Axis TRH-TSH-T3/T4

TRH, thyrotropin-releasing hormone

Characteristics
- Peptide with central effects – neuromodulation, thermoregulation
- Peripheral effects

Hypothalamo-hypophyseal axis
- Regulation of TSH and PRL secretion (prolactinemia, galactorea)

Clinical significance
- In the past – hyperthyroidis diagnosis (hypothalamic X hypophyseal causes)
- Possible role in depression treatment, spinal muscular atrophy and amyotrophic lateral sclerosis
- Treatment of some syndromes (West, Lannox-Gastaut, early infantile epileptic encephalopathy)

Regulation of secretion

- Neural control
- Circadian rhythm (maximum between 21:00 and 5:00 and between 16:00 and 19:00, peaks in 90–180 min intervals
- Temperature (cold) – higher synthesis among people from colder regions in winter – together with ANS (catecholamines)
- Stress – TRH synthesis and secretion inhibition (indirect negative feedback loop between glucocorticoids and effect on hippocampus)
- Starvation – TRH secretion decrease („saving“ energy); effect of leptin
- Body mass - POMC (-) and ARGP (+) system

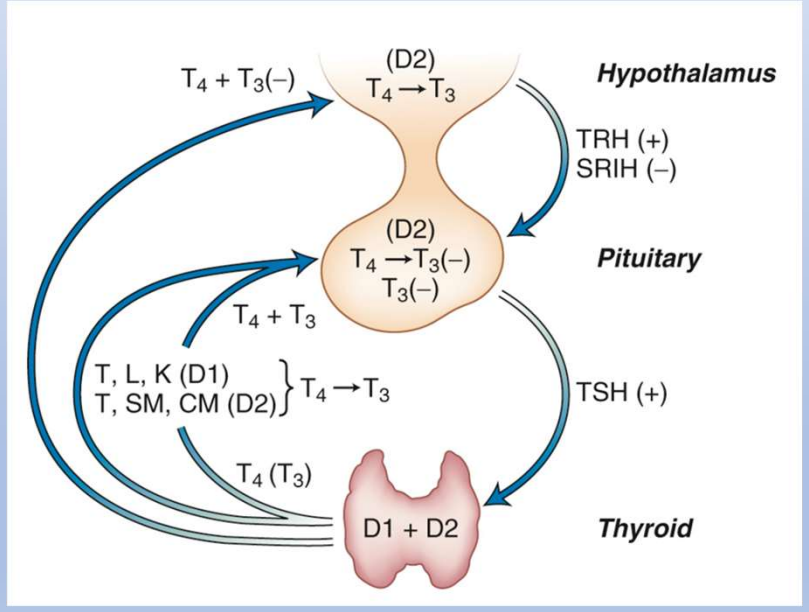
TSH, thyroid stimulating hormone

Characteristics
- Heterodimer
- Negative feedback T3 – inhibition of α subunit transcription; dopamine (α and β)
- Positive feedback – TRH
- Co-translational glycosylation and folding (- T3, + TRH)

TSH
- Half-life ca 30 min
- Pulsatile secretion (2-3 h), circadian rhythms (peak between 23:00 and 5:00)
- Magnitude changes – starvation, disease, surgery
- Leptin, ADH, GLP-1, glucocorticoids, α-adrenergic agonists, prostaglandins, TRH (+)
- T3/T4, dopamine, gastrin, opioids, glucocorticoids (high doses), serotonin, CCK, IL-1β a 6, TNF-α, somatostatin (-)

Function
- Stimulation of thyroid hormones synthesis
- „Growth hormone“ for thyroid gland

Clinical significance
- TSH deficiency (mutation in genes coding TRH and TSH receptors)
- Analogues of somatostatin
- ! (+) cortisol metabolism



Feedback mechanism!

Thyroid gland

- *Glandula thyroidea* (15 - 20 g, frontal side of trachea under thyroid cartilage
- Two lobes connected by thyroidal isthmus, *lobus pyramidalis*
- Strong vascularization
- Round follicles (acini) with one layer of **follicular cells (T3/T4)**
- Cavity filled with colloid
- Capillaries with fenestrations
- **Parafollicular (C-) cells (calcitonin)**
- From day 29 of gravidity (Tg), T4 – 11th week

Follicles are the basic functional units of thyroid gland

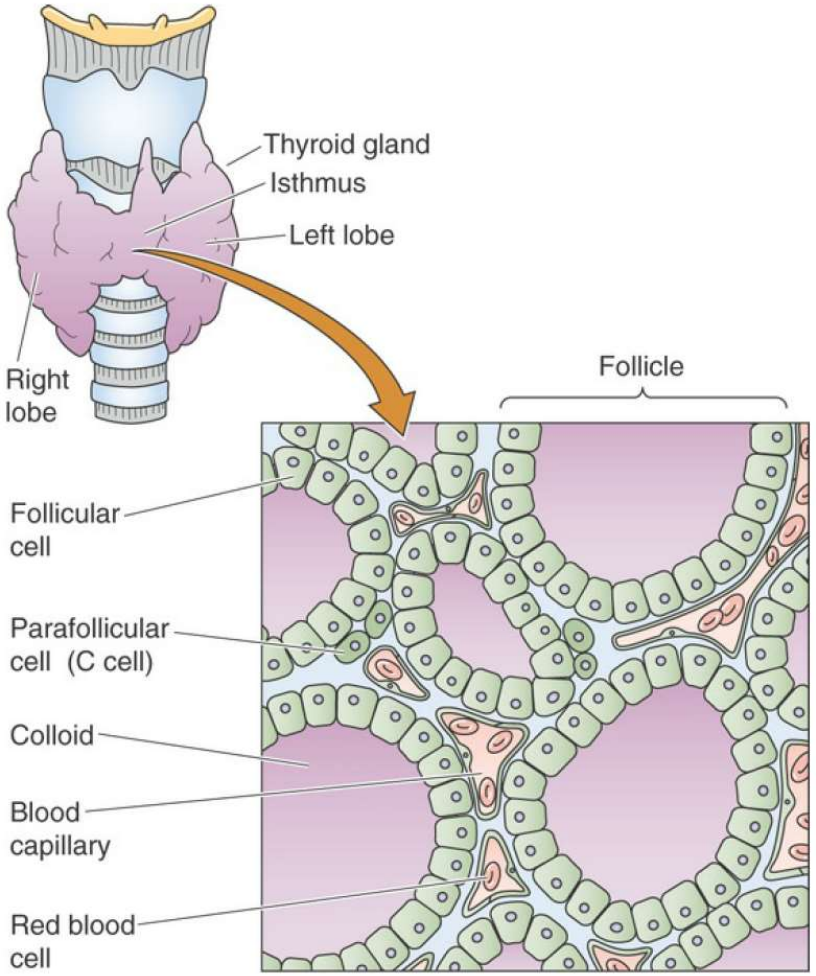
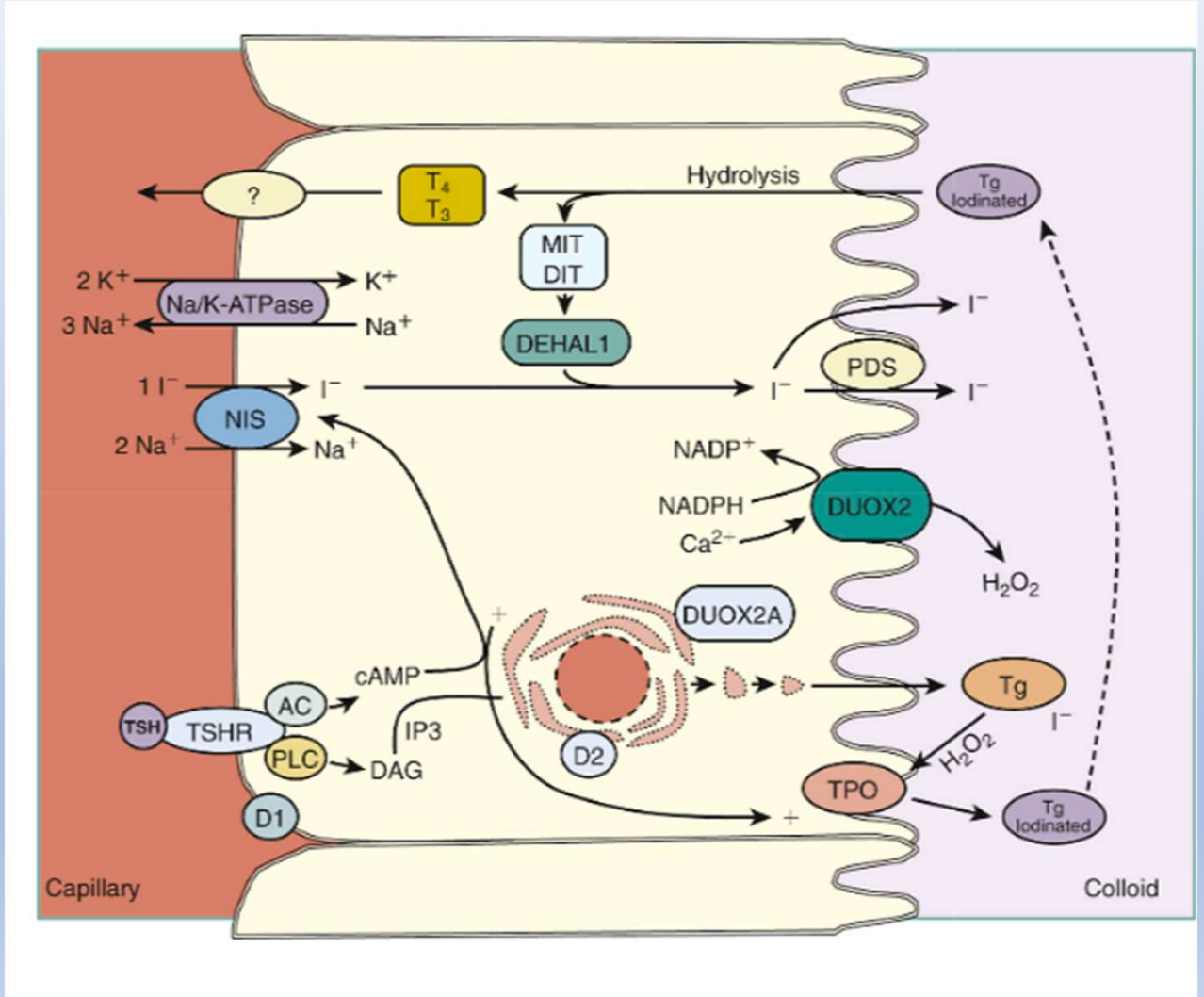


Figure 49-1 Structure of the thyroid gland. The thyroid gland is located anterior to the cricoid cartilage in the anterior neck. The gland comprises numerous follicles, which are filled with colloid and lined by follicular cells. These follicular cells are responsible for the trapping of iodine, which they secrete along with thyroglobulin—the major protein of the thyroid colloid—into the lumen of the follicle.

Iodine and hormone secretion – general view

- NIS (Na^+/I^- symporter)
- PDS (pendrin)
- TPO (thyroidal peroxidase)
- TG homodimers and their iodation – MIT and DIT
- DUOX1 and 2 – together with TPO oxidation of iodide and transportation to TG structure
- TPO - connection DIT+DIT (T4) or DIT+MIT (T3)
- Pinocytosis and phagolysosomes
- Deiodation of MIT and DIT – DEHAL1 (iodotyrosine dehalogenase)

- Other proteins (TSHR)
- Transcriptional factors (TTF-1, TTF-2, PAX8, HNF-3)

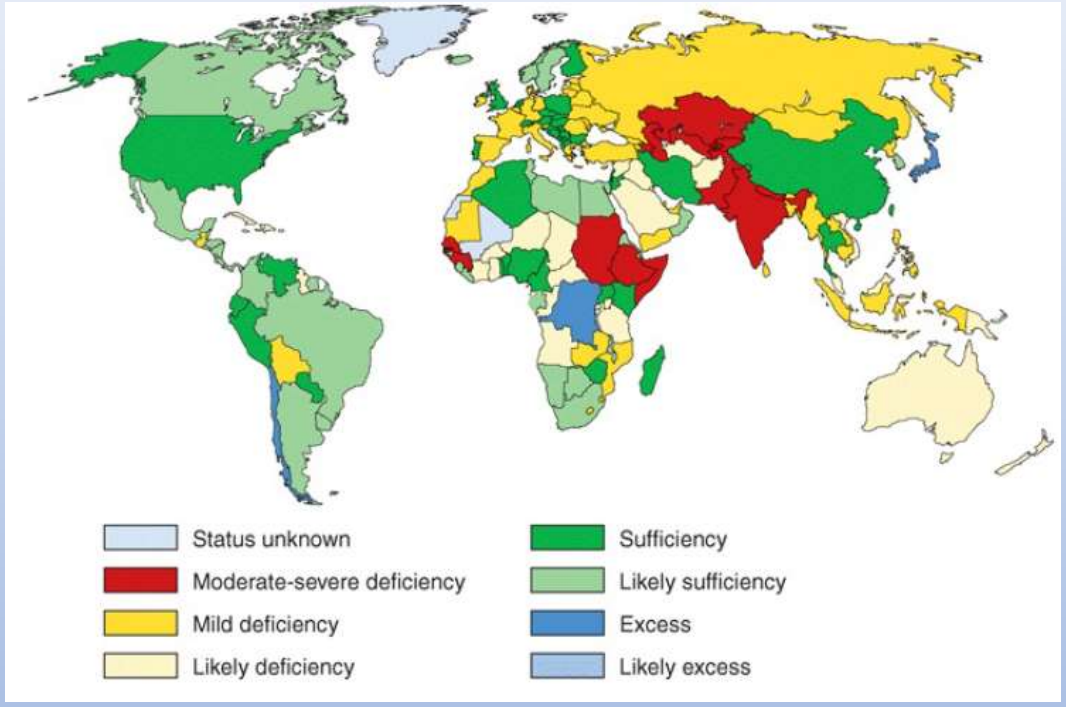


Dietary iodine

Recommended Daily Intake	
Adults	150 µg
During pregnancy	200 µg
Children	90-120 µg
Typical Iodine Daily Intakes	
North America (1992)	75-300 µg
Chile (1981)	<50-150 µg
Belgium (1993)	50-60 µg
Germany (1993)	20-70 µg
Switzerland (1993)	130-160 µg

- Bioavailability of organic and inorganic I
- breast milk
- I^- filtered with passive reabsorption 60 – 70 %
- loss through stool (10 – 20 µg/day)

- Highest daily intake in Japan (several mg)
- In many countries on decrease – eating habits



Clinical relevance
- Endemic goiter
- Endemic cretinism

Iodine fate in follicular cells

NIS
- Concentration of I in follicular cells
- Transport of other ions (TcO_4^-, ClO_4^-, SCN^-) – clinical significance
- Salivary glands, mammary gland, choroid plexus, gastric mucosa, cytotrophoblast, syncytiotrophoblast
- Loss of ability to concentrate I in thyroid gland tumors
- TSH
    - (+) transcription
    - (+) prolonged stay in PM

Pendrin
- also kidneys (Cl^-/HCO_3^- exchanger) and inner ear

Chloride channel 5 (ClCn5)
- ?

DEHAL1
-MIT and DIT, iodine recyclation

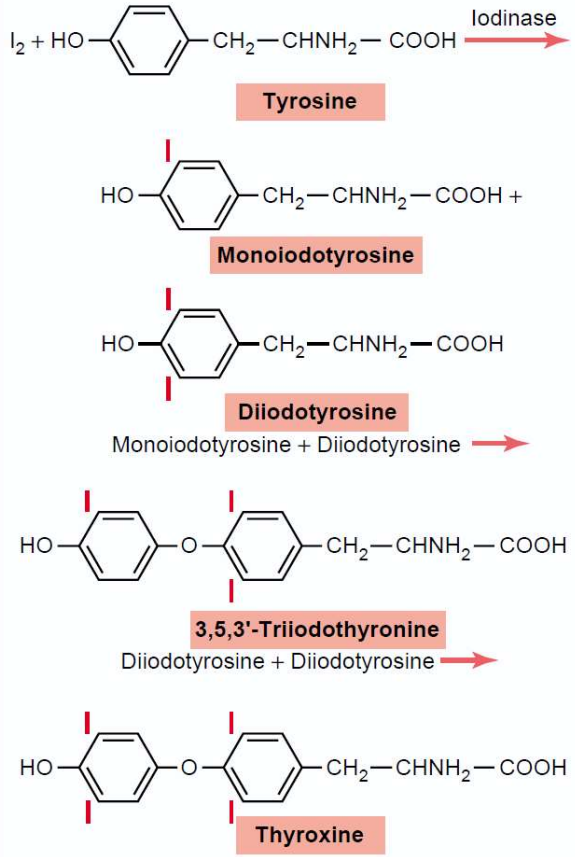
IYD
-iodotyrosine deiodinase
-MIT (+++), DIT (+)

Clinical relevance
-Mutation
-Thiourea derivatives – methimazole, carbimazole, propylthiouracil (TPO)

Oxidation, organification of iodine and MIT/DIT synthesis

- Organification = incorporation I in MIT and DIT
- TPO in cooperation with DUOX1 and DUOX2 – peroxide generation
- DUOX1/2 – NADPH, Ca^{2+}-dependent oxidases
- generation of I_2 and I^+
- DUOXA2 – maturation and DUOX2 incorporation
-TSH stimulation

- T3 and T4 –TPO catalysis
- Tg – tyreoglobulin, 660 kDA homodimer
- Tg – 134 tyrosines / 25 – 30 iodinated / only 3, resp. 4, participate in T4 and T3
- 3 – 4 molecules of T4 in Tg (physiological conditions)
- Only 1 T3 in Tg



T3 and T4 secretion

- High supply vs low daily turnover (about 1 %)
- Supply ca 5000 μg T4 – euthyroid state for ca 50 days

- Macropinocytosis and **micropinocytosis** (apical membrane)
- Endocytosis
- Selective proteolysis (cathepsin D and D-like thiol proteases, active at low pH)
- Release from Tg in lysosomes
- T4 available to deiodases D1 and D2 – modulation of systemic conversion?
- Inhibition of T4 secretion by iodide

TSH and T3, T4 secretion
- TSHR
    - TSH binding
    - TRAb (TSHR-stimulating antibody)
    - TBAb (thyroid-blocking antibodies)
    - LH (+)
    - hCG (+)

- PLC + Ca^{2+}
    - iodide efflux, peroxide generation, iodation of Tg

-PKA
    - iodide uptake
    - Tg transcription
    - transcription and generation of TPO and NIS

T3 and T4 transport

TBG
- Glycoprotein
- One binding site for iodothyronine
- Half-life ca 5 days

Transthyretin
- Binds one T4 molecule, low affinity
- Half-life ca 2 days
- CSF – relevance ?

Albumin
- Low affinity
- Little relevance for T3/T4 transport (max. 10 %)

Other – lipoproteins (3 – 6 %)

Parameter	Thyroxine-Binding Globulin	Transthyretin	Albumin
Molecular weight of holoprotein (kDa)	54,000	54,000 (4 subunits)	66,000
Plasma concentrations (μmol/L)	0.27	4.6	640
T_4 binding capacity as μg T_4/dL	21	350	50,000
Association constants of the major binding site (L/mol)			
T_4	1×10^{10}	7×10^7	7×10^5
T_3	5×10^8	1.4×10^7	1×10^5
Fraction of sites occupied by T_4 in euthyroid plasma	0.31	0.02	<0.001
Distribution volume (L)	7	5.7	7.8
Turnover rate (% day)	13	59	5
Distribution of iodothyronines (% protein)			
T_4	68	11	20
T_3	80	9	11

T_3, triiodothyronine; T_4, thyroxine.

Low solubility of iodothyronines determines their reversible binding and transport by plasmatic proteins.

TBG concentration and saturation is the main free-T4 determinant.

T4/T3 transport across PM and their cell fate*

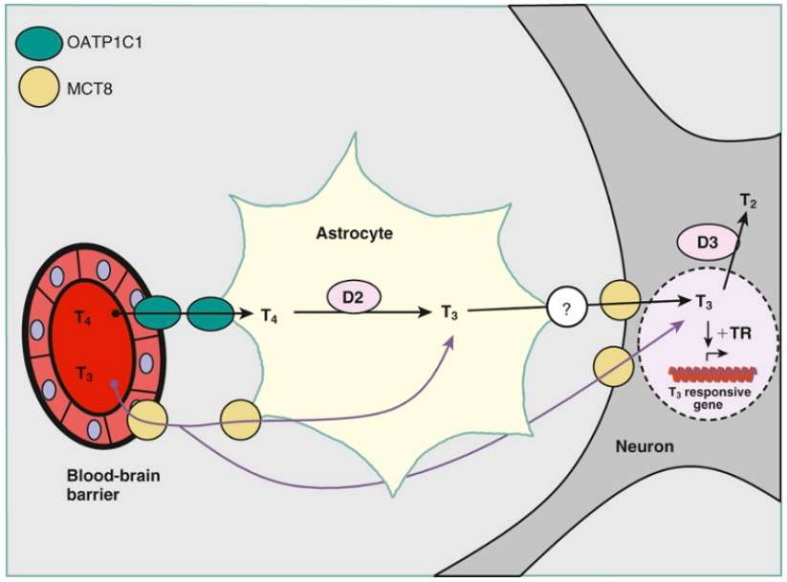
Transport systems:

- MCT8 (monocarboxylate transporter 8)
- MCT10 (monocarboxylate transporter 10)

} Expression in various tissues — T3, T4, rT3

- OATP1C1 (organic anion transporting polypeptide 1C1) (HEB)

} CNS (astrocytes) — T4



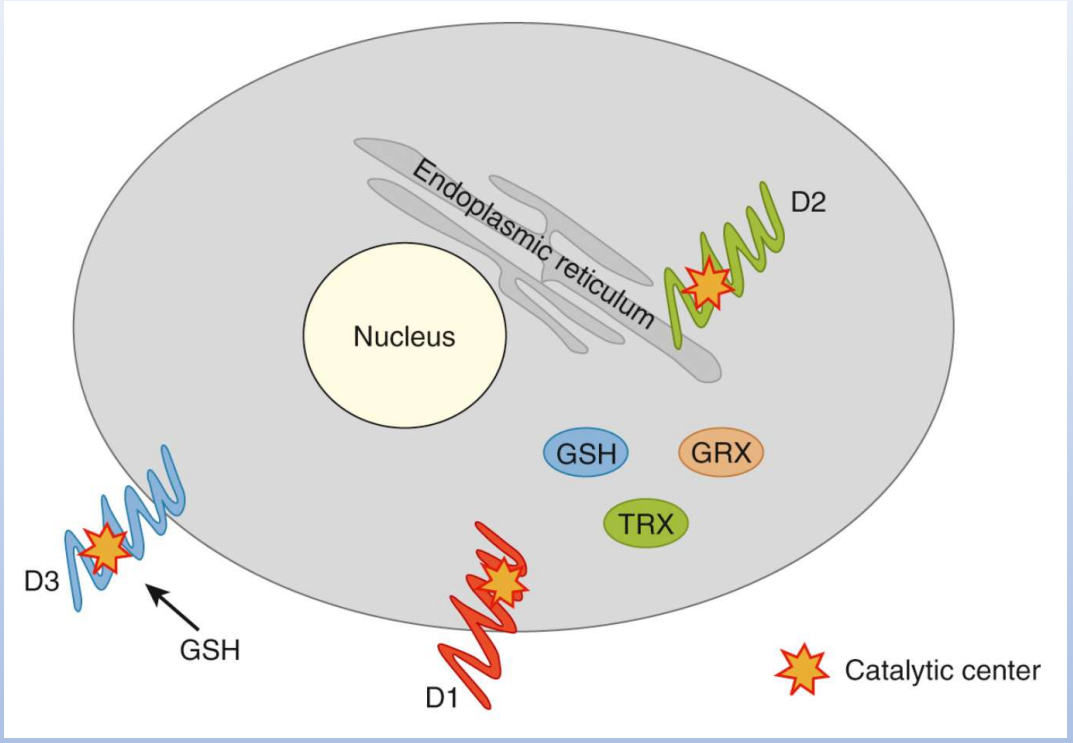
Two-way transport of T3

Role of deiodinase type II

Extrahypophyseal tissues
- 90 % T3 in cytosol
- 10 % T3 in nucleus

Hypophysis
- 50 % T3 in cytosol
- 50 % T3 in nucleus

Deiodination and (seleno-)deiodinases*

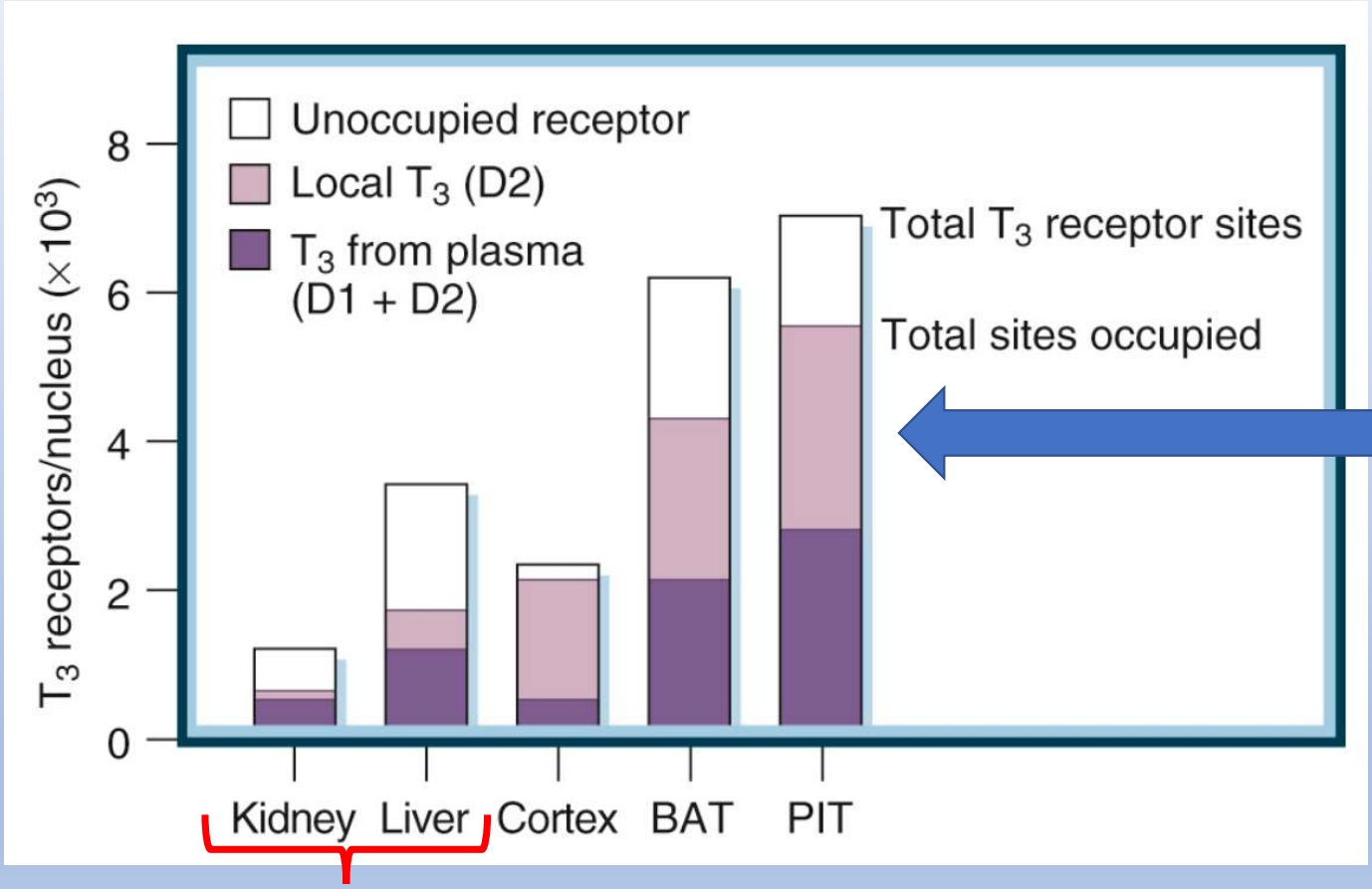


- all deiodinases require thiol presence as cofactor (glutathione (GSH), thioredoxin (TRX), glutaredoxin (GRX))
- D1 - main source of plasmatic T3
- D3 - most important „deactivating“ enzyme over-expressed in tumor tissue

Parameter	Type 1 (Outer and Inner Ring)	Type 2 (Outer Ring)	Type 3 (Inner Ring)
Physiologic role	rT_3 and T_3S degradation, the source of plasma T_3 in thyrotoxic patients	Provide intracellular T_3 in specific tissues, a source of plasma T_3	Inactivate T_3 and T_4
Tissue location	Liver, kidney, thyroid, pituitary (?) (not CNS)	CNS, pituitary, BAT, placenta thyroid, skeletal muscle, heart	Placenta, CNS, hemangiomas, fetal or adult liver, skeletal muscle
Subcellular location	Plasma membrane	Endoplasmic reticulum	Plasma membrane
Preferred substrates (position deiodinated)	rT_3 (5′), T_3S (5)	T_4, rT_3 (5′)	T_3, T_4 (5)
K_m	rT_3, 10^{-7}; T_4, 10^{-6}	10^{-9}	10^{-9}
Susceptibility to PTU	High	Absent	Absent
Response to increased T_4	↑	↓	↑

BAT, brown adipose tissue; CNS, central nervous system; K_m, Michaelis-Menten constant; PTU, 6-n-propylthiouracil; rT_3, reverse triiodothyronine; T_3, triiodothyronine; T_3S, T_3SO_4; T_4, thyroxine.

Sources of intracellular T3 and T4



D2 as a source of supplementary nucleic T3

T3 supply critical for tissues:
- cortex
- BAT
- PIT

Physiological relevance:
- Normal development
- Thyroid gland function regulation
- Cold

Clinical relevance
- Amiodarone (D1/D2 (-))
- Propylthiouracil (D1 (-))
- Glucocorticoids (D3 (+))

Preferential plasmatic T3 utilization

Physiological effects of thyroid hormones

- Non-nuclear receptors
- Interactions with adaptor proteins

- cAMP
- MAPK
- Ca^{2+}-ATPase (+)
- Na^{+}/H^{+} antiporter (+)

Cell response

- Regulation of transcriptional activity

- Normal growth and development
- Regulation of metabolism

Organ-specific effects of thyroid hormones

Bones
- increase of bone turnover
- regulation of activity of osteoblasts/clasts, chondrocytes
- hyperthyroidism – risk of osteoporosis

Cardiovascular system
- Inotropic and chronotropic effect
- (+) cardiac output and IVF
- (-) vascular resistance
- changes in transcriptional activity:
  - -Ca^{2+}-ATPase
  - -Phospholamban
  - -Myosin
  - –β-AR (upregulation and sensitivity)
  - -G-proteins, AC
  - -Na^{+}/Ca^{2+} exchanger
  - -Na^{+}/K^{+}-ATPase
  - -Voltage-gated ion channels

GIT
- (+) resorption of monosaccharides
- (+) motility

Adipose tissue
- (+) differentiation of adipose tissue, adipocytes proliferation
- (+) lipogenic enzymes
- (+) cell accumulation of lipids
- (+) uncoupling proteins, uncoupling of oxidative phosphorylation
- Hyperthyroidism (+) lipolysis
  - (+) β-AR
  - (-) phosphodiesterase activity
  - (+) cAMP

  } (+) activity HSL
- Hypothyroidism (-) lipolysis

Liver
- regulation of triglyceride, lipoprotein and cholesterol metabolism
- (+) fatty acids metabolism
- (+) gluconeogenesis
- (+) mitochondrial respiration

CNS
- expression of genes related myelination, cell differentiation, migration and signaling
- Axonal growth and further development

Metabolic effects of thyroid hormones

Saccharides

- increased glucose resorption
- Increased utilization of Glu in tissues
- Increased liver gluconeogenesis
- Increased glycolysis

- hyperthyroidism = postprandial hyperglycaemia
- hypothyroidism = inbalances in glycaemia

Lipids

- increased activity of lipoprotein lipase
- Increased synthesis of LDL receptor in hepatocytes
- increased synthesis of fatty acids (nonesterified)
- increased beta-oxidation
- hypothyreosis = proatherogenic changes!

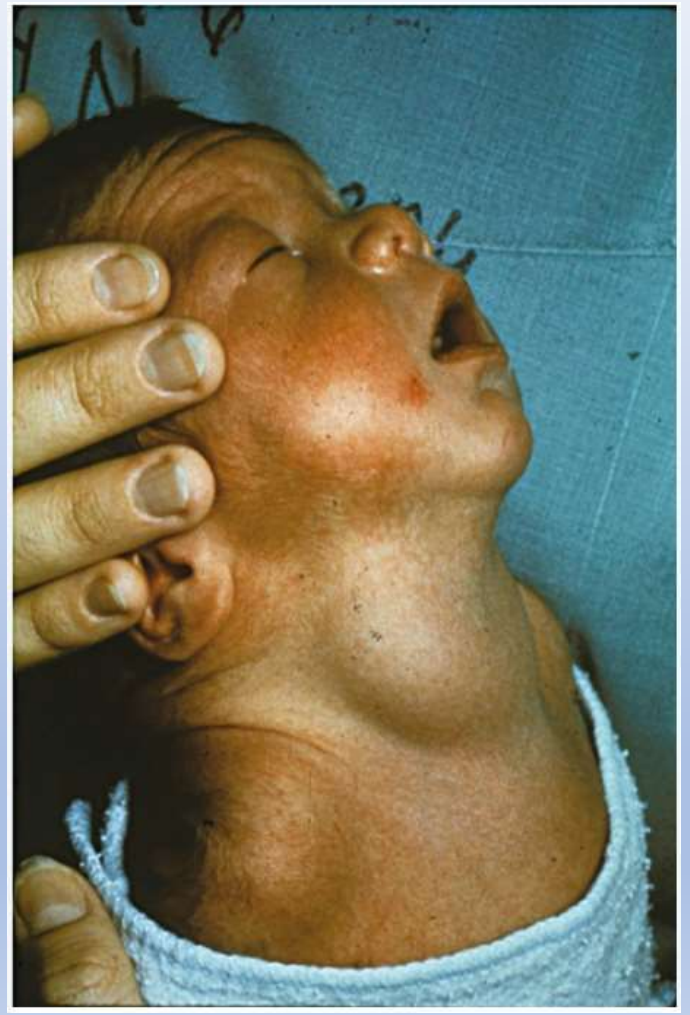
Proteins

- Proteoanabolic effect (mainly during intrauterine development and the first year after birth – brain)
- hyperthyroidism = protein catabolism!

Thyroid hormones and iodide deficit and excess

Deficit
- Rapid T4 decrease, TSH increase
- No change in T3
- Increased synthesis of NIS, TPO, Tg, organification of iodide and Tg turnover
- Increase D2 in CNS, hypothalamus and hypophysis
- Stimulation of follicular cells (TSH)
- Long-term deficit – decreased D3
- Decrease supplementation under 75 µg/day (China, India, Indonesia, Africa)
- hypothyroidismus

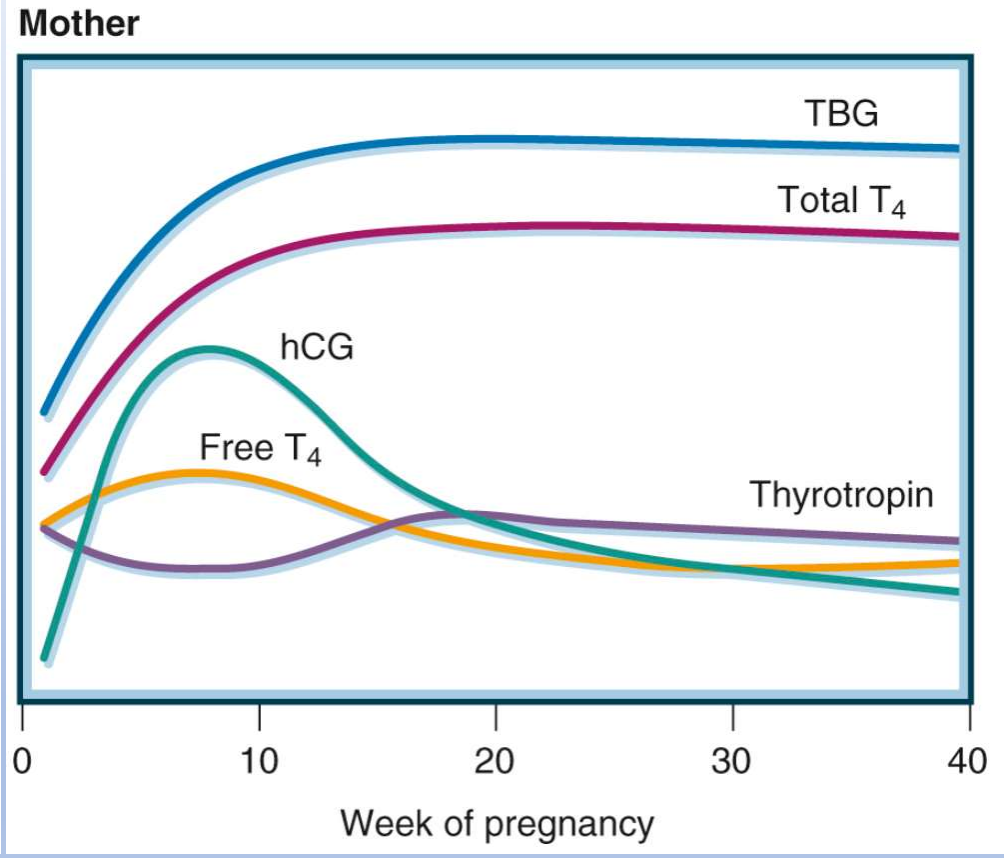
Excess
- At first increase, then decrease of iodide organification (Wolff–Chaikoff effect)
- Long-term high iodide supplementation = hypothyroidism and goitre
- decreased NIS generation
- Immediate inhibition of thyroid hormones secretion



Functions of thyroid gland in fetus and newborn*

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T_4 and T_3; ↑ T_4 production
↑ Plasma volume	↑ T_4 and T_3 pool size; ↑ T_4 production; ↑ cardiac output
D3 expression in placenta and (?) uterus	↑ T_4 production
First trimester ↑ in hCG	↑Free T_4; ↓ basal thyrotropin; ↑ T_4 production
↑ Renal I^- clearance	↑ Iodine requirements
↑ T_4 production; fetal T_4 synthesis during second and third trimesters	
↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

D3, type 3 iodothyronine deiodinase; I^-, plasma iodide; hCG, human chorionic gonadotropin; T_3, triiodothyronine; T_4, thyroxine.



Thyroid gland and development stages*

Fetal thyroid gland - qualitative and quantitative differences

- 10-fold higher T4 production
- D1 (-), D3 (+; liver, skin, tracheobronchial system, urothelial system, GIT epithelium) – T3(-), rT3 (+)
- D2 – generation of T3 in tissues
- Start at the beginning of the 3rd trimester
- TSH during whole development higher than in mother
- Almost no interaction with mother (exception placental transport of T4), high expression of D3 in uterus and placenta

Thyroid gland in newborns - qualitative and quantitative differences

- Increased TBG level
- Lower T4 levels compared to mother
- Low T3 level in serum, increased levels of rT_3 and T_3SO_4
- Rapid increase TSH 2 – 4 hours after birth, decrease in 48 hours
- Rapid increase T_4, T_3, Tg – 24 hours (+D1 a D2, adrenergic stimulation of D2 in BAT)

Thyroid gland and aging

- Normal T4 level, decreased T3 level
- TSH according to iodide supplementation
- Benefit of decreased thyroid hormones - longevity

Thyroid gland functions during disease and starvation*

Starvation
- Decreased plasmatic T3, increased rT3, T4 no change
- Upregulation of D3
- Decreased oxygen consumption
- Slower heart rate
- More positive nitrogen balance

= mechanisms to save energy and proteins

- Chronic malnutrition – decreased plasmatic T3

Severity of Illness	Free T_3	Free T_4	Reverse T_3	TSH	Probable Cause
Mild	↓	N	↑	N	↓ D2, D1
Moderate	↓↓	N, ↑↓	↑↑	N, ↓	↓↓ D2, D1, ? ↑ D3
Severe	↓↓↓	↓	↑	↓↓	↓↓ D2, D1, ↑ D3
Recovery	↓	↓	↑	↑	?

D1 through D3, iodothyronine deiodinases; N, no change; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone (thyrotropin).

Disease
- Changes in T4 to T3 D2) conversion – TSH binding
- IL-6
- Increased intra-/extracellular ROS = changes in deiodinase activity – decreased T4 to T3 conversion
  BUT! no change in D3
- potential therapy – infusion of TSH + GHRP2

- Bipolar disorder – (+) TSH, (-) T4
- Severe depression – (-) TSH, (+) T4

Hormones and thyroid gland

Glucocorticoids
- Decreased pulsatile secretion of TSH and TRH secretion
- Increased activity (expression) of D3

Sex steroids
- Estrogens
  - increased TBG
  - TSH (+ 15 – 20 %)
- Androgen
  - decreased TBG

GH
- (+) T3, (-) T4
- Deiodinase

Glucocorticoids
Excess
Decrease TSH, TBG, TTR (high-dose) Decrease serum T_3/T_4 and increase rT_3/T_4 ratios Increase rT_3 production (? ↑ D3) Decrease T_4 and T_3 secretion in Graves disease
Deficiency
Increase TSH
Estrogen
Increase TBG sialylation and half-life in serum Increase TSH in postmenopausal women Increase T_4 requirement in hypothyroid patients
Androgen
Decrease TBG Decrease T_4 turnover in women and reduce T_4 requirements in hypothyroid patients
Growth Hormone
Decrease D3 activity

D3, type 3 deiodinase; rT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; TSH, thyrotropin; TTR, transthyretin.

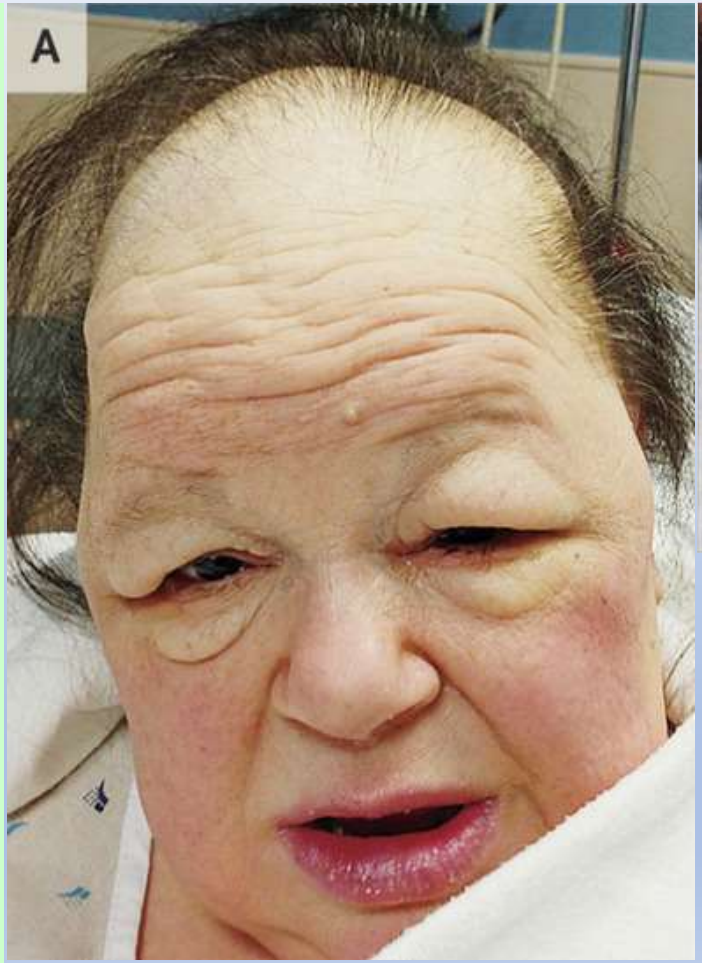
Hypothyroidism

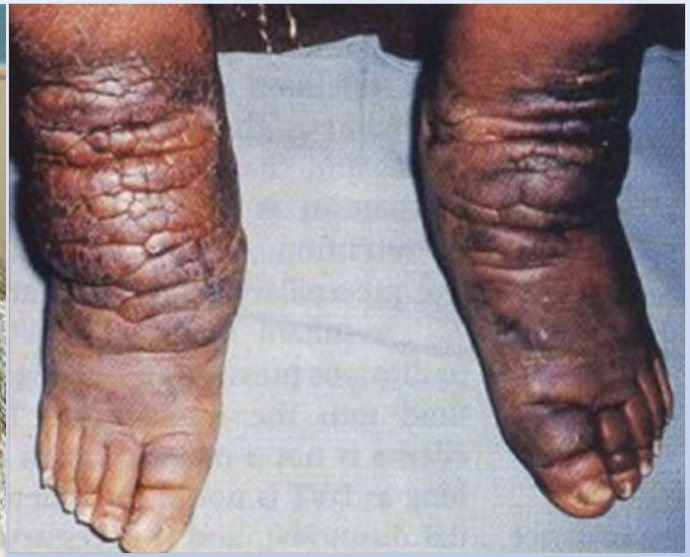
Disruptions of HYP-ADH-TG axis including mutations
Goitrogens and treatment

Primary versus **secondary**

- Cold sensitivity
- Dry cold skin
- Slower movements
- Slow quiet speech
- Bradycardia
- Water retention

- **Psychomotoric retardation** (children)
- **Myxedema** (accumulation of protein complexes, polysaccharides, hyaluronic acid and chondroitin sulfuric acid in skin)
- Hypothyroidism since birth = **cretinism**

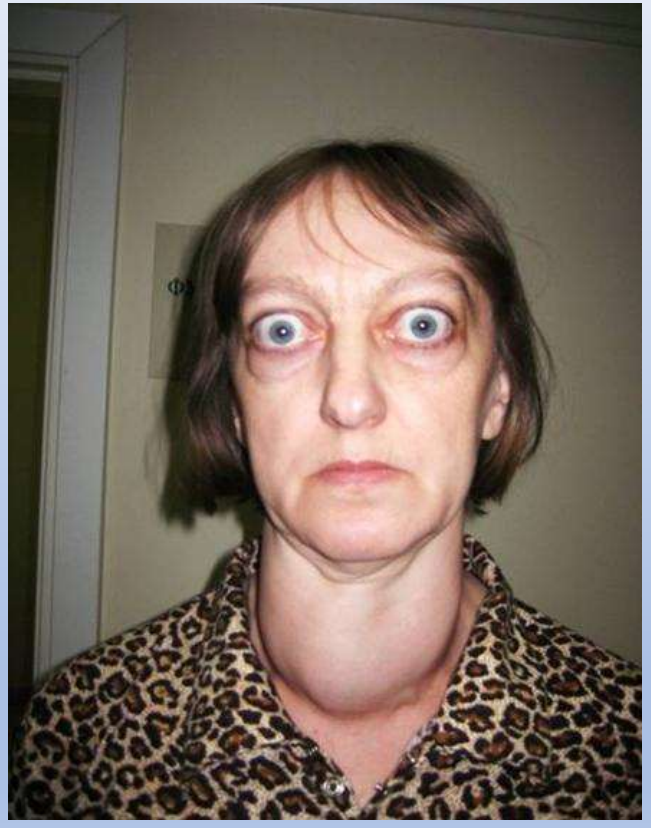


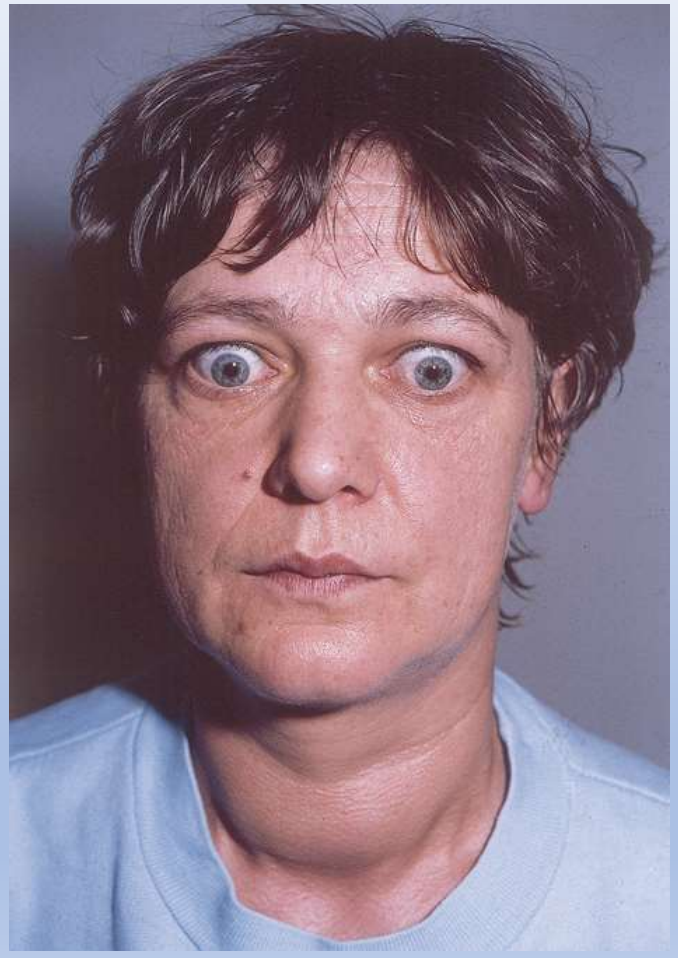


Hypothyroidism

Graves disease, **diffusion toxic goiter**, toxic nodular goiter, inappropriate pharmacotherapy, excessive iodide intake, thyroiditidis, follicular carcinoma, tumors producing TSH

- increased BMR
- Changes in catecholamines reactivity
- **Exophthalmos -** infiltration of lymphocytes and periocular fibroblasts into extraocular muscles and tissue
- unrest
- **Tachycardia**
- Hyperventilation





Hypo- versus hyperthyroidismus

Parameter	Hypothyroidism	Hyperthyroidism
BMR	(-)	(+)
Carbohydrate metabolism	Gluconeogenesis (-) Glycogenolysis (-) Glycemia (N)	Gluconeogenesis (+) Glycogenolysis (+) Glycemia (N)
Protein metabolism	Proteosynthesis (-) Proteolysis (-)	Proteosynthesis (+) Proteolysis (+) Muscle mass (-)
Lipid metabolism	Lipogenesis (-) Lipolysis (-) Serum cholesterol (+)	Lipogenesis (+) Lipolysis (+) Serum cholesterol (-)
Thermogenesis	(-)	(+)
Autonomic nervous system	Plasmatic catecholamines (N)	Increased reactivity – β-AR (+) Plasmatic catecholamines (-)

Examination of hypothalamus – adenohypophysis – thyroid gland axis

TSH – immumometric methods

Overall T3 and T4 – immunochemical methods (immunoassays)

Free T3 and T4

rT3

Antibody levels - (anti-Tg, anti-TPO, TSIs – thyroid-stimulating immunoglobulins

Thyroid nodules – ultrasound, biopsy, scan – I-123, Tc-99