METABOLISM OF WATER AND MINERALS

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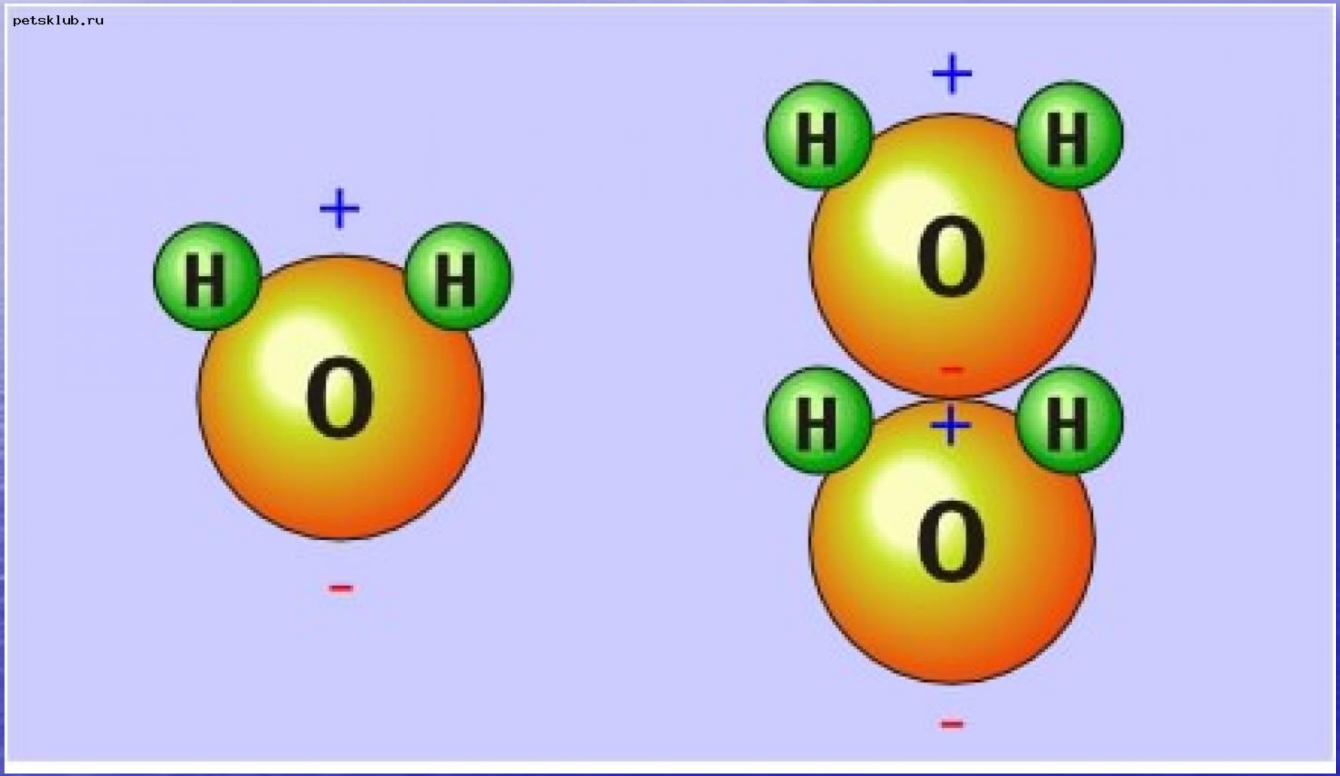

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Role of water in the body

1. Takes part in enzyme-catalyzed reactions and digestion of nutrients (hydrolysis, hydratation)

2. Separates the polar functional groups (structural) - forms cell membranes

3. Forms hydrate layer of molecules and ions – facilitates solubility of compounds (proteins, enzymes) and their transport

4. Forms active volume of cells and extracellular space (turgor)

5. Determines state of body fluids (blood, lymph, sweat, urine, bile), maintains blood pressure

6. Thermoregulatory

7. Transport medium

Daily water balance

INTAKE

FOOD – 0.8-1.0 L

DRINKING – 0.5-1.7 L

25-30 ml/kg body weight.
For children under 1 -
100-165 ml/kg body weight,

METABOLIC WATER – 0.2-0.3 L

TOTAL: 1.5-3.0 L

OUTPUT

1. URINE – 0.6-1.6 L
2. SWEAT – 0.5-0.9 L
3. FECES – 0.1-0,2 L
4. LUNG SURFACE - 0.3-0.5 L

Obligatory water loss ~
1400 ml per day.

TOTAL: 1.5-3.0 L

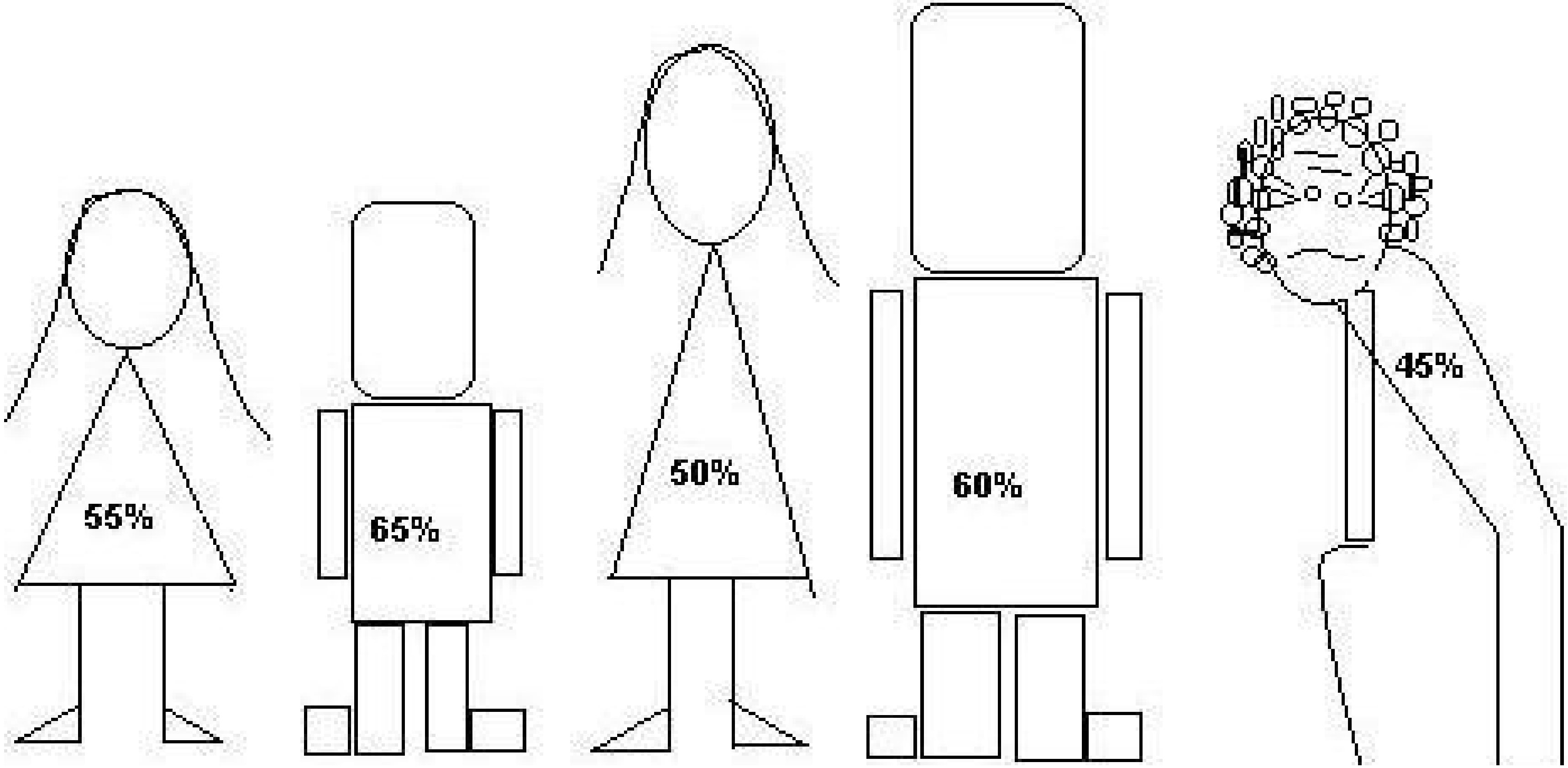
Total body water (TBW)

55-60 % of body weight in adults.

Women have a **lower TBW than men** due to a **higher proportion of body fat** (the same rule – for people having **overweight**).

Young children and **pregnant women** have an **increased TBW**,

as we age, our bodies gradually dry up



Distribution of water in the body (WATER COMPARTMENTS):

A. **Extracellular liquid** (1/3 or 20% body weight);
   - Interstitial (26%);
   - Blood plasma (7%)

B. **Intracellular liquid** (2/3 (67%) or 40% body weight).
   - plasma and interstitial liquid: similar composition
   - extra- and intracellular: different (permeability of membranes to certain ions, transport systems)

- In neonatals, ECL is 1/3, ICL is 2/3 of TBW

C. **Third space** (preformed cavities):
   - Cerebrospinal fluid < 1%;
   - Other transcellular liquid (~1%);
     - saliva, bile, secretion in GIT, synovial fluid, fluid in the pleural, peritoneal and the pericardial cavity

Water homeostasis

Maintaining a **constant composition of the internal environment of the human body** – is absolutely essential.

This is one of the **vital functions** such as breathing or blood circulation.

Basic components of the internal environment

1) Constant volume
2) Constant tonicity and **constant ionic composition**
3) Constant pH (acid-base balance)

Water production at rest:

- **100 g** of fat produce over **100 ml** of water,
- **100 g** of protein — approx. **40 ml** of water,
- **100 g** of carbohydrates — **55 ml** of water.

Activation of catabolism of metabolic fuels and energy metabolism leads to increase of production of endogenous (metabolic) water.

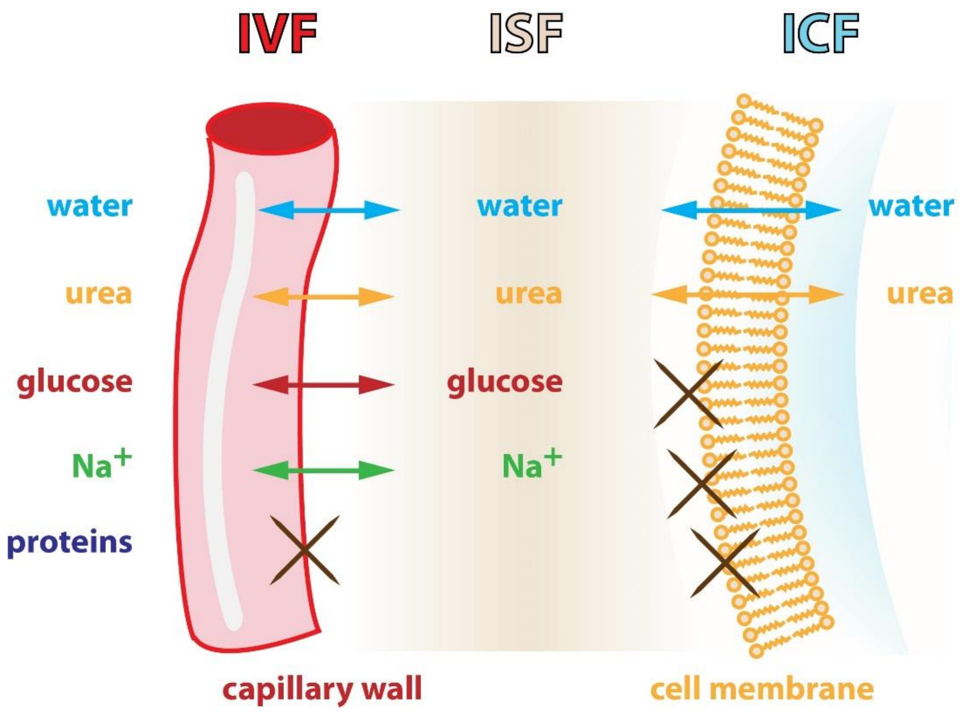
Volume and osmolality of body fluids

Total concentration of mineral and organic substances determines osmotic pressure

Osmolality - osmotic pressure exerted by the dissolved substances (mmol / kg of a solvent)

Water moves **from** a compartment of lower osmolality **to** the compartment of higher osmolality until the osmotic pressure becomes identical

– volume of both **extracellular** and **intracellular** fluid depends on the amount of substances **dissolved** in these compartments



Osmolality of **extracellular space** is created mainly by **Na^+**.

Under pathological condition, **glucose** and **urea** may contribute in plasma osmolality.

Part of the osmotic pressure created by **proteins (albumin)** - **oncotic pressure**.

decrease of **oncotic pressure** in the blood

- moves water from plasma to interstitial space - edema

Volume and osmolality of body fluids

Normal osmolality of blood – **280-300 mmol/kg** (mOsm)

Calculated osmolality = 2 [Na^+] + [glucose] + [urea]

Comparison of measured and calculated osmolality - **osmotic gap** (**OG**):

Osmotic gap = measured osmolality – calculated osmolality

OG is comprised of substances other than Na, glucose and urea – normal range is **4-12 mmol/l**.

OG increases in:

1) **Accumulation of foreign substances to the human body** – **poisoning** (e.g., ethanol, ethylene glycol)

2) **Accumulation of substances**, **which are commonly found in the body, but their metabolism is altered** – excessive catabolism in diabetes mellitus type 1 (ketone bodies etc.).

Regulation of sodium and water balance at renal level

main regulatory mechanisms:

- **simple feedback** via **antidiuretic hormone (ADH, vasopressin)**
- thirst inducement

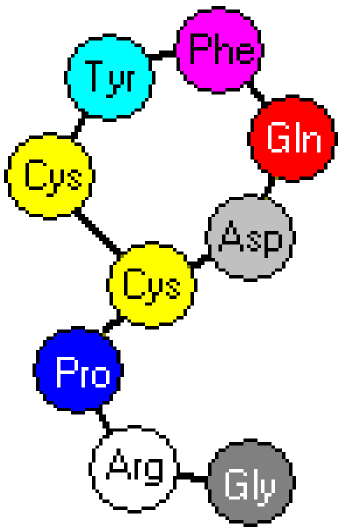
1. **ADH antidiuretic hormone – hormone of neurohypophysis, activates water reabsorption by the kidney**

2. **Aldosterone – hormone of adrenal cortex**
   (stimulates sodium reabsorption).

3. **Natriuretic peptides – facilitates sodium excretion**
   (decrease Na^+ reabsorption)
   causes vasodilatation, decreases blood pressure

Vasopressin
Antidiuretic hormone (ADH)

Oligopeptide, 9 amino acids, production in HYPOTHALAMUS



Antidiuretic hormone

Neurons of lateral hypothalamus - **center of thirst**. are able to monitor the **osmolality**.

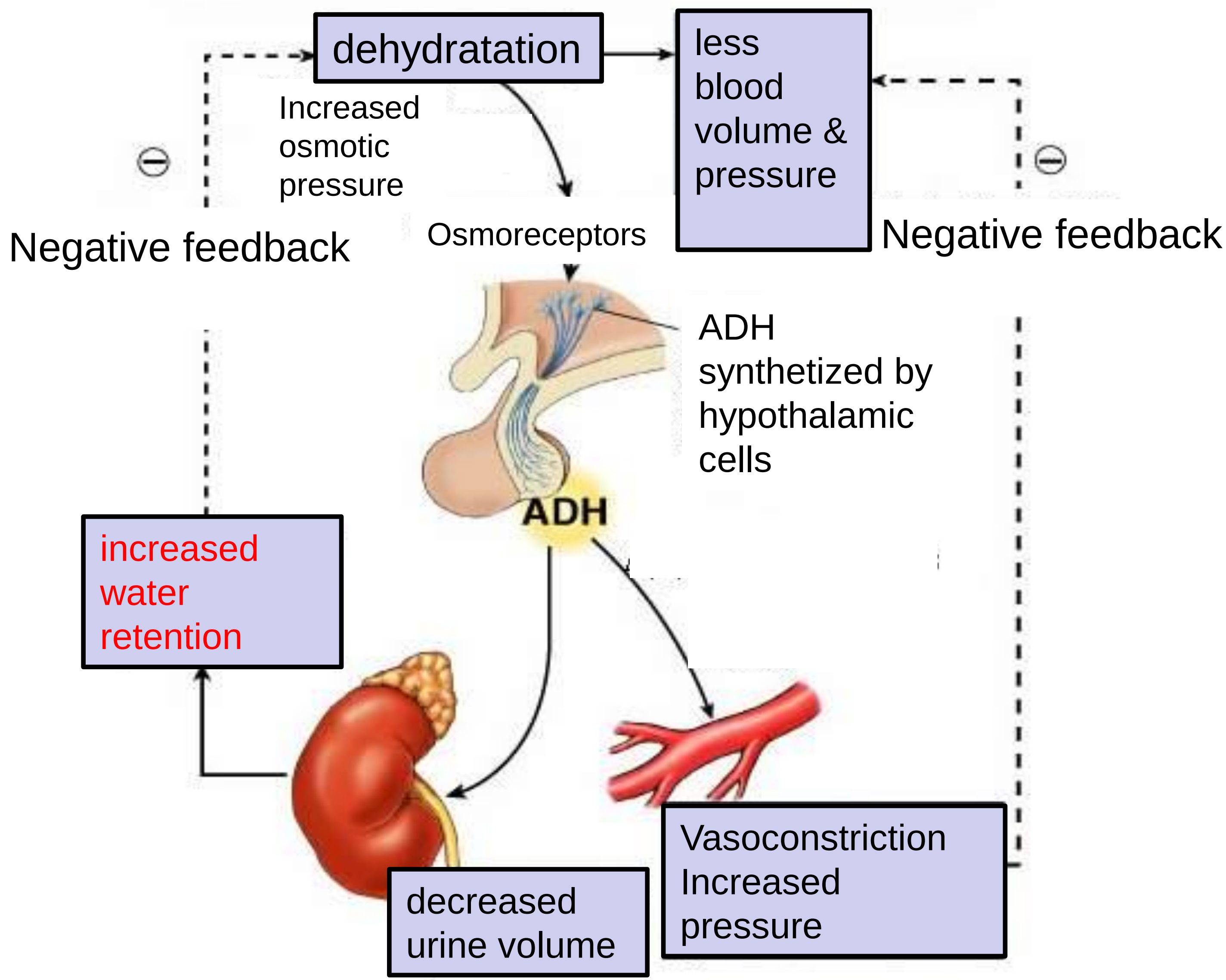
In hyperosmotic environment - **shrinkage** of cells (diffusion of water into extracellular compartment), inducing a **feeling of thirst**.

Neurons of **supraoptic area** - osmoreception. Increase activity in hyperosmotic fluid, release **ADH** from axons in the **neurohypophysis** into blood.

Target for ADH in kidneys: **cells of distal tubuli** and **collecting ducts**

carry **V2 membrane receptors for ADH**, through cAMP -- incorporation of **aquaporins-2** (channels for water) to the apical membranes of cells.
water moves by osmotic gradient from the **lumen of the nephron into the hyperosmolar environment of the kidney medulla**.
The result: **increase in urine osmolality, decrease in body osmolality**.

INFLUENCE OF ADH ON VOLUME OF BODY FLUIDS AND BLOOD PRESSURE



Disorders of antidiuretic hormone secretion

diabetes insipidus:

insufficient secretion of ADH or absence of its receptors

excessive diuresis (polyuria – up to 30 liters per day)

excessive thirst (polydipsia).

SIADH (Syndrome of Inappropriate ADH secretion, Schwartz-Bartter syndrome):

excessive secretion of ADH.

water retention, **hypoosmolarity** and **dilutional hyponatremia**. In more severe conditions **brain damage** develops due to the **edema**.

tumors producing ectopic ADH.

Clinical significance of plasma osmolality

Isotonic solutions

the most frequently encountered in practice:

a) Normal saline (NS) – **0,9% NaCl**, 154 mmol/l Na^+ and Cl^-
b) 5% glucose – free water remains after glucose metabolism
– **de facto hypotonic solution**
c) Ringer's and Hartmann's solution – **ionic composition similar to plasma**

Hypotonic solution

may cause **hemolysis** and **brain edema**

Hypertonic solutions

can irritate the wall of blood vessels and cause **damage to the CNS** **(pontine myelinolysis)**

REGULATION OF ALDOSTERONE SECRETION (RENIN-ANGIOTENSIN SYSTEM)

Angiotensinogen Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu (~400 more amino acids)

↓ RENIN (kidney, juxtaglomerular cells) – stimulated by **hypotension or decreased Na^+ level**

Angiotensin I Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu

↓ CONVERTING ENZYME - **ACE** (lungs)

ANGIOTENSIN II Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

↓ AMINOPEPTIDASE

Angiotensin III Arg-Val-Tyr-Ile-His-Pro-Phe

↓ ANGIOTENSINASES

Degradation products

ANGIOTENSIN II stimulates aldosterone secretion by adrenal glands

Inhibitors of ACE are used for treatment of hypertension.

MAIN MACROELEMENTS OF THE BODY

CONTENT IN WHOLE BODY $> 10^{-2}$ mole

- POTASSIUM
- SODIUM
- CALCIUM
- MAGNESIUM
- CHLORINE
- PHOSPHORUS

DAILY REQUIREMENTS IN MACROELEMENTS FOR ADULTS (g per day)

Na^{+}	2,0-3,0
K^{+}	2,0-5,0
Ca^{2+}	0,7-0,8
Mg^{2+}	0,22-0,26
Cl^{-}	3,0-5,0
P	0,7

Water-electrolyte (or salt) metabolism

Water balance of the body is tightly bound to **electrolyte** balance

Effective concentration of free ions is important

Ions may be bound to other compounds

(Ca and Mg bound to proteins, Na - in subcellular structures).

Sodium

- maintaines osmotic pressure of extracellular liquid,

Deficiency cannot be replenished by other cations

130-150 mmol/L

Shifts in Na^+ levels in body fluids →
osmotic pressure changes →
fluids volume changes

< Na^+ extracellular → **>** water moves to cells.
> Na^+ → **>** water moves from cells.

Na^+ in the cell determines membrane potential (cell exitability)

Aldosterone and estrogens	increase reabsorption of Na^+
Progesterone	increases Na^+ excretion

Regulation of Na^+ by the natriuretic peptides

ANP (**atrial natriuretic peptide**)
BNP (**brain natriuretic peptide**).

- Significant **vasodilating** effects,
- **increase natriuresis** (inhibit reabsorption of Na^+ in distal tubuli) and **diuresis**
- **reduce sympathetic activity**.

secreted by cells of the **heart** – the heart is therefore an endocrine organ.

ANP: by **atrial cardiomyocytes**

the stimulus is **increased wall stress** in the atria (**increased venous return**).

BNP: by **cardiomyocytes in heart ventricles**

the signal is increased **tension in the wall** of the ventricle or ventricular **dilatation.**

Natriuretic peptides mediate the body's response to **excess Na^+ and increased blood volume**

Levels of natriuretic peptides, predominantly the N-terminal fragment of **proBNP (NT – proBNP)**, are measured

- to **rule out** heart failure in people who present with sudden difficulty in breathing or
- to determine the **prognosis of patients with known heart failure**.

Potassium

K^+ level inside and outside the cells plays major role in the
cardiovascular function **(extremely important)**,
muscles and nerve system,
motor function and secretion of the digestive tract
excretory function of the kidney

98% of potassium is **in cells**. Ionized form facilitates membrane potential.

- Normal levels in plasma **3.5-4.9 mmol/l**

  < 3.5 mmol/l – hypokalemia

  > 5.5 mmol/l - hyperkalemia

main source is **vegetable diet** (fruits and vegetables)

Losses of K^+: **urine** – U-K^+ = ~ 45 mmol/l, **feces** – 12-18 mmol/day.

Regulation of K^+ in the body

1) Regulation of the distribution of K^+ between ECF and ICF – is responsible for acute shifts in K^+:

a) Energetic state of cells, Na^+/K^+-ATPase: low energy → high K^+

b) pH: **K^+** level increases in acidosis and decreases in alkalosis.

2) Regulation of the K^+ excretion in distal kidney tubuli – **aldosterone increases K^+ excretion**

Going of **K^+** out from cells depends on increase in protein and glycogen breakdown

Rapid anabolism after prolonged catabolism can lead to severe hypokalemia

Hyperkalemia

1) Renal failure leads **to inadequate secretion of K^+** by the kidneys
2) The failure of the adrenal cortex (low aldosterone - Addison's disease).

Symptoms
muscle weakness
abnormal ECG
K^+ values over 7,0 mmol/l are indications for **hemodialysis**.
Higher values can be fatal: **sudden cardiac arrest** resulting from **ventricular fibrillation**.

Hypokalemia

1) Hyperaldosteronism or long-term treatment with glucocorticoids (in high quantities have similar effects as aldosterone)
2) Diuretic overdose (furosemide)
3) GIT fluid losses – diarrhea

Symptoms
muscle weakness (up to paralytic ileus)
heart rhythm disorders

Calcium (1,5% of body weight, 99% in bones)

Necessary for:

- excitability of nerve and muscle cells,
- muscle contraction
- membrane permeability,
- blood clotting,
- **second messenger, Ca-binding proteins, activator of PKC**.
- facilitates **release of mediators** in nervous tissue, hormone secretion.
- decreases permeability of capillaries (anti-allergic action)

Normal concentration in the blood - 2 – 2.75 mmol/l.

Concentration in blood depends on pH:

- in acidosis Ca^{2+} level increases.
- in alkalosis — Ca^{2+} level falls – deeply increased exitability of nerves and muscles → tetany

Hypocalcemia

1) Hypovitaminosis D or hypoparathyroidism

2) Chronic kidney failure

Damaged kidneys fail to form calcitriol (1-hydroxylation) – reduced intestinal absorption of Ca^{2+}.

Inadequate excretion of phosphates → phosphate accumulation → even higher disbalance in Ca/P ratio.

3) Malabsorption

Symptoms: **cramps** (Ca^{2+} stabilizes cell membranes, thus increasing neuromuscular irritability).

Hypercalcemia

hyperparathyroidism

bone diseases (e.g. tumors).

Symptoms: polyuria, somnolence, muscle fatigue and constipation.

Can lead to cardiac arrest in systole.

Magnesium

Mg^{2+}- second major intracellular cation.

50% – in bones,

- **49%** - in cells of tissues,
- **1%** outside the cells.

In blood – **0.7-1 mmol/l**, > 60% in ionized form.

< 0.5 mmol/l - CNS impairments,

< 0.2 mmol/l – clonic convulsion, death.

Magnesium found in over 300 enzymes (all **kinases** use **Mg^{2+}**)

- furnish protein synthesis;
- maintains functional state of cell membranes
- decrease exitability of nerves and muscles
- depressive action on the mental functions.

induction of hypermagnesemia used **as a therapy** in preeclampsia and other seizure disorders

Chlorine

Main extracellular anion.

Concentration in blood plasma **90-105 mmol/l** Cl^-

- **maintaining acid-base balance – exchange for HCO_3^-**
  - losses of Cl^- - body replaces them by the bicarbonates → alkalosis,
  - retention of Cl^- - bicarbonate levels decrease) → acidosis
- participates in the formation of resting potential of excitable cells.

Essential for HCl formation in the stomach

Immune cells can utilize the **H_2O_2-myeloperoxidase-Cl^- system** in the **destruction of phagocytosed microorganisms**.

Phosphates (700 g)

main intracellular anions
(intracellular / extracellular = 40 / 1)

Norman level in blood is **0.94-1.44 mmol/l**
50% of inorganic phosphates found in bones
Together with Ca^{2+} form main mineral matrix of bone tissue

Essential component of cell membranes
play key role in metabolism

Included into co-enzymes,
nucleic acids
phosphorylated proteins and lipids
second messengers,
macroergic compounds,
Buffer

Sulfates

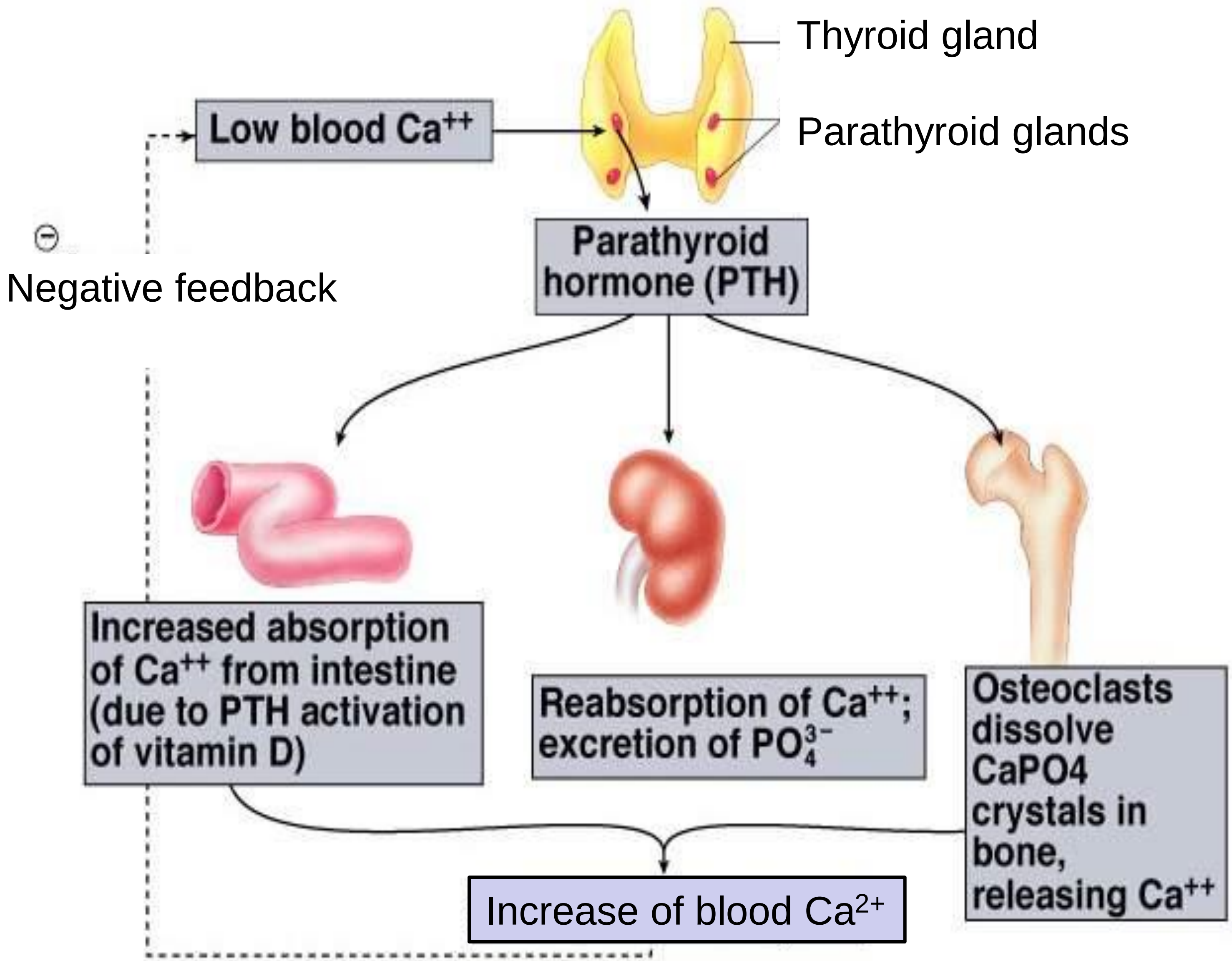
In cells found in numerous biologically active substances

Active form – **3'-Phosphoadenosine-5'-phosphosulfate (PAPS) –** coenzyme in sulfotransferase reactions

Plasma concentration of inorganic sulfates – **0.3-1.5 mmol/l**

Essential for detoxication in liver

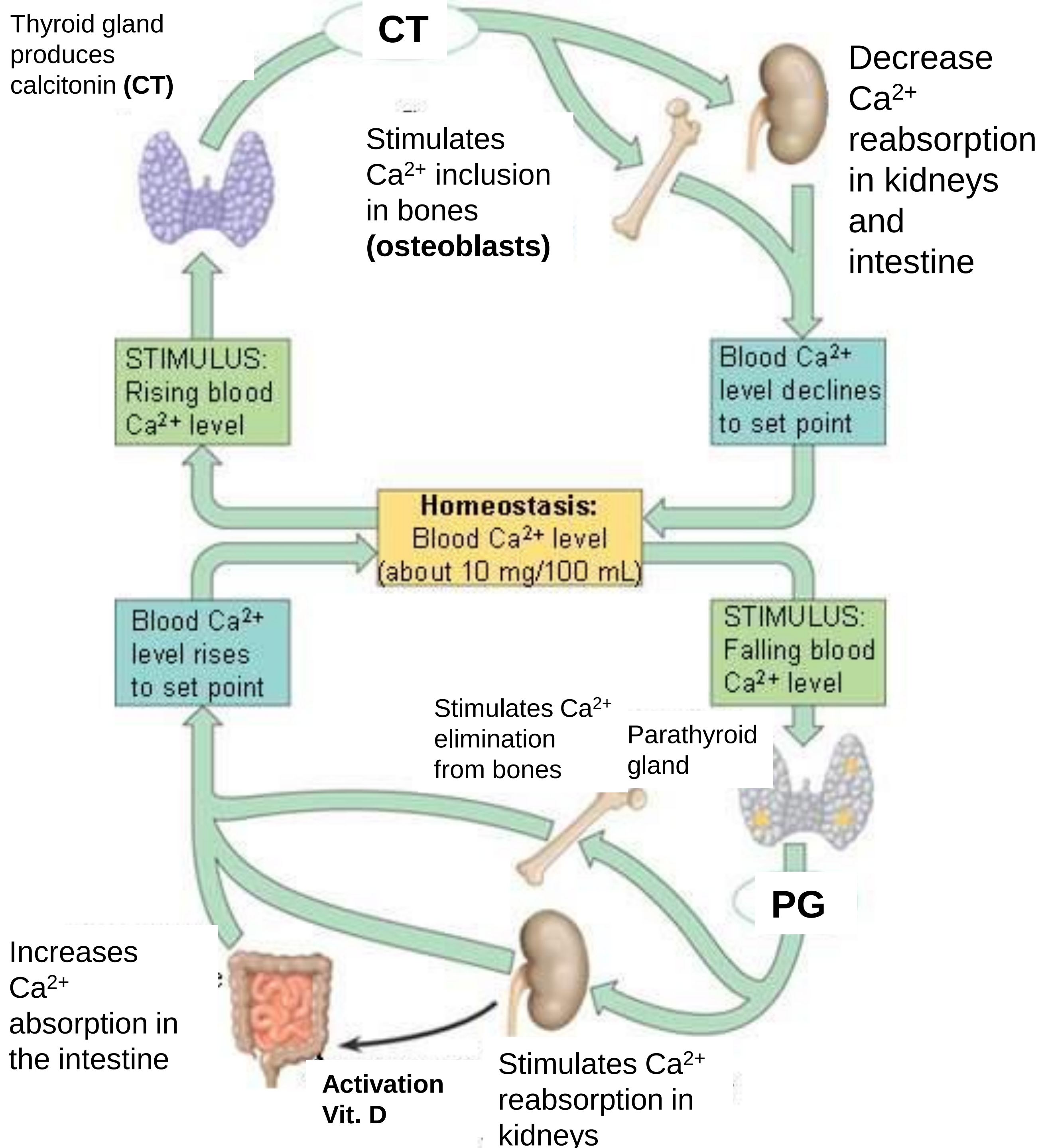
Parathormone and its target organs



Ca^{2+} metabolism

Parathormone and calcitonin effects

hormone	stimulus	target organ	General effect
Parathormone	Decreased Ca^{2+} in blood	Intestine Kidney Bones	Increase of Ca^{2+} level in blood
Calcitonin	Increased Ca^{2+} in blood	Bones Kidney	Decrease of Ca^{2+} level in blood



Thyroid gland produces calcitonin **(CT)**
CT
Stimulates Ca^{2+} inclusion in bones **(osteoblasts)**
Decrease Ca^{2+} reabsorption in kidneys and intestine
STIMULUS: Rising blood Ca^{2+} level
Blood Ca^{2+} level declines to set point
Homeostasis: Blood Ca^{2+} level (about 10 mg/100 mL)
Blood Ca^{2+} level rises to set point
STIMULUS: Falling blood Ca^{2+} level
Stimulates Ca^{2+} elimination from bones
Parathyroid gland
PG
Increases Ca^{2+} absorption in the intestine
Activation Vit. D
Stimulates Ca^{2+} reabsorption in kidneys

ESSENTIAL MICROELEMENTS

CONTENT IN WHOLE BODY 10^{-3} TO 10^{-6} mole

Cofactors	regulatory role	function not known
ZINC	MANGANESE	SILICON
IRON	CHROMIUM	VANADIUM
COBALT	IODINE	FLUORIDE
COPPER		LITHIUM
MOLYBDENIUM		ARSENIC
SELENIUM		

BIOLOGICAL ROLE OF CERTAIN MICROELEMENTS

Iron (4-5 g) – oxygen transport and storage,
cytochromes, oxidative phosphorylation
catalase, peroxidases
transport proteins – **ferritin, transferrin**
deficiency: anemia

Copper (80-120 mg) – oxidases, antioxidant activity, synthesis of collagen and elastin
transport protein in plasma: **ceruloplasmin**

Zinc (1-2 g) – found in > 300 enzymes, gene expression
complex with insulin

Manganese (12-20 mg) – antioxidant activity, glycosylation, carbohydrate metabolism

Chromium (6 mg) – optimize tolerance to glucose
binding of insulin to receptor

Selenium (14 mg) – antioxidant activity **(SeC – glutathione peroxidase),** cancer protection

Molybdenium (10 mg) – metabolism of purines (xanthine oxidase) ans sulfur

Iodine (10-20 mg) – thyroid hormones, 6-iodolactone

Fluoride – bone system and teeth

Cobalt (1,5 mg) – part of vitamin $\mathbf{B_{12}}$