Kidneys in regulation of homeostasis

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Homeostasis

= maintainance of stable conditions in the internal body environment

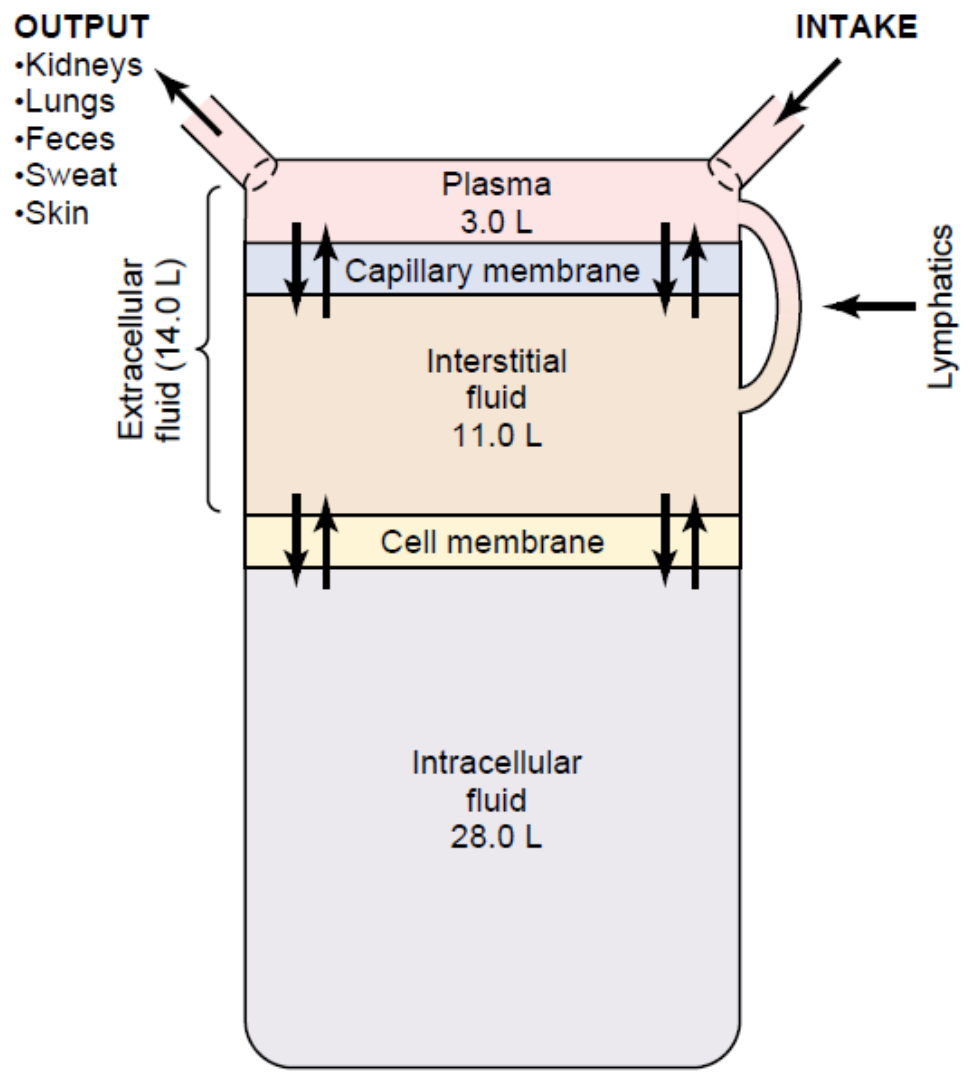
Maintainance of Constant Volume and Composition of Body Fluids

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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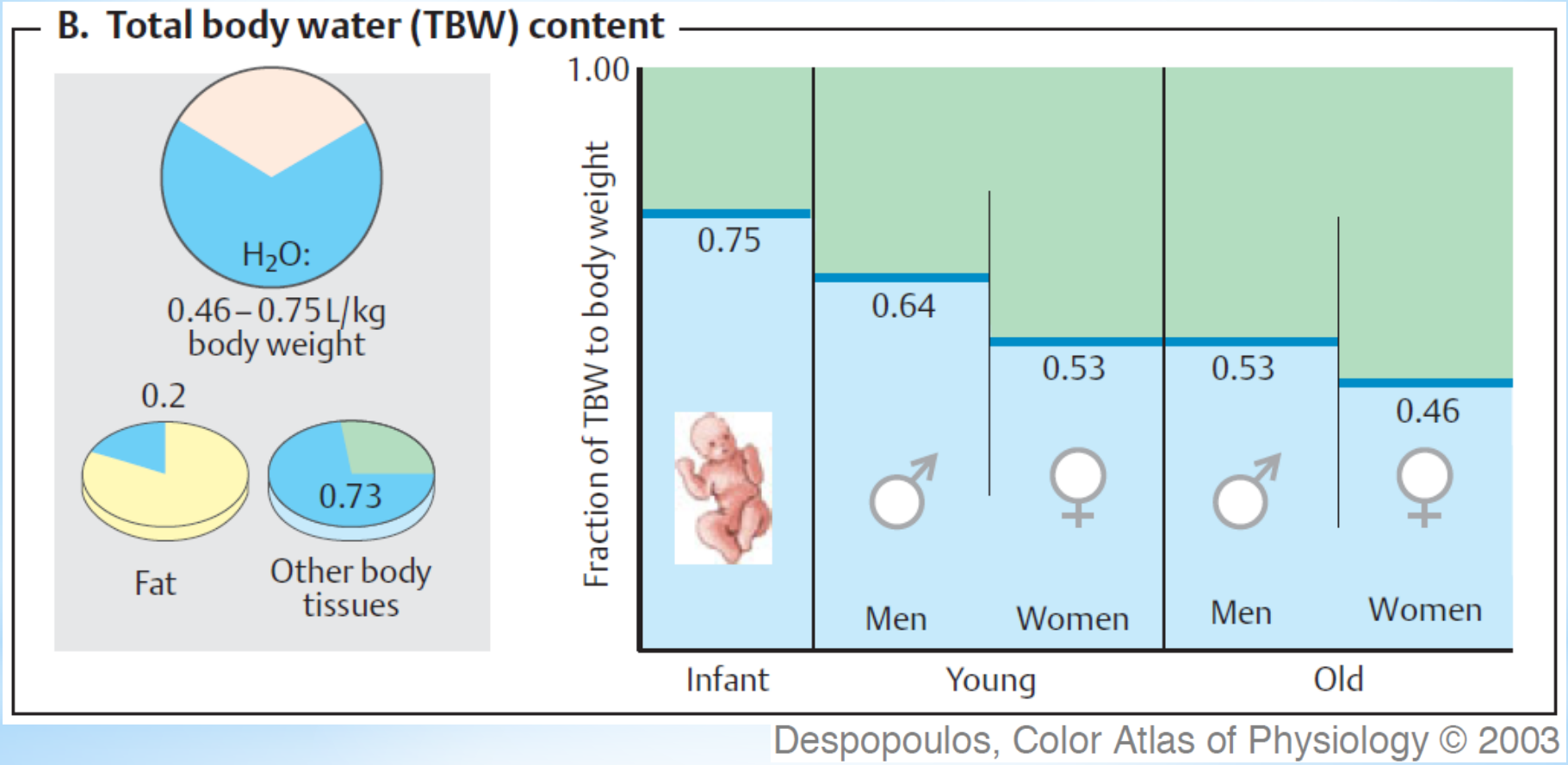
Body Fluids – Types and Volumes



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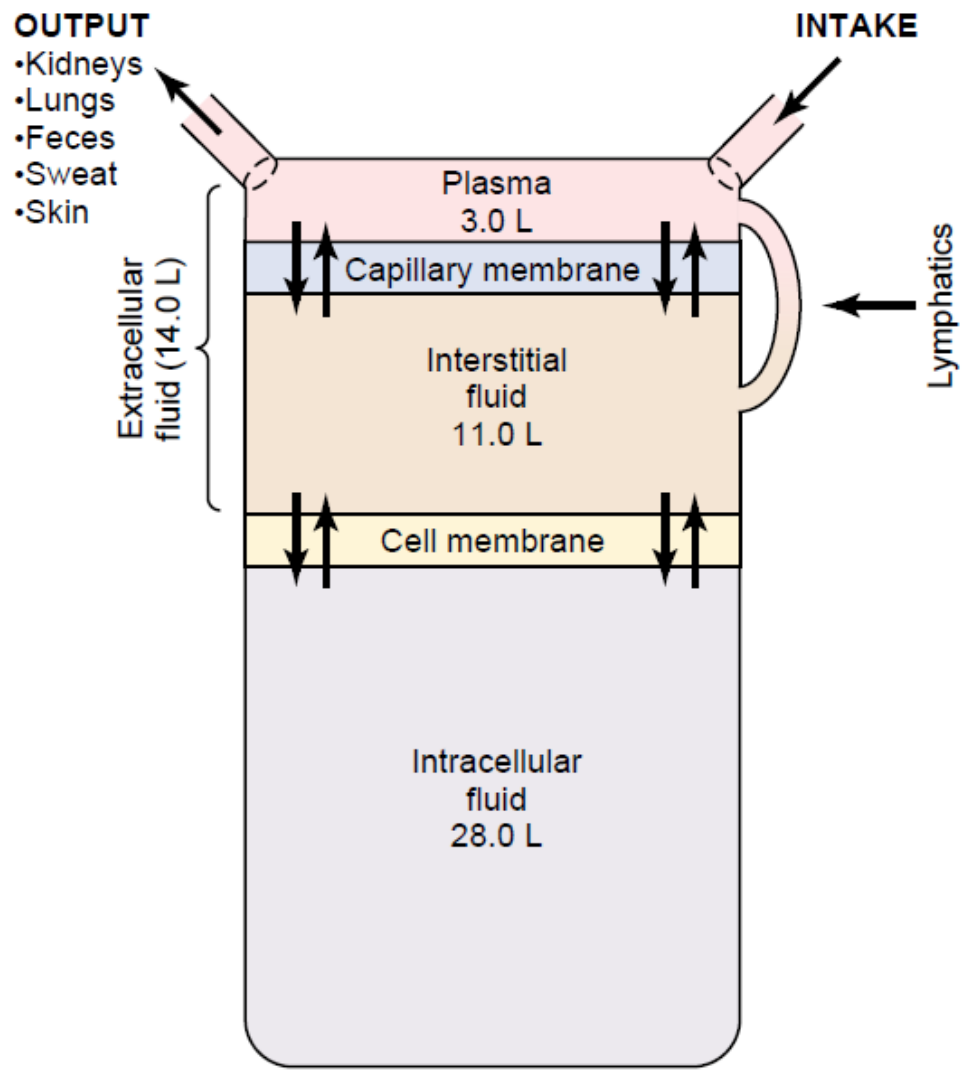
Body Fluids – Types and Volumes

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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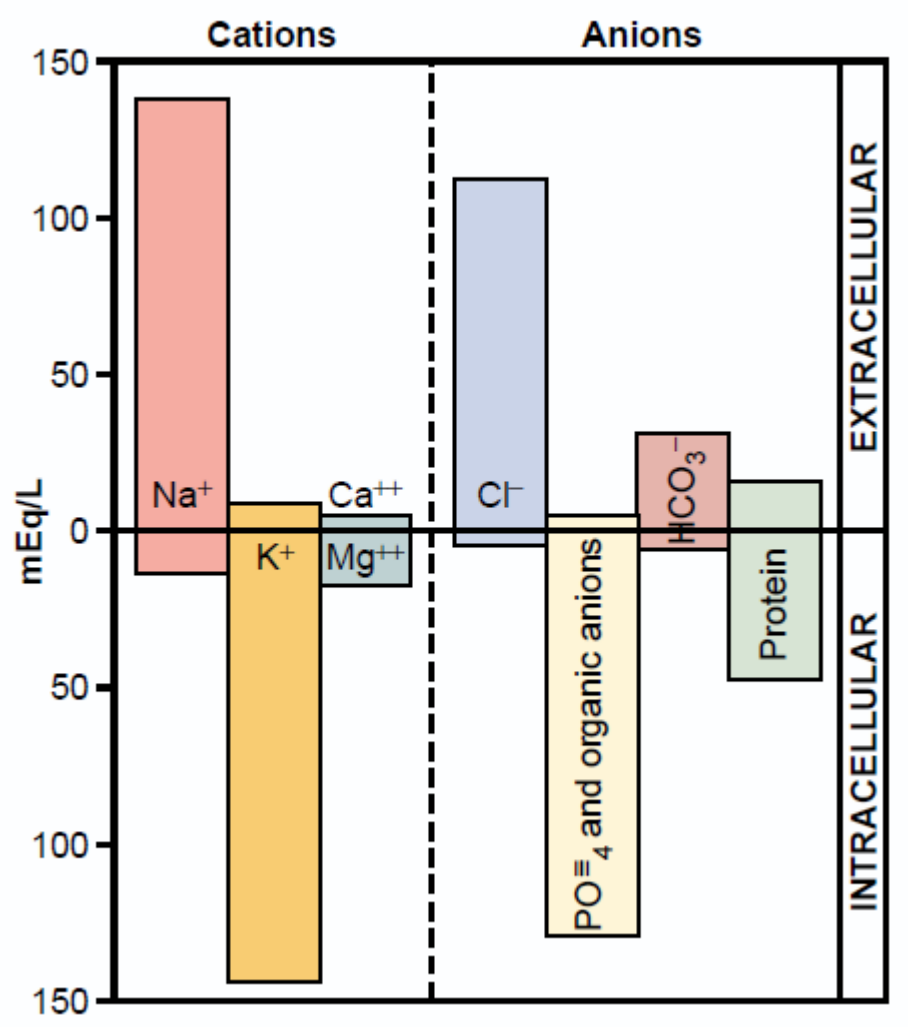
Body Fluids – Composition

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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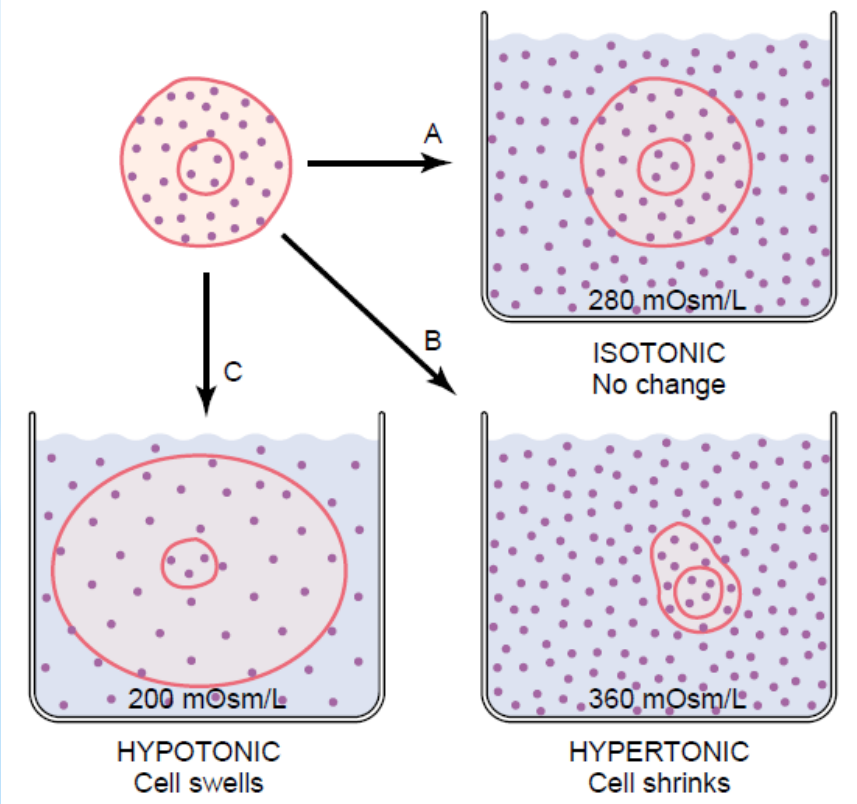
Body Fluids – Composition

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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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

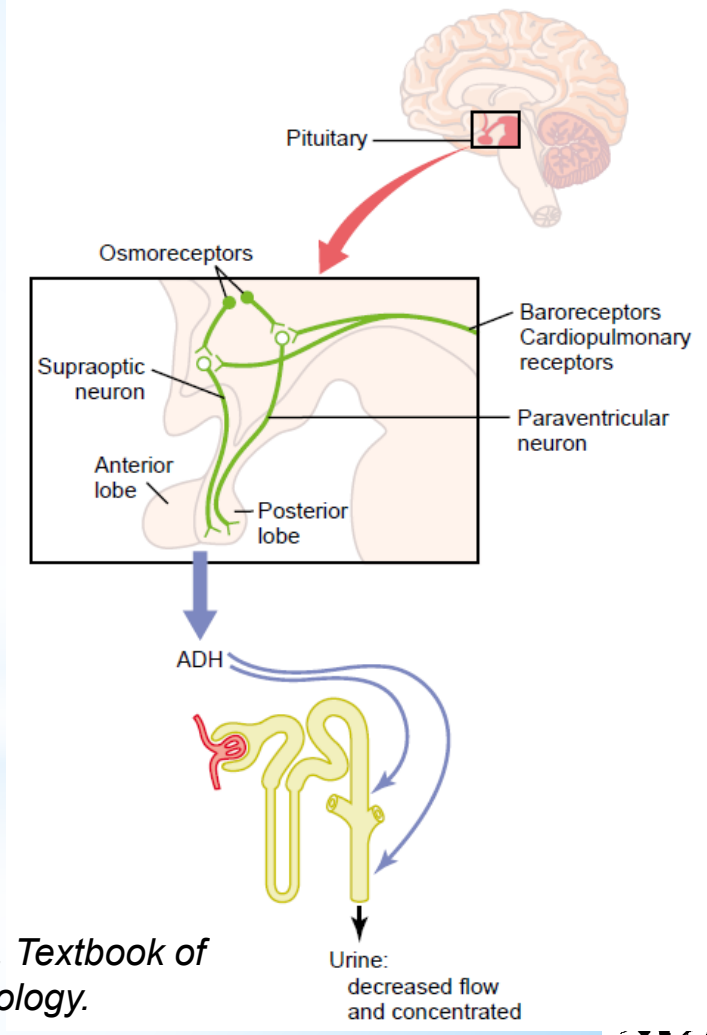
(vasopressin)

- 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

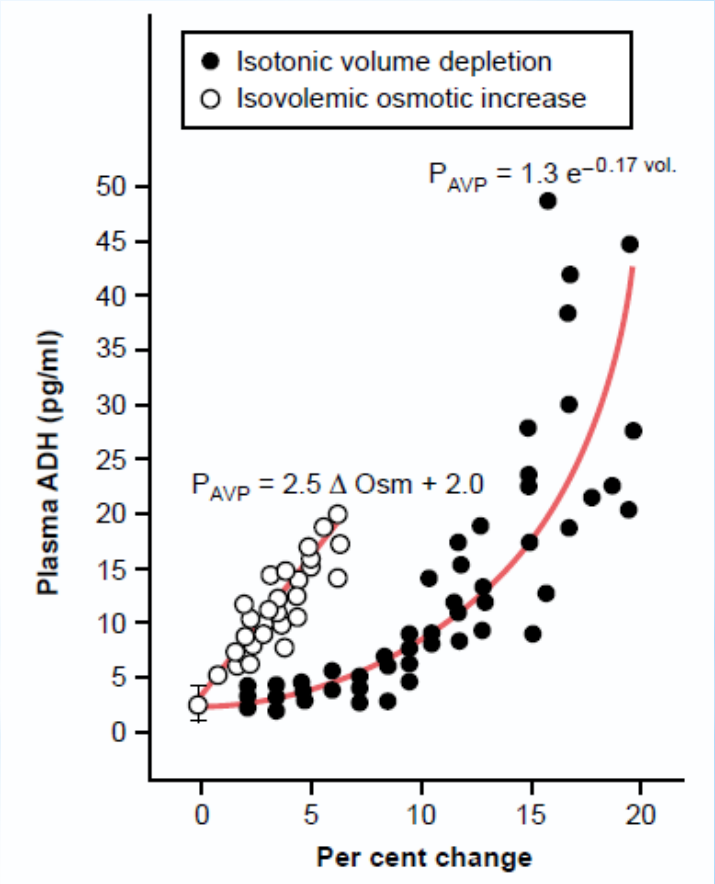
Antidiuretic Hormone

(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

Antidiuretic Hormone

(vasopressin)

- pathology:

↑ SIADH

↓ *diabetes insipidus*

Humoral Regulation of Body Fluids

Aldosteron

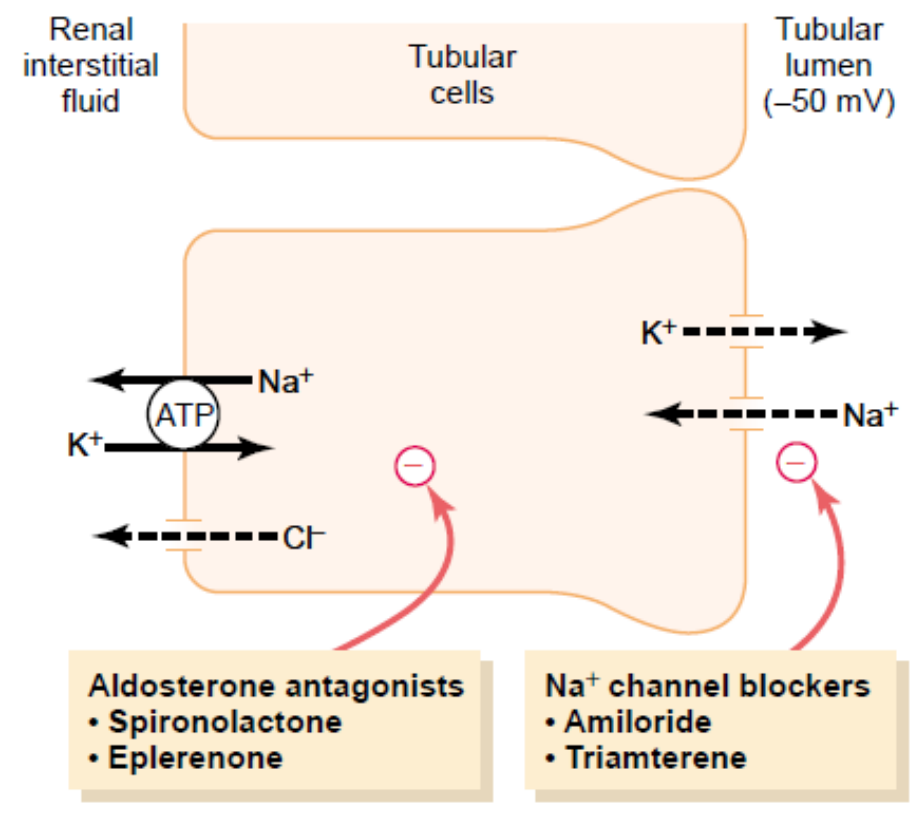
- the most important steroid with the mineralocorticoid effect

- mechanism of action:

  binding to the mineralocorticoid receptor → binding of the hormone-receptor complex to DNA → mRNA → synthesis of proteins:

  - namely Na^+/K^+-ATPase
  - ↑ number of amiloride-inhibited Na^+-channels in the membrane of target cells

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



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  - 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:

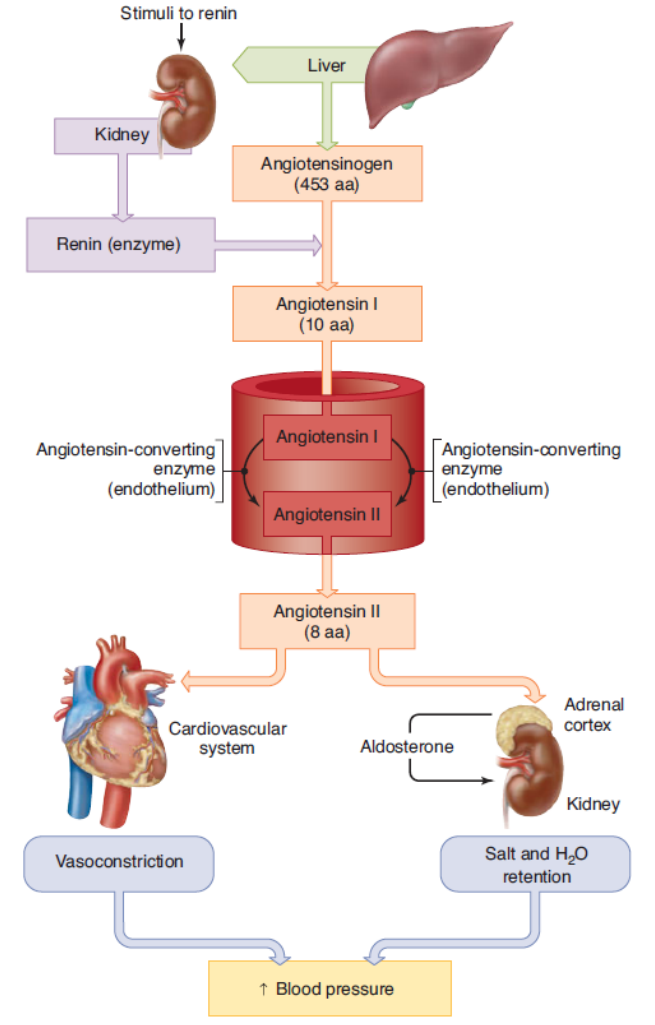
  → ↑ Na^+ reabsorption from urine, sweat, saliva, gastric juice
  → ↑ K^+ urine excretion, ↑ acidity of urine (exchange for Na^+)
  → ↑ K^+ content and ↓ Na^+ content in muscle and brain cells

- regulation of its secretion:

  - ACTH from the adenohypophysis (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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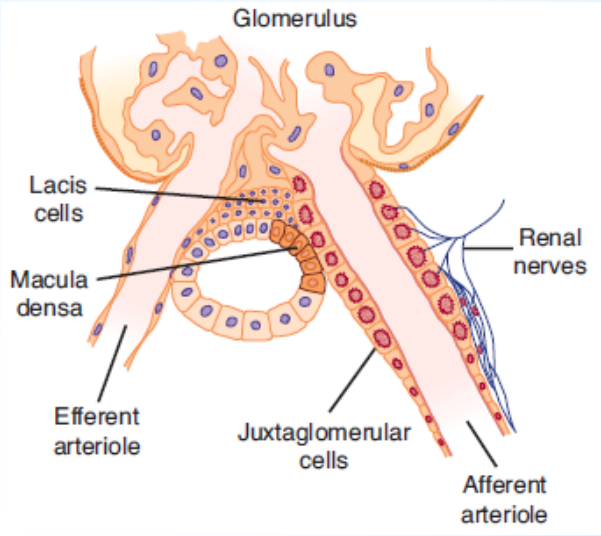

Humoral Regulation of Body Fluids

Aldosteron

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

Humoral Regulation of Body Fluids

Aldosteron - Pathology

Primary hyperaldosteronism (Conn´s syndrome)

- tumors of adrenal cortex which secretes aldosteron

→ heavy K^+ depletion
→ hypertension
→ ECF expansion (without edemas, without marked hypernatremia – redundant salts released by the so called escape phenomena)

→ at a prolonged K^+ depletion:
- →renal damage → polyuria (the hypocalemic nephropathy)
- →muscle weekness
- →metabolic alkalosis → ↓ plasmatic concentration of Ca^{2+} → latent or fully developed tetany
- →glucose intolerance

Humoral Regulation of Body Fluids

Aldosteron - Pathology

Primary hyperaldosteronism (Conn´s syndrome)

- tumors of adrenal cortex which secretes aldosteron

Secondary hyperaldosteronism

- patients with the congestive heart failure, nephrosis, liver cirhosis, renal artery constriction, hypertension, with the salt-losing form of adrenogenital syndrome

Hyporeninemic hypoaldosteronism

Pseudohypoaldosteronism

Humoral Regulation of Body Fluids

Atrial Natriuretic Peptide

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

- secreted by atrial cardiomyocytes, found also in the brain

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:

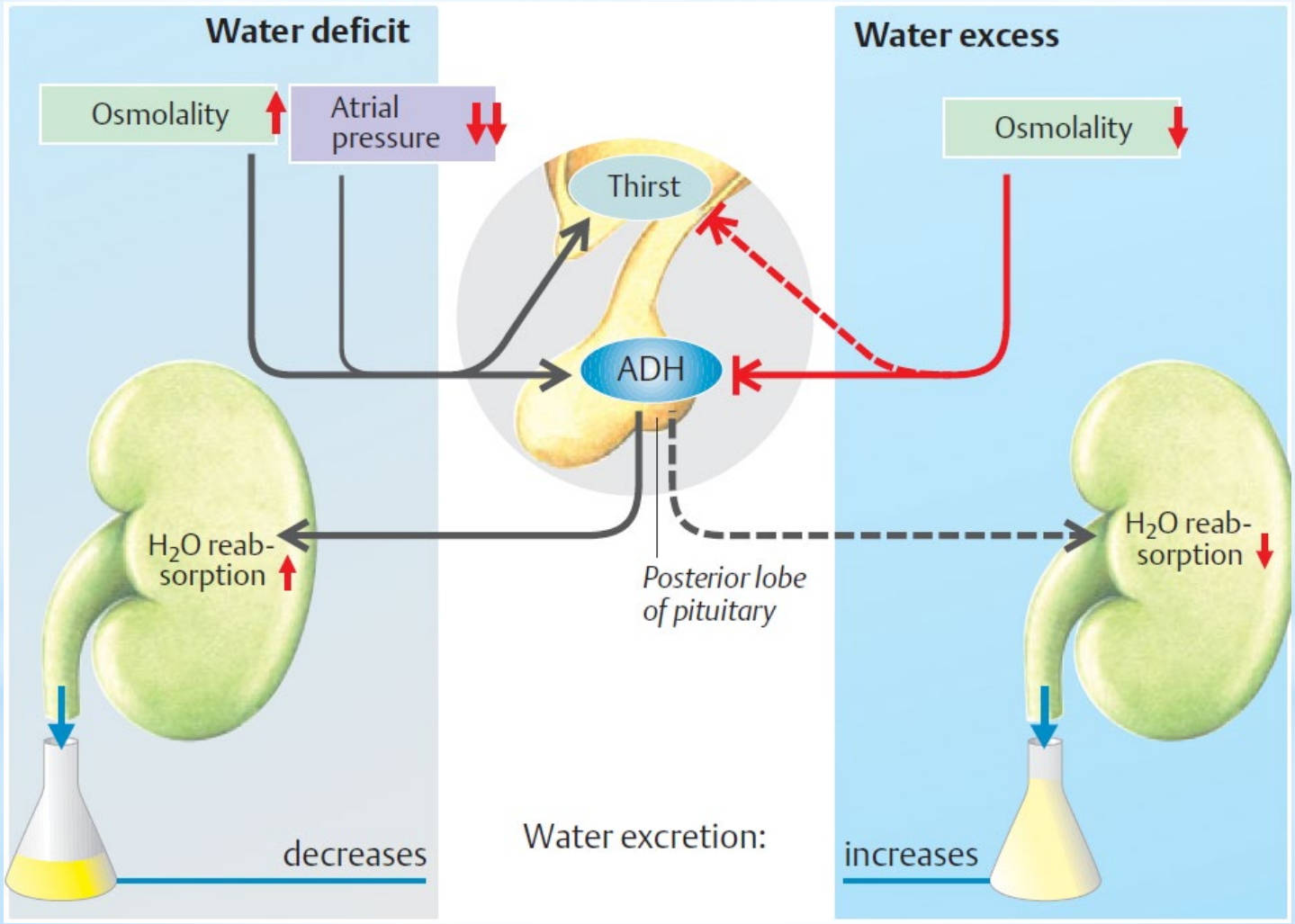
↑ - ↑ ECF volume (atrial cells´ stretch at higher atrial filling)

↓ - ↓ CVP at orthostasis

Humoral Regulation of Body Fluids

Water Homeostasis

water intoxication



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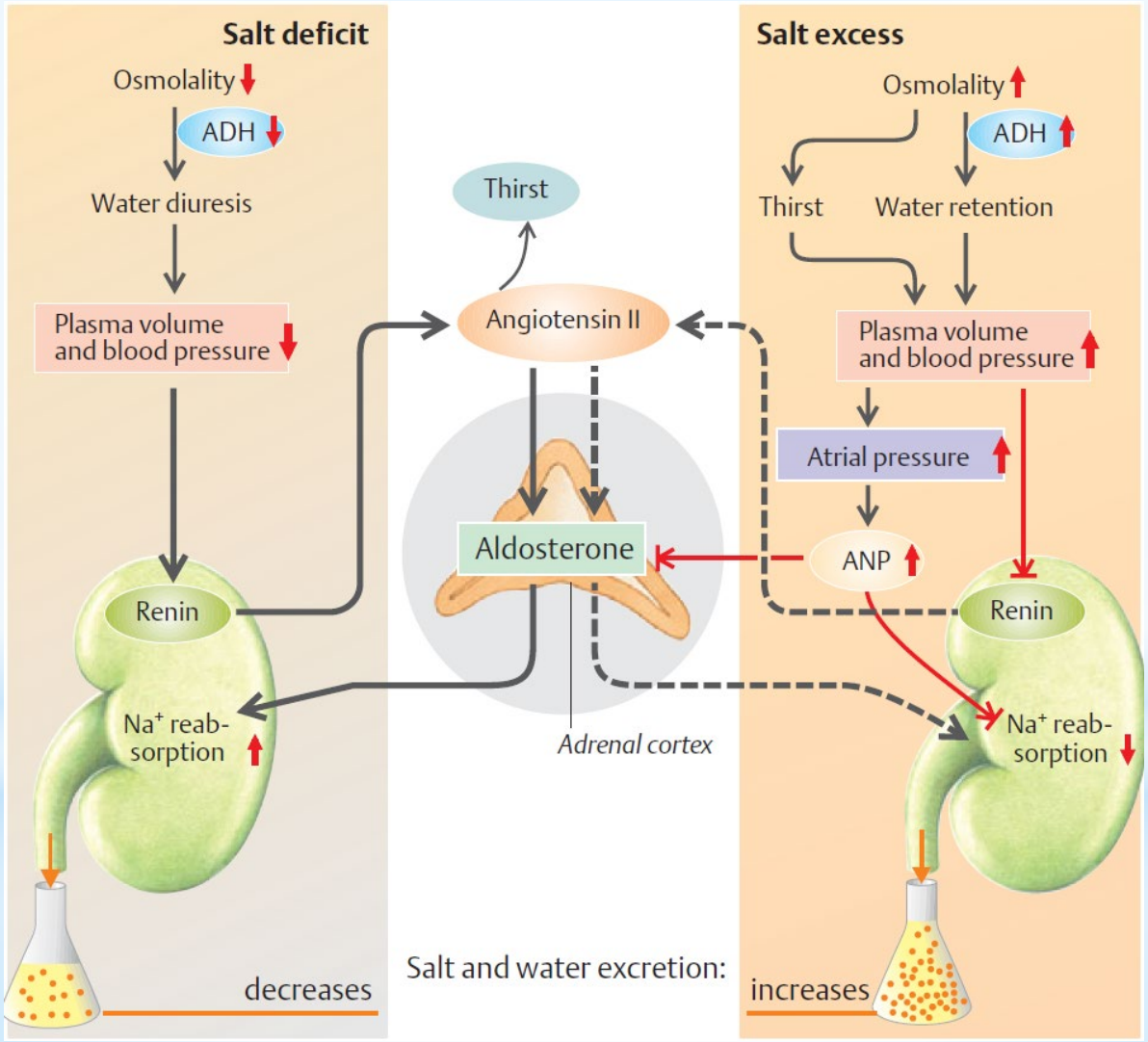
Humoral Regulation of Body Fluids

Salt Homeostasis



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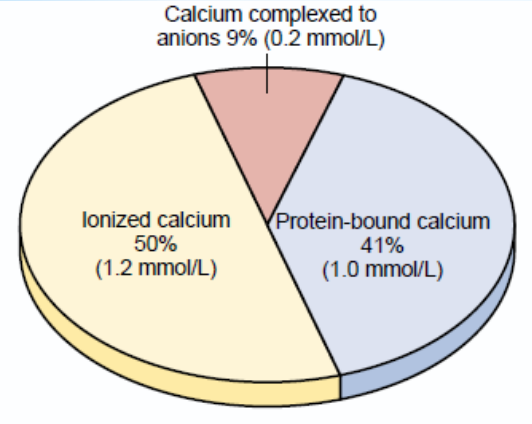
Humoral Regulation of Body Fluids

Calcium in the Body



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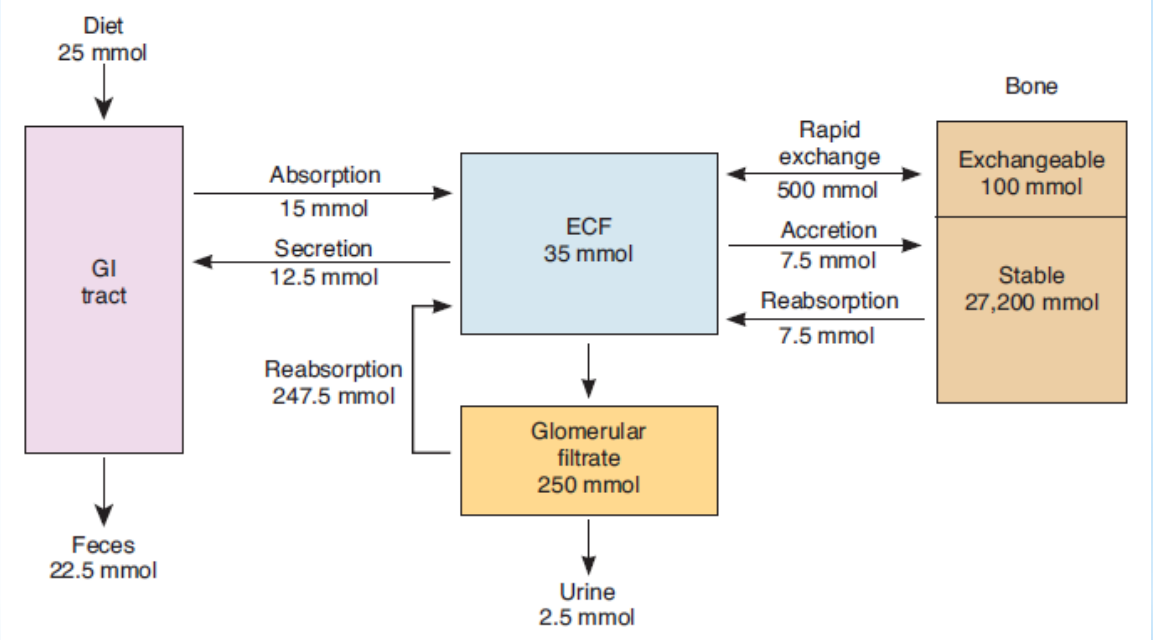

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hypocalcemia

hypercalcemia

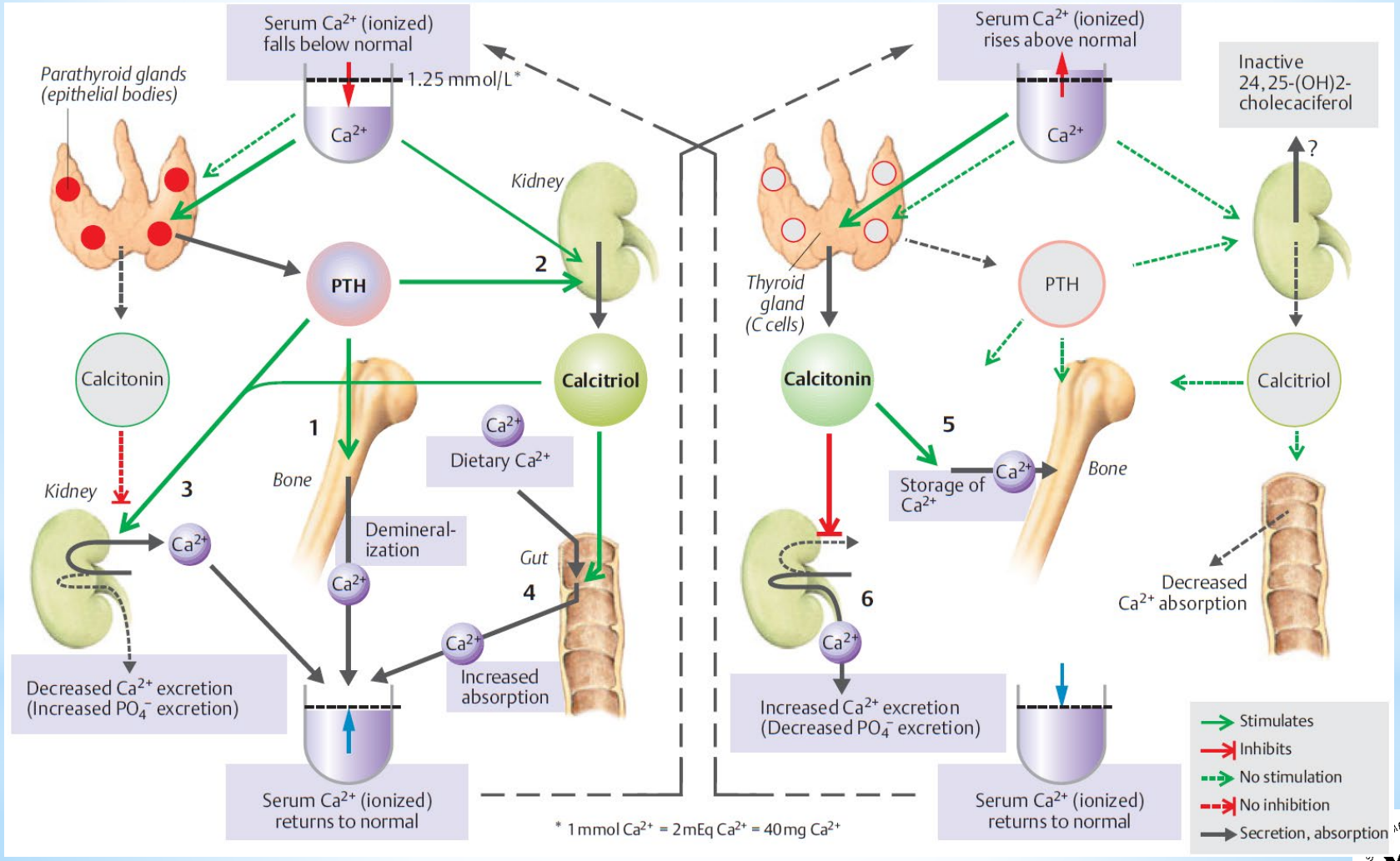
Humoral Regulation of Body Fluids

Hormonal Regulation of Calcemia

Parathormone
Vitamin D
Calcitonin

Humoral Regulation of Body Fluids

Hormonal Regulation of Calcemia



Acid-Base Balance
- Regulation by Kidneys -

Acid-Base Balance and its Regulation

acid — substance releasing H^+ (*e.g.* $H_2CO_3 \rightarrow H^+ + HCO_3^-$)

base — substance binding H^+ (*e.g.* $HCO_3^- + H^+ \rightarrow H_2CO_3$; proteins)

$[H^+]$

- influences activity of almost all enzymatic systems
- very low compared to the concentration of other ions; $[H^+]$ = 40 nEq/l but for example $[Na^+]$ = 142 mEq/l
- thus, its changes has to be much smaller (3-5 nEg/l) $\Rightarrow$ precise regulation of $[H^+]$ is necessary!

Since $[H^+]$ is a very small number, its negative logarhithm is used:

$$pH = -\log [H^+] = -\log 0.000\,000\,040 = 7.4$$

The value of pH is thus inversely proportional to $[H^+]$.

Change of pH by 1 ~ change of $[H^+]$ 10-times bigger!

Acid-Base Balance and its Regulation

Physiological value of pH:

- arterial blood pH = 7.4
- venous blood pH = 7.35 (CO_2 from tissues)
- ICF pH = 6.0 – 7.4 (according to the cell type)
- urine pH = 4.5 – 8.0

The value of pH 6.8 – 8.0 can be survived for several hours!

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^+:

  buffer + H^+ $\rightleftharpoons$ H - buffer

  $\uparrow[H^+]$ direction to the right favoured till free buffer is available

  $\downarrow[H^+]$ 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 Buffers

1) Bicarbonate buffer

- the most important buffer system
- weak acid H_2CO_3 and its salt $NaHCO_3$

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- + Na^+$$

- the most powerful (despite not expected to be so powerful, pK = 6.1)

2) Phosphate buffer

- an important buffer system of the renal tubular fluid and of the intracellular fluid (high concentration + pH nearer to pK = 6.8)
- $H_2PO_4^-$, HPO_4^{2-}

3) Protein buffer

- an important buffer of an important buffer system of (conc. + pK)

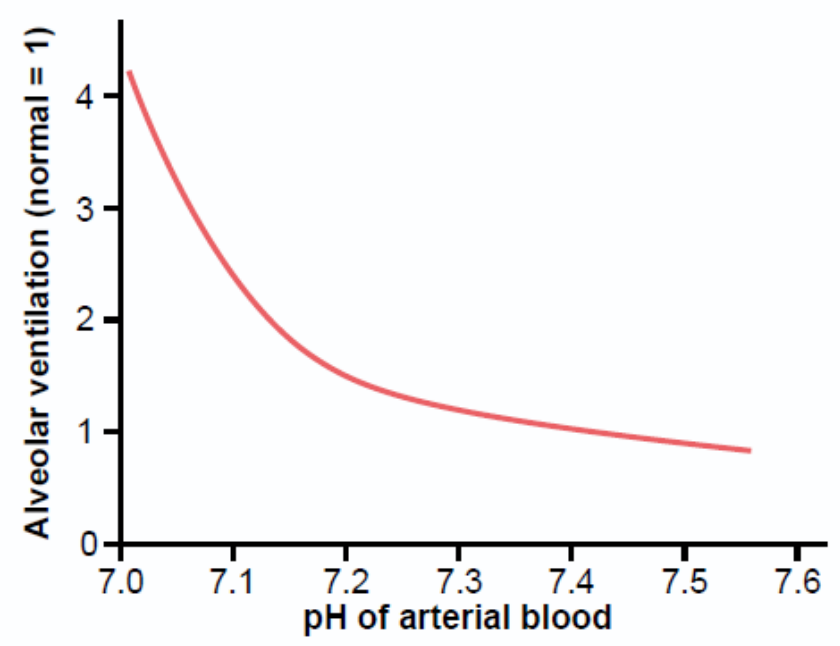
60 – 70% of the buffer capacity of body fluids sites in the cells and is dependent on proteins!

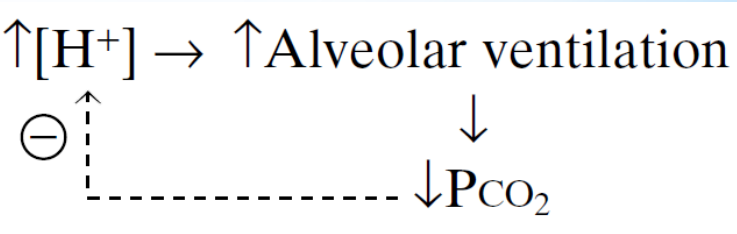
Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Lungs

- by the hyper- or hypoventilation

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





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

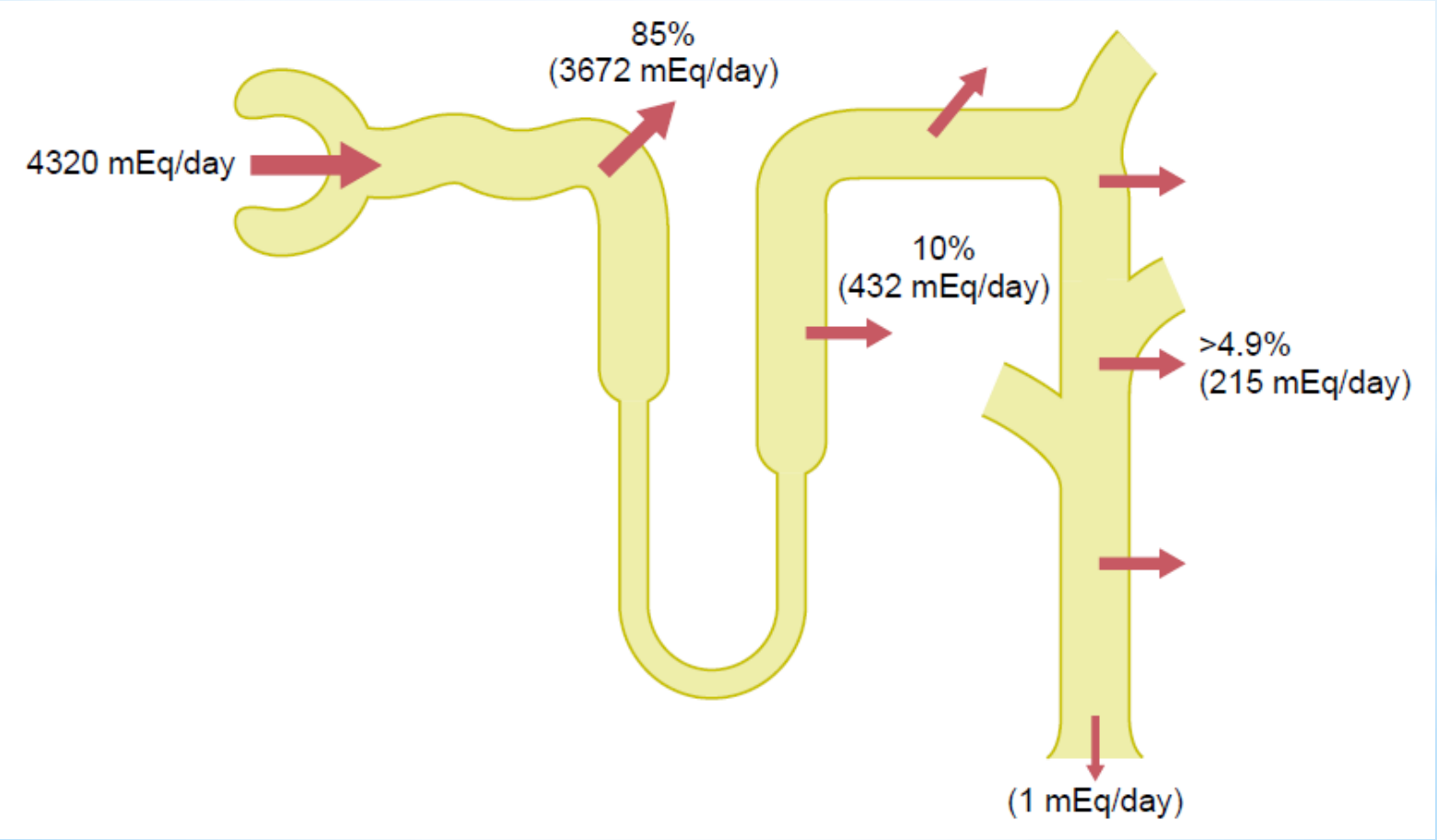
  GFR 180 l/day, $[HCO_3^-]_{plasma}$ 24 mEq/l $\rightarrow$ 4320 mEq HCO_3^- filtered per day – almost all ordinarily reabsorbed
- a high amount of H^+ still secreted in renal tubules

  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

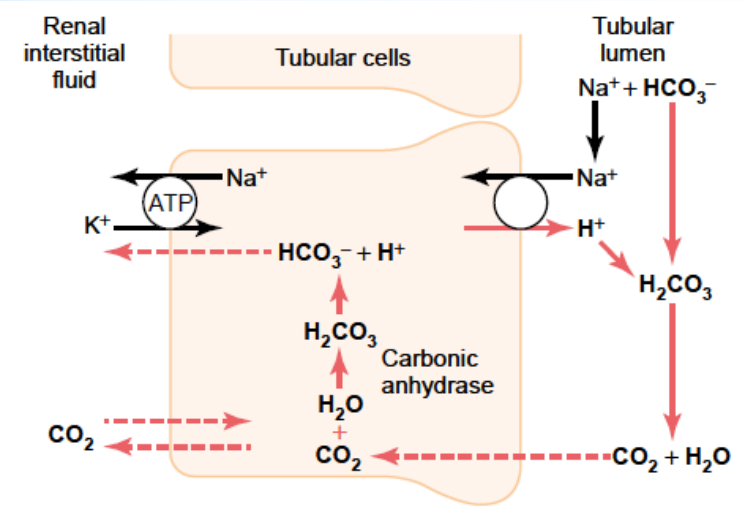
1) Secretion of H^+
2) Reabsorption of HCO_3^-



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:

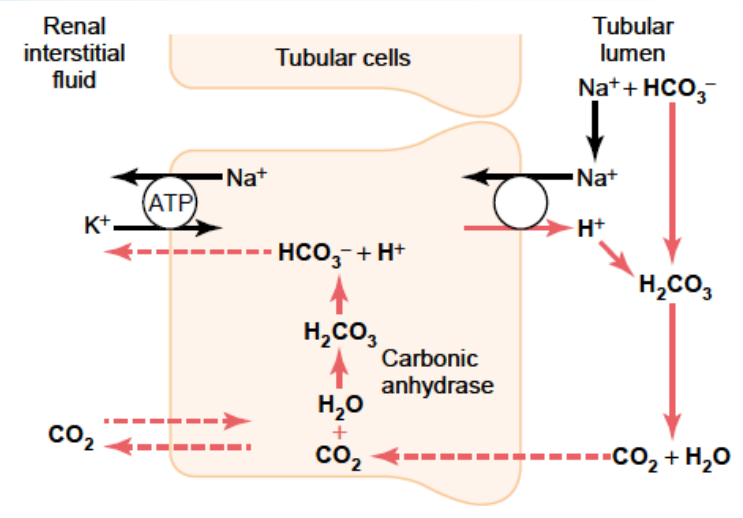
- Na^+-HCO_3^- co-transport
  (the proximal tubule)
- Cl^--HCO_3^- exchanger
  (the end of proximal tubule and the following parts of tubulus except for the thin loop of Henle)

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

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

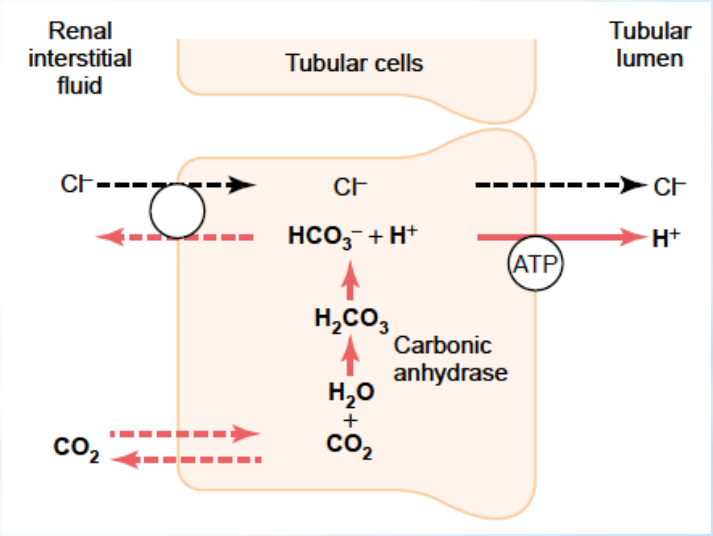
- in the proximal tubule, thick loop of Henle and at the beginning of the distal tubule



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)

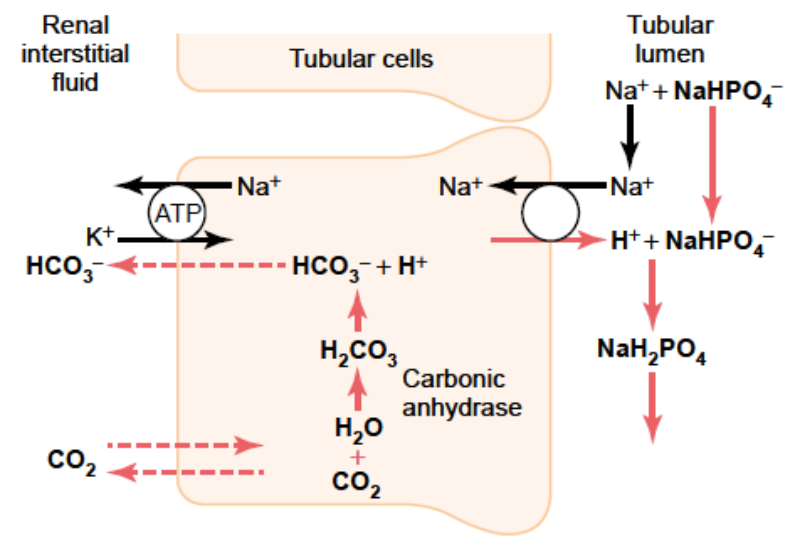
acidification of urine

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

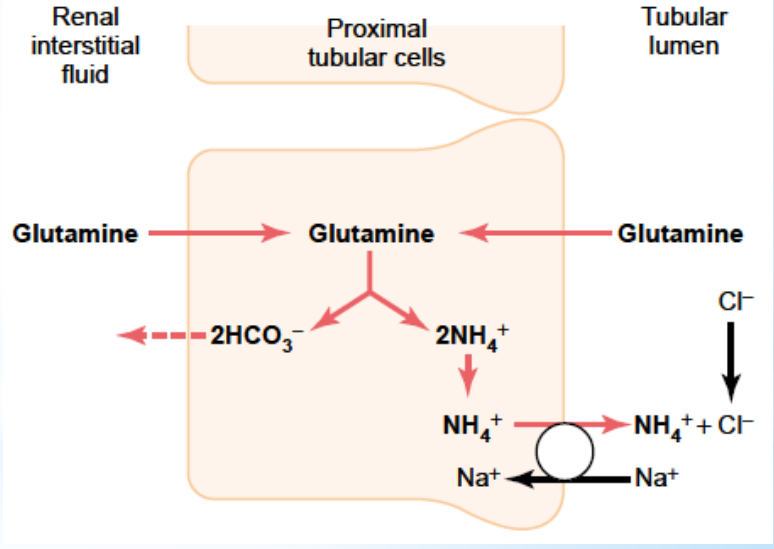
1) Secretion of H^+
2) Reabsorption of HCO_3^-
3) Production of HCO_3^- *de novo*

- 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

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2) Reabsorption of HCO_3^-
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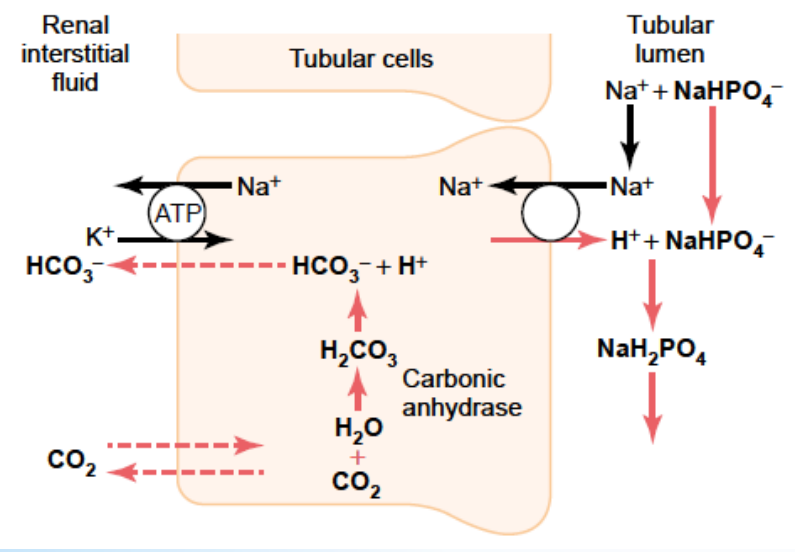

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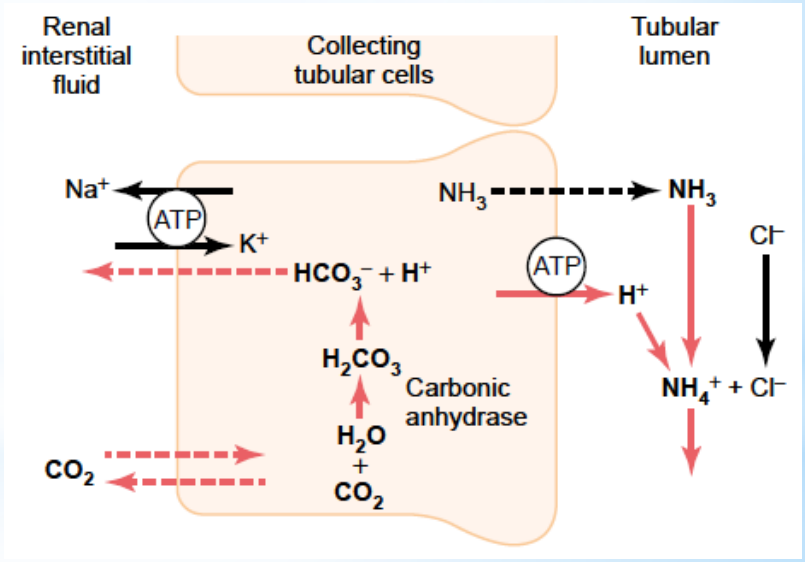


the collecting duct (permeable for NH_3 but far less for NH_4^+ - excreted by urine)

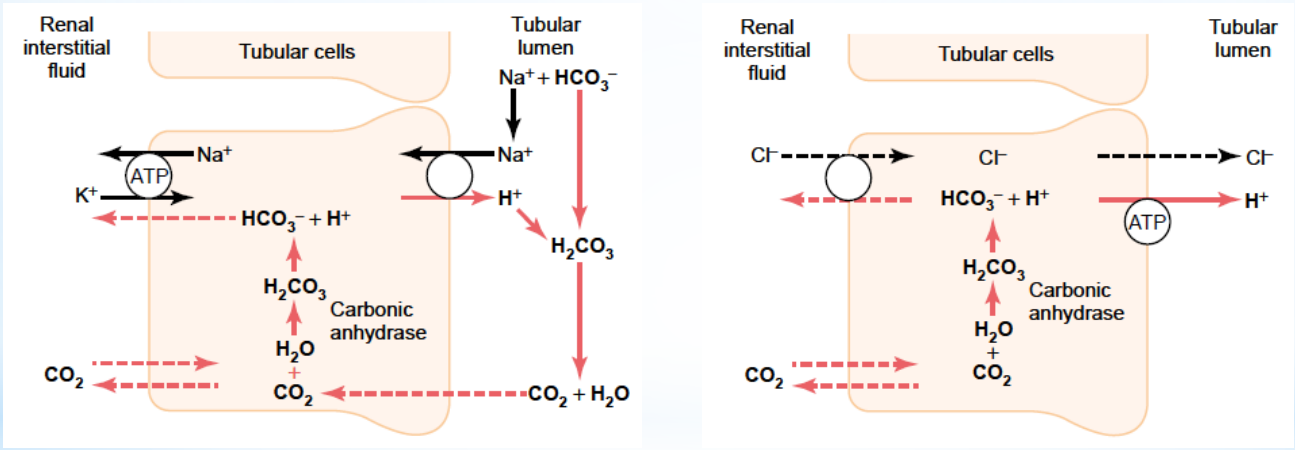
50% of H^+ secretion and HCO_3^- formed *de novo*!

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 active H^+ secretion in intercalated cells of collecting ducts, also through Na^+/H^+ antiport; Conn´s syndrome - alkalosis)

Acid-Base Balance and its Regulation

Regulation of Acid-Base Balance by Kidneys

Regulation of H^+ secretion

Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

RAS

↑ activity of Na^+/H^+ antiport

↑ activity of H^+ ATPase

↓

tendency to 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

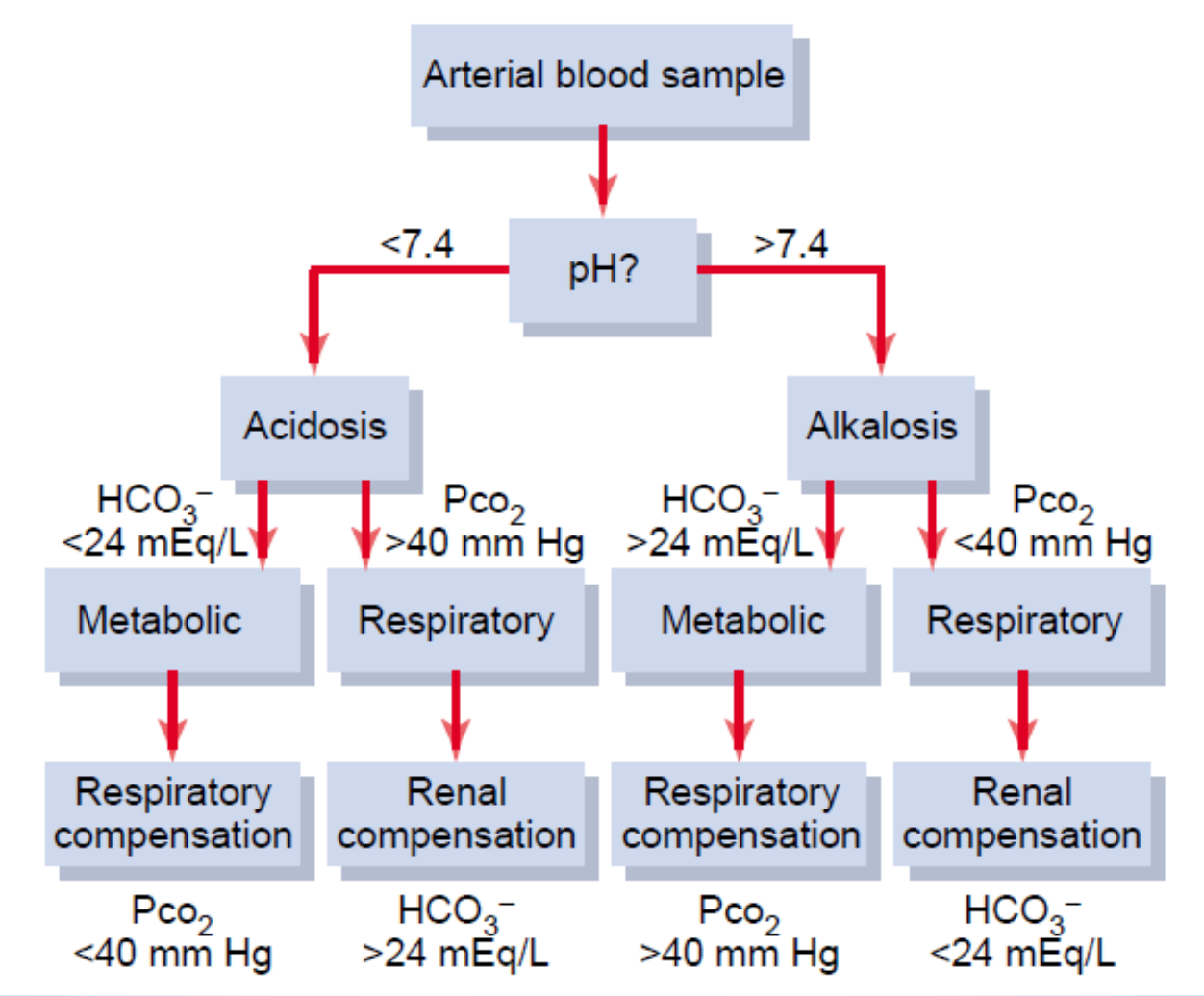
Alkalosis – correction by kidneys

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

- 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

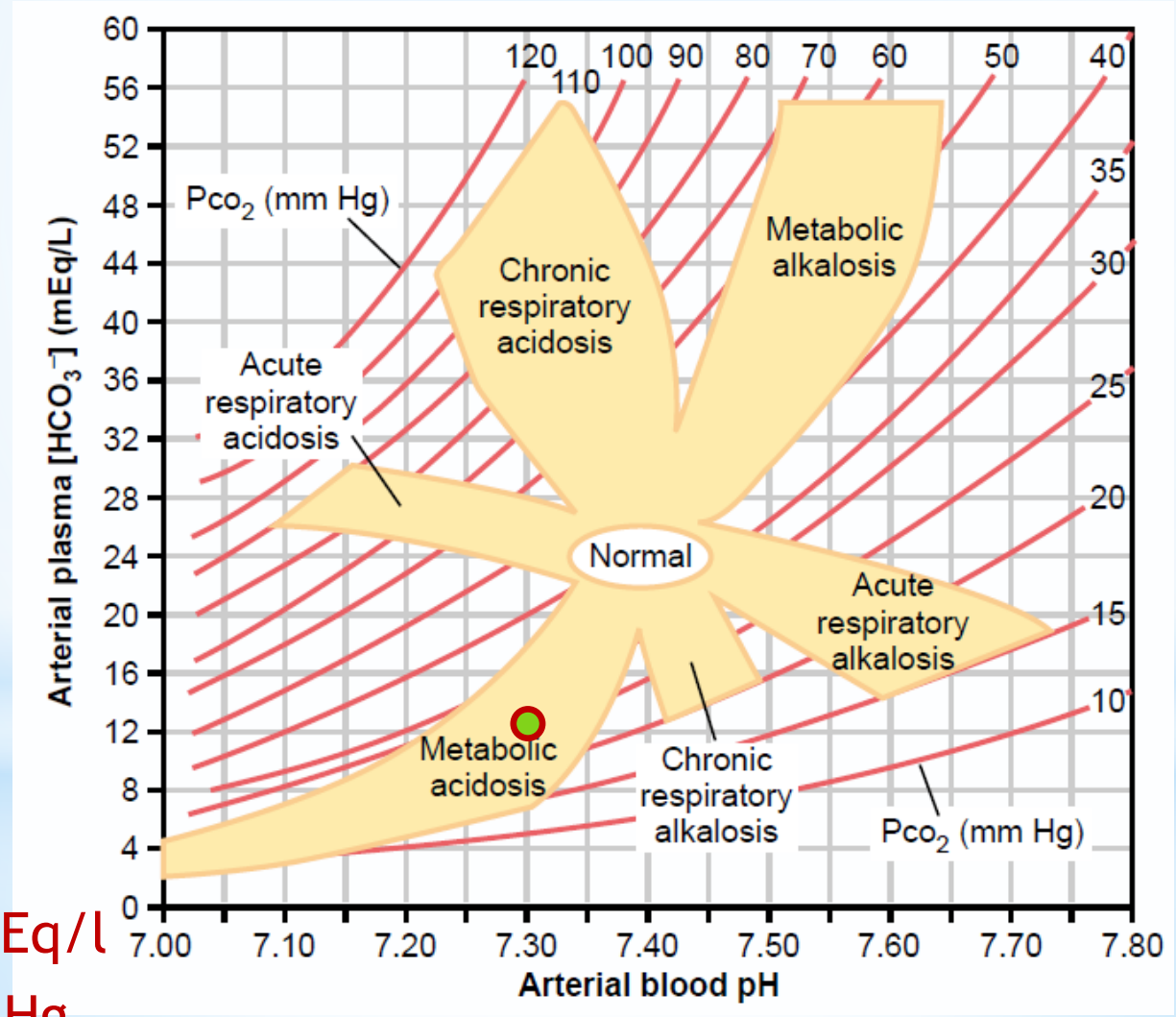
Acid-Base Balance and its Regulation

Diagnostics



Acid-Base Balance and its Regulation

Diagnostics



pH: 7,3

HCO_3^-: 12 mEq/l

P_{CO2}: 25 mmHg