Regulation of Renal Functions
Kidneys
in Regulation of Homeostasis

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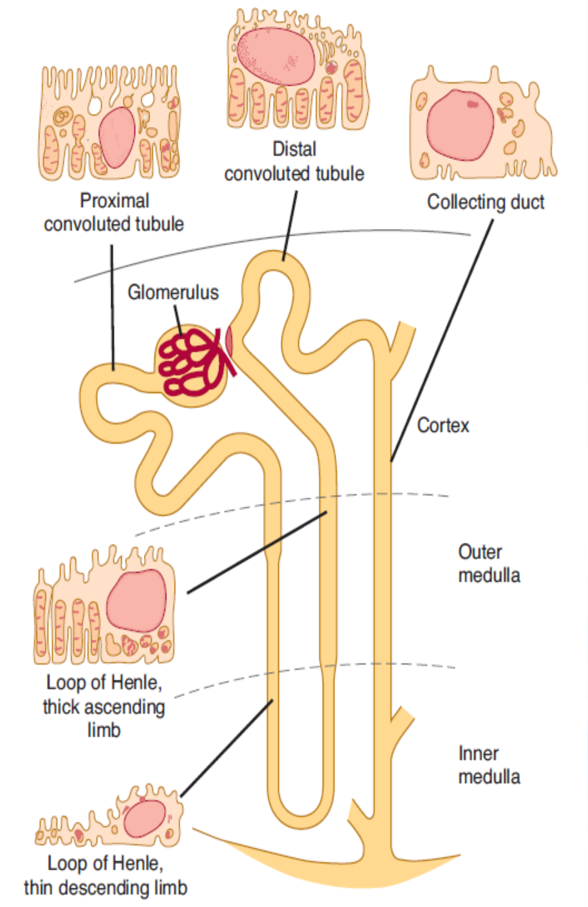
This presentation includes only the most important terms and facts. Its content by itself is not a sufficient source of information required to pass the Physiology exam.

Regulation of Renal Functions



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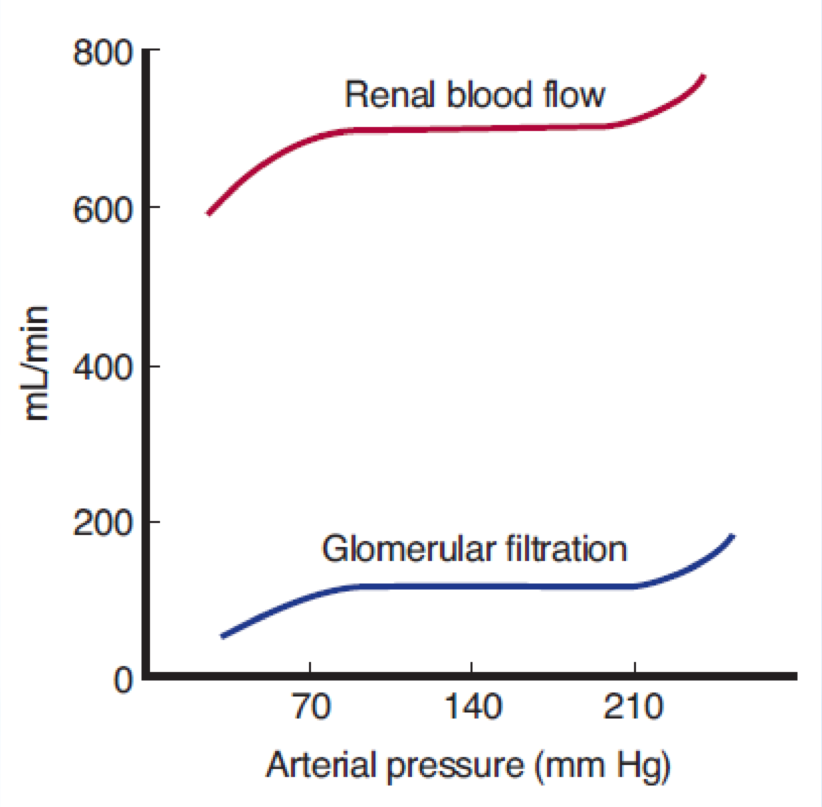
Regulation of Renal Blood Flow

1) Myogenic Autoregulation
2) Neural Regulation
3) Humoral Regulation



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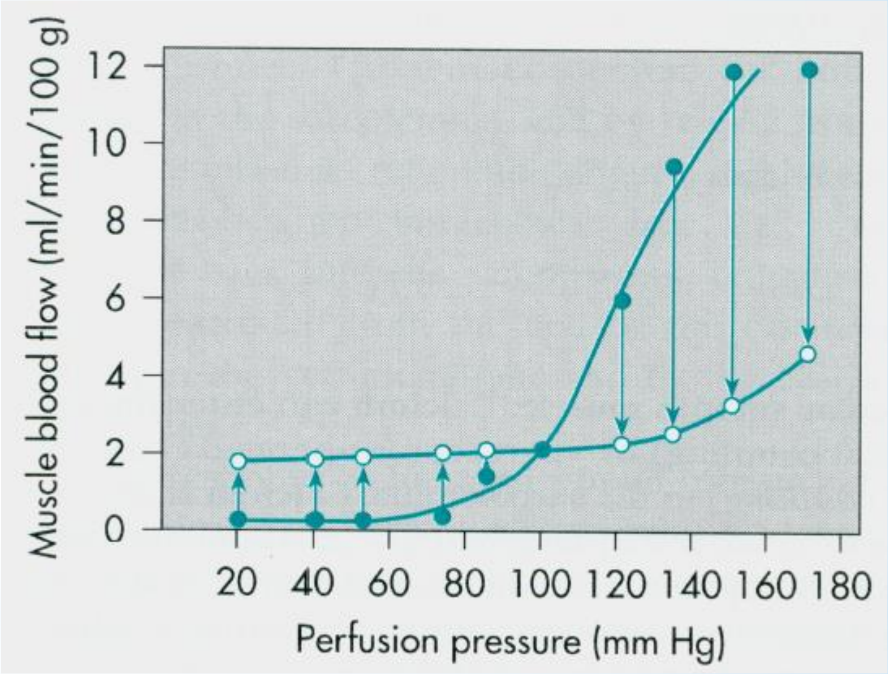
Regulation of Renal Blood Flow

1) Myogenic Autoregulation

- dominates
- provides stable renal activity by maintaining stable blood flow at varying systemic pressure (stable glomerular pressure and, thus, also stable glomerular filtration rate)



Regulation of Renal Blood Flow

2) Neural Regulation

- conformed to demands of systemic circulation
- renal blood flow forms 25% of the cardiac output, thus, it considerably influence BP
- **sympathetic system - norepinephrine**

light exertion (both emotional and physical) + upright body posture → ↑ sympathetic tone → ↑ tone of *v. aff.* and *eff.* → ↓ renal blood flow but without ↓ GFR (↑ FF)

higher ↑ of sympathetic tone - during anesthesia and pain - GFR may already ↓

in healthy people – minor impact

Regulation of Renal Blood Flow

3) Humoral Regulation

- contribute to regulation of systemic BP and regulation of body fluids
- **norepinephrine, epinephrine** (from adrenal medulla) → constriction of aff. and eff. arterioles → ↓ renal blood flow and GFR
  in agreement with ↑ activity of sympathetic system
  (small impact with the exception of serious conditions, for example serious bleeding)

Regulation of Renal Blood Flow

3) Humoral Regulation

- contribute to regulation of systemic BP and regulation of body fluids
- **norepinephrine, epinephrine** (from adrenal medulla)

  $\rightarrow$ constriction of aff. and eff. arterioles $\rightarrow \downarrow$ renal blood flow and GFR
- **endothelin**

  constriction of aff. and eff. arterioles $\rightarrow \downarrow$ renal blood flow and GFR

  released locally from the impaired endothel (physiological impact - hemostasis; pathologically increased levels at the toxemia of pregnancy, acute renal failure, chronic uremia)

Regulation of Renal Blood Flow

3) Humoral Regulation

- contribute to regulation of systemic BP and regulation of body fluids
- **NO** (from the endothel)

  continual basal production → vasodilation in the kidney → stable renal blood flow and GFR

- **prostanglandins (PGE_2, PGI_2), bradykinin**

  → vasodilation

  minor impact under physiological conditions

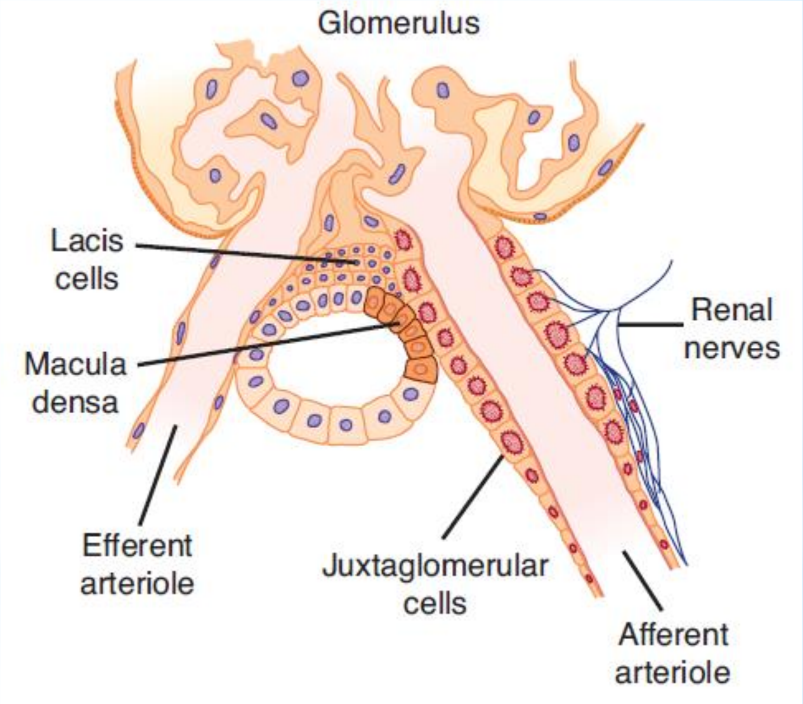
  decrease the effect of vasoconstrictive substances which reduce marked ↓ of renal blood flow and GFR

  non-steroidal anti-inflammatory agents during stress (surgery, ↓ fluid volume) may → notably ↓ GFR

Regulation of Renal Blood Flow

3) Humoral Regulation

- contribute to regulation of systemic BP and regulation of body fluids
- **Renin-Angiotensine System**



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Regulation of Renal Blood Flow

3) Humoral Regulation

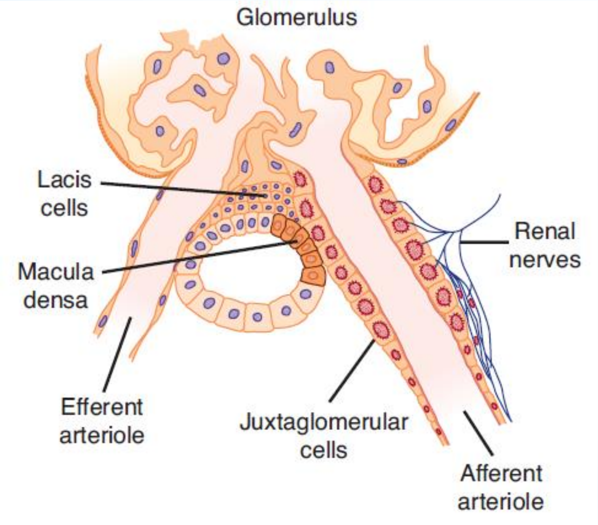
Tubuloglomerular Feedback

- provides constant NaCl load in the distal tubule, prevents excessive changes of renal excretion

Regulation of Renal Blood Flow

3) Humoral Regulation

Tubuloglomerular Feedback



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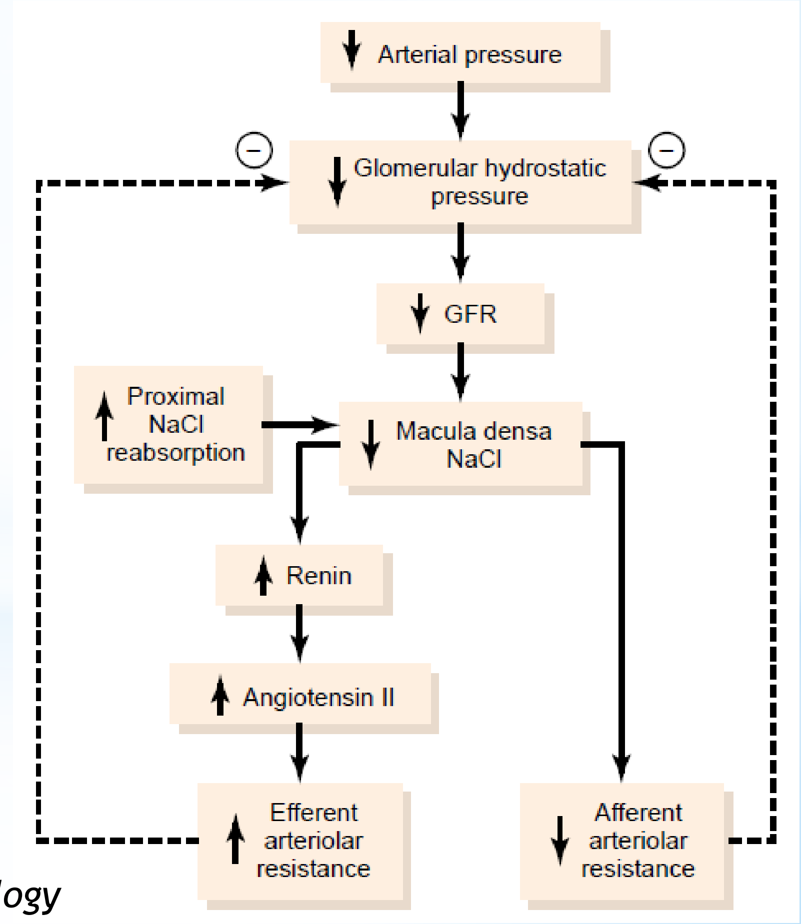

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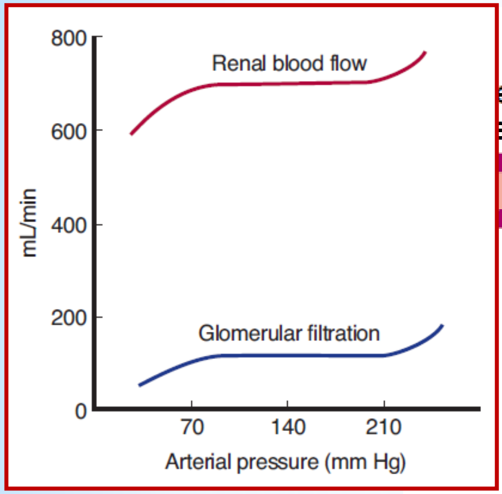
Regulation of Glomerular Filtration

$$GFR = K_f \cdot \text{net filtration pressure}$$



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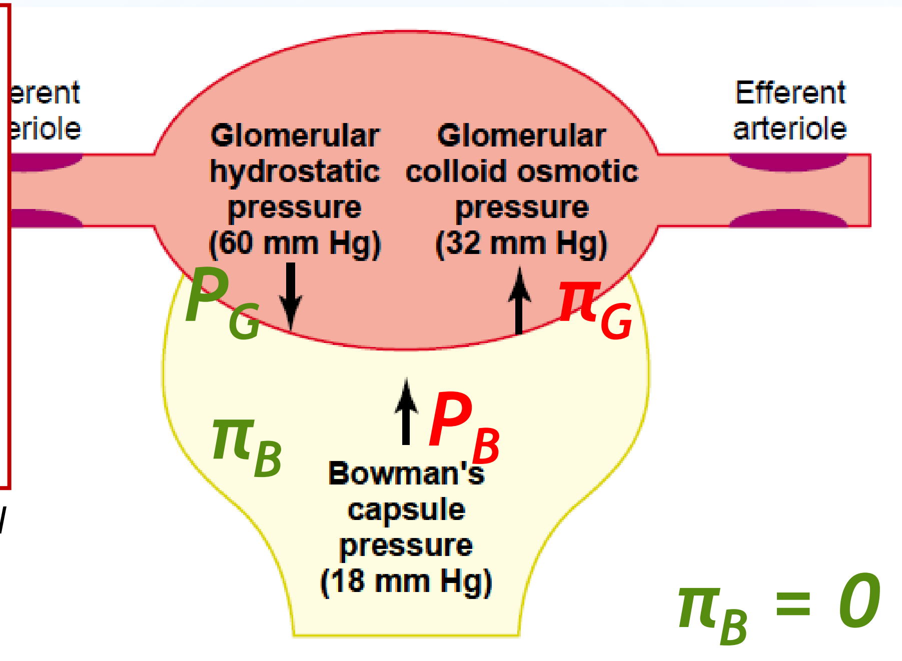

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Under physiological conditions:

net filtration pressure = $P_G + \pi_B - P_B - \pi_G = 60 + 0 - 18 - 32 = 10$ mmHg

$$GFR = K_f \cdot (P_G + \pi_B - P_B - \pi_G)$$

Regulation of Tubular Reabsorption

- controls balance between the glomerular filtration and tubular reabsorption

1) Local Regulation
2) Neural Regulation
3) Humoral Regulation

Glomerulotubular Balance

- ↑ tubular reabsorption rate at ↑ load of fluid flowing through tubules (prevention of overload of distal parts of tubulus)
- namely in the proximal tubule
- local mechanisms (present even in isolated proximal tubule)
- mechanisms not fully known (changes of physical forces?)

Regulation of Tubular Reabsorption

1) Local Regulation

Physical Forces in Peritubular Capillaries and in Renal Intersticium

- tubular reabsorption is controlled by hydrostatic and coloid osmotic forces (similary to GFR)

$$GFR = K_f \cdot \text{net filtration pressure}$$

$$TRR = K_f \cdot \text{net reabsorptive force}$$

Regulation of Tubular Reabsorption

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Physical Forces in Peritubular Capillaries and in Renal Interstícium

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$$GFR = K_f \cdot \text{net filtration pressure}$$

↓

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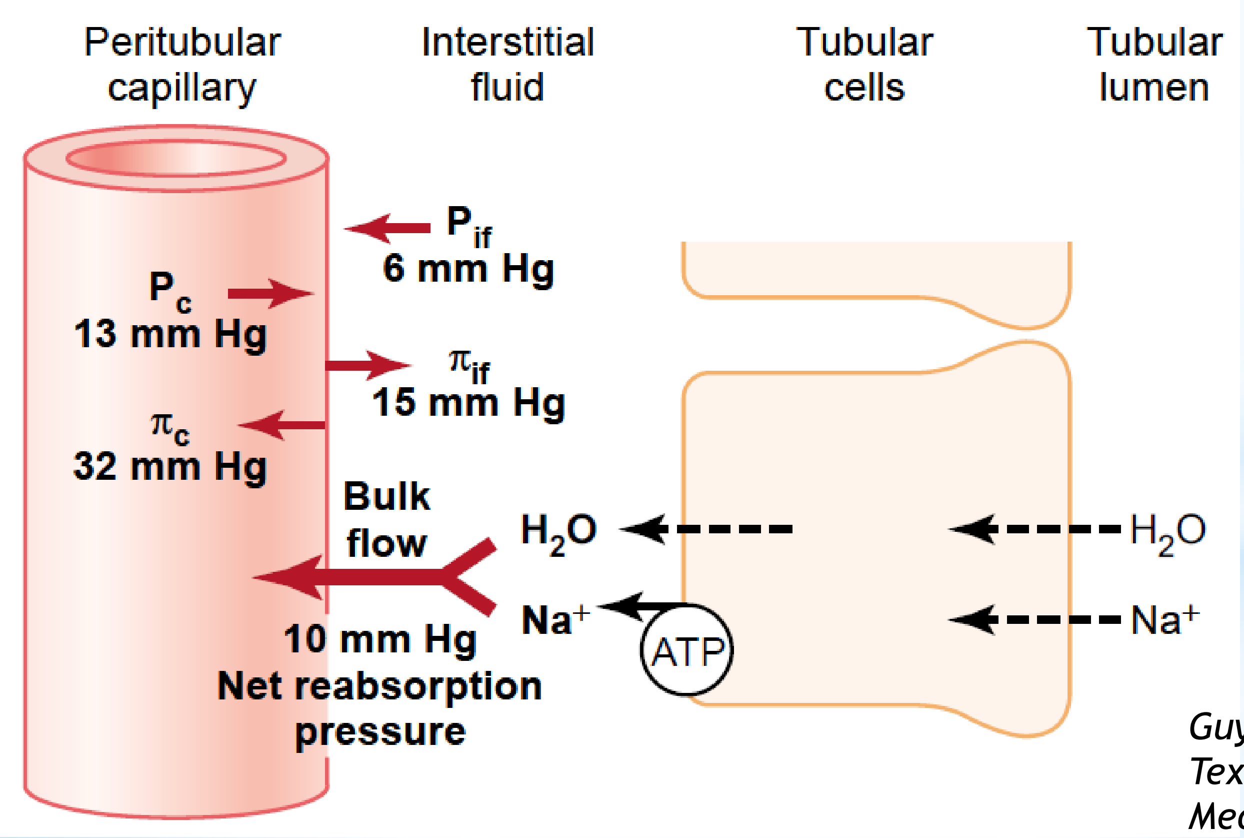
Regulation of Tubular Reabsorption

1) Local Regulation

Physical Forces in Peritubular Capillaries and in Renal Intersticium



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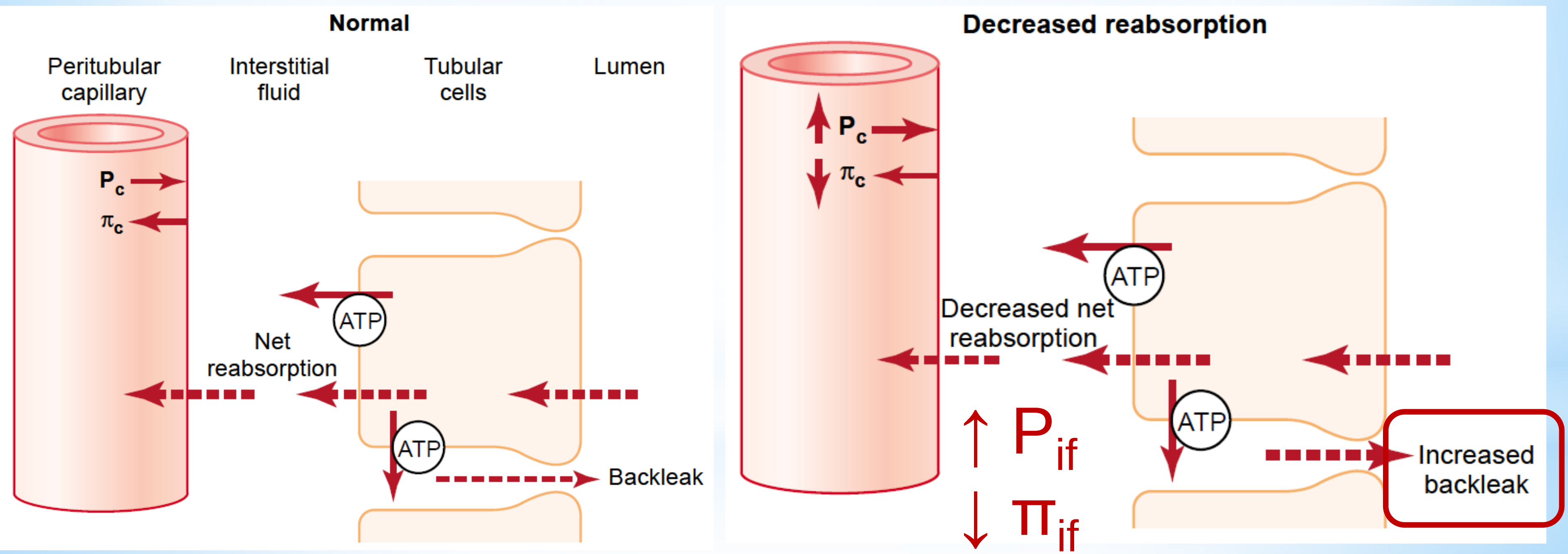
Regulation of Tubular Reabsorption

1) Local Regulation

Physical Forces in Peritubular Capillaries and in Renal Intersticium – changes in intersticium (P_{if}, π_{if})



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↑ reabsorption → ↓ P_{if} a ↑π_{if} → ↓ *backleak*

Regulation of Tubular Reabsorption

2) Hormonal Regulation

- impact – separate regulation of reabsorption/excretion of particular solutes (other mechanisms are nonspecific – influence the total TRR)

Aldosteron

Angiotensine II

Natriuretic peptides (namely ANP)

Antidiuretic hormone

Parathormone

Urodilatin (renal NP)

Regulation of Tubular Reabsorption

3) Neural Regulation

Sympathicus

→ ↑ reabsorption of salt and water

- during a small ↑ of its activity (α-rec. in epithelia):

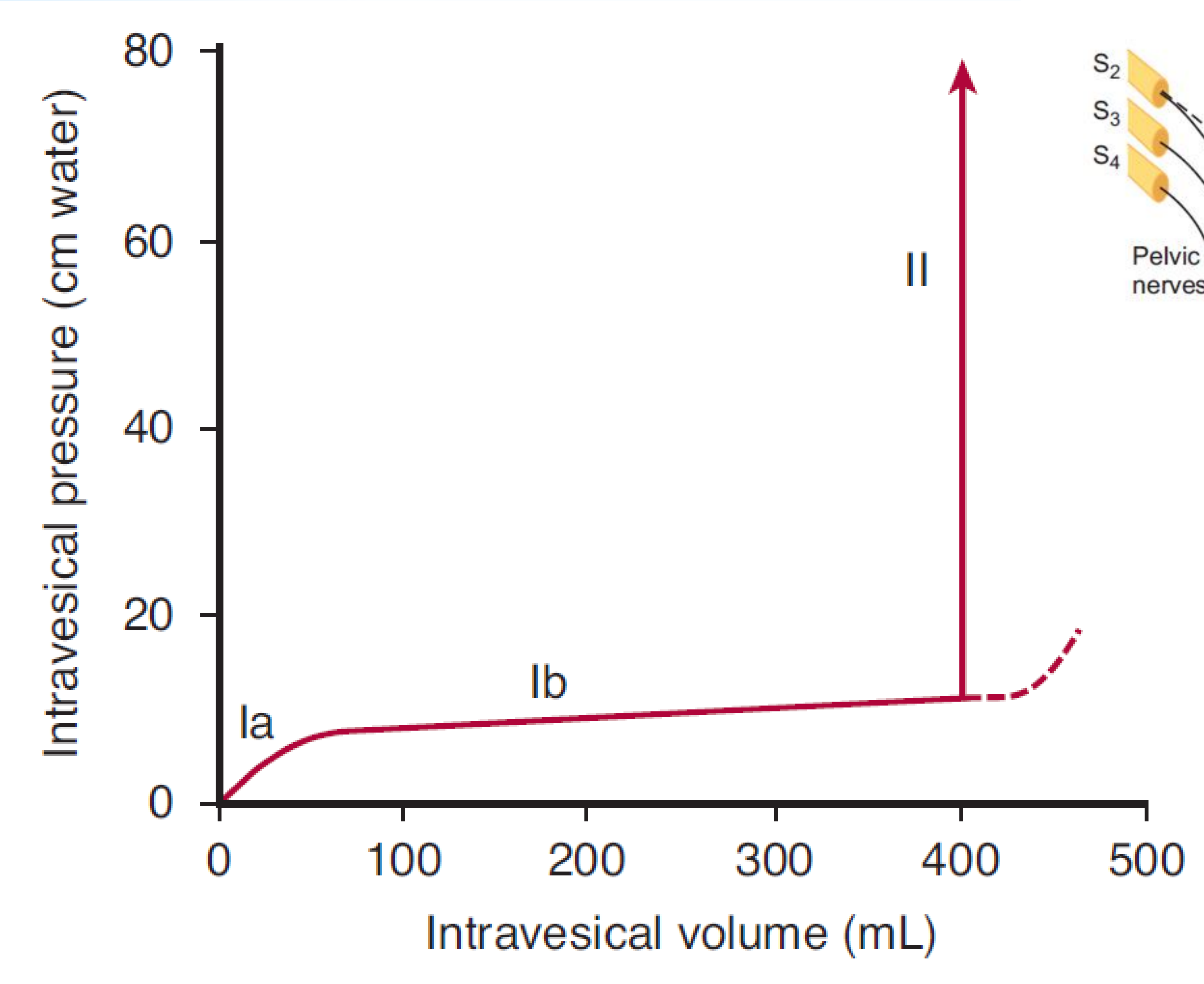
  directly through ↑ reabsorption of Na^+ in the proximal tubule, in the ascending loop of Henle and may be also in the distal parts of tubulus

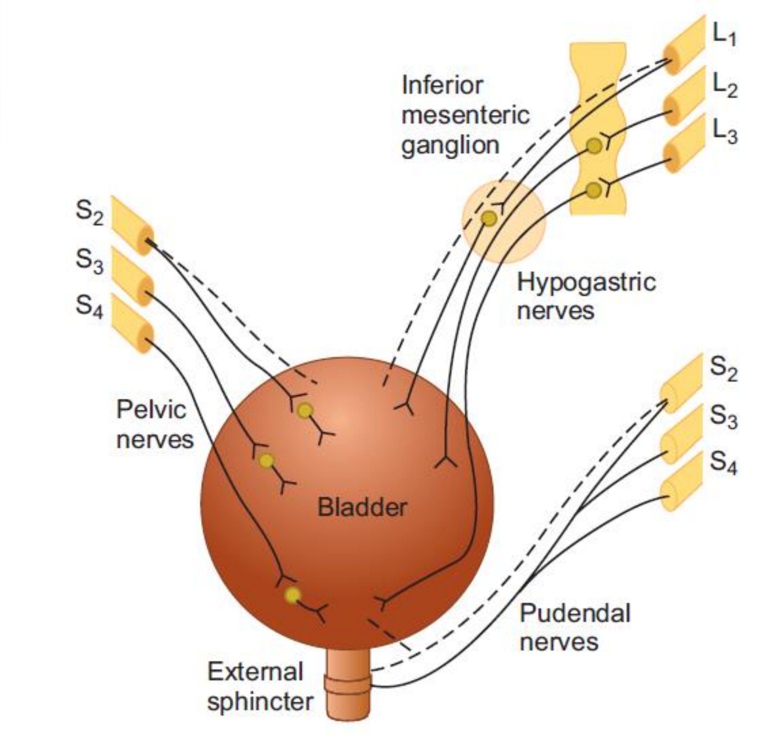
- during a notable ↑ of its activity indirectly:

  → constriction of aff. and eff. arterioles → ↓ renal blood flow → ↓ P_c → ↑ TRR

Filling and emptying of the bladder

cystometrogram





Kidney
in Regulation of Homeostasis

Homeostasis

= maintainance of stable conditions in the internal body environment

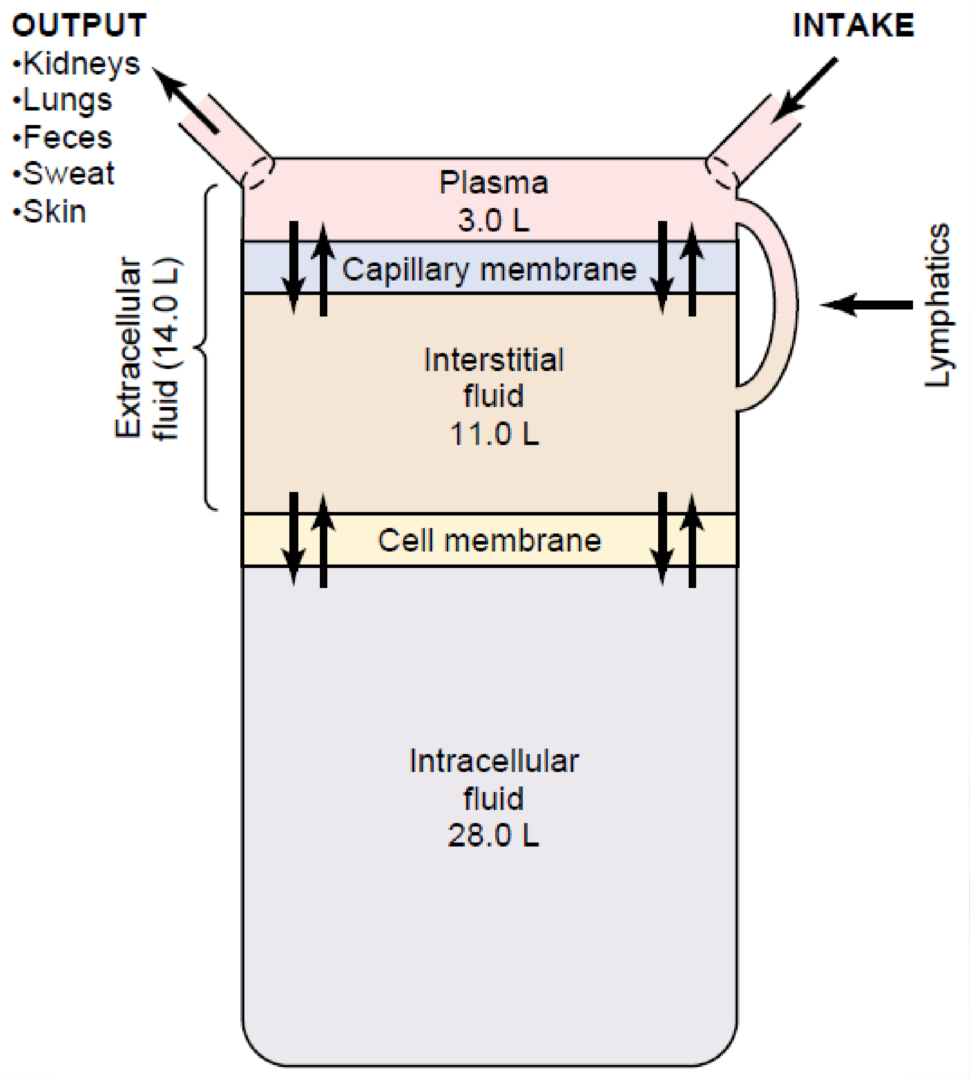
Maintainance of Constant Volume and Composition of Body Fluids

Maintainance of Acid-Base Balance

Constant Volume and Composition of Body Fluids - Regulation by Kidneys -

Body Fluids – Types and Volumes

Body fluids occupy ~60% of the body weight.



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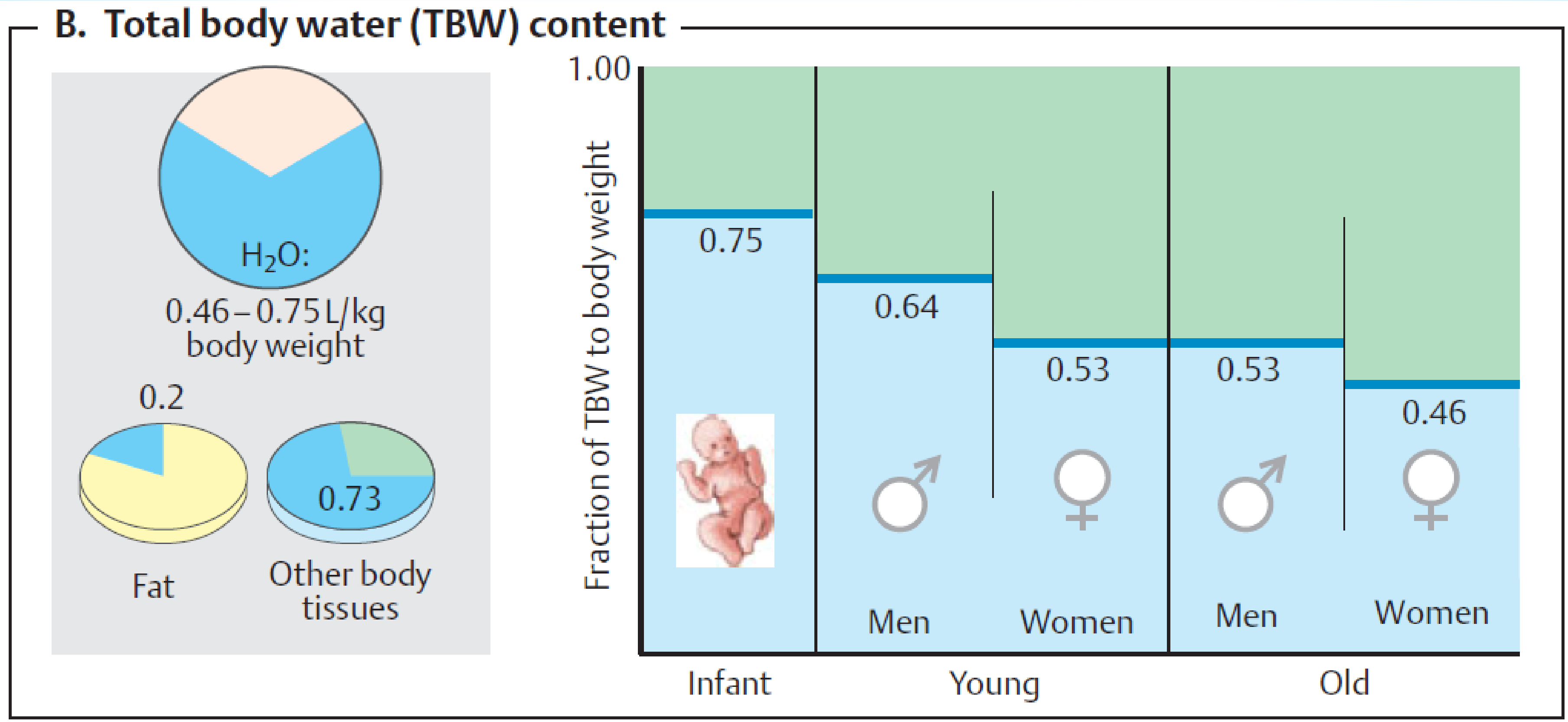
Body Fluids – Types and Volumes



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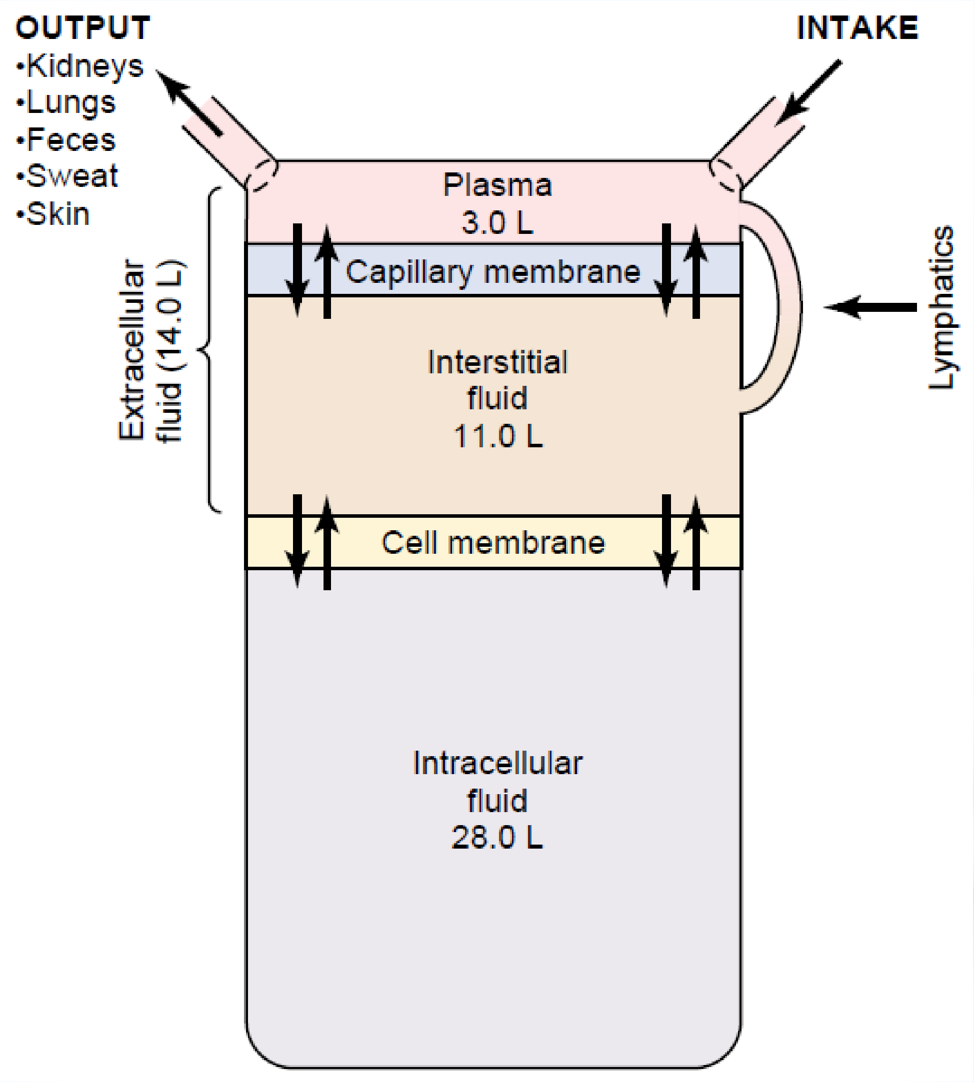
Body Fluids – Types and Volumes

Body fluids occupy ~60% of the body weight.

Transcellular fluid (1-2 l) – special type of ECF. (peritoneal, pericardial, synovial, cerebrospinal and intraocular fluid)



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5% of the body weight

15% of the body weight

40% of the body weight

Body Fluids – Types and Volumes

Balance between Input and Output of Fluid

Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

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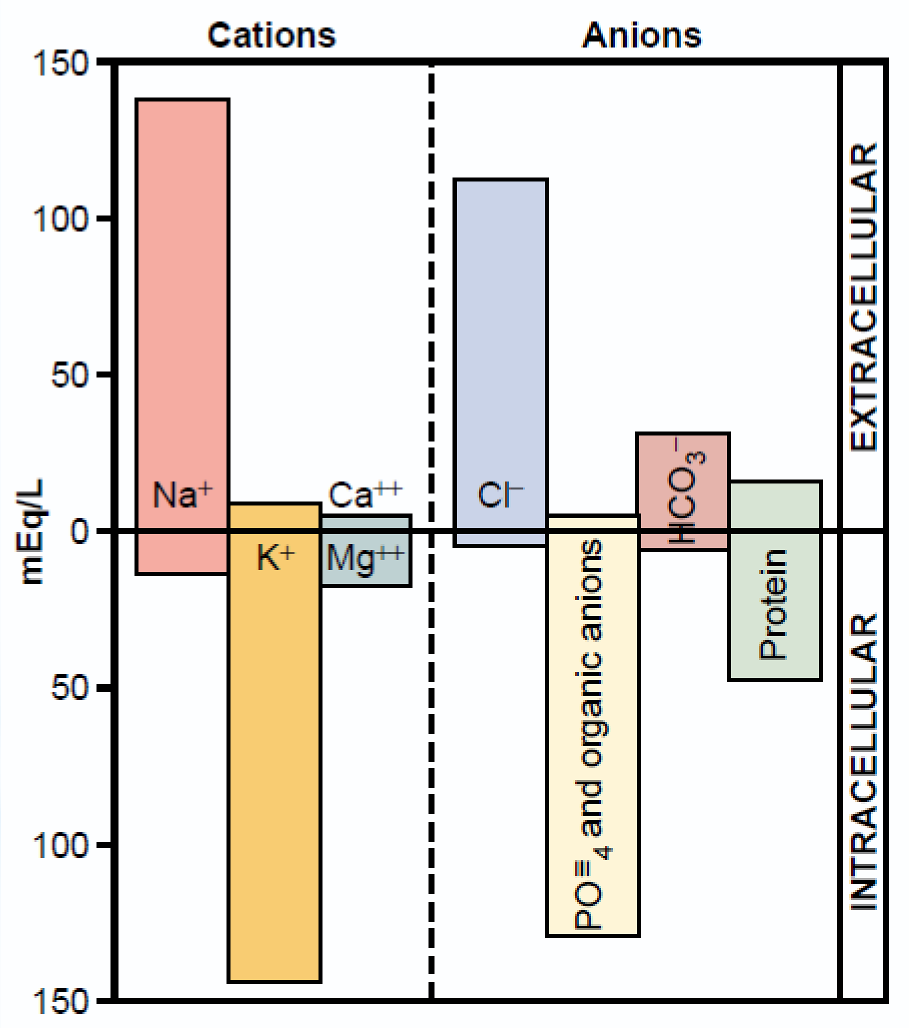
Body Fluids – Composition

ECF vs. ICF



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Body Fluids – Composition

plasma vs. ISF

	Plasma ($mOsm/L\ H_2O$)	Interstitial ($mOsm/L\ H_2O$)
Na^+	142	139
K^+	4.2	4.0
Ca^{++}	1.3	1.2
Mg^+	0.8	0.7
Cl^-	108	108
HCO_3^-	24	28.3
HPO_4^-, $H_2PO_4^-$	2	2
SO_4^-	0.5	0.5
Phosphocreatine		
Carnosine		
Amino acids	2	2
Creatine	0.2	0.2
Lactate	1.2	1.2
Adenosine triphosphate		
Hexose monophosphate		
Glucose	5.6	5.6
Protein	1.2	0.2
Urea	4	4
Others	4.8	3.9

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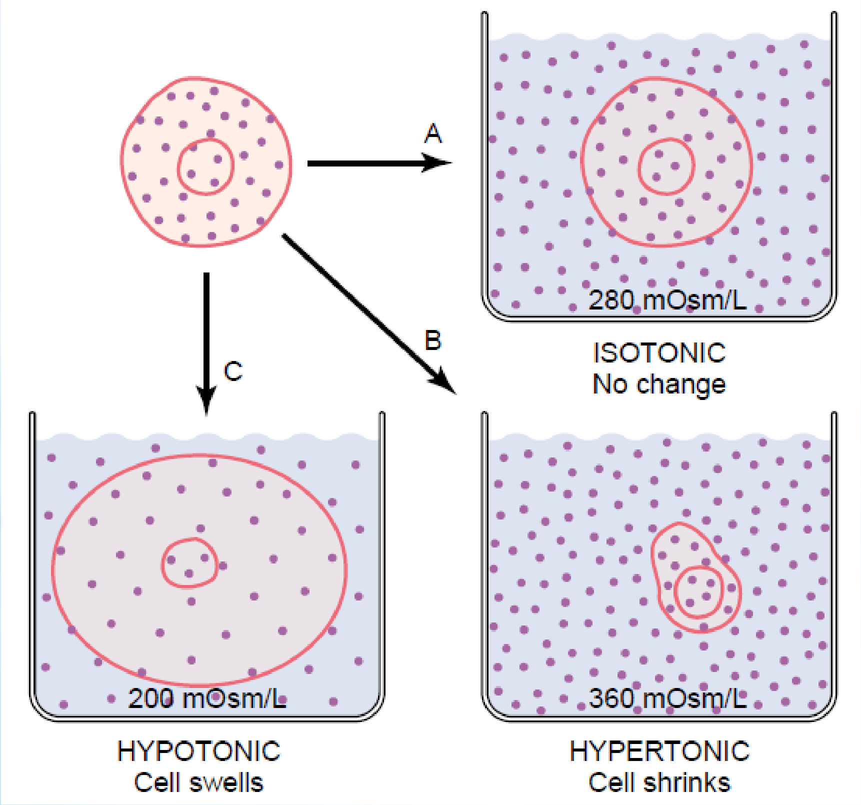
Body Fluids – Composition

osmolality 285 mosm/kg H_2O

↑ ↑ NaCl intake, loss of water → water leaves cells (shrinking of cells)

↓ ↓ NaCl intake, ↑ water input → water sucked into cells by osmosis (cell edema)



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↓ ↓ NaCl intake, ↑ water input → water sucked into cells by osmosis (cell edema)

Precise regulation of osmolality of ESF is necessary!

- **osmoreceptors**
- **kidneys** (target organ for the action of hormones below)
- **antidiuretic hormone**

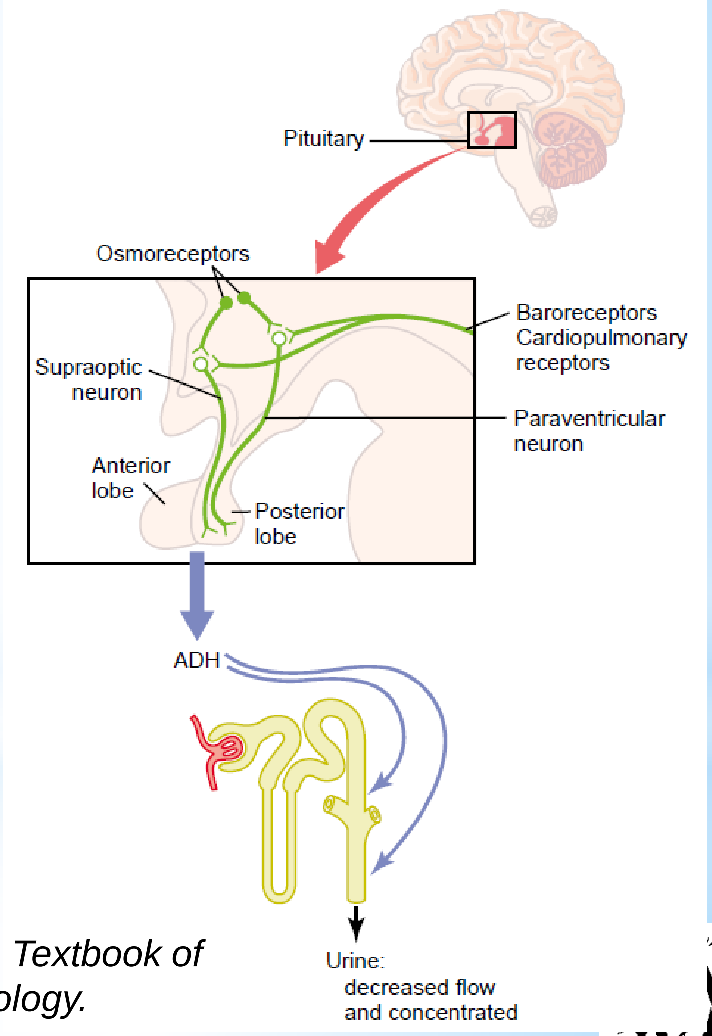
- **aldosteron**
- **natriuretic peptides**

Humoral Regulation of Body Fluids

Antidiuretic Hormone

(vasopressin)

- effects:
  - → water reabsorption in kidneys (collecting duct, aquaporin 2)
  - → control of blood pressure (water reabsorption, vasoconstriction)
  - → ↑ glycogenolysis, mediator in the brain, ↑ secretion of ACTH in adenohypophysis



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Humoral Regulation of Body Fluids

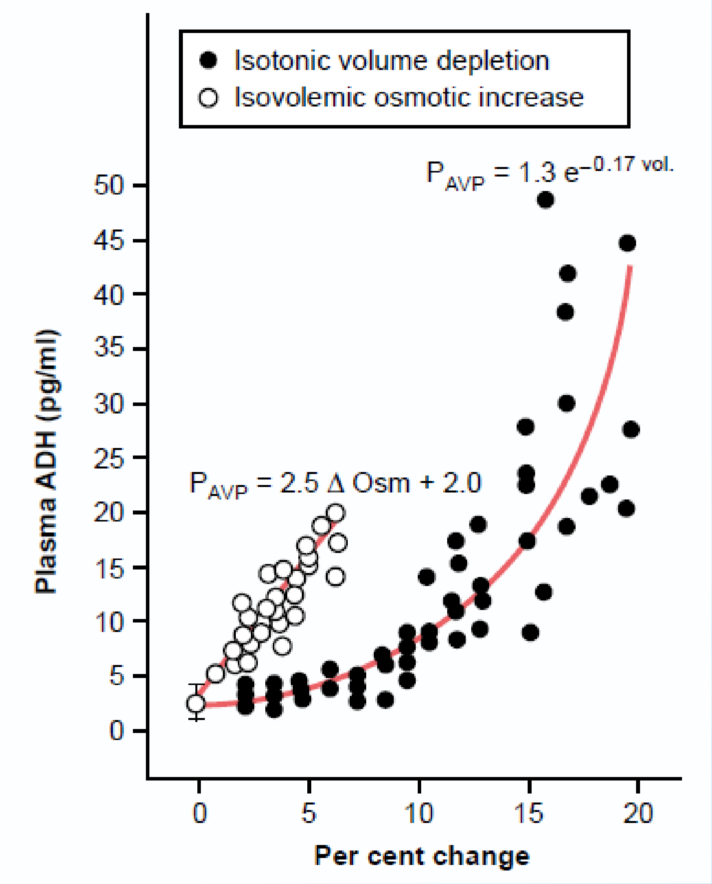
Antidiuretic Hormone

(vasopressin)

- regulation of secretion:

↑
- ↑ osmolality
- ↓ volume of ECF
- pain, emotions, stress (surgical), physical exertion; standing
- nausea, vomitting
- angiotensine II
- morphin, nicotine, barbiturates, …

↓
- ↓ osmolality, ↑ volume of ECF
- alcohol; antagonists of opioids



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Humoral Regulation of Body Fluids

Aldosteron

- the most important steroid with the mineralocorticoid effect

- mechanism of action:

binding to the mineralocorticoid receptor $\rightarrow$ binding of the hormone-receptor complex to DNA $\rightarrow$ mRNA $\rightarrow$ synthesis of proteins:

- namely Na^+/K^+-ATPase
- ↑ number of amiloride-inhibited Na^+-channels in the membrane of target cells
- ↑ activity of H^+-pump in collecting ducts of the renal cortex
- ↑ activity of Na^+/H^+-antiport in both distal and proximal parts of nephrons

Start of the effect even 10 – 30 min after release of the hormone!

Humoral Regulation of Body Fluids

Aldosteron

- the most important steroid with the mineralocorticoid effect

- effects:

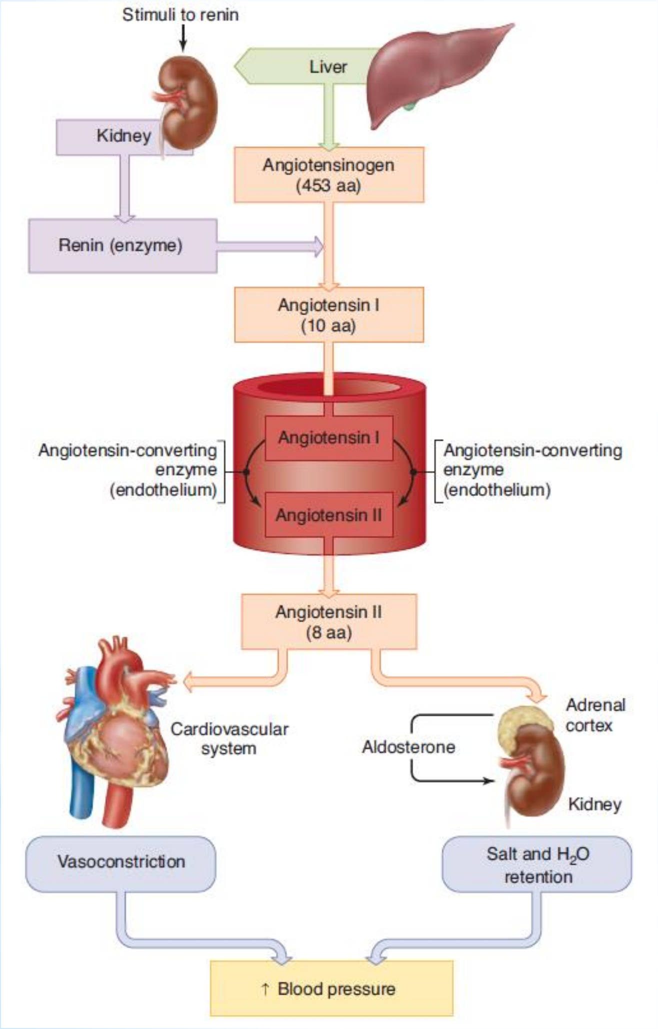
→↑ Na^+ reabsorption from urine, sweat, saliva, gastric juice
→↑ K^+ urine excretion, ↑ acidity of urine (exchange for Na^+)
→↑ K^+ content and ↓ Na^+ content in muscle and brain cells

- regulation of its secretion:

  - ACTH from the adenohypophysis (a transient effect)
  - direct stimulatory effect of ↑ plasmatic concentration of K^+ (even a small change – even after a meal rich for K^+ - fruit, vegetable) and ↓ Na^+ (only a big change)
  - renin-angiotensine-aldosteron system

Humoral Regulation of Body Fluids

Renin-Angiotensine-Aldosteron System



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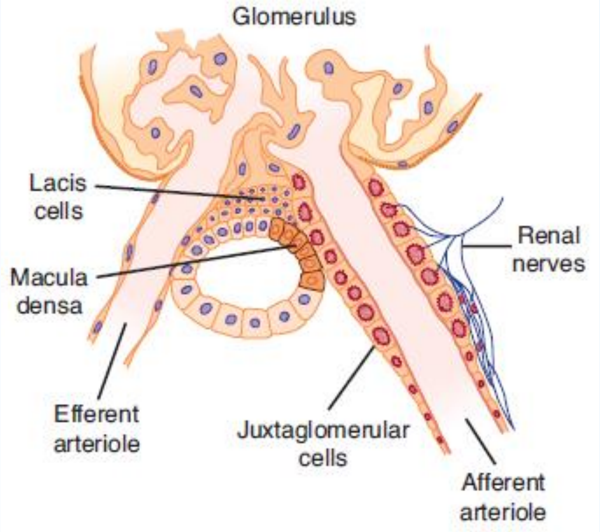

Humoral Regulation of Body Fluids

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  - renin-angiotensine-aldosteron system
  - atrial natriuretic peptide (inhibition of renin secretion, ↓ reactivity of *zona glomerulosa* to angiotensine II)
  - other hormones od adenohypophysis (besides ACTH; maintenance of reactivity of *zona glomerulosa*)

Humoral Regulation of Body Fluids

Atrial Natriuretic Peptide

- one of natriuretic peptides (BNP – cardiac ventricles, CNP – brain)
- secreted by atrial cardiomyocytes, found also in the brain
- receptors (ANPR-A – the highest affinity to ANP, ANPR-B – CNP, ANPR-C – all NP)
- short half-life

Humoral Regulation of Body Fluids

Atrial Natriuretic Peptide

- one of natriuretic peptides (BNP – cardiac ventricles, CNP – brain)

- effects (through ↑ cGMP): → ↓ **BP** (also through the brain stem)

→ natriuresis (1. ↑ GFR – increased area for the filtration through relaxation of mesangial cells, 2. ↑ Na^+ excretion – decrease tubular Na^+ reabsorption)

→ ↓ reactivity of vascular smooth muscles for vasocontrictive substances

→ inhibition of renin secretion, ↓ reactivity of *zona glomerulosa* for stimuli ↑ aldosteron secretion

→ inhibition of ADH secretion → ↑ water excretion

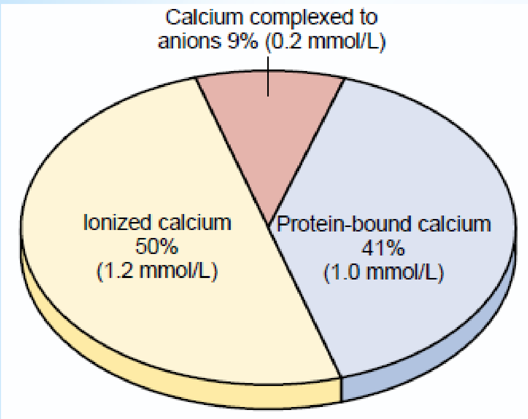
- regulation of its secretion:

↑ - ↑ ECF volume (atrial cells´ stretch at higher atrial filling)

↓ - ↓ CVP at orthostasis

Humoral Regulation of Body Fluids

Calcium in the Body



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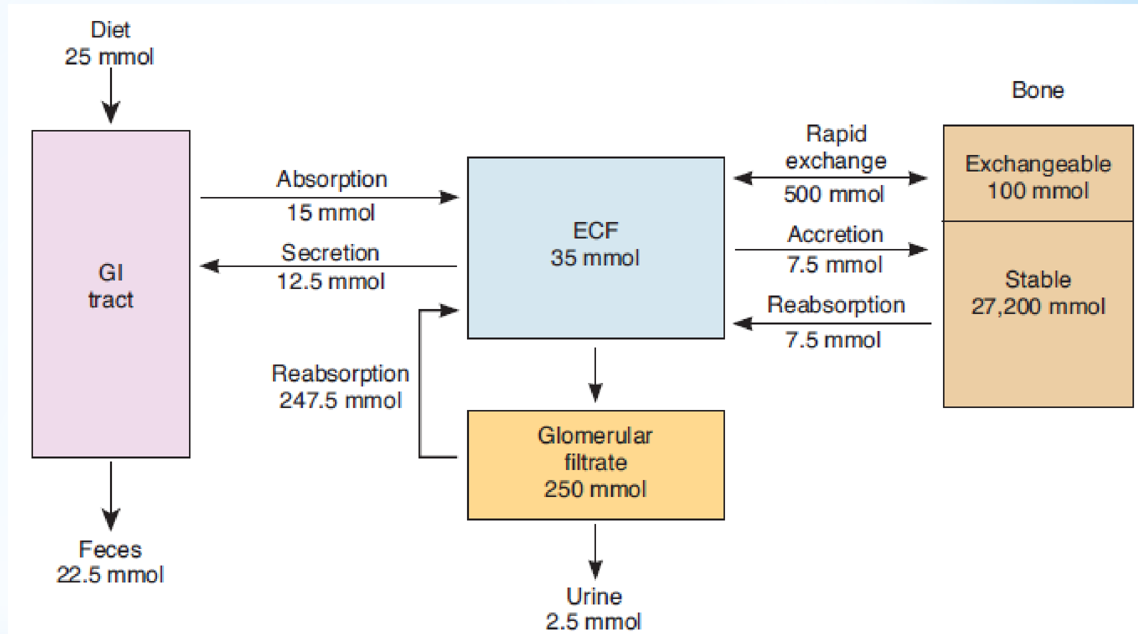

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hypocalcemia

hypercalcemia

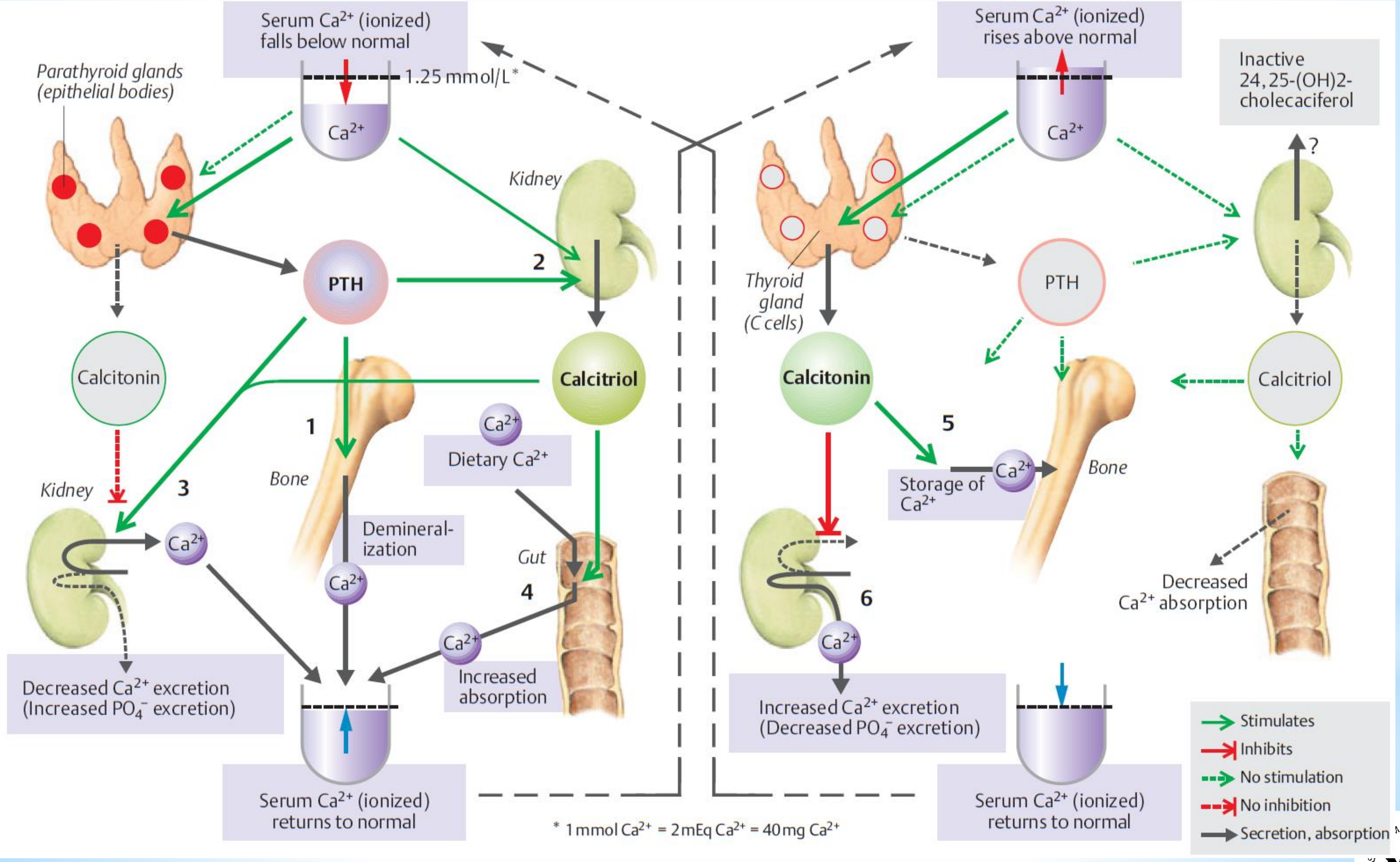
Humoral Regulation of Body Fluids

Hormonal Regulation of Calcemia

Parathormone
Vitamin D
Calcitonin

Humoral Regulation of Body Fluids

Hormonal Regulation of Calcemia



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Acid-Base Balance

- Regulation by Kidneys -

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Acid-Base Balance and its Regulation

Acid-base balance is regulated by:

1) Buffers
   - fast regulation (seconds)
   - pH changes attenuated by binding and release of H^+:

   $$\text{buffer} + H^+ \rightleftharpoons \text{H - buffer}$$

   ↑[H^+] direction to the right favoured till free buffer is available

   ↓[H^+] direction to the left favoured, H^+ released

2) Lungs
   - fast regulation (minutes even hours)
   - elimination of CO_2 from the body ($H_2CO_3 \rightarrow H_2O + CO_2$)

3) Kidneys
   - slower regulation (hours even days) but the most powerful
   - elimination of acids and bases from the body

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

- by excretion of acid or alkalic urine
- a high amount of HCO_3^- still filtered in the glomerulus

  GFR 180 l/day, $[HCO_3^-]_{plasma}$ 24 mEq/l $\rightarrow$ 4320 mEq HCO_3^- filtered per day – almost all ordinarily reabsorbed
- a high amount of H^+ still secreted in renal tubules

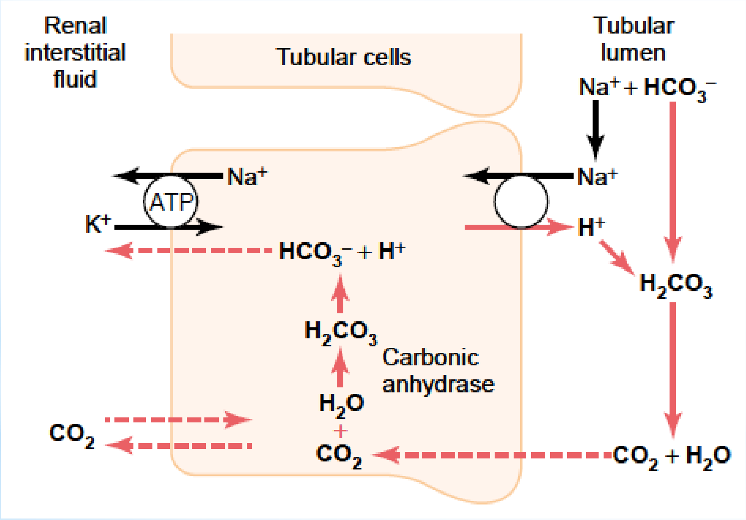
  about 80 mEq of non-volatile acids are formed in the course of metabolic processes per day – have to be excreted by kidneys
- filtered HCO_3^- / secreted H^+

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

1) Secretion of H^+
2) Reabsorption of HCO_3^-

- in the proximal tubule, thick loop of Henle and at the beginning of the distal tubule



Na^+/H^+-antiport

>90% HCO_3^- reabsorbed – only a slight acidification of the urine!

Reabsorption of HCO_3^- across the basolateral membrane facilitated by:

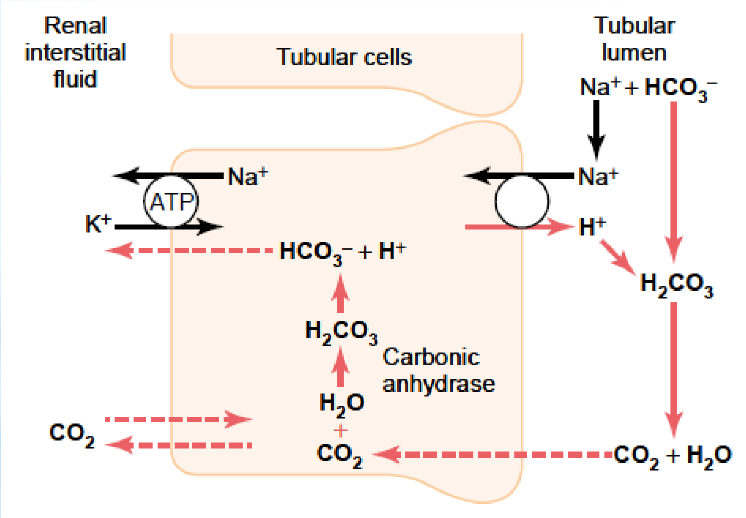
- Na^+-HCO_3^- co-transport (the proximal tubule)
- Cl^--HCO_3^- exchanger (the end of proximal tubule and the following parts of tubulus except for the thin loop of Henle)

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

1) Secretion of H^+
2) Reabsorption of HCO_3^-

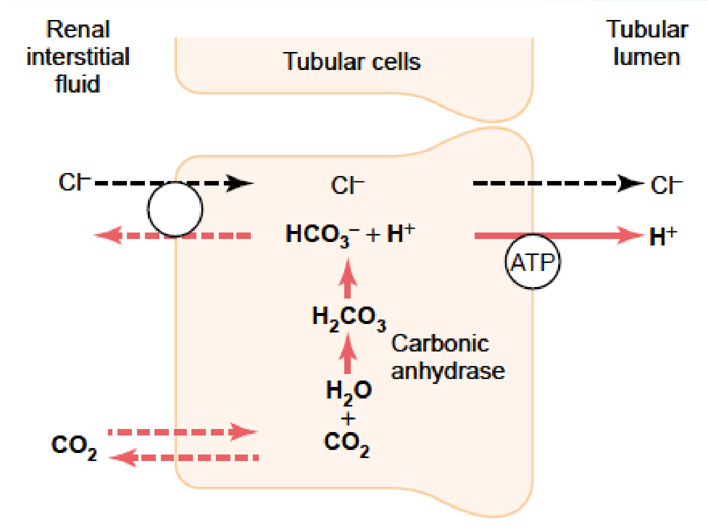
- in the proximal tubule, thick loop of Henle and at the beginning of the distal tubule



Na⁺/H⁺-antiport

>90% HCO_3^- reabsorbed – only a slight acidification of the urine!

- in the final part of distal tubule and in the collecting duct



primary active transport of H^+ (intercalated cells)

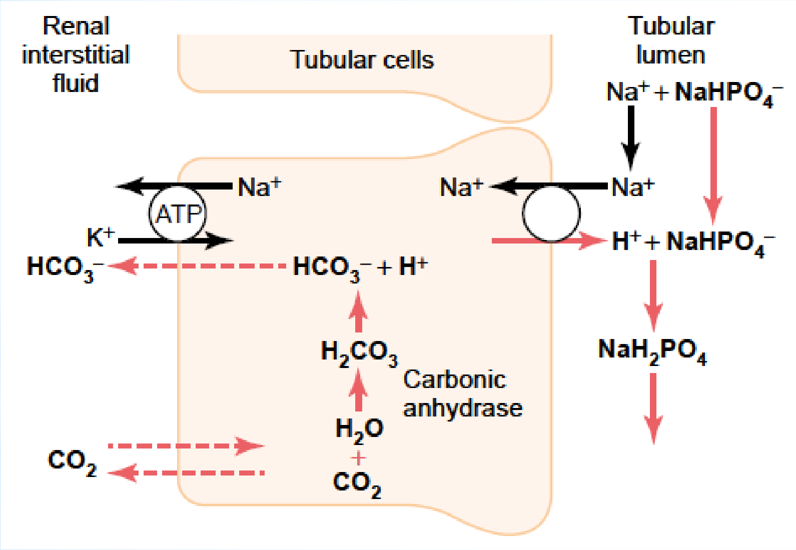
acidification of urine

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

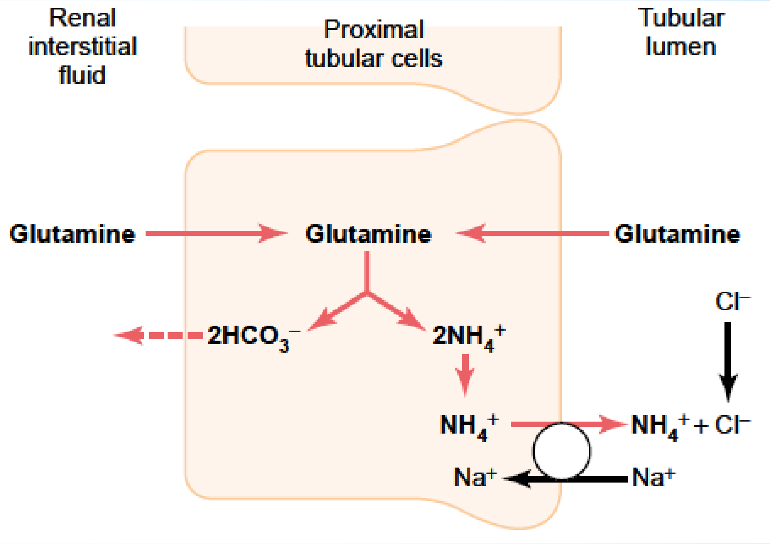
1) Secretion of H^+
2) Reabsorption of HCO_3^-
3) Production of HCO_3^- *de novo*

❖ Phosphate buffer (HPO_4^{2-}, $H_2PO_4^-$)



HPO_4^{2-} and $H_2PO_4^-$ are reabsorbed less than water ⇒ their concentration in the tubular fluid gradually rises

❖ Ammonium buffer (NH_3, NH_4^+)



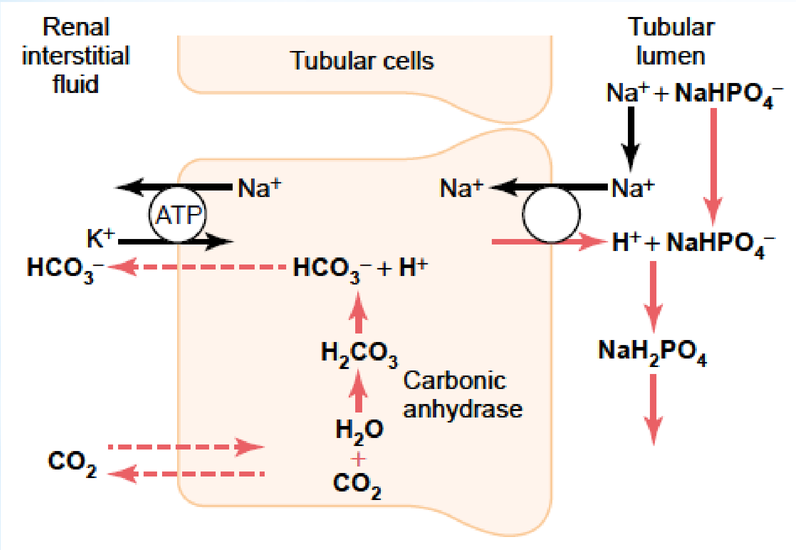
NH_4^+ originates from glutamine – the proximal tubule, thick ascending loop of Henle and distal tubule

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

1) Secretion of H^+
2) Reabsorption of HCO_3^-
3) Produkce nového HCO_3^-

❖ Phosphate buffer (HPO_4^{2-}, $H_2PO_4^-$)



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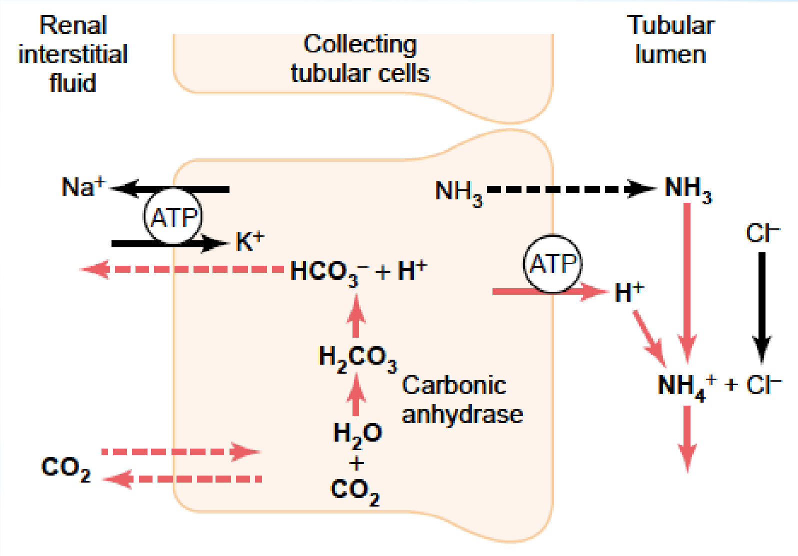


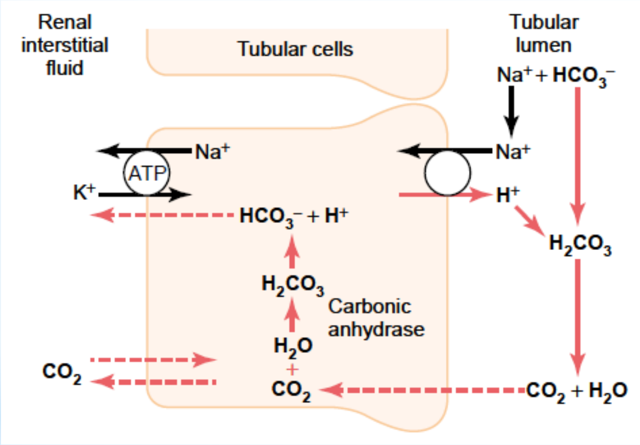
the collecting duct (permeable for NH_3 but far less for NH_4^+ - excreted by urine)
50% of H^+ secretion and HCO_3^- formed *de novo*!

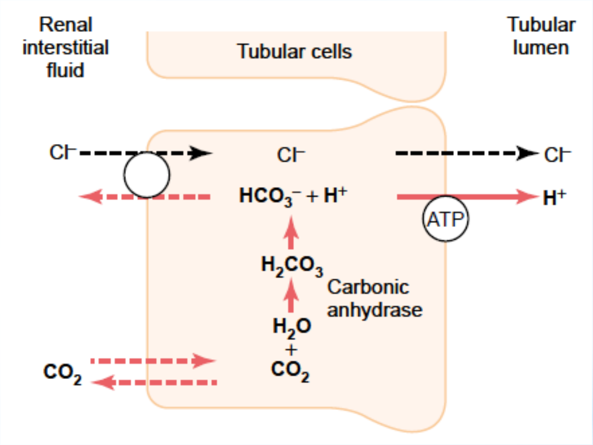
Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

Regulation of H^+ secretion

↑ - ↑ **pCO_2 in ECF** (respiratory acidosis; direct stimulation due to ↑ formation of H^+ in tubular cells)





- ↓ **pH in ECF** (respiratory or metabolic acidosis)
- ↑ **secretion of aldosteron** (stimulates H^+ secretion in intercalated cells of collecting ducts; Conn´s syndrome - alkalosis)

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

Acidosis - correction by kidneys

$$\downarrow \text{pH} = 6.1 + \log \frac{HCO_3^-}{0.03 \times P_{CO2}} \downarrow$$

- metabolic acidosis: due to $\downarrow HCO_3^-$
  renal correction : $\downarrow HCO_3^-$ in ECF $\rightarrow \downarrow$ filtered $HCO_3^- \rightarrow$ complete reabsorption of HCO_3^- + its formation *de novo* (HCO_3^- not excreted) + $\uparrow H^+$ excretion $\rightarrow$ pH normalization
- respiratory acidosis: due to $\uparrow P_{CO2}$ (hypoventilation)
  renal correction: $\uparrow P_{CO2}$ in ECF $\rightarrow \uparrow P_{CO2}$ in tubular cells $\rightarrow \uparrow$ formation of H^+ and HCO_3^- in tubular cells $\rightarrow \uparrow H^+$ secretion + $\uparrow HCO_3^-$ reabsorption $\rightarrow$ pH normalization

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

Alkalosis – correction by kidneys

$$\uparrow \ pH = 6.1 + \log \frac{HCO_3^-}{0.03 \times P_{CO2}} \ \uparrow$$

- metabolic alkalosis: due to $\uparrow$ HCO_3^-
  renal correction: $\uparrow$ HCO_3^- in ECF $\rightarrow$ $\uparrow$ filtered HCO_3^- $\rightarrow$ incomplete HCO_3^- reabsorption (lack of H+) $\rightarrow$ $\uparrow$ HCO_3^- excretion by urine $\rightarrow$ pH normalization

- respiratory alkalosis : due to $\downarrow$ P_{CO2} (hyperventilation)
  renal correction: $\downarrow$ P_{CO2} in ECF $\rightarrow$ $\downarrow$ P_{CO2} in tubular cells $\rightarrow$ $\downarrow$ formation of H^+ and HCO_3^- in tubular cells $\rightarrow$ $\downarrow$ H^+ secretion + $\downarrow$ HCO_3^- reabsorption $\rightarrow$ pH normalization