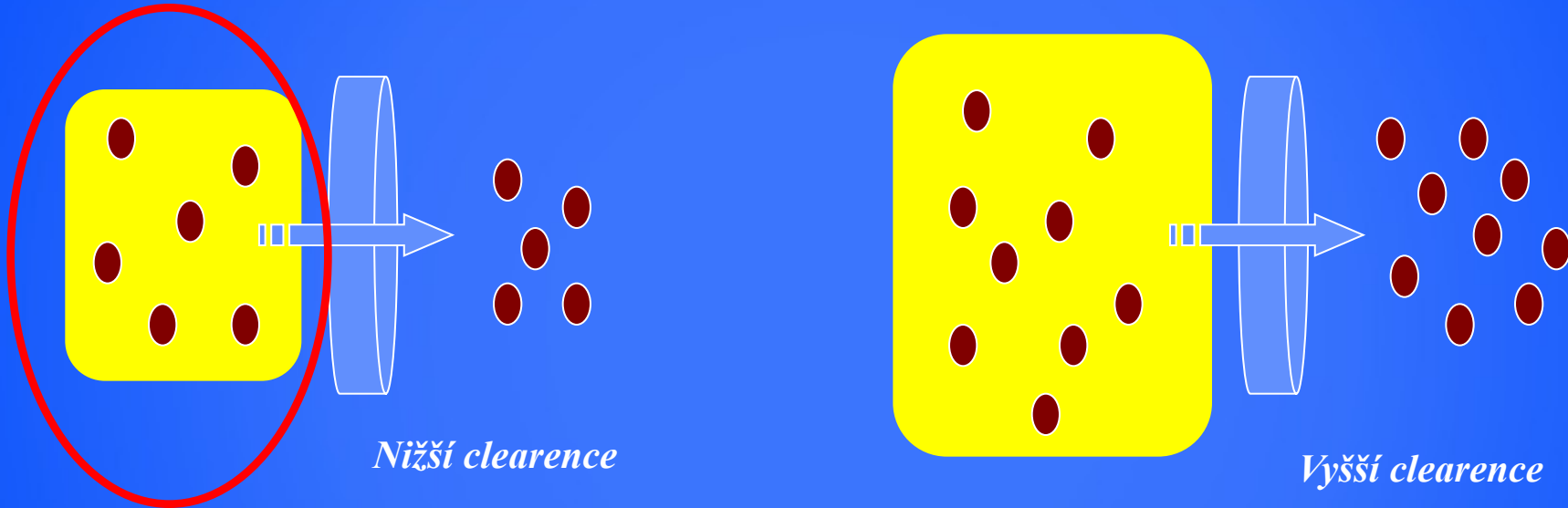
Obr. 8.63 Vztah tlaku v močovém měchýři a objemu močového měchýře (bližší podrobnosti viz text)



<b>základní vlastnosti moči</b>		
<b>vlastnost</b>	<b>fyziologická hodnota</b>	<b>jednotka</b>
pH	4,5–7,8	
specifická hmotnost	1002–1035	kg/m <sup>3</sup>
denní diuréza	500–1500	ml/den
vyučování látek močí		
<b>látka</b>	<b>vyložené množství</b>	<b>jednotka</b>
proteiny	25–70	mg/den
močovina	334–586	mmol/den
kreatinin	8,8–17,0	mmol/den
glukóza	0	mmol/den

# Základní funkční vyšetření ledvin

*Clearance (očistění) = objem plazmy, který je zbaven dané látky za jednotku času (ml/s ; ml/min)*



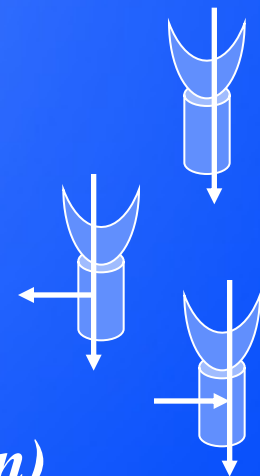
*1) Clearance látky pouze filtrované (endogenní kreatinin, inulin)*

*= GFR 1-2 ml/s*

*2) Clearance látky filtrované a resorbované (glukóza, Na)*

$$C_{krea} > C_{glu}$$

*3) Clearance látky filtrované a secernované (PAH, penicilin)*

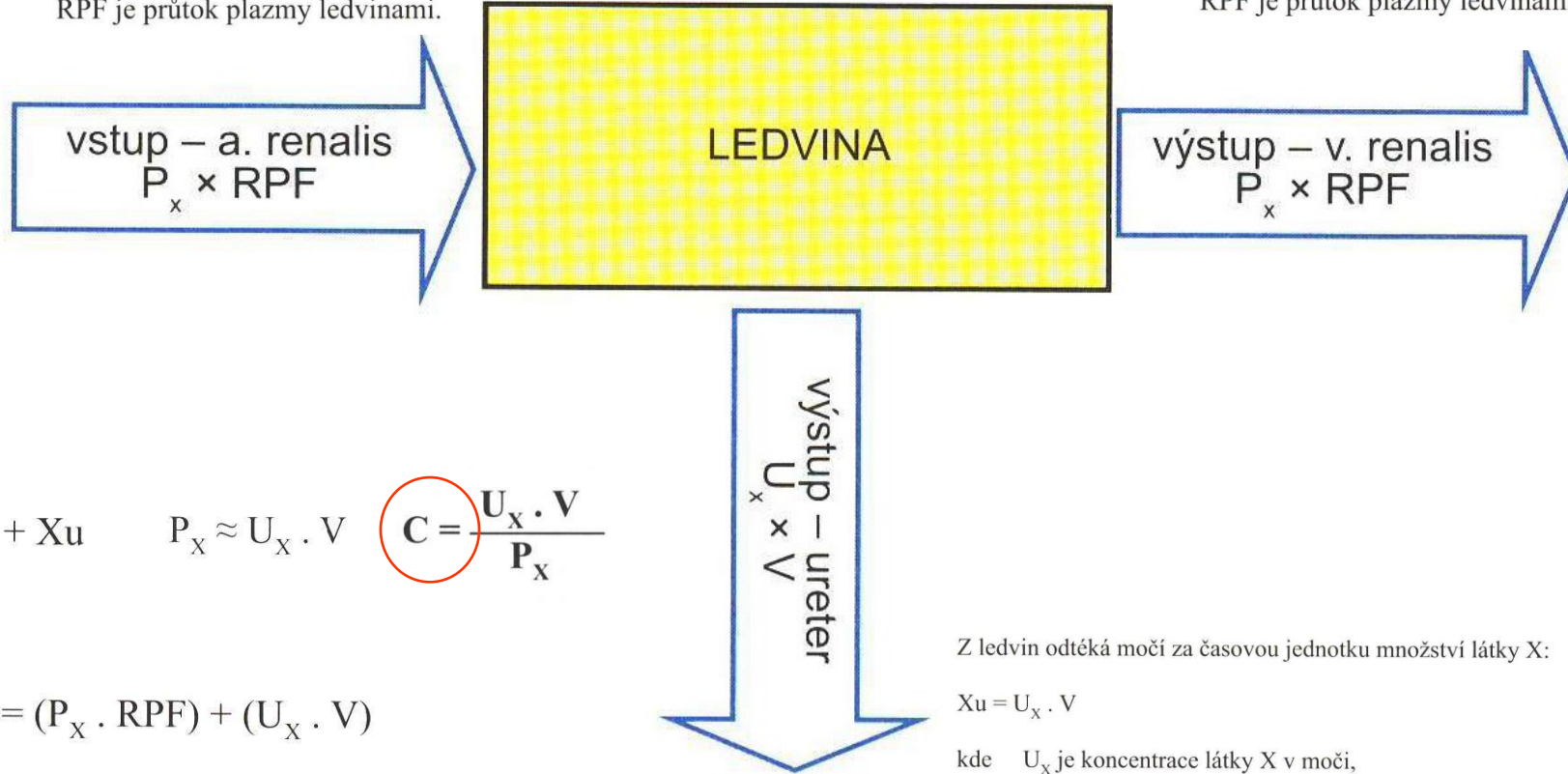


$$X_a = P_x \cdot RPF$$

kde  $P_x$  je koncentrace látky X v plazmě,  
RPF je průtok plazmy ledvinami.

$$X_v = P_x \cdot RPF$$

kde  $P_x$  je koncentrace látky X v plazmě,  
RPF je průtok plazmy ledvinami.



$$X_a = X_v + X_u \quad P_x \approx U_x \cdot V \quad C = \frac{U_x \cdot V}{P_x}$$

neboli

$$P_x \cdot RPF = (P_x \cdot RPF) + (U_x \cdot V)$$

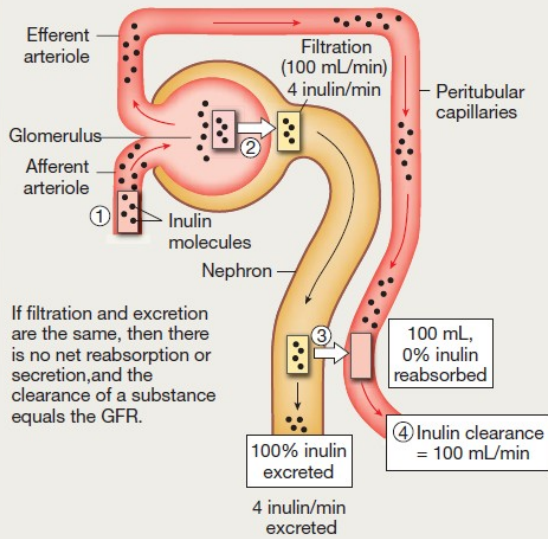
Z ledvin odtéká močí za časovou jednotku množství látky X:

$$X_u = U_x \cdot V$$

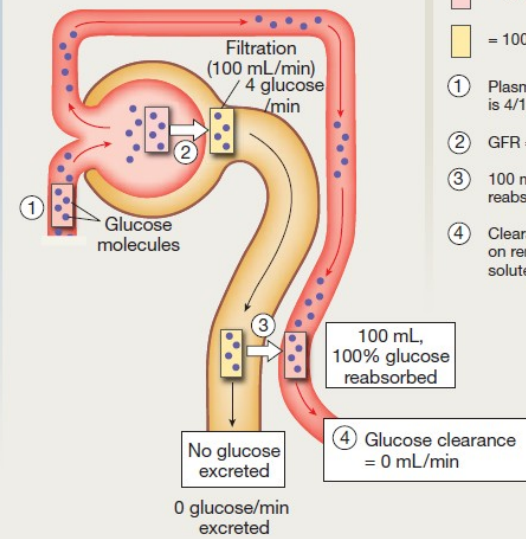
kde  $U_x$  je koncentrace látky X v moči,  
 $V$  je průtok moči vývodnými močovými cestami.

**Obr. 8.67** *Koncept clearance vychází ze zákona zachování hmoty: množství látky, které do ledviny za časovou jednotku vstoupí, ji také musí opustit (samozřejmě, že látka není v ledvinách ani produkována, ani metabolizována)*

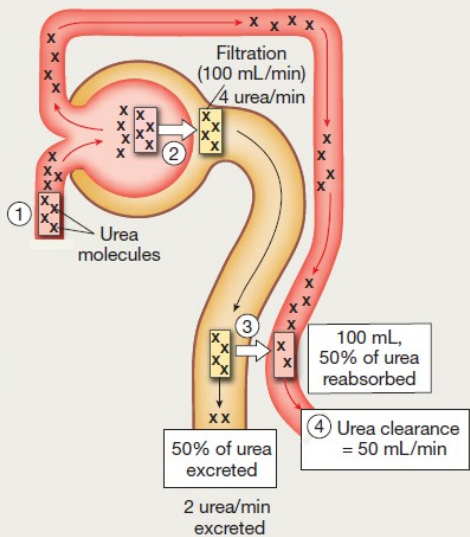
(a) Inulin clearance is equal to GFR.



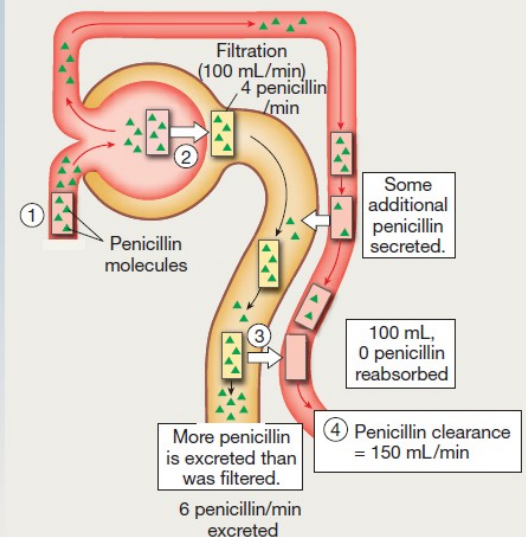
(b) Glucose clearance: Normally all glucose that filters is reabsorbed.



(c) Urea clearance is an example of net reabsorption. If filtration is greater than excretion, there is net reabsorption.



(d) Penicillin clearance is an example of net secretion. If excretion is greater than filtration, there is net secretion.



## Hodnocení GFP (velikost glomerulární filtrace)

- látka, která je pouze filtrována, a nepodléhá dále žádnému tubulárnímu procesu
- Inulin, kreatinin

## Hodnocení RPF (průtok plazmy ledvinou)

- látka, která je filtrována v glomerulech a secernována v tubulech
- malé množství látky, které bude vyloučeno při jediném průtoku krve ledvinou
- Kyselina para-aminohippurová

## Průtok krve ledvinou RBF - Z hodnoty hematokritu RBF = RPF/(1-Ht)

## Use of Clearance to Quantify Kidney Function

Term	Equation	Units
Clearance rate ( $C_s$ )	$C_s = \frac{U_s \times V}{P_s}$	ml/min
Glomerular filtration rate (GFR)	$GFR = \frac{U_{\text{inulin}} \times V}{P_{\text{inulin}}}$	
Clearance ratio	$\text{Clearance ratio} = \frac{C_s}{C_{\text{inulin}}}$	None
Effective renal plasma flow (ERPF)	$ERPF = C_{\text{PAH}} = \frac{U_{\text{PAH}} \times V}{P_{\text{PAH}}}$	ml/min
Renal plasma flow (RPF)	$\begin{aligned} RPF &= \frac{C_{\text{PAH}}}{E_{\text{PAH}}} = \frac{(U_{\text{PAH}} \times V / P_{\text{PAH}})}{(P_{\text{PAH}} - V_{\text{PAH}}) / P_{\text{PAH}}} \\ &= \frac{U_{\text{PAH}} \times V_{\text{PAH}}}{P_{\text{PAH}} - V_{\text{PAH}}} \end{aligned}$	ml/min
Renal blood flow (RBF)	$RBF = \frac{RPF}{1 - \text{Hematocrit}}$	ml/min
Excretion rate	$\text{Excretion rate} = U_s \times V$	mg/min, mmol/min, or mEq/min
Reabsorption rate	$\begin{aligned} \text{Reabsorption rate} &= \text{Filtered load} - \text{Excretion rate} \\ &= (GFR \times P_s) - (U_s \times V) \end{aligned}$	mg/min, mmol/min, or mEq/min
Secretion rate	$\text{Secretion rate} = \text{Excretion rate} - \text{Filtered load}$	mg/min, mmol/min, or mEq/min

S, a substance; U, urine concentration; V, urine flow rate; P, plasma concentration; PAH, para-aminohippuric acid;  $P_{\text{PAH}}$ , renal arterial PAH concentration;  $E_{\text{PAH}}$ , PAH extraction ratio;  $V_{\text{PAH}}$ , renal venous PAH concentration.



# DALŠÍ FUNKČNÍ VYŠETŘENÍ LEDVIN

## VYŠETŘENÍ KONCENTRAČNÍ SCHOPNOSTI LEDVIN

- **VYŠETŘENÍ SCHOPNOSTI LEDVIN KONCENTROVAT MOČ**
- *Pacient nepije a nedostává potraviny obsahující větší množství vody (ovoce) po dobu max. 36 hodin = koncentrační pokus žízněním*
- *Moč se sbírá ve čtyřhodinových intervalech (po 12 hodinách)*
- *Ukončení před dosažením hranice pro určitý věk*
- *Před posledním vzorkem se odebírá rovněž krev*
- *Hodnotí se její hustota (1.026 – 1.032 g/cm<sup>3</sup>)*
- *Co zjišťujeme? Schopnost vyplavit ADH*

## TEST S ADIURETINEM

- *syntetický analog antidiuretického hormonu*
- *sběr moči každé 4 hodiny*
- *opakovaně změření osmolality moči*
- *Schopnost distálního tubulu a sběrného kanálku reagovat na ADH*

## VYŠETŘENÍ ZŘEĎOVACÍ FUNKCE LEDVIN

### ACIDIFIKAČNÍ A ALKALIZAČNÍ TESTY

- *Změna pH moči až v tubulech - proximální - resorpce HCO<sub>3</sub><sup>-</sup>, distální sekrece H<sup>+</sup>*

*Acidifikační test - chlorid amonný v dávce 2 mmol/kg, sběr moči každou hodinu, měří se pH moči, dobrá acidifikační schopnost pokles pH pod 5,5; Snížená konc.schopnost u tubulární acidózy I. typu*

*Alkalizační test - hydrogenuhličitan sodný v dávce 2 mmol/kg, sledování pH moči, při nárustu nad 7,8, přesné stanovení pH moči a pCO<sub>2</sub>, výpočet HCO<sub>3</sub><sup>-</sup>; změny u renální tubulární acidózy II. typu*

*Index aktivní sekrece H<sup>+</sup> podle rozdílu pCO<sub>2</sub> krvi a moči  
(norma pCO<sub>2</sub> nad 3,3 kPa, FEHCO<sub>3</sub><sup>-</sup> nad 0,15)*