

Thyroid hormones and antithyroid drugs

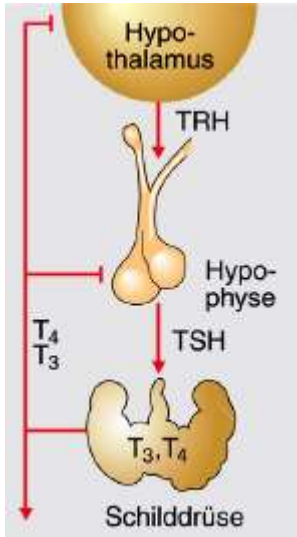
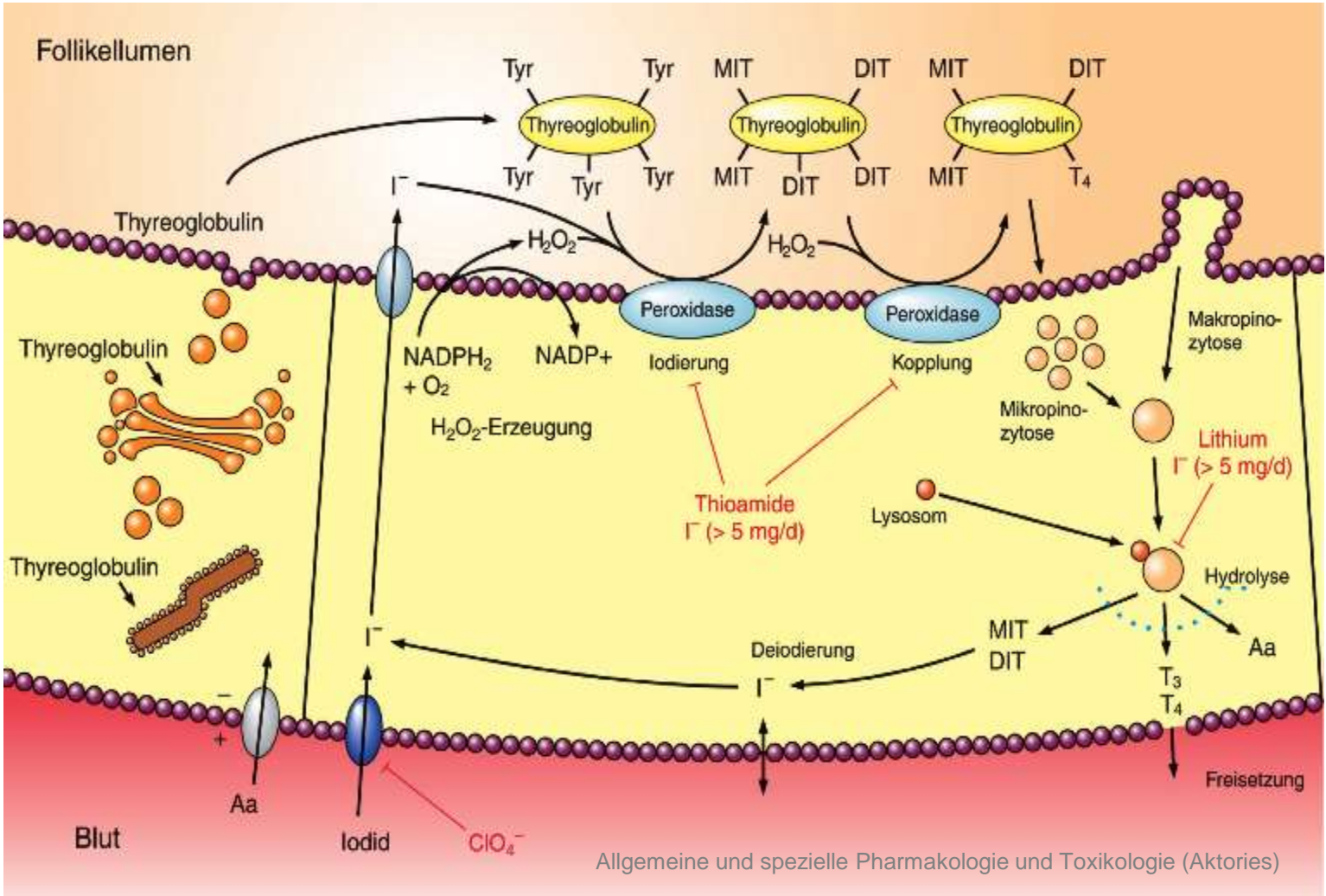
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Synthesis of thyroid hormones



Effects T₃ (and T₄)

- nuclear receptors – gene transcription
 - T₃ is the active hormone (10x higher affinity compared with T₄)
 - T₄ is converted to T₃ in periphery (deiodinase)
- lack of thyroid hormones – failure of somatic and mental development
- influence on metabolism of glucose, proteins, lipids, vitamins, nucleic acids, ions, etc.
- modulation of endocrine effects
- increased O₂-consumption, heat production, increased synthesis of Na⁺/K⁺-ATPase,
- increased basal metabolic rate
- increased glycogen synthesis and glycogen amount in muscle and liver
- changes in lipid profile: FFA ↑, Cholesterol and TG ↓
- high doses – inhibition of protein synthesis and increased proteolysis
- heart rate, oxygen consumption ↑ because of increased expression of β receptors

Iodine

- essential mineral nutrient, intake with diet, drinking water as anorganic iodine salts; daily requirement: 150 µg
- treatment of iodine deficiency
 - iodized salt
 - iodine salt preparations (KI) 100-250 µg /d
- indications
 - prophylaxis of iodine deficiency
 - treatment of endemic goitre
 - radioactive disaster (100 mg iodine!! – 130 mg KI)
- adverse effects
 - up to 300µg usually not problematic,
 - more than 1g/d can cause skin and mucous membrane irritations (Iodismus);
 - iodine induced hypertyreosis
 - allergy
- high doses – transient blockade of the release of thyroid hormones

Goitre

- Struma
 - most common thyroid disease
- cause: iodine deficiency
- clinical symptoms: abnormal enlargement of the thyroid gland
 - risks: difficulty of swallowing and breathing, hoarseness (hoarse voice), nodes and cysts
- treatment
 - early phase: iodine substitution (iodine salt preparations)
 - thyroid hormone preparations – thyroid gland is relieved, goitre is reduced

Hyperthyreosis

Symptoms

- **Subjective symptoms:** nervousity, anxiety, insomnia, tremor, palpitations, heat intolerance, increased GI motility
- **Objective symptoms:** weight loss, increased glucose, tachyarrhythmias, hair loss, cholesterol reduced, wet and warm skin; in case of Basedow: exophthalmus, pretibial edemas

Causes

Immunological (Graves' disease)

- TSH-receptor-antibodies stimulate the thyroid gland

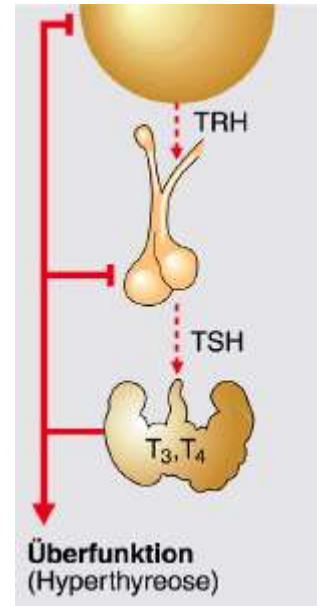
Multinodular goitre (Thyroid adenoma)

- nodules grow up and secrete thyroid hormone autonomously

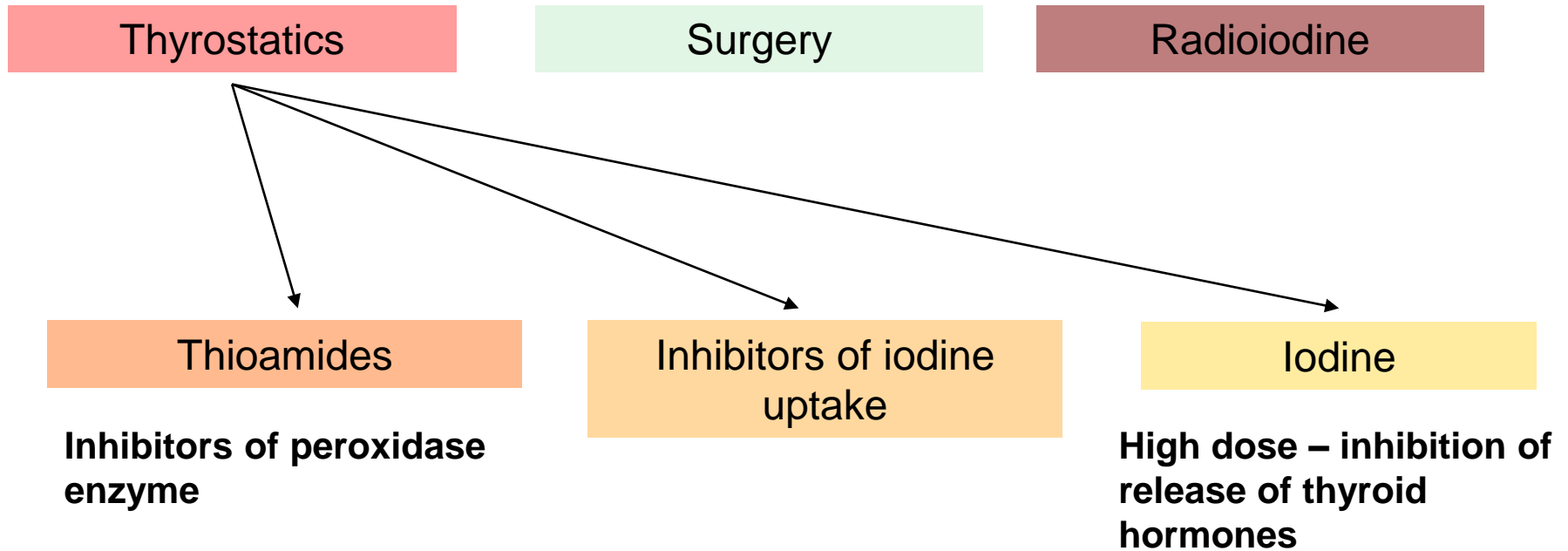
Hypersecretion of thyroid stimulating hormone

- pituitary adenoma, T₃-resistent

Thyroid cancer (rare)

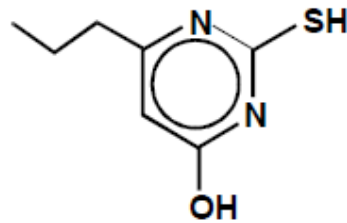


Treatment of hyperthyreosis

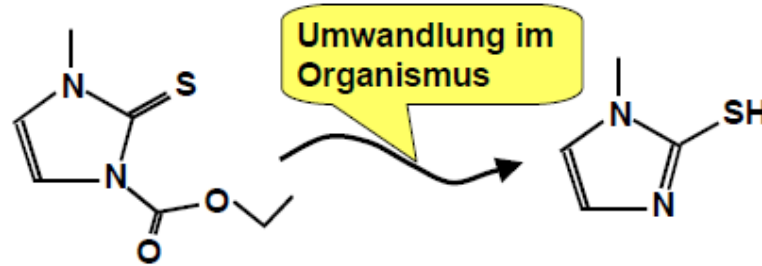


Inhibitors of peroxidase (Thionamides)

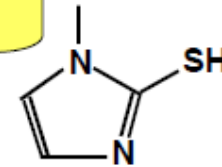
Wirkstoffe (Thioamide, Thioharnstoff-Derivate)



Propylthiouracil,



Carbamizol,



Thiamazol

- Carbimazol and thiamazol (methimazol) are about 10 x stronger as propylthiouracil
- Mechanism of action
Blockade of Thyroid-Peroxidase (both functions)
onset - 1-4 weeks (first the previously synthesized hormones will be released)

Inhibitors of peroxidase (Thionamides)

- Pharmacokinetics

- metabolism: oxidation and glucuronid conjugation
- half life of thiamazol: 4-6 h, but duration of action: 24 h
- half life of propylthiouracil: 2 h, - 6x daily
- all cross the placenta, propylthiouracil has lower amount in breast milk

- Adverse effect

- agranulocytosis, (leukopenia) – usually first 2-6 weeks
- allergy
- hypothyreosis

Inhibitors of iodine uptake

- perchlorate (ClO_4^-), and thiocyanate (SCN^-) are competitive inhibitors of the Na/I cotransporter
- Na-perchlorate can be used in case of hyperthyreosis
- adverse effects
 - allergy
 - gastric mucosal irritation
 - aplastic anemia, agranulocytosis, thrombopenia
 - nephrotic syndrome

Iodine treatment in case of hypertyreosis

- Iodine in high dose (>5mg/d) inhibits the release of T₄ and T₃. (mechanism of action is not clear)
 - onset: 24 h. max.: 10-15 d; after that gradual decrease in the effects
- Radioiodine therapy
 - ¹³¹I – β emission
 - selective uptake into the thyroid gland
 - treatment of Graves' disease, adenomas and iodine storing cancers
 - adverse effect: hypothyreosis (80%)
 - duration of the treatment: 5-14 d, onset: 10-12 weeks
 - contraindications: children, pregnancy

Treatment of hyperthyreosis (summary)

- Graves' disease:
 - Thioamides: up to 1-1,5 years (in case of intolerance, adverse effects: perchlorate)
 - in case of recidiva (50%) surgery or radioiodine
- Multinodular goitre (Thyroid adenoma)
 - first choice: surgery or radioiodine
 - preparation for surgery: thioamides + high-dose-iodine
- Iodine-induced hypertyreosis (e.g. contrast agents)
 - thioamides + perchlorate (high dose)
- Thyroid storm
 - Thioamides iv., high dose
 - β -blockers
 - Glucocorticoides
 - high-dose-iodine
 - Acute surgery (thyroidectomy)

Hypothyreosis

Causes

Immuntyreoditis (Hashimoto), postoperative, drug-induced

Subjective symptoms

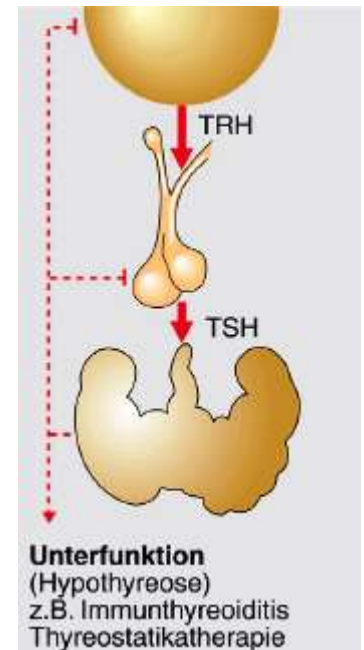
disabilty, weakness, lethargy, avolition,
fatigue, feeling cold, poor memory,
constipation

less frequently: mental depression, weight gain, cardiac problems, hair loss,
poor appetite, joint pain

Objective symptoms

dry skin, hoarseness, slow speech, dry and rough hair, bradycardia, delayed
relaxation of tendon reflexes

less frequently: swelling of the tongue, cardiomegaly, hypertension,
myxedema



Substitution of thyroid hormones

- Thyroxin, T₄

First choice

1x/d, 30 – 60 min before breakfast

(resorption is reduced by food)

Indications:

- Hypothyreosis: start with 12,5-50 µg/d, gradually increase to 100-200 µg/d
monitor: TSH (2 mIE/l) – with the exception of secondary hypothreoidism
- Congenital hypothyroidism (test immediately after birth) 12,5-50 µg /d
- Myxedema coma: 500µg iv. immediately, than 100µg/d iv.
- relapse prevention after resection of goiter
- Suppressive treatment in endemic goitre
- Suppressive treatment and substitution after surgery of thyroid cancer

Adverse effects: in case of overdosing hyperthyreosis (heart!)

- Triiodthyronin, T₃

for a constant hormone level 5 – 6 dosis/day would be necessary

– only in case of deiodinase problem