PATHOPHYSIOLOGY OF THE THYROID GLAND

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Content

1. MORPHOLOGY OF THE THYROID GLAND

The thyroid gland (*glandula thyroidea*) is localised ventrally in the neck. It consists from two lobes (left and right) connected by an isthmus. In some people, the third lobe, *lobus pyramidalis*, protrudes from the isthmus between both basic lobes (Fig. 1).

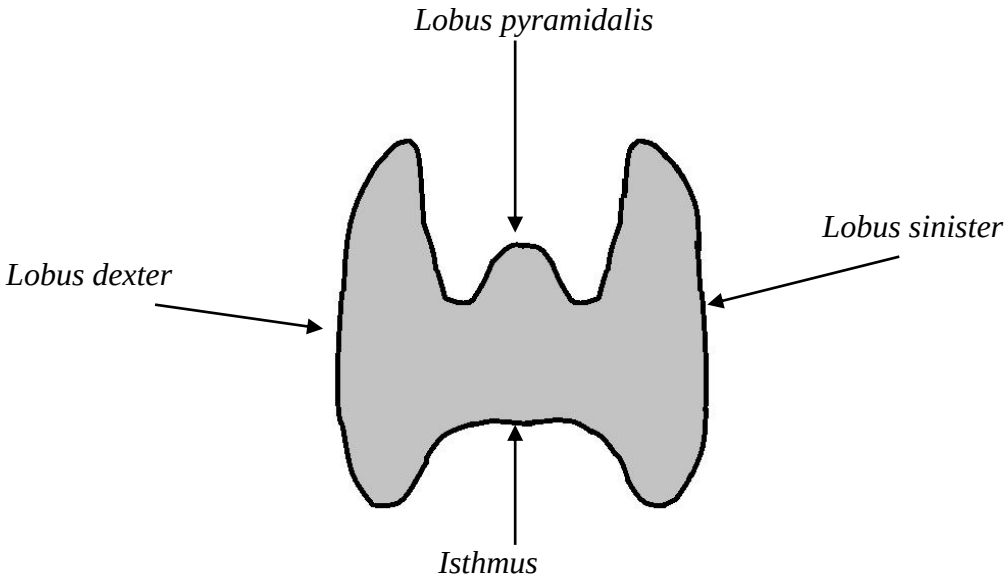

Fig. 1: Schematic depiction of thyroid gland anatomy.

Parenchyma of the thyroid gland consists of follicles, wall of which is composed of one layer of the follicular cells (Fig. 2). The follicles are filled with a colloid. Between the follicles, the parafollicular cells are localised.

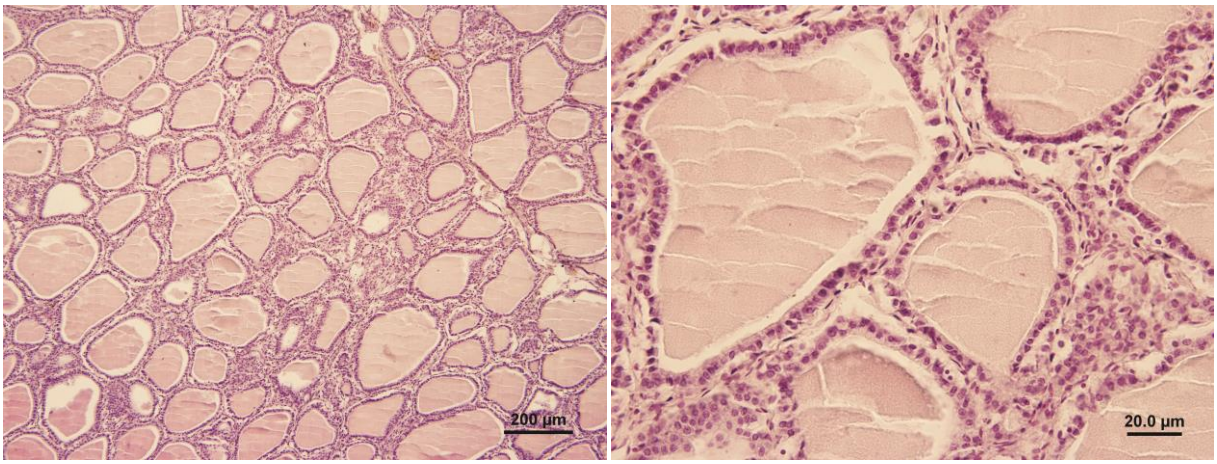

Fig. 2: Histological structure of the thyroid gland.

2. THYROID GLAND FUNCTION

The thyroid gland is an endocrine structure and its function is hormone production. Follicular and parafollicular cells produce different hormones and also their regulation is different. From functional point of view, thyroid gland consists of two independent endocrine structures.

Follicular cells:
- synthesis and secretion of T-hormones (see Thyroid gland and T-hormones)
- processes and functions related to T-hormone production
    - iodide uptake, conversion to iodine, iodine transport to colloid
    - thyroglobulin synthesis and its transport to colloid
    - colloid endocytosis and release of T-hormones to the blood

Parafollicular cells:
- **c**alcitonin production (see Thyroid gland and calcitonin)

3. THYROID GLAND AND T-HORMONES

T-hormones

(Fig. 3)
- tetraiodothyronine (T4 = thyroxin)
- triiodothyronine (T3)
- reverse triiodothyronine (rT3) – ineffective, but can bind to and block the T3-receptors

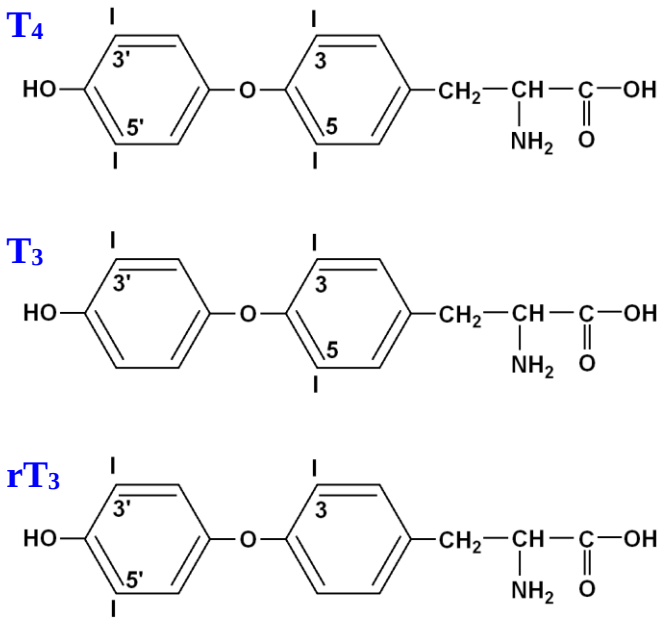

Fig. 3: T-hormone structure

Protein binding of T-hormones

In the blood, 99% of T-hormone molecules are bound to proteins:
- thyroxine binding globulin (TBG)
- albumin

- thyroxine binding prealbumin (TBPA)
- transthyretin

There is a balance between the bound and free fraction (Fig. 4). The free fraction is physiologically active including its effect in the feedback regulatory mechanisms. Protein-bound fraction represents a reserve pool from which the free fraction can be quickly replenished.

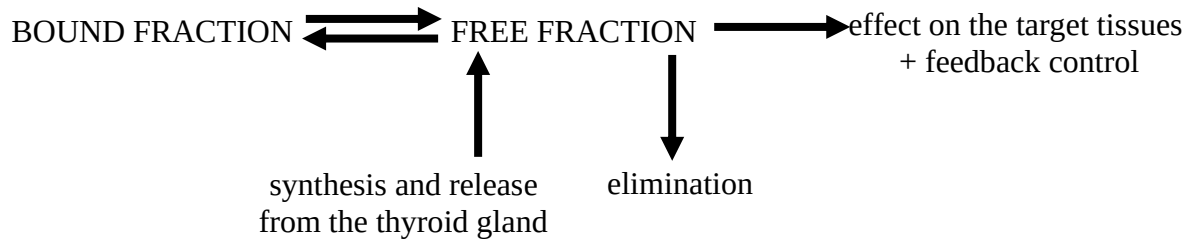

Fig. 4: Balance between the free and bound fraction of the T-hormones.

Changes of binding protein concentrations lead to changes of binding capacity for the T-hormones. Total amount of T-hormones in the blood can be then also changed. However, a new balance it is established and the concentration of the free hormones level of which determines the effect on the tissues as well as the feedback control is normal. Thus, the patient is usually clinically euthyroid. Hyper- or hypofunction of the T-hormones is manifested only transiently during fast changes of the binding proteins.

Thyroid gland function regulation

Thyroid gland function (that related to T-hormones) is controlled by the **hypothalamus–pituitary–thyroid gland axis** (Fig. 5).

Hypothalamus:
The hypothalamus produces two hormones regulating production of the thyroid stimulating hormone (TSH) in the adenohypophysis
- thyroliberin (TRH, thyrotropin-releasing hormone) – stimulation of TSH release from the adenohypophysis
- somatostatin – inhibition of TSH release from the adenohypophysis

The effect of the TSH is more apparent. Therefore, in the case of interruption of the connection between the hypothalamus and the hypophysis (leading to restriction of transport of hypothalamic statins and liberins to the adenohypophysis), TSH production falls due to lacking stimulating effect of the TRH.

Adenohypophysis:
-produces thyroid stimulating hormone (TSH)

Effects of the TSH on the thyroid gland:
- increase of iodide uptake
- increases T3 and T4 synthesis
- increases secretion of the thyroglobulin to the colloid
- increases colloid endocytosis
- increases incorporation of the iodine
- increases blood perfusion of the thyroid gland
- after long-lasting action, it causes thyroid gland hypertrophy

Free T3 and T4 play a role in the feedback control. They inhibit TRH production and block TRH-induced increase of the TSH level.

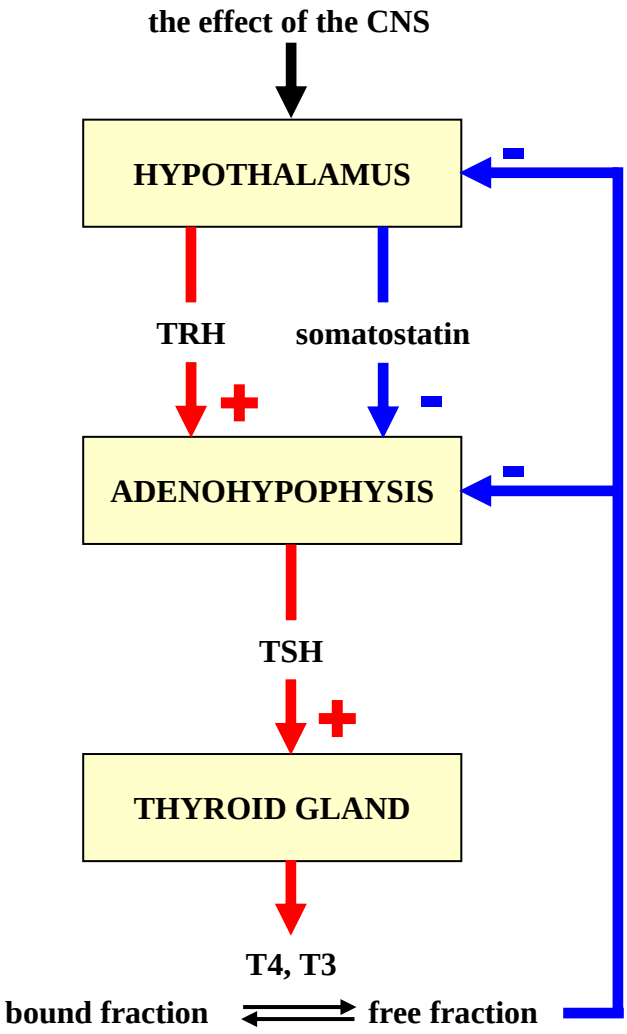

Fig. 5: Scheme of thyroid gland function control

Factors influencing T-hormone regulation:
Stress, heat → ↓ TRH → ↓ TSH
Cold → ↑ TRH → ↑ TSH (plays a role in the newborns, less in the adults)

Effect of the T-hormones

T-hormones act through **nuclear receptor** hTR-α1, hTR-α2, hTR-β1, hTR-β2.
hTR-α2 does not bind T3 and its function is not clear. T3 activates the receptors stronger than T4 and is more efficient. The mechanism of the effect is through control of gene expression and synthesis of appropriate proteins in the cell.

Effects of the T-hormones:
- Na^+/K^+ -ATPase activity increase
- Metabolic rate increase (oxygen consumption and heat production increase)
- Vasodilation in the skin leads to reduction of peripheral resistance.

- Increased expression of α-MHC (myosin heavy chain) and decreased expression of β-MHC in the myocardium what lead leads to increased speed of heart contractions.
- Increased intensity of lipolysis.
- Increased expression of LDL receptors
- Increased protein catabolism
- Faster carbohydrate resorption
- Increased DPG (2,3 diphosphoglycerate) level in the erythrocytes facilitating O_2 dissociation from the haemoglobin
- Increased expression of the β-adrenergic receptors → catecholamine effect enhancement (increased cardiac output, increased heart rate, increased activity of the activating reticular formation system). Manifestations of hyperthyroidism mediated by these mechanisms can be mitigated by β-blockers.
- During the development, there are also important effects on growth, tissue maturation and CNS development CNS (synaptogenesis, myelination).

T-hormone metabolism

(Fig. 6)

- T3 and T4 are conjugated in the liver.
- Deiodination of the T4 – iodine cleavage and thereby transformation to T3 or rT3 and then to various forms of the diiodothyronine. Various forms of deiodinase (DI) catalyse deiodination in different positions of the molecule. 5´DI catalyses iodine cleavage in the 5´ position and transforms the T4 to T3. 5DI catalyses T4 transformation to rT3. 5´DI is a selenoprotein and, thus, it is dependent on sufficient amount of selenium in the organism.
  5´DI activity decreases in following situations: selenium deficiency, burns, injuries, malignity, liver cirrhosis, renal failure, myocardial infarction, fever, starvation. Decreased 5´DI activity leads to reduction of T4 transformation to T3. T4 is then more accessible as a substrate for 5DI and is transformed to inactive rT3 (see also Euthyroid sick syndrome).

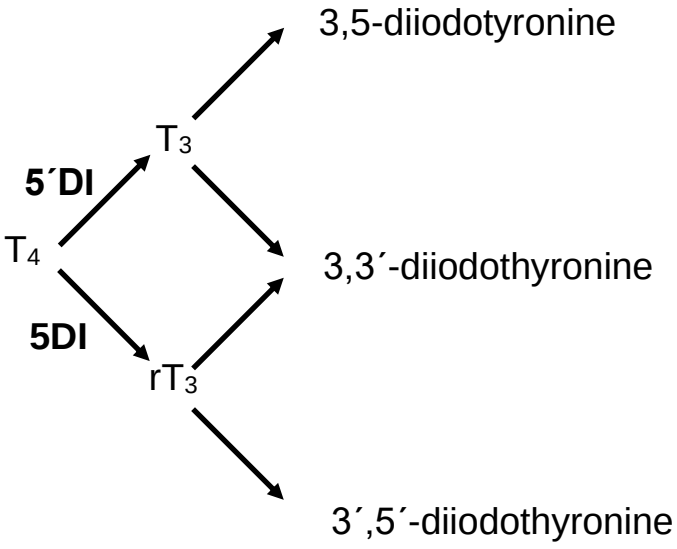

Fig. 6: The effect of deiodinases on the thyroxin.

3.1. THYROID GLAND DISORDERS

According to the impact on functions of the thyroid gland and the level of T-hormone effect on the target tissues, diseases of the thyroid gland can lead to following states:

1. **Hyperthyroidism** = increased thyroid gland function (increased effect of T-hormones)
2. **Hypothyroidism** = decreased thyroid gland function (decreased effect of T-hormones)
3. **Euthyroid state** = normal function of the thyroid gland (normal intensity of T-hormone effect)

In the course of some diseases, the function of the thyroid gland can develop and switch consecutively between all these states. For instance, autoimmune destruction of the gland can first cause uncontrolled release of T-hormones from damaged thyroid gland tissue. As the mass of the tissue is reduced consecutively, the state turns to euthyroid (function of the residual tissue plus uncontrolled release form tissue being destroyed is equal to normal secretion). Finally, small amount of residual thyroid gland tissue provides low t-hormone secretion leading to hypothyroidism.

The main general causes of thyroid gland diseases and disorders of its function:

- Developmental disorders
- Injuries
- Thyroidectomy (due to malignant tumours, Graves-Basedow disease)
- Tumours – both malignant or benign, with or without production of T-hormones by the tumour tissue
- Inflammations – infectious, autoimmune (note: the follicular content is isolated from the immune system, thus immune tolerance to certain antigens has not been developed; some thyroid gland lesions can enable contact between these antigens and the immune system inducing an autoimmune process)
- Disorders of thyroid gland regulation (disorders in the hypothalamus or adenohypophysis, Resistance to T-hormon in the adenohypophysis) and primary functional disorders (iodine deficiency, **Chyba! Nenalezen zdroj odkazů.**, inborn disorders of T-hormone synthesis)

Goitre

= enlarged thyroid gland

General causes and mechanisms: hyperplasia of thyroid gland cells, increased content of fibrous tissue in the gland, tumours, inflammatory infiltration

Goitre classification according to the function and potential causes of individual goitre types:

- **Hyperfunction goitre** – Graves-Basedow disease, adenoma
- **Hypofunction goitre** – iodine deficiency, tumours, enzymatic defect, goitregenes, inflammations
- **Eufunction goitre** – moderate iodine deficiency, fibrosis, **Chyba! Nenalezen zdroj odkazů.**

Note: Some of the causes can lead to more types of goitre. It depends on the intensity of the factor or stage of the pathological process (e.g. moderate iodine deficiency leads to eufunction goitre while severe lack of iodine causes hypofunction goitre).

Goitre classification according to the geographic distribution and potential causes of individual goitre types:

- S**poradic goitre** – sporadic occurrence in a particular region

- **Endemic goitre** – frequent occurrence in particular regions due to specific local conditions (e.g. lack of iodine in the soil and rock, and thus, lack of iodine in water and locally produced food)

Besides potential changes of thyroid gland function, goitre can be manifested with mechanical difficulties – breathing and swallowing problems due to compression of the airways and oesophagus respectively (first of all retrosternal goitre).

Ectopic goitre is a thyroid gland tissue localized in an abnormal localization out of the normal thyroid gland. It is usually a developmental anomaly when an islet of the tissue is retained along the trajectory of travel of the thyroid gland during its ontogenetic. Thyroid gland can also differentiate inside the teratoma. Ectopic goitre does not have to be a problem. On the other hand, it should be considered that pathological processes typical for the thyroid gland can affect also in this ectopically localized thyroid tissue (hypersecretion of hormones, tumours).

Thyroid nodes

- benign or malignant tumours
- cold nodes – do not produce T-hormones
- hot nodes – produce T-hormones

Resistance to T-hormones

- disorder of sensitivity of the tissues to T-hormones
- mutation of hTR-β receptor encoding gene

In dependence on tissues which are resistant to the T-hormones, there are 3 potential situations:

1. **Resistance in both the periphery and adenohypophysis** – the most often option
   - high level of TSH as well as T3 and T4
   - usually no severe manifestations of hypothyroidism
     – High levels of T3 and T4 compensates for lower hTR-β receptor sensitivity and the hTR-α receptor works normally.
2. **Resistance only in the adenohypophysis**
   - high or normal TSH level not reacting by decrease to administration of T-hormones
   - high T3 and T4
   - increased metabolic rate
3. **Resistance only in the periphery**
   - rare
   - normal levels of TSH as well as T3 and T4 (feedback control works normally)
   - manifestation of hypothyroidism because insensitive tissues are insufficiently stimulated by normal T3 and T4 levels

Antithyroid substances

= substances inhibiting thyroid gland activity (thyrostatic drugs)
- e.g. derivates of thiourea and mercaptoimidazole

Mechanisms of their effect is interference with iodide uptake and block of organic binding of iodine.

Because their intake can lead to goitre development, they are also called **goitregenes**. There are also natural goitregenes such as progoitrin contained in cruciferous vegetables

(Brassicaceae). In the gut, progoitrin is activated to goitrin. Long-lasting consummation of large amounts of cruciferous vegetables could lead to goitre.
High doses of iodide have mild and transient inhibitory effect on iodide binding (Wolff-Chaikoff's effect). This effect is stronger in thyrotoxicosis.
Some of the antithyroid substances are used for therapy of hyperthyroidism.

3.2. SYNDROMES OF THYROID GLAND FUNCTION DISORDERS

3.2.1. Hypothyroidism

= lack or insufficient effect of T-hormones
Disorders leading to hypothyroidism can be localised on different levels of thyroid gland function regulation or it could be due to target tissue insensitivity. Important indicator is the level of TSH, potentially also TRH.

There are following types of hypothyroidism:

1. Primary disorders of the thyroid gland (primary hypothyroidism)
   - Lack of T-hormones due to the primary problem leads elevation of TSH level (negative feedback) but the damaged thyroid gland is not able to enhance T-hormone production to an adequate level.
   - E.g. direct damage of the thyroid gland of any aetiology and mechanism, iodine deficiency, antithyroid substances)
2. Disorder of the adenohypophysis (secondary hypothyroidism)
   - The problem arises from damage of the adenohypophysis of any aetiology resulting in decreased THS secretion. Due to adenohypophysis lesion, there is often also disorder of other pituitary hormones
   - TSH level is reduced. The thyroid gland reacts to TSH administration with an increase of T-hormone production. On the other hand, TRH administration has no effect since the adenohypophysis is not able to react with adequate TSH secretion.
3. Disorder of the hypothalamus (tertiary hypothyroidism)
   - The problem arises from damage or dysfunction of the hypothalamus, damage of the connection between the hypothalamus and adenohypophysis disabling transportation of hypothalamic hormones (including TRH) to the hypophysis.
   - There is low level of TSH as well as low level of TRH. The thyroid gland reacts to TSH or TRH administration with an increase of T-hormone production.
4. Disorder of receptors in the tissues
   – inability of target tissues to respond to T-hormones (see Resistance to T-hormon)

<u>Euthyroid sick syndrome</u>

- It is an adaptation of the organism to severe situation (severe diseases, injuries, surgery, burns, malnutrition). It reduces energy consumption to be to spare resources.
- T4 level is normal, T3 is reduced, inactive rT3 is elevated (see metabolism of T-hormones and role of individual types of deiodinases), TSH level is normal (or slightly elevated).
- The patient shows manifestations of hypothyroidism.
- The state is normalized after healing the primary disease.

Due to a role of T-hormones in the ontogenetic development, hypothyroidism has different manifestations and consequences in the childhood and in the adulthood.

Hypothyroidism in the adults (called also myxoedema)

Causes
- Iodine deficiency – e.g. endemic goitre
- Thyroidectomy, ablation by radioisotopes
- Inflammations of the thyroid gland – e.g. the Hashimoto thyroiditis (autoimmune), purulent thyroiditis
- Antithyroid substances
- Secondary (disorder of the adenohypophysis) or tertiary (disorder of the hypothalamus) causes

Manifestations of hypothyroidism in adults
- Decreased basal metabolism – 40% reduction in athyreosis (i.e. complete absence of T-hormones); many of the following manifestations are consequences of reduced metabolic rate
- Moderate reduction of the body weight temperature, poor cold tolerance
- Decreased cardiac output, increased peripheral resistance, bradycardia
- Deposition of mucopolysaccharides in the myocardium, reduced myocardial contractility leading even to heart failure, pericardial effusion
- Fatigue
- Muscle weakness and stiffness
- Prolonged reaction time of the reflexes
- Slower mental processes, memory deficit, apathy
- Dry, cold skin
- Myxoedema = oedema of the skin, subcutis and also other tissues due to accumulation of mucopolysaccharides, retention of sodium and water
- Carotene accumulation in the blood → yellow skin (but not the sclera; in icterus, sclera is also yellow)
- Fragile and coarse hair
- Hoarse voice
- Anaemia
- Constipation
- Hypercholesterolemia

Myxoedema coma
= enhanced life-threatening manifestation of hypothyroidism
It can be provoked by another associated disease (e.g. infection).

Hypothyroidism in children (cretinism)

Causes
- Aplasia or hypoplasia of the thyroid gland
- Iodine deficiency during gravidity (if it is in the frame of a frequent occurrence in certain region due to lack of iodine in the soil it is called endemic cretinism)
- Maternal antithyroid antibodies passing through the placenta
- Inborn disorders of T-hormone synthesis (enzymatic defect)
- Foetal hypopituitary hypothyroidism

Manifestations of hypothyroidism in children = cretinism
- Mental retardation

- Disproportional nanism – retardation of growth of the bones, delayed ossification of epiphyseal cartilages; in absence of T-hormones, secretion and effect of the growth hormone is decreased.

A newborn with thyroid gland hypofunction mother has normal T-hormone level is normal at the time of birth! Normal intrauterine development is enabled by T-hormones from the mother passing through the placenta. After the birth when this supply is stopped, the consequences of T-hormone deficiency start to develop. Therefore, timely substitution therapy could prevent cretinism development.

Hypothyroidism that arises later during childhood leads to intermediate forms between cretinism and myxoedema in dependence on the age (the higher the age, the closer it is to adult form).

3.2.2. Hyperthyroidism, thyrotoxicosis

= high level or excessive effect of T-hormones

Causes

1. Primary disorders of the thyroid gland (primary hyperthyroidism):
   - Graves-Basedow disease
   - Tumours (often adenoma) of the thyroid gland – toxic nodular goitre – autonomous secretion of the hormones
   - Thyroiditis – transient hyperfunction due to uncontrolled release of the hormones from the gland tissue being destroyed (with further reduction of functioning tissue it turns to hypothyroidism)
2. Disorder in the adenohypophysis (secondary hyperthyroidism) – TSH overproduction
   - adenoma of the adenohypophysis –
3. Disorder in the hypothalamus (tertiary hyperthyroidism) – TRH overproduction
4. Thyreotoxicosis factitia – exogenous T-hormone in high doses

Manifestations

- Increased basal metabolism (10-100%); many of the following manifestations are consequences of increased metabolic rate.
- Hot climate intolerance
- Body weight loss, but hyperphagia
- Fine finger tremor, insomnia, nervousness, emotional lability, hyperactivity, shortage of reaction time of reflexes
- Increased metabolic rate leads to increased need of vitamins. Therefore, vitamin deficiency syndromes can develop despite normal vitamin intake (relative insufficiency).
- Increased cardiac output, reduced peripheral resistance
- Tachycardia, potentially arrhythmias (atrial fibrillation!)
- Potential cardiomyopathy
- Muscle weakness, in long-lasting severe hyperthyroidism even myopathy
- Weakness of the intercostal muscles can lead to respiratory insufficiency.
- After glucose intake, rapid elevation of glycemia followed by rapid normalization (T-hormones accelerate saccharide resorption in the gut. It leads to rapid increase of glycemia that stimulates insulin release. Insulin induces fast normalization of glucose level.)
- Decreased cholesterol level (T-hormones increase LDL receptor expression in the liver and thereby they increase elimination of LDL from the blood.)

Thyrotoxic crisis

= a life-threatening enhancement of hyperthyroidism manifestations

In can be provoked by another simultaneous disease or stress state (e.g. infection, surgery). Surgical manipulation with the hyperfunction goitre can lead to release of high quantity of T-hormones.

Graves-Basedow disease

- The most frequent cause of the hyperthyroidism, more frequent in women
- An autoimmune disease
- Autoantibodies against the TSH receptor – These autoantibodies stimulate the receptor! Thus, they have similar effect on the thyroid gland like TSH. This leads to the main manifestations of the disease.
- **Manifestations:**
  - Hyperthyroidism and all its manifestations
  - **Chyba! Nenalezen zdroj odkazů.** (growth of the glad as a response to TSH receptor stimulation)
  - Ophthalmopathy – the autoantibodies also attack retroorbital tissue including the oculomotor muscles; inflammation of these leads to exophthalmos
  - Stellwag's symptom = low frequency of eye blinks or incomplete eyeblinks
  - Moebius's symptom = disorder of eyeball convergence
  - Rosenbach's symptom = tremor of the eyelid when closed
  - In the extreme cases even vison disorders

4. THYROID GLAND AND CALCITONIN

Via calcitonin secretion, the thyroid gland participates in calcium metabolism control. Nevertheless, calcitonin is much less important than parathormone having in principle the opposite effect. Therefore, this part of the thyroid gland has lower clinical importance that T-hormone secretion.

Calcitonin

- A hormone produced by the parafollicular cells of the thyroid gland
- A peptide (32 aminoacids) with a high interspecific variability of the aminoacid sequence. Solomon calcitonin has twenty-fold more active in humans than the human calcitonin (therapeutic potential)
- A short biological half-life (less than 10 minutes)

Control of calcitonin secretion

- Stimulation by calcium level: at low plasmatic calcium levels (< 95 mg/l), calcitonin is not released, then its production increases with increasing calcemia
- Stimulation by β-adrenergic agonists, dopamine, oestrogens, gastrin

Calcitonin effect (Fig. 7)

- Calcitonin receptors are in the bones and kidneys.
- It induces decrease of Ca^{2+} and PO^{4-} blood levels.
- It inhibits bone resorption (it is a direct effect because it inhibits osteoclasts even *in vitro*).
- It increases urinary calcium excretion.

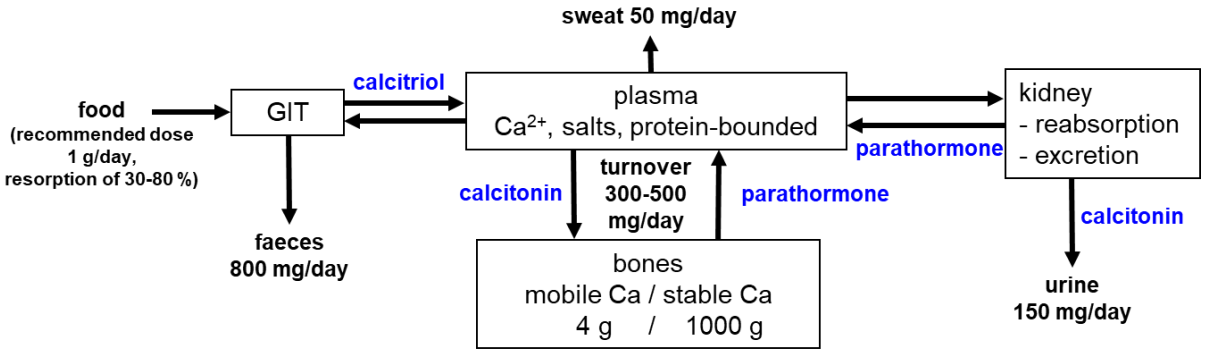

Fig. 7: Scheme of calcium metabolism

Calcitonin importance

Calcitonin has only minor long-term effects on calcemia in adult people.
After thyroidectomy, bone density and calcemia remain normal if the parathyroid glands remain preserved and functioning.
No syndrome due to calcitonin deficiency has been described.
Furthermore, high calcitonin levels in medullary carcinoma of the thyroid gland (originating from the parafollicular cells) does not cause any symptoms related to calcium metabolism.
Young people have higher calcitonin levels having probably a role in skeleton development.
It is also hypothesized that calcitonin prevents postprandial hypercalcemia and protects bones of women from calcium loss during pregnancy and lactation.

Clinical importance of calcitonin

- Paget's disease treatment
- Osteoporosis treatment