

PATHOPHYSIOLOGY OF WATER AND MINERAL METABOLISM

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1. WATER IN THE ORGANISM

Water is a fundamental component of the inner environment of living organisms. It is a dissolvent and vehicle for other substances. It is also a basic component of blood plasma and thus a carrier of blood elements.

For maintenance of a stable volume of body fluids balance between intake and loss of water is crucial (Fig. 1). Nevertheless, not only total water content in the body but also its distribution in individual compartments (Fig. 2), adequate exchange of water between the compartments and its osmolality are important. For water transfer across the cell membrane osmotic pressure is a determining factor (see also below). For maintenance of water in the vessels, oncotic pressure of plasmatic proteins (i.e. also inability of the proteins to pass through the vessel wall under normal conditions) and hydrostatic pressure are important.

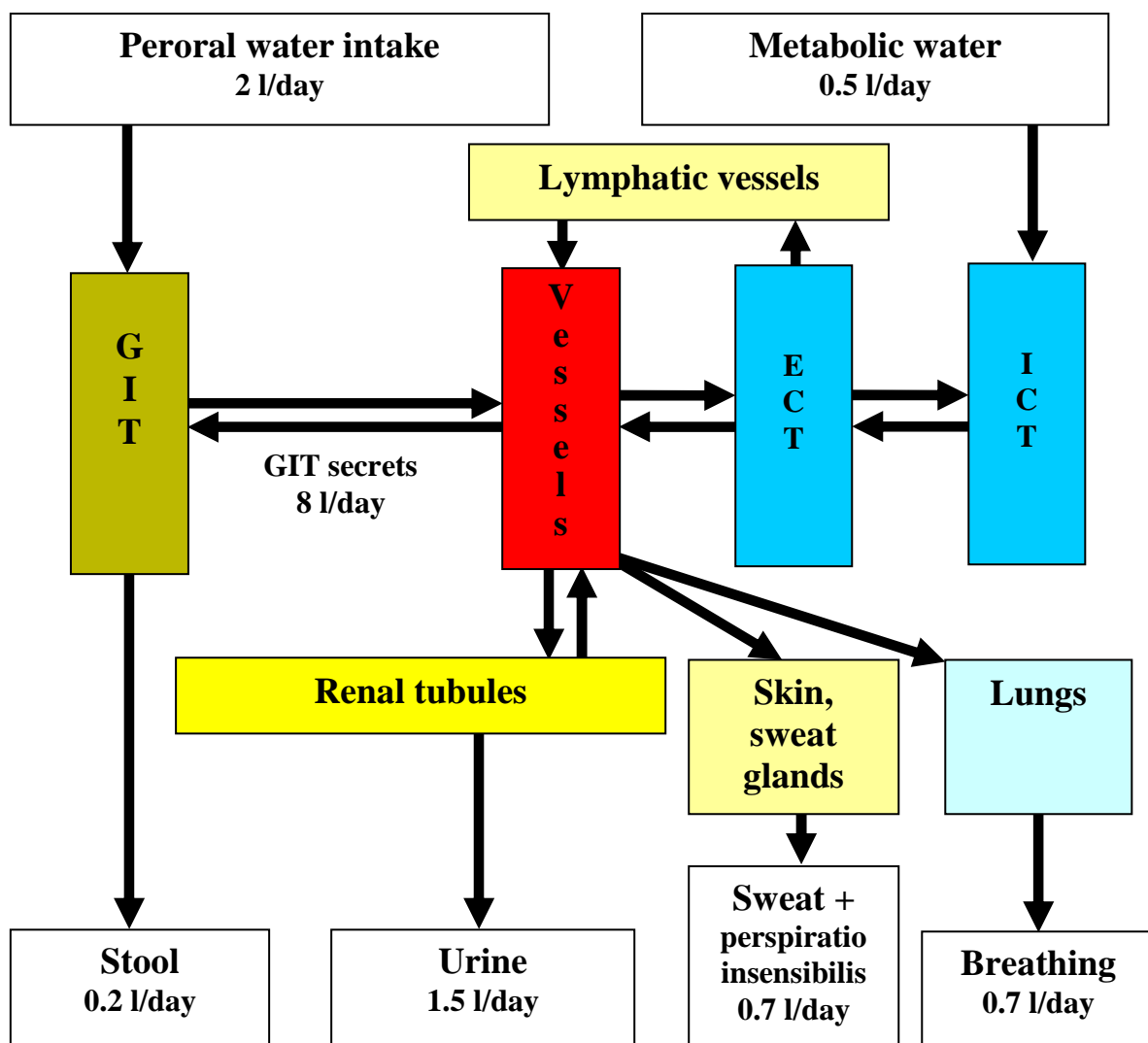


Fig. 1: Scheme of distribution of water in the organism.

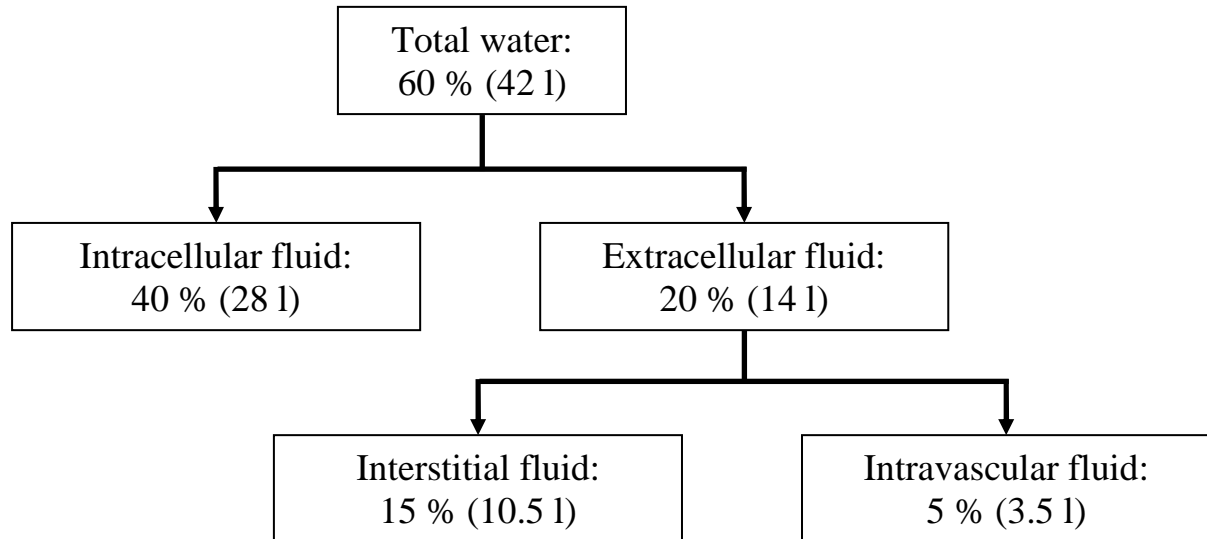


Fig. 2: Water in the organism and its distribution in individual compartments under physiological conditions – expressed as % of the body weight (absolute volume in a 70 kg human).

2. CHANGES OF BODY WATER VOLUME

Hyperhydration and dehydration arise from imbalance between intake and loss of fluids.

Causes of hyperhydration:

- 1) Excessive water intake
 - Excessive drinking (beer)
 - Infusion
- 2) Reduced fluid excretion
 - Kidney function disorder (oliguria, anuria)

Causes of dehydration:

- 1) Insufficient fluid intake
 - No access to water source (desert, immobilization – motor disorder, incarceration in a restricted area without water, disorders of consciousness)
 - Difficulties with water intake (injury of the oral cavity, oesophagus)
 - Lack of thirst sensation
- 2) Increased fluid loss
 - Kidney disorder (polyuria)
 - Diarrhoea, vomiting
 - Sweating, burns
 - Bleeding
 - Transfer of fluids into other compartments (oedema, ileus, ascites, inner bleeding)

Water penetrates cell membrane due to osmotic pressure. It moves from the compartment with lower osmolality into the compartment with higher osmolality. To change intracellular fluid volume (ICT), a difference of osmolality between ICT and extracellular fluid (ECT) is necessary. Thus, change of ICT volume develops when ECT osmolality changes, but not in the case of isotonic hyperhydration or dehydration. As a consequence of these rules, reduction

of ICT volume develops during hypertonic hyperhydration, while ICT expands during hypotonic dehydration.

| Hyperhydration | | | | |
|----------------|---|-----------------------|-------------------|-------------------|
| Received fluid | Examples | ECT osmolality change | ECT volume change | ICT volume change |
| Isotonic | Drinking isotonic fluid (some types of mineral water, sports drinks) Infusion of isotonic solutions (physiological saline) | - | ↑ | - |
| Hypertonic | Drinking hypertonic fluid (e.g. very sweet drinks) Infusion of hypertonic solution (e.g. mannitol) | ↑ | ↑ | ↓ |
| Hypotonic | Pure water drinking, tea | ↓ | ↑ | ↑ |
| Dehydration | | | | |
| Lost fluid | Examples | ECT osmolality change | ECT volume change | ICT volume change |
| Isotonic | Vomiting, sweating, diarrhoea | - | ↓ | - |
| Hypertonic | Osmotic diuresis (diabetic urine, diuretics) | ↓ | ↓ | ↑ |
| Hypotonic | Loss of hypotonic urine (diabetes insipidus) | ↑ | ↓ | ↓ |

Tab. 1: Types of hyperhydration and dehydration and changes of osmolality of extracellular fluid (ECT) and changes of volume of extracellular fluid and intracellular fluid (ICT).

3. OEDEMA

Oedema (= swelling) = accumulation of fluid in the tissue, enlargement of volume of the tissue due to water accumulation

The oedema can be interstitial or intracellular.

The oedema increases pressure in the tissue. It is marked namely in compartments surrounded by a rigid capsule and thus with a limited space (e.g. skull cavity, muscles enclosed between fibrous septa). Increase of the pressure in the tissue leads to reduction of the perfusion pressure and consequently reduction of blood perfusion of the tissue. Interstitial oedema also increases distances between the cells and distances from the cells to the capillaries that provide nutrition (extension of diffusion trajectories, reduction of oxygen pressure). This

influences negatively communication between the cells and metabolite exchange of nutrients and metabolites.

The fluid can be accumulated also in body cavities:

- ascites = fluid in the peritoneal cavity
- hydrothorax = fluid in the pleural cavity
- hydropericardium = fluid in the pericardial cavity

Generalized oedema = anasarca

3.1. Mechanisms of oedema development

- Increase of hydrostatic pressure of the blood
 - Blood congestion in heart insufficiency (failure)
 - Block of blood flow in the veins (thrombosis, compression of the vein by a tumour, in the portal region also liver cirrhosis)
 - Vein insufficiency (often in lower extremities; dilatation of the veins and insufficiency of the vein valves → fusion of columns of fluid formerly separated by the valves – higher fluid column means higher hydrostatic pressure according to the formula $p = h \times \rho \times g$)
 - Increase of ECT volume including expansion of intravascular fluid volume
- Decrease of oncotic pressure of the plasma - hypoproteinaemia (liver insufficiency, proteinuria, protein malnutrition)
- Increased vessel wall permeability
 - Inflammation (including allergic inflammation)
 - Affection of vessel wall by hypoxia (e.g. in advanced stages of circulatory shock; nevertheless, in this case it is a generalized event and the most important problem is hypovolemia due to transudation of the fluid from the vessels to the tissues)
- Reduction of lymphatic drainage of the extracellular fluid
 - Obstruction of the lymphatic vessels after inflammation (repeated streptococcal infection)
 - Infiltration of the lymphatic nodes by a tumour
 - Obstruction of the lymphatic vessels by parasites (filariasis)

3.2. Classification of the oedemas according to the nature of primary disease

- **Cardiac**
 - Accumulation of fluid in the areas in front of the relatively weaker part of the heart (i.e. in the left heart insufficiency in the pulmonary circulation, in the right heart insufficiency in the systemic circulation)
 - Cardiac oedema can be promoted by the secondary hyperaldosteronism (reduction of kidney perfusion as a consequence of the left heart failure activates the renin - angiotensin – aldosterone system), which leads to retention of water in the organism.
- **Renal**
 - Retention of water in oliguric form of the renal failure
 - Hypoproteinaemia as a consequence of proteinuria
 - Secondary hyperaldosteronism – in renal artery stenosis, or as a result of kidney perfusion reduction in hypovolemia due to transfer of fluid into the interstitium (the oedema contributes this way to retention of water in the organism what subsequently supports oedema development)
- **Hepatic**

- Hypoproteinaemia
- Development of the ascites as a consequence of portal hypertension
- Secondary hyperaldosteronism as a consequence of 1) reduction of kidney perfusion in hypovolemia due to transfer of water into the interstitium and the peritoneal cavity (i.e. due to activation of the renin – angiotensin – aldosterone system) and 2) slow inactivation of aldosterone by the diseased liver
- **Lymphatic**
 - Reduction of drainage of the tissue fluid by the lymphatic system
- **Venous**
 - Increase of hydrostatic pressure in the vessels in vein obstruction or insufficiency
- **Inflammatory**
 - Increased vessel permeability during inflammation

4. ENDOCRINE CONTROL OF WATER METABOLISM AND ITS DISORDERS

4.1. Vasopressin (antidiuretic hormone, ADH)

4.1.1. Vasopressin effects

- Mediated by V1A, V1B and V2 receptors

V1A - vasoconstriction

V1B – in the adenohypophysis – increases ACTH secretion

V2 – antidiuretic effect, transfer of aquaporins (water channels) from the cytoplasm into the luminal membrane of the cells of the renal collecting ducts; thereby the cells become water permeable

4.1.2. Regulation of vasopressin secretion

- Osmoreceptors in the anterior hypothalamus
- Stimuli increasing ADH secretion:
 - Increased ECT osmolality
 - Decreased blood pressure (hypovolemia)
 - Stress, physical activity, pain

4.1.3. Disorders of vasopressin secretion and effects

Diabetes insipidus

a) Central diabetes insipidus

- Lack of vasopressin
- Causes: hypothalamus damage, hypothalamic-hypophyseal tract damage, neurohypophysis damage (often only transient disorder), mutation of the prepropressophysin-encoding gene
- Manifestation: polyuria (up to 20 l/day), polydipsia,
- If water is not supplied in adequate amount dehydration develops very quickly.

b) Renal diabetes insipidus

- Inability of the kidneys to react to vasopressin secretion of which is not deteriorated
- Causes:
 - Mutation of the V2 receptor encoding-gene
 - Mutation of the aquaporin-2 encoding-gene

- Similar manifestation develops in acquired disorders of tubular function in which water resorption is reduced.
- Manifestation is similar like in the central diabetes insipidus with polyuria. Vasoconstriction effects of vasopressin remain preserved.

Syndrome of inappropriate secretion of ADH

(SIADH, Schwartz-Bartter's syndrome)

Causes: ectopic secretion by a tumour (small cell lung carcinoma), brain affection, pulmonary diseases

Pathogenesis:

- Water retention
- \uparrow ECT \rightarrow \downarrow aldosterone \rightarrow \uparrow Na^+ loss \rightarrow hyponatremia

Consequences: \rightarrow weakness, confusedness, cramps, coma

Partial compensation by increased atrial natriuretic peptide (ANP) secretion. Therefore, there are usually no severe oedemas.

4.2. Aldosterone

The main human mineralocorticoid, produced by the adrenal cortex (zona glomerulosa)

4.2.1. Aldosterone function

- Increases reabsorption of Na^+ in the kidneys, from sweat, saliva and GIT secrets
- Increases excretion of K^+ + a H^+ (alkalosis) – exchanged with Na^+

Normal levels of aldosterone-controlled parameters:

- Natremia: 130 – 148 mmol/l
- Kaliemia: 3.8 – 5.4 mmol/l

4.2.2. Regulation of aldosterone secretion

- 1) Secretion of aldosterone is stimulated by increase of K^+ (even small changes), decrease of Na^+ (marked changes) - negative feedback
- 2) Renin – angiotensin – aldosterone system (complex negative feedback)

Stimulation of renin secretion:

- Increased intraarteriolar pressure in the juxtaglomerular cell area
- Decreased delivery of Na^+ and Cl^- into the distal tubule
- Prostaglandins
- The sympathetic system and circulating catecholamines

Inhibition of renin secretion:

- Angiotensin II (feedback)
- Increased intraarteriolar pressure in the juxtaglomerular cell area

- 3) ACTH – transient effect (1-2 days) on aldosterone secretion (partially caused by renin decrease due to hypervolemia); permanent effect on deoxycorticosterone
In the case of hypophysis damage, basal secretion of aldosterone is normal, but its increase during stress is missing
- 4) ANP – inhibition of renin secretion, \downarrow of sensitivity of zona glomerulosa to angiotensin II

4.2.3. Disorders of aldosterone secretion and effects

Addison disease

Causes: Bilateral damage of adrenal glands (about 80-90% of adrenal cortex tissue must be damaged)

- Autoimmune processes
- Infection (TBC)
- Haemorrhage (meningococcus-induced sepsis)
- Ischemia and necrosis (shock)
- Amyloidosis, sarcoidosis, hemochromatosis
- Inborn hypoplasia
- Insensitivity to ACTH

Consequences:

↓ mineralocorticoids, ↓ glucocorticoids, ↓ adrenal androgens, ↑ ACTH
 → Loss of Na⁺ and water, retention of K⁺, reduced resistance to stressors

Manifestations:

- Dehydration (↓ ECT), hyperkalemia
- Decreased resistance to stressors
- Hypoglycemia after starvation
- Skin and mucous membrane hyperpigmentation (deliberation of ACTH secretion is connected with increased production of MSH – melanocyte stimulating hormone which has a common precursor with ACTH)

Chronic Addison disease

- Loss of Na⁺ → loss of water → hypovolemia
 - 1) hypotension, orthostatic hypotension
 - 2) decreased glomerular filtration and increased ADH → reduced loss of water → hyponatremia
- Retention of K⁺ → risk of arrhythmia
- Due to the lack of glucocorticoids: fatigue, anorexia, body weight loss

Addisonian crisis is a life-threatening escalation of Addison disease manifestations.

Its consequences that can lead to the death of the patient are:

- Hypovolemia → May even lead to hypovolemic shock
- Hyperkalemia → May lead to malignant arrhythmias (ventricular fibrillation!)
- Renal failure due to kidney hypoperfusion
- Laboratory examination finds: hyponatremia, hyperkalemia, hypoglycemia, elevated creatinine, elevated urea

Primary hyperaldosteronism (Conn's syndrome)

- Hyperproduction of aldosterone independent on regulatory mechanisms.

Cause: adenoma or bilateral hyperplasia of the adrenal cortex

Consequences: increased retention of Na⁺ and water, increased excretion of K⁺ and H⁺, decrease of renin

Manifestations:

- Hypertension
- Oedemas – usually not severe because of compensation by increased secretion of ANP
- Usually no hyponatremia because retention of Na⁺ and water is roughly proportional and ANP increases excretion Na⁺ (acts against aldosterone)
- Hypokaliemia – extrasystols, U- wave, low T, muscle weakness, even paralysis of respiratory muscles, paralytic ileus, rhabdomyolysis, damage of renal tubules
- Alkalosis –increased neuromuscular irritability

Secondary hyperaldosteronism

- It is a secondary consequence of disorders that are not in the adrenal cortex.

Mechanisms of secondary hyperaldosteronism development:

- 1) Activation of the renin - angiotensin – aldosterone system
 - a) Reduction of kidney perfusion
 - Hypovolemia due to loss of fluid (dehydration, bleeding...) - physiological compensatory mechanism
 - Hypovolemia due to water transfer into other compartments (oedema, ascites, ileus...)
 - Stenosis of the renal artery
 - Left heart insufficiency (decreased cardiac output that restricts perfusion of the organs including the kidney)
 - b) - Bartter's syndrome = hyperplasia of the juxtaglomerular apparatus
 - Ectopic production of renin by a tumour that increases its level.
 - c) - Hyponatremia
- 2) Disorder of aldosterone elimination by the liver (in liver diseases)
 - Participation in hepatic oedema development

Increased level of renin and angiotensin II differentiates the secondary hyperaldosteronism from the primary hyperaldosteronism (hypokalemia is less marked, less frequent arterial hypertension).

4.3. Natriuretic peptides

Natriuretic peptides increase excretion of sodium and thus, also excretion of water by the kidneys.

- Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), natriuretic peptide type C (CNP)

ANP is the most important. Dilatation of the heart atria due to increased intravascular fluid volume is a stimulus for ANP secretion. Its role is to protect against hypervolemia by these mechanisms:

- \uparrow excretion of Na^+ by the kidney
 - Dilatation of vas afferens and relaxation of mesangial cells $\rightarrow \uparrow$ glomerular filtration
 - Inhibition of reabsorption of Na^+
- Increased capillary permeability \rightarrow extravasation of fluid into the tissues $\rightarrow \downarrow$ blood pressure
- Inhibition of renin secretion
-

ANP plays a role in **pathogenesis of some disorders**. Its level is secondarily elevated e.g. in the Conn's syndrome (primary hyperaldosteronism), when aldosterone overproduction leads to Na^+ and water retention. Subsequent expansion of intravascular fluid volume stimulates production of ANP which, on the other hand, increases excretion of sodium and water and thus, it compensates for Na^+ and in part for water retention induced by aldosterone. Similarly, in the syndrome if inappropriate ADH secretion, expansion of water in the body induces increased secretion of ANP that compensates partially for water retention but enhances hyponatremia.

5. SODIUM METABOLISM

Sodium is the main extracellular cation.

Normal natremia: 130 – 148 mmol/l

Intake by food (meat)

Excretion by urine, stool, sweat

50% bounded in the bone tissue, this part is not easily exchangeable with other compartments

50% in ECT, quickly exchangeable

The main function of sodium: Maintenance of ECT volume, important contribution to ECT osmolality, participates in action potential – fast sodium current is a component of the action potential (phase of depolarization and transpolarization)

Hyponatremia: Higher deficit of Na^+ than deficit of water in the ECT.

Hypernatremia: Higher deficit of water than deficit of Na^+ in the ECT.

5.1. Sodium depletion

Arises in renal or extrarenal loss of sodium:

- Osmotic diuresis (e.g. glycosuria)
- Lack of aldosterone
- Loss of fluid from the GIT (diarrhoea, vomiting)
- Intensive sweating (when loss of water is compensated by drinking pure water)
- Drainage of ascitic fluid

Consequence: ↓ ECT volume and blood volume, ↑ haematocrit, ↑ concentration of plasmatic proteins, circulatory failure

Depletion of sodium in the organism is not the same as hyponatremia. Hyponatremia means decreased concentration of Na^+ in ECT and can arise not only from loss of sodium (in relation to its depletion), but also by dilution due to water retention (e.g. SIADH) or due to excessive water intake. On the other hand, sodium depletion does not need to be accompanied by hyponatremia, if there is also proportional loss of water.

5.2. Sodium retention

Causes:

- High intake of NaCl in the food or by infusion (newborns, renal hypofunction!)
- Hyperaldosteronism
- Renal insufficiency with reduced glomerular filtration

Consequence: retention of adequate amount of water (→ oedema), plasmatic concentration of Na^+ does not need to be changed!

6. POTASSIUM METABOLISM

Potassium is the main intracellular cation. Nevertheless, maintenance of extracellular potassium level in a narrow range is essential for the organism.

Normal kaliemia: 3.8 – 5.4 mmol/l

Intake by food (vegetable, fruits)

Excretion by urine and stool

Only 2% of potassium is stored in the ECT, 98% of the total amount is in the cells.

The organism controls potassium level in the ECT by 2 mechanisms:

- Change of potassium distribution between the ECT and ICT (change of Na^+/K^+ pump activity)
- Change of amount of potassium excreted by the kidneys

6.1. Hypokalemia and potassium depletion

In hypokalemia, potassium pool in the organism does not need to be reduced always (some amount of potassium moves from the ECT into the cells - the effect of epinephrine, aldosterone, insulin, alkaline pH – exchange of K^+ with H^+)!

On the other hand, general potassium depletion could be accompanied by hyperkalemia (e.g. in diabetic ketoacidosis – transfer of potassium from the cells maintains high potassium level in the ECT despite its total amount in the organism is reduced, see also below: distribution hyperkalemia)!

Causes:

- Decreased potassium intake
- Redistribution of potassium between the ECT and ICT (insulin, epinephrine, aldosterone, accelerated catabolism, long-lasting acidemia – transfer of K^+ from the cells into the ECT and its loss)
- Increased extrarenal loss of potassium (sweating, diarrhoea)
- Increased renal loss of potassium

Manifestations:

- Neuromuscular: muscle weakness, constipation or even paralytic ileus, rhabdomyolysis with myoglobinuria, risk of paralysis of respiratory muscles (kaliemia less than 2 mmol/l)!
- Cardiac: disorders of heart impulse transmission (RT interval prolongation, ST segment depression, T wave flattening, enhancement of U wave)
- Peripheral circulation: tendency to vasodilation and decrease of systemic blood pressure
- Renal: ↓ sensitivity to ADH, polyuria
- Acid-base balance: transfer of H^+ into the cells (extracellular alkalosis, intracellular acidosis)
- Endocrine: ↓ aldosterone production, ↑ prostaglandin E2 production, ↑ renin synthesis → angiotensin II and aldosterone production, ↓ insulin secretion, ↓ sensitivity of peripheral tissues to insulin

6.2. Hyperkalemia and potassium retention

Clinically important hyperkalemia if K^+ in the ECT is over 6 mmol/l, dangerous over 7 mmol/l.

Causes:

- Increased peroral or parenteral potassium intake leads to retention only at simultaneous renal insufficiency.
- Decreased elimination of potassium (renal disorder, hypocorticalism, potassium sparing diuretics)

So-called distribution hyperkalemia: transfer of potassium from the cells into the ECT (acidosis, catabolic states, insulin deficit, beta-blockers, haemolysis)

So-called pseudohyperkalemia: incorrect blood sample taking – long strangulation of the extremity and ischemia (transfer of potassium from the muscles into the blood)

Manifestation:

- Changes of impulse transmission in the heart, even cardiac arrest
- ECG manifestations: high spiked T wave, prolonged PQ interval and QRS complex
- Paresthesia, muscle weakness, muscle twitches, loss of deep muscle reflexes

7. CALCIUM METABOLISM

Calcium: In the body we have 1.1 kg of calcium

(99% in the bones, teeth, calcemia 2.25 – 2.75 mmol/l)

The importance of calcium: the bones, teeth, action potential, neuromuscular irritability, muscle contraction, blood coagulation, second messenger...

| | | | | | |
|-----------------------------|-----|----------------|-------------|---|-------------|
| Total plasmatic Ca (mmol/l) | 2.5 | Diffusible | 1.35 (54 %) | Ca ²⁺ | 1.20 (48 %) |
| | | | | HCO ₃ ⁻ , citrate,... | 0.15 (6 %) |
| | | Non-diffusible | 1.15 (46 %) | albumin | 0.92 (37 %) |
| | | | | globulin | 0.23 (9 %) |

Tab. 2: Forms of calcium in the plasma.

Regulation of calcemia: parathormone (+ parathormone related peptide = PTHrP – in utero), calcitonin, calcitriol

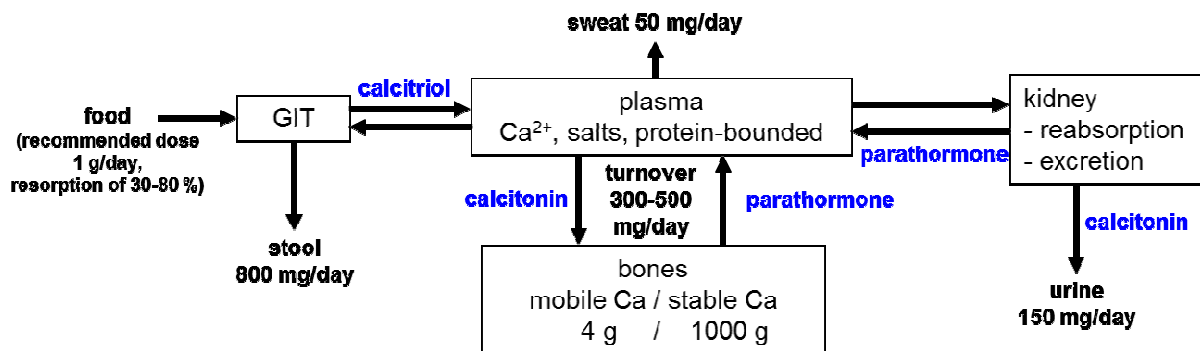


Fig. 3: Scheme of calcium metabolism with depicted effects of individual hormones.

7.1. Hypocalcemia

Manifestation:

- Opaque eye lens (phacosotasmus), trophic disorders of the skin and nails
- Paresthesia
- Tetany: Increased neuromuscular irritability, persisting and spontaneous muscle contractions, namely limb muscles (carpopedal spasms), signs of Chvostek, Trousseau, Erb, laryngospasm!!!, respiratory muscle camps!!!, even generalized cramps

Disorders of blood coagulation due to hypocalcemia do not appear *in vivo*. The patient would die earlier because of severe tetany.

Causes and mechanisms of hypocalcemia and tetany

- Hypocalcemic tetany – due to hypocalcemia – hypoparathyroidism, insensitivity of parathormone receptors
- Lack of calcium with (almost) normal calcemia (calcemia is maintained by parathormone-mediated mobilization of calcium from the bones)
 - rickets, osteomalacia
 - lack of calcium in food
 - malabsorption syndrome
- Latent tetany – manifestation of tetany is provoked by some overload (other simultaneous disease, gravidity, lactation).
- Phosphate and citrate tetany – after intravenous administration of sodium phosphate or citrate – exchange of Na^+ with Ca^{2+} (this mechanism is used to block blood clotting *in vitro*)
- \uparrow pH (e.g. hyperventilation) \rightarrow shift of Ca to unionized fraction and proteins (increased binding capacity of plasmatic proteins for Ca^{2+} ions instead of H^+ ions) \rightarrow tetany at normal total calcemia
- Hyperphosphatemia - Ca^{2+} and PO_4^{3-} are poorly soluble and the plasma is almost saturated solution \rightarrow product of concentrations of both ions ($[\text{Ca}^{2+}] \times [\text{PO}_4^{3-}]$) is constant and increase of concentration of one of them leads to drop of concentration of the latter one. Therefore, \uparrow PO_4^{3-} (e.g. renal disorder) \rightarrow Ca^{2+} storage in the bones \rightarrow \downarrow calcemia \rightarrow \uparrow PTH \rightarrow conversely, Ca mobilization from the bones \rightarrow renal osteoporosis

7.2. Hypercalcemia:

Manifestation:

- Increased muscle contraction power, decrease of neuromuscular irritability
- Hypertension, QT-segment shortening, increased myocardial contractility, arrhythmia (ventricular extrasystoles), cardiac arrest in the systolic phase
- Memory disorders, vomiting, anorexia
- Renal damage – first reversible functional disorder of the tubules \rightarrow reduction of concentration capacity of the kidneys, later glomerular filtration disorder and renal failure
- Nephrolithiasis, ectopic calcifications

Ectopic calcifications develop in tissues with alkaline pH, in which calcium is less soluble. In general, these tissues or organs are those, in which acid substances are secreted and therefore in the tissue pH increases. They are: the kidney that excretes acid metabolites, the lungs in which carbon dioxide is exhaled and the stomach which produces hydrochloric acid.

Causes:

- Hyperparathyroidism
- Paraneoplastic syndrome in some malignant tumours that produce parathormone related peptide (PTHrP)
- Metastases into the bones
- Intoxication with D vitamin

7.3. Hormones controlling calcium metabolism

7.3.1. Parathormone (PTH)

A peptide produced by 4 parathyroid glands localized on the dorsal surface of the thyroid gland.

Regulation of parathormone secretion:

- Feedback control of parathormone secretion by calcemia:
 - Decrease of Ca^{2+} level triggers fast (seconds) release of PTH from secretion granules
 - Longer (hours) decrease of Ca^{2+} level enhances expression of PrePro-PTH (precursor of parathormone) encoding gene what leads to further increase of PTH.
 - Long-lasting (days, weeks) drop of Ca^{2+} level induces hyperplasia of the parathyroid gland. It increases their functional capacity enabling more intensive parathormone synthesis and more marked increase of its level in the blood.
- Stimulation by phosphate
- Inhibition by calcitriol which reduces mRNA for PrePro-PTH.
- β -adrenergic stimulation
- For normal PTH secretion magnesium is necessary!

Effects:

- Increase of calcium and decrease of phosphate in the plasma
- Release of calcium from the bones
 - Direct and fast release mobile calcium
 - After longer activity, calcium is released by resorption of bone tissue.
- Stimulation of the both osteoclasts and osteoblasts (more osteoclasts than osteoblasts)
- Increase of reabsorption of calcium in the distal renal tubules. But in hyperparathyroidism loss of calcium is often increased due to its increased filtration in the glomeruli (due to its high plasmatic concentration).
- Increased excretion of phosphates by the kidneys (decreased resorption in the proximal tubules)
- Increase of calcitriol production that enhances calcium resorption in the gut.

Hypoparathyroidism

Primary hypoparathyroidism

Causes:

- Removal or damage of the parathyroid gland during thyroid gland surgery (the symptoms occur 2-3 days after the surgery)
- Autoimmune process
- Wilson's disease, hemochromatosis
- Agenesis of the parathyroid glands
- Mutation of the PrePro-PTH-encoding gene
- Activation mutation of the Ca^{2+} receptor gene leading to increase of sensitivity of the parathyroid glands to feedback effect of Ca^{2+} = familiar hypercalciuric hypocalcemia

Manifestation:

- Hypocalcemia with all its consequences including tetany, hyperphosphatemia

Secondary hypoparathyroidism

The problem is not localized directly in the parathyroid glands. It is a response to other disorders

Causes:

- A consequence of lack of Mg^{2+}
- Hypercalcemia inhibiting parathormone release:
 - D hypervitaminosis – direct inhibition of PTH secretion and stimulation of calcium mobilization from the bones that also inhibits PTH secretion.
 - PTHrP (humoral hypercalcemia in malignity) – manifestation of hyperparathyroidism, but PTH is low.
 - Bone metastases releasing calcium from destroyed bones (local osteolytic hypercalcemia)

Pseudohypoparathyroidism

- Disorder of sensitivity of the tissues to PTH – mutation of genes encoding the receptors (Albright's disease) or G-proteins.

Hyperparathyroidism

Primary hyperparathyroidism

Manifestations:

- Increased Ca^{2+} , increased PTH in the plasma
- So called hyperparathyroid osteodystrophy: Increased turnover of calcium in the bones with generally negative balance, reduction of bone mass (osteoporosis), risk of bone fractures

Causes:

- Hyperplasia, adenoma or carcinoma of the parathyroid glands
- MEN 1 (multiple endocrine neoplasia, Wermer's syndrome) = prolactinoma, hyperplasia of the parathyroid glands, tumours of the pancreas producing gastrin
- MEN 2a – hyperparathyroidism, thyroid gland carcinoma, pheochromocytoma
- Familial hyperparathyroidism – inactivation mutation of the Ca^{2+} receptor leading to a disorder of feedback inhibition of PTH secretion (heterozygotes: familial benign hypocalciuric hypercalcemia, homozygotes: neonatal severe primary hyperparathyroidism)

Manifestations:

- Hypercalcemia, bone changes – fractures, bone reconstruction
- Chronic course (sometimes only increased fatigue and muscle weakness)
- Osteodystrophia fibrosa, morbus Recklinghausen
 - Adenoma of the parathyroid gland overproducing PTH
 - Soft bones, fractures, brown tumours, pseudocysts

Secondary hyperparathyroidism

The mechanism of its origin is: hypocalcemia that stimulates secretion of PTH and even leads to hyperplasia of the parathyroid glands.

- Decreased Ca and increased PTH levels in the plasma

Causes:

- Hypovitaminosis D
- Chronic renal failure (hyperphosphatemia → decreased Ca^{2+} , decreased calcitriol synthesis)
- Malabsorption

7.3.2. Calcitonin

See pathophysiology of the thyroid gland.

No known syndromes arising from calcitonin lack or excess. In the case of its abnormal secretion (high or low) normal calcemia is maintained by the effects of parathormone secretion of which adapts to the particular conditions.

7.3.3. 1,25-dihydroxycholecalciferol (calcitriol)

A vitamin (its intake with food is necessary) and also a hormone (endogenous production, secretion into the blood)

Lipid soluble vitamin, steroid

Endogenous production represents about 80% of the need, intake with food represents about 20 % of the need (sea fish, vegetable).

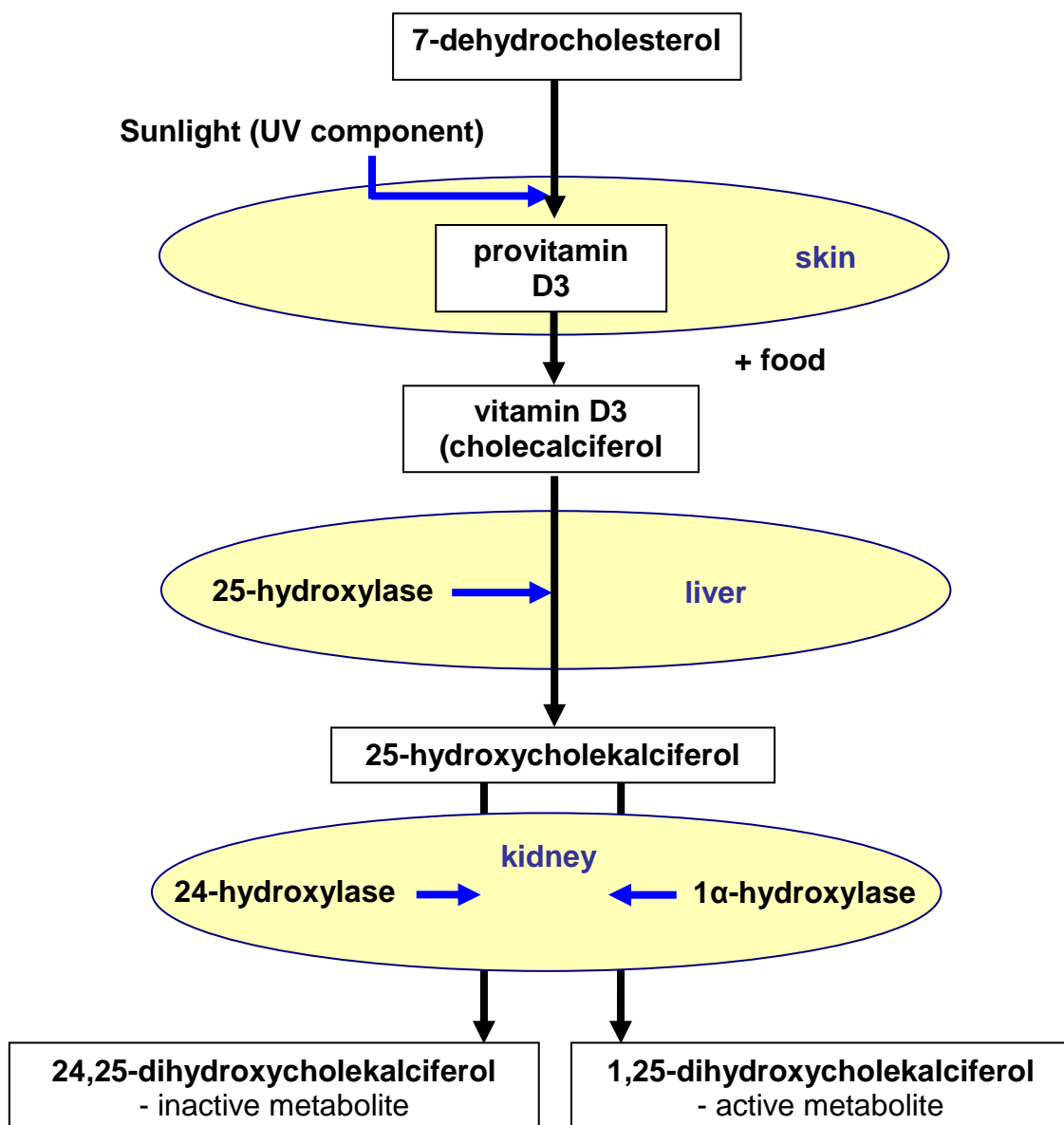


Fig. 4: Scheme of vitamin D metabolism.

Production regulation:

- Parathormone increases calcitriol synthesis in the kidneys.
- Prolactin – stimulation of 1 α -hydroxylase

- Stimulation by growth hormone
- Phosphates – inhibition of 1α -hydroxylase
- Calcitriol stimulates 24-hydroxylase and thereby it supports production of less active 24,25-dihydroxycholecalciferol

Effects of calcitriol:

- Control of expression of genes encoding calbindin-D protein family in the gut, brain and kidneys
- Calbindin-D facilitates transfer of Ca^{2+} across the gut epithelium.
- Facilitation of reabsorption of Ca^{2+} in the kidneys.
- Mobilization of Ca^{2+} and PO_4^{3-} from the bones by increase of osteoclast number, but also stimulation of the osteoblasts. At higher calcitriol concentrations, release of Ca is dominant.
- Receptors for calcitriol are in the gut, kidneys, bones, skin, lymphocytes, monocytes, skeletal muscles, myocardium, mammary gland, adenohypophysis
- Differentiation of cells of the immune system and keratinocytes in the skin
- Probably regulation of growth and synthesis of growth factors

Hypervitaminosis D

→ Excessive resorption of calcium in the gut

Cause: overdose of vitamin D

Manifestations:

It leads to hypercalcemia with all its symptoms and complications.

- Anorexia, nausea, vomiting
- Polyuria, polydipsia
- Weakness, nervousness, pruritus
- Affection of the kidneys
- Metastatic calcifications

Hypovitaminosis D

→ Insufficient calcium resorption in the gut → disorder of bone matrix calcification

In the childhood = **rickets (rachitis)**

- poor bones, bone deformities
- tooth defects
- hypocalcemia

In the adulthood = **osteomalacia**

Causes

- Lack of provitamins in the food
- Lack of Sunshine
- Mutation of 1α -hydroxylase-encoding gene = **vitamin D-resistant rickets type I.**
 - Does not react to vitamin D, however, reacts to 1,25-dihydroxycholecalciferol.
- Mutation of the receptor-encoding gene = **vitamin D-resistant rachitis type II.**
 - Does not react neither to vitamin D nor to 1,25-dihydroxycholecalciferol.

7.3.4. Other hormones influencing calcium metabolism

- **Growth hormone** – increases calcium resorption in the gut more than it increases calcium excretion with urine
- **Estrogens** – prevent osteoporosis by a direct effect on the osteoblasts
- **T-hormones** – hypercalcemia, calciuria, osteoporosis

- **Insulin** – increases bone matrix building