Thyroid hormones – Synthesis and action

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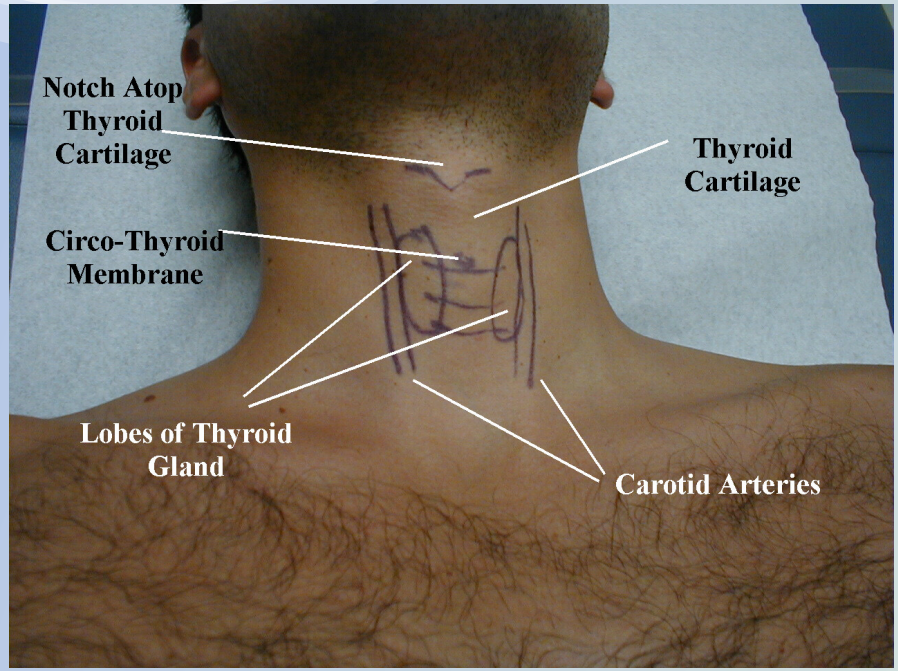
Thyroid gland

The thyroid gland is a midline structure located in the anterior neck.



- The second largest endocrine gland
  - 20 grams in adult
  - Each lobe
    - 2-2.5cm in width and thickness
    - 4cm in height
  - Isthmus
    - 0.5cm thick
    - 2cm height and width

Thyroid gland

The thyroid gland is divided into two lobes connected by the isthmus, which crosses the midline of the upper trachea at the second and third tracheal rings.

In its anatomic position, the thyroid gland wraps around the cricoid cartilage and tracheal rings.

On either side of the thyroid lies the **carotid artery**

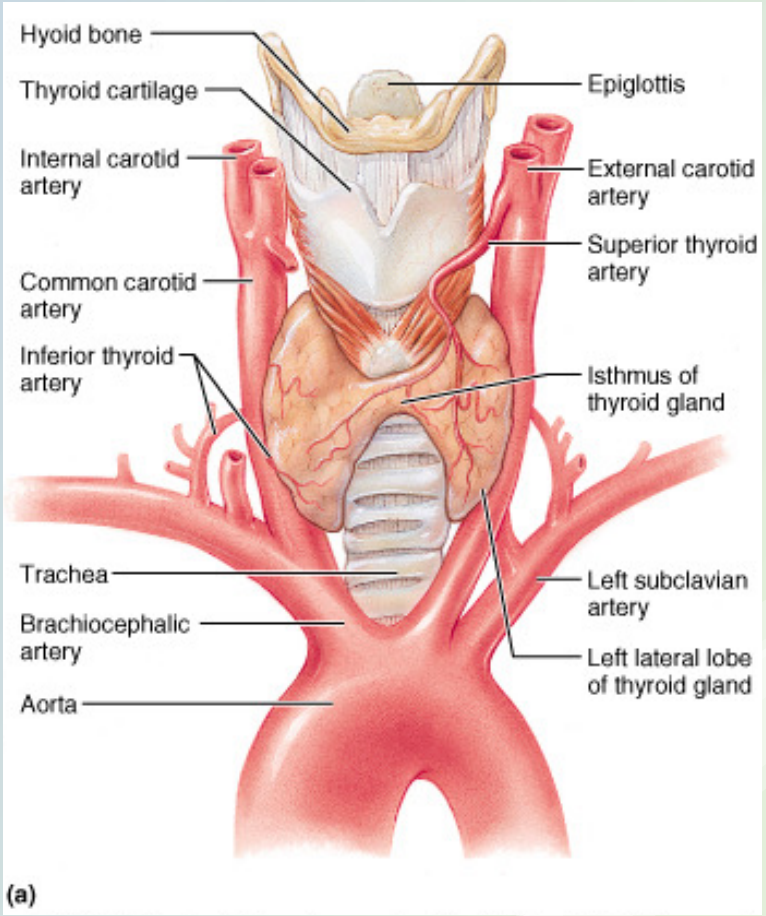
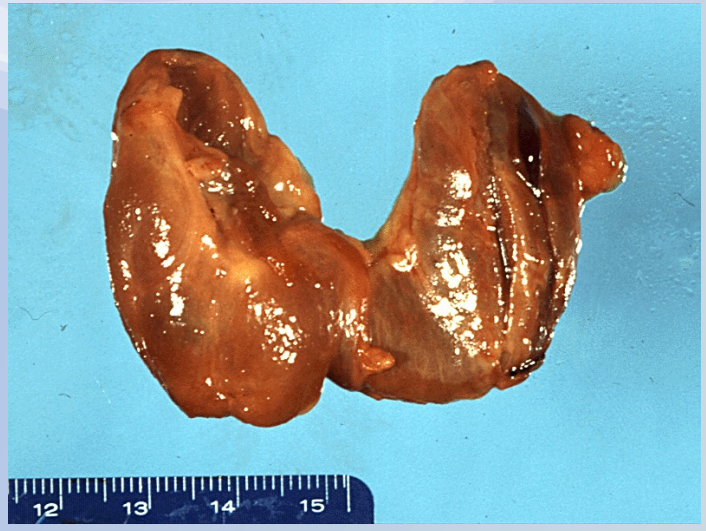
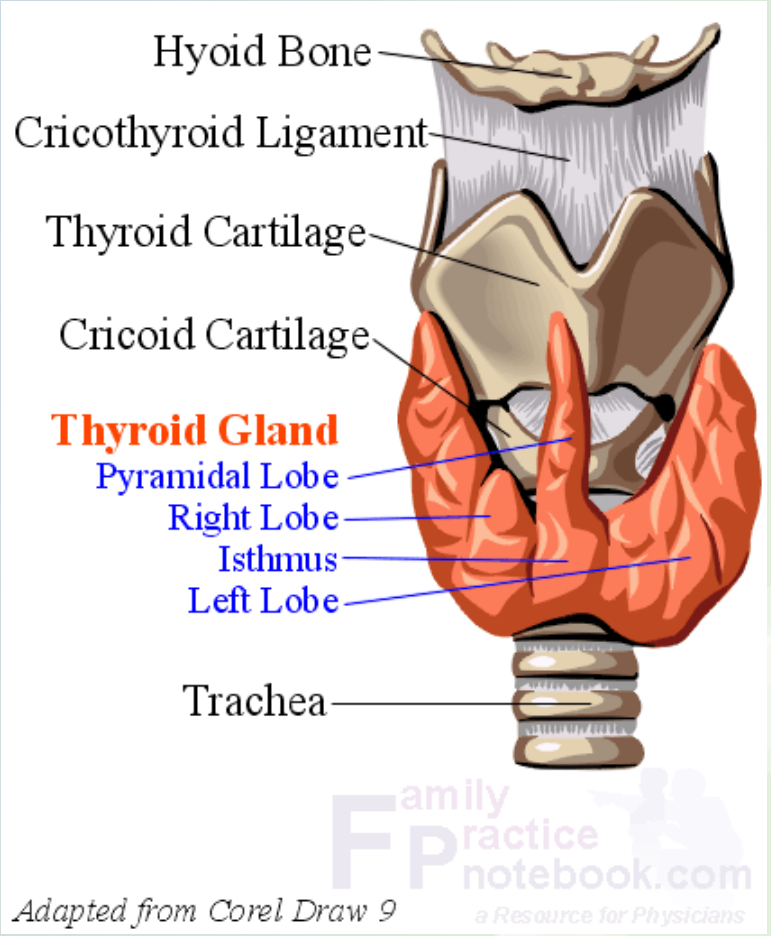


Figure 15.8a

Thyroid gland



Pyramid lobe represents a persistent remnant of the thyroglossal duct



Thyroid gland

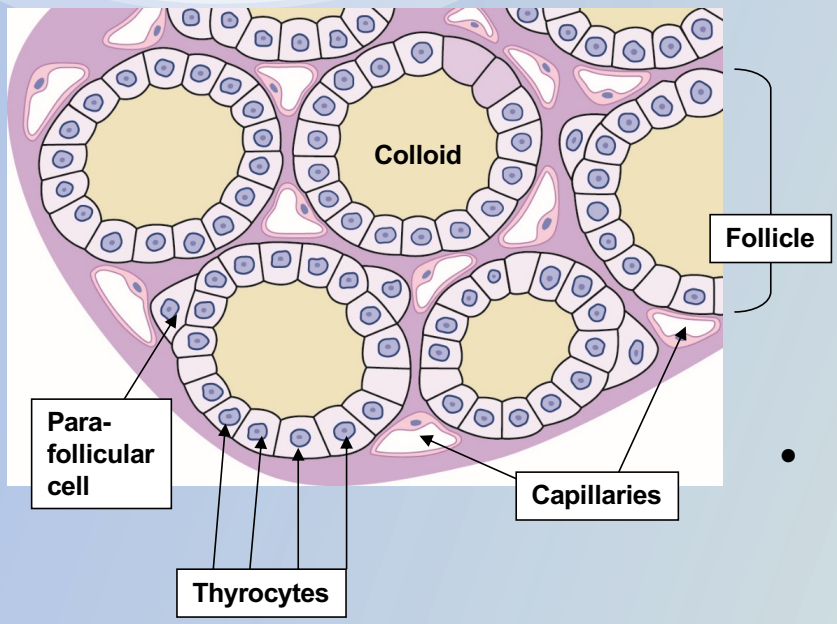
Structure : It consists of many follicles.

Each of these follicles is a set of cells that lie on a basement membrane and form a lumen. The lumen contains a glycoprotein called colloid (thyroglobulin) . There are also extrafollicular hormone-secreting cells called C cells (different embryonic origin).

Hormones that are produced and secreted by thyroid gland :

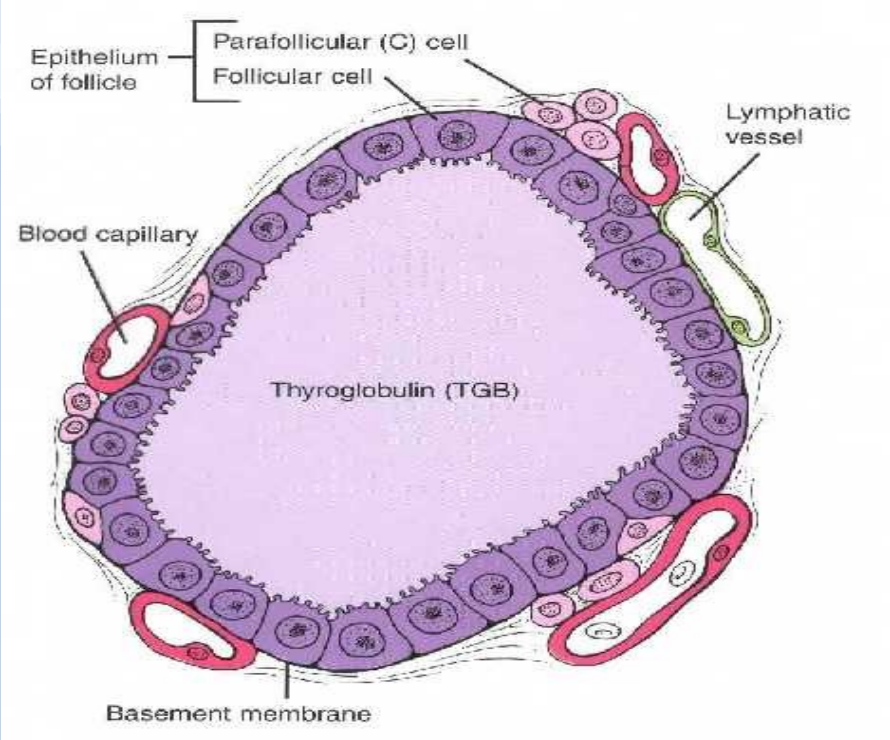
- Thyroxine (T_4) follicular cells
- Triidothyronine (T_3) follicular cells
- calcitonin C cells

Microscopic Structure of the Thyroid



- Thyroid follicles
  - 20 µm in diameter
  - Outer layer of thyroid epithelial cells (thyrocytes)
    - Synthesis of thyroid hormones
  - Colloid in the lumen
    - Depot of thyroid hormones coupled to the carrier protein thyroglobulin
- Parafollicular or C cells
    - Secretion of calcitonin (regulates calcium balance together with parathyroid hormone PTH)

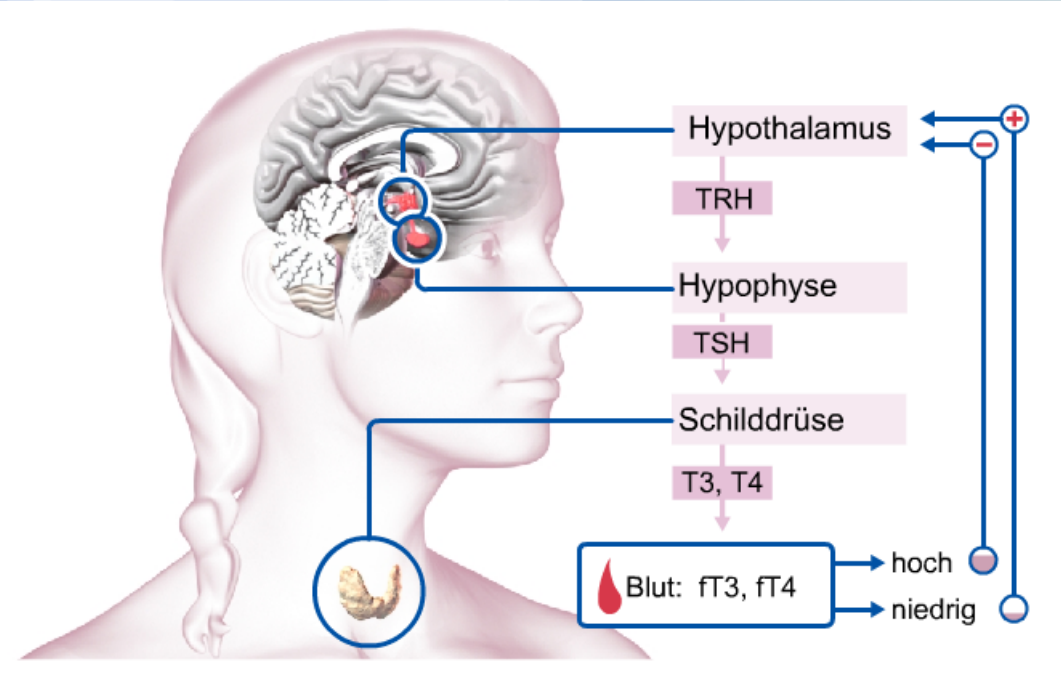
Microscopic Structure of the Thyroid



Histologically, the thyroid gland is organized as epithelial cells surrounding colloid-containing pools, called follicles. Depending on the activity of the gland the epithelial cells can be tall cuboidal (active) of flattened (inactive)

Regulation of Production of Thyroid Hormones

The Negative Feedback Loop



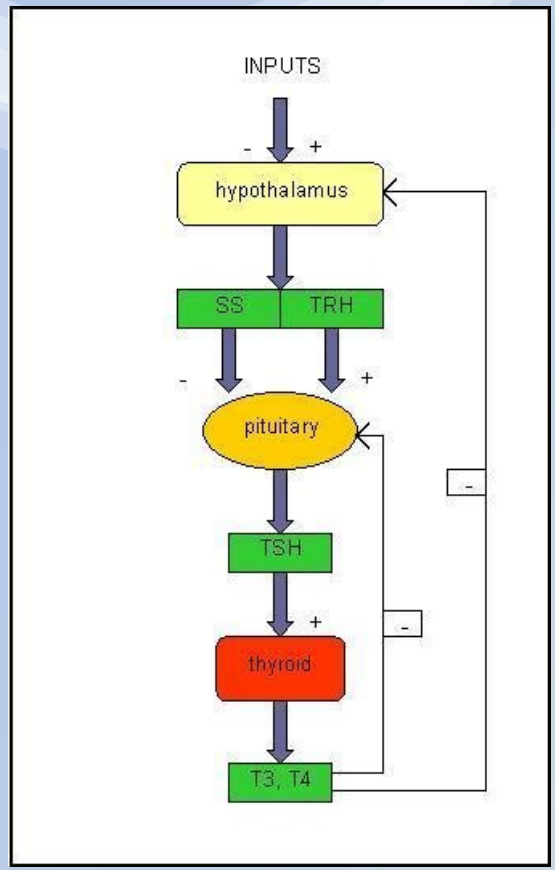
Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus (paraventricular nucleus) and regulates TSH production.

Thyroid-Stimulating Hormone (TSH) is secreted by the pituitary and regulates thyroid hormone production, secretion and growth.

Thyroid gland produces and secretes 2 hormones: thyroxine (T4) and triiodothyronine (T3).

Regulation of Production of Thyroid Hormones

The Negative Feedback Loop



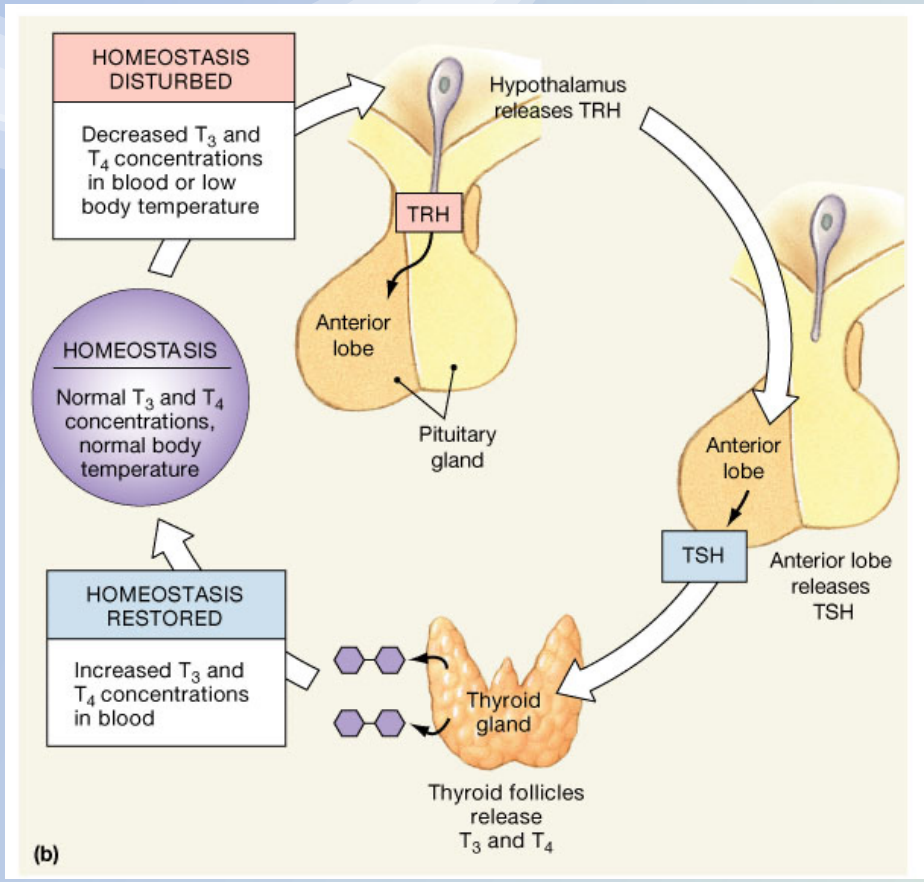
Somatostatin (growth hormone-inhibiting hormone (GHIH)) is produced by **neuroendocrine cells of the ventromedial nucleus of the hypothalamus**.

Thyrotropin-releasing hormone (TRH) is a common prolactin-releasing factor that regulates the synthesis and secretion of prolactin

In any case of hyperprolactinemia we firstly exclude primary hypothyroidism (through blood tests)

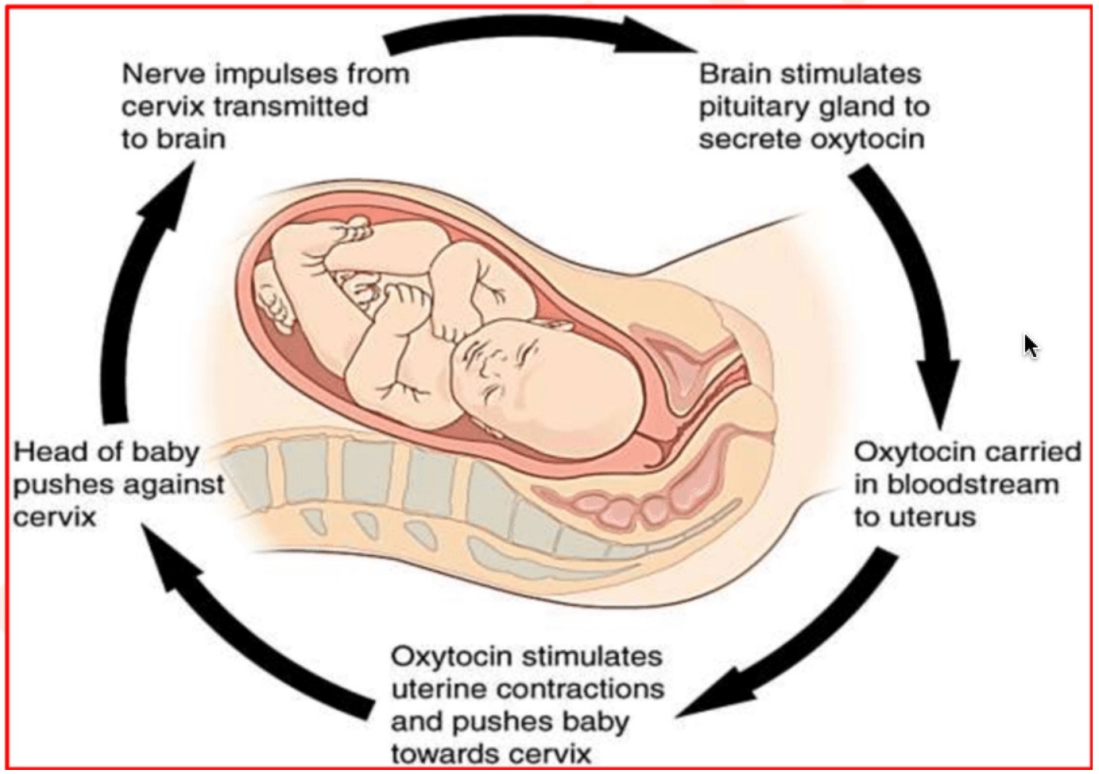
Regulation of Production of Thyroid Hormones

The Negative Feedback Loop



The negative feedback loop between circulating thyroid hormone and the neuroendocrine system (hypothalamus and pituitary gland) is the fundamental mechanism preserving thyroid hormone homeostasis.

Examples of Positive Feedback Loops

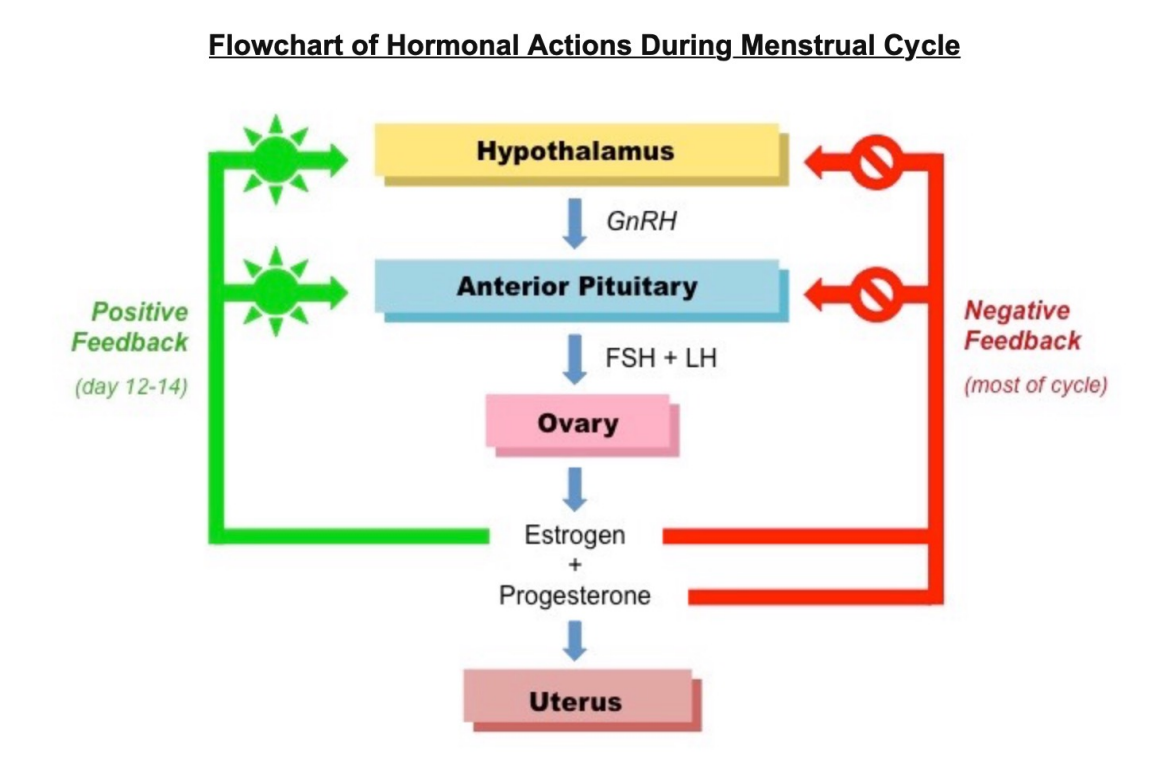


Positive Feedback Loop Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

The release of oxytocin from the posterior pituitary gland during labor is an example of positive feedback mechanism.

Oxytocin stimulates the muscle contractions that push the baby through the birth canal. The release of oxytocin result in stronger or augmented contractions during labor.

Examples of Positive Feedback Loops



Midcycle (during the menstrual cycle) (~ day 12), estrogen stimulates the anterior pituitary to secrete hormones (positive feedback)

This positive feedback results in a large surge of luteinizing hormone (LH) and a lesser surge of FSH

LH surge causes the dominant follicle to rupture and release an egg (secondary oocyte) – this is called ovulation

Synthesis of thyroid hormones- Iodide

- 50 mg of iodides are needed per year
  - 1 mg/week (150µg/ day for adults and adolesences)
- Iodide content of foods differs depending on geochemical conditions
- Major dietary iodine sources today are sea fish, seafood, iodised salt and dairy products

  - 250 µg for pregnant and lactating women

- 1/5 of ingested iodine utilized for hormone synthesis

Synthesis of thyroid hormones- Iodide

- Most thyroid hormone circulating in the blood is bound to transport proteins. Only the free (unbound) hormone is biologically active
- The half-life of T_4 is 5–8 days due to the high protein binding
- When TBG is abnormally high or low, measuring total thyroid hormone levels (TT_4, TT_3) can be misleading

Free T_4 (fT_4)	0.04%
Free T_3 (fT_3)	0.4%
Bound to thyroxine-binding globulin (TBG)	70%
Bound to transthyretin or ‘thyroxine-binding prealbumin’	10–15%
Paraalbumin	15–20%

Synthesis of thyroid hormones

Thyroid hormone synthesis occurs within the follicles of the thyroid gland.

The following steps involved in thyroid hormone synthesis:

(1) inorganic iodide is transported into the gland. The active transport of iodide into the follicular cells is mediated by the sodium iodide symporter (NIS) as the first crucial step in thyroid hormone synthesis

Several mutations in NIS have been identified in individuals with hypothyroidism-associated with impaired iodide uptake.

In these patients, a diffuse or nodular goiter with impaired or highly reduced radioiodine uptake is observed.

Synthesis of thyroid hormones

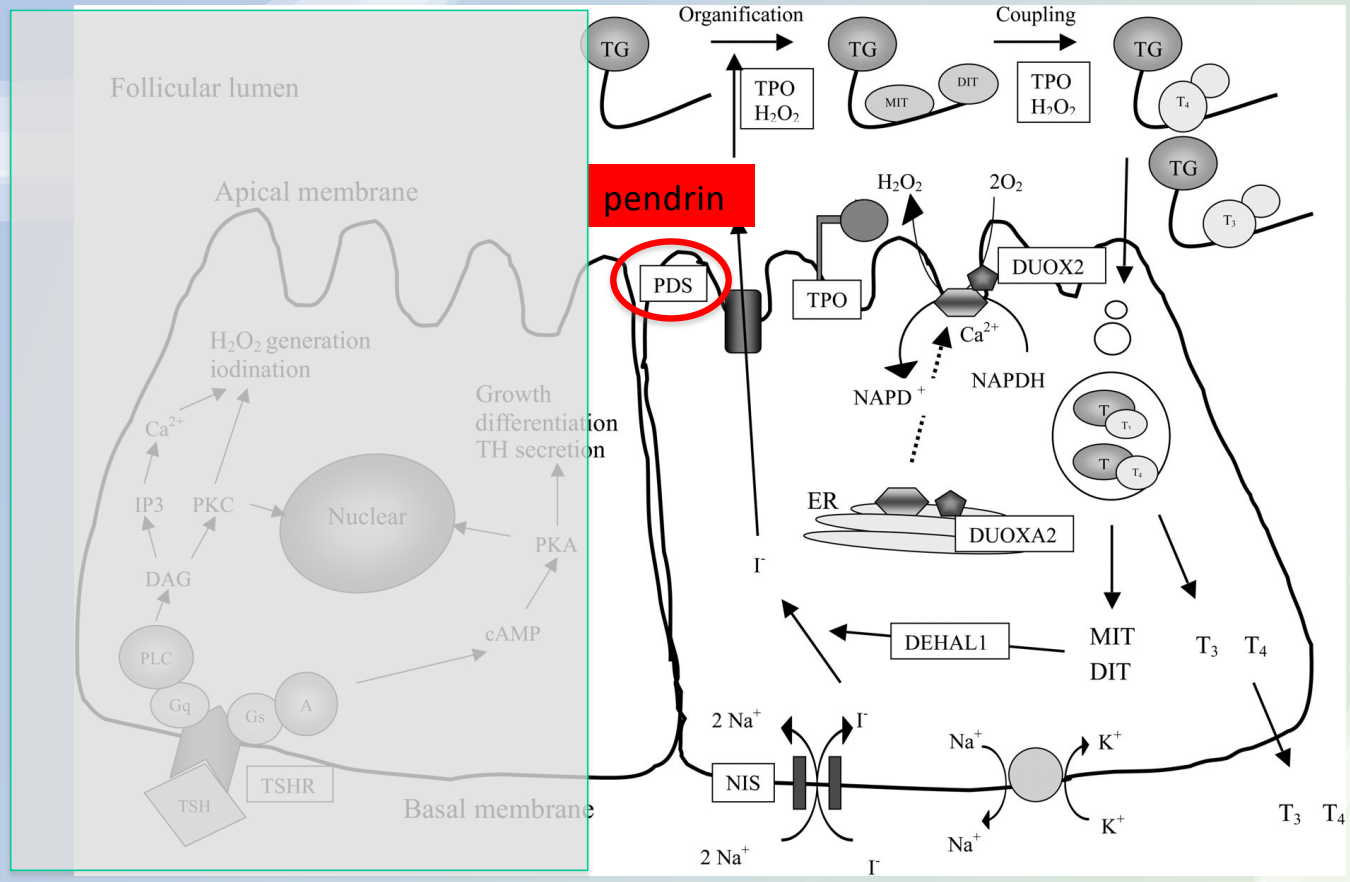
Thyroid hormone synthesis occurs within the follicles of the thyroid gland.

The following steps involved in thyroid hormone synthesis:

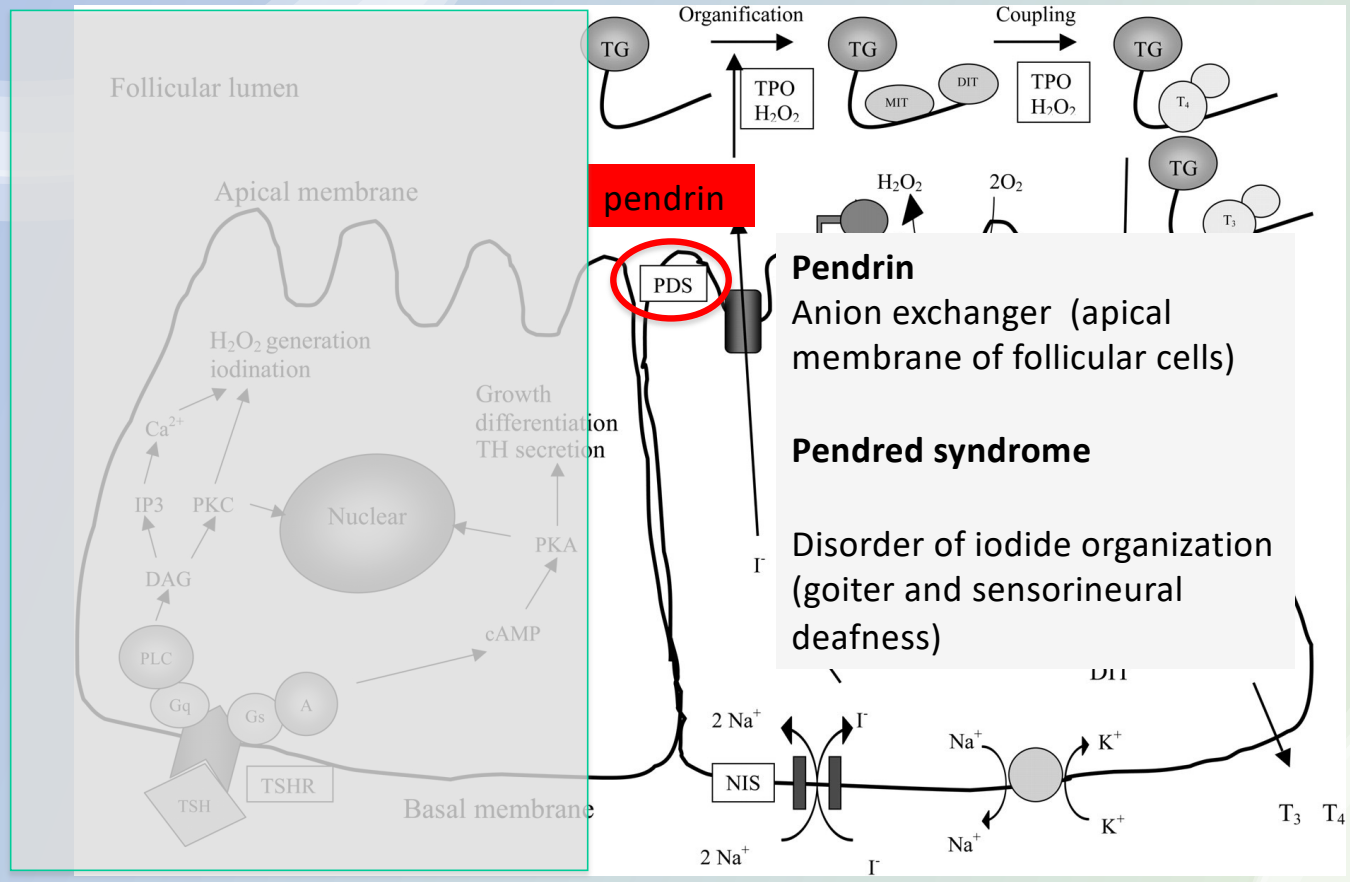
1a) The Iodide taken up by the thyrocytes is transported through the apical membrane by the anion transporter (chloride/iodide transporter), pendrin (SCL26A4) and most likely by other transport systems not yet identified.

Mutations in the *SCL26A4* gene cause Pendred's syndrome, is inherited in an autosomal recessive manner and is characterized by partial iodide organification defect , with or without goiter and hypothyroidism

Synthesis of thyroid hormones



Synthesis of thyroid hormones



Pendrin
Anion exchanger (apical membrane of follicular cells)

Pendred syndrome

Disorder of iodide organization (goiter and sensorineural deafness)

Synthesis of thyroid hormones

Thyroid hormone synthesis occurs within the follicles of the thyroid gland.

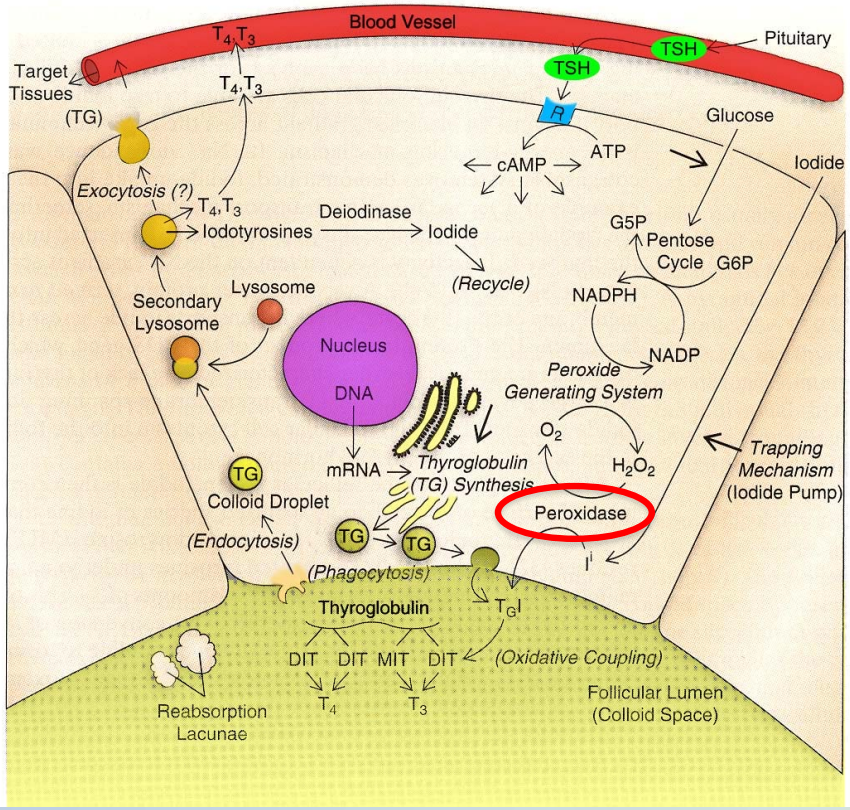
2) intrathyroidal iodide is oxidized to iodine under the influence of H_2O_2 (hydrogen peroxide) and peroxidase (TPO);

The oxidation of iodide requires hydrogen peroxide that is synthesized outside the cell at the apical border.

TPO is a membrane-bound enzyme. It is also a common target antigen in autoimmune thyroid disease (AITD) (thyroiditis Hashimoto)

Synthesis of thyroid hormones

Figure 13.4 Summary scheme of thyroid hormone biosynthesis and secretion.



NADPH as a reducing agent.

Synthesis of thyroid hormones

Thyroid hormone synthesis occurs within the follicles of the thyroid gland.

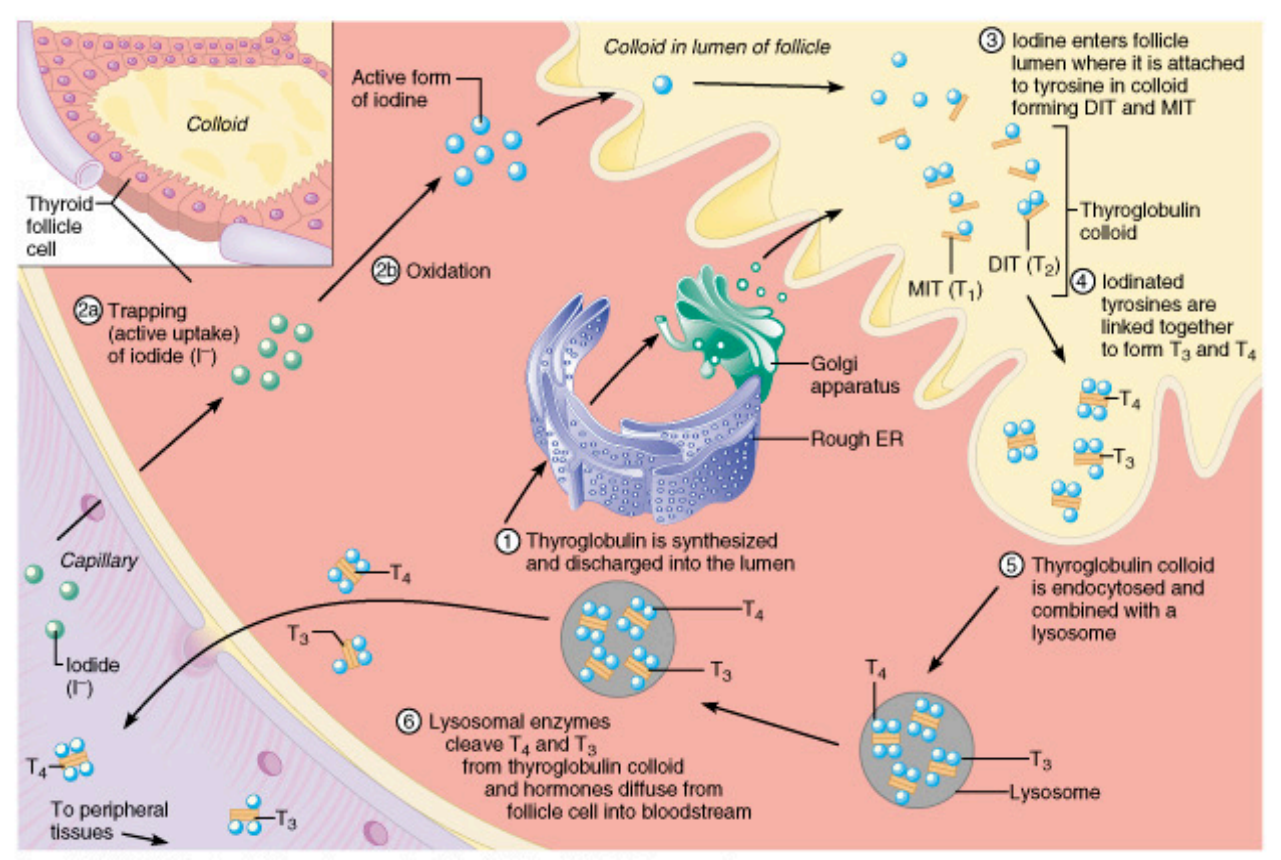
3) iodine is bound in tyrosine residues of thyroglobulin,
forming monoiodotyrosine (MIT) and diiodotyrosine (DIT) (organification)

4) the iodotyrosines are enzymatically coupled to form thyroxine (T4)
and triiodothyronine (T3)

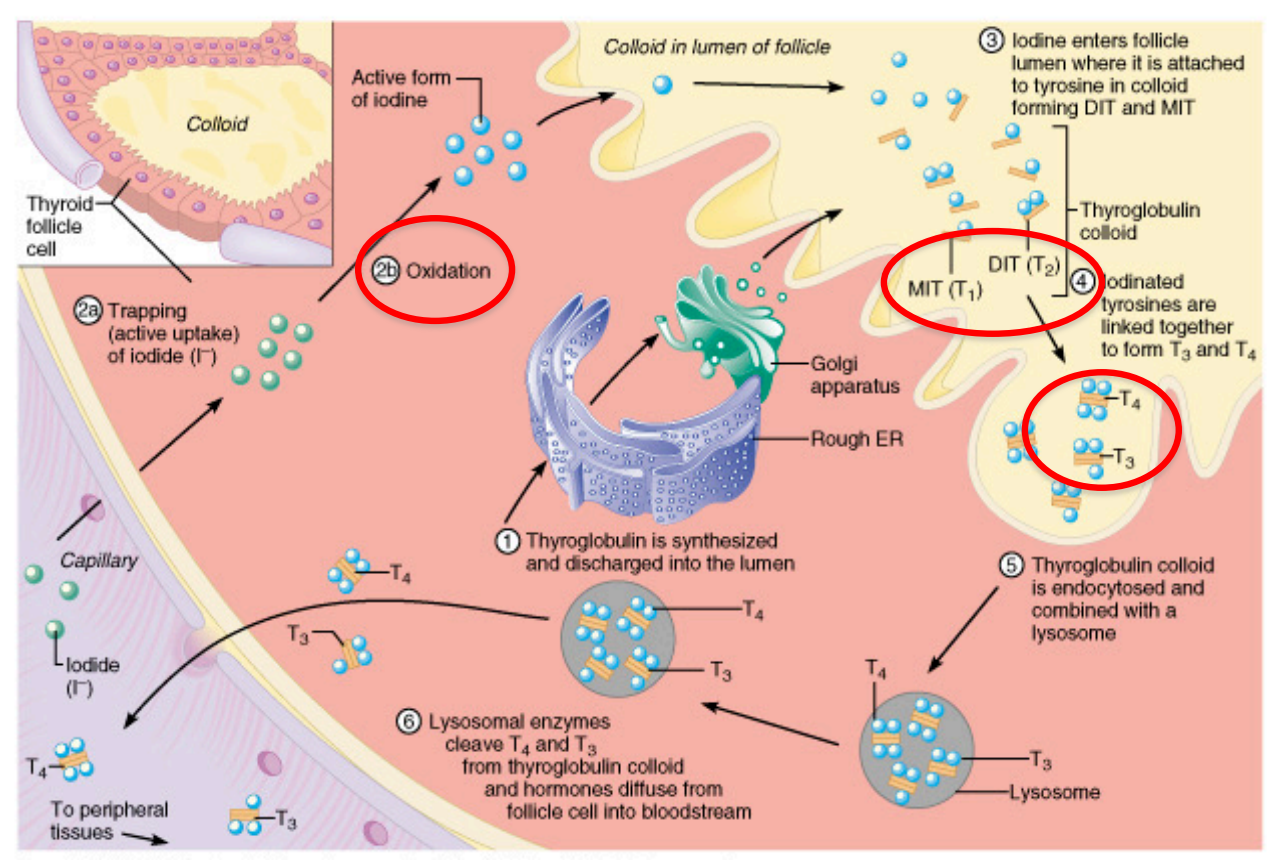
5) the iodothyronines, T4 and T3, are stored in thyroglobulin until released into the circulation

6) lysosomal enzymes cleave the T4 and T3 from thyroglobulin colloid and hormones diffuse from follicle cell into bloodstream

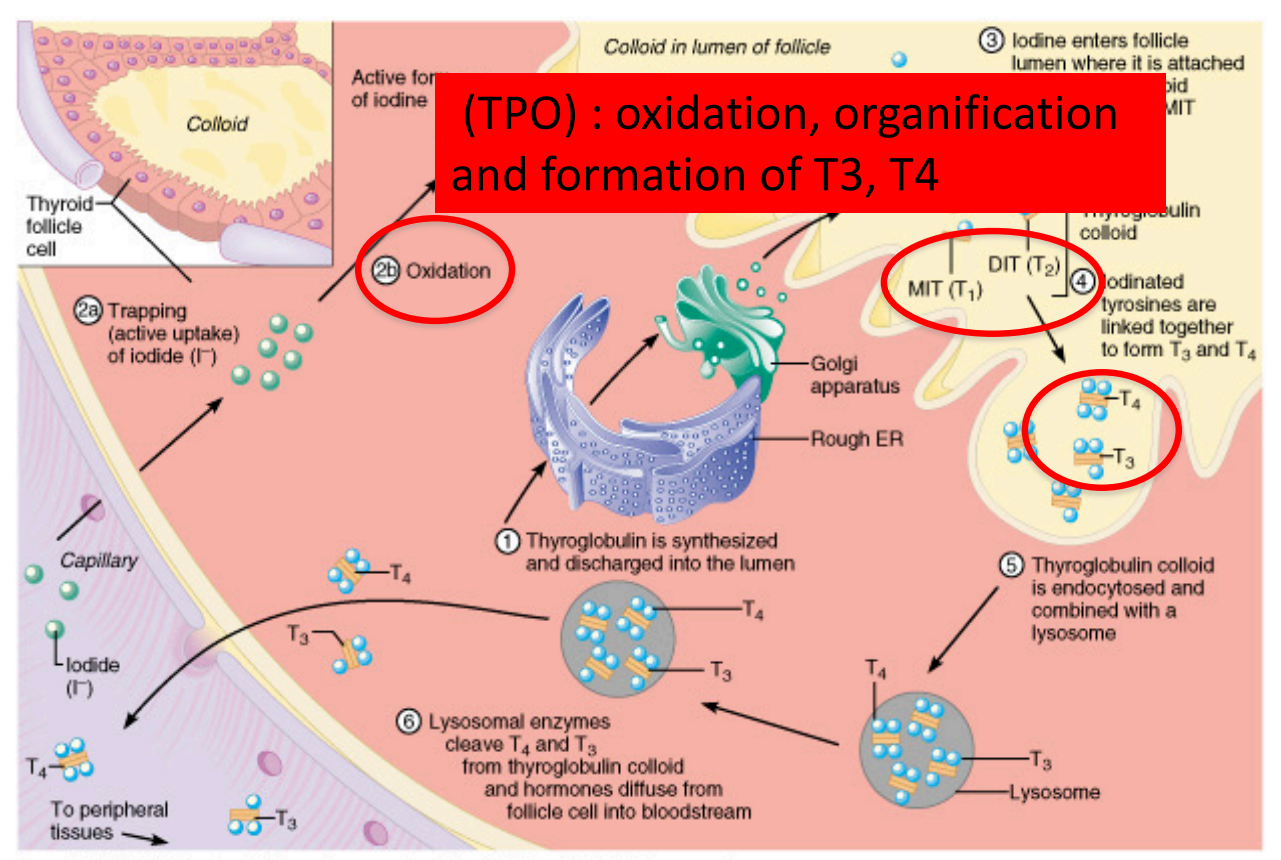
Synthesis of thyroid hormones



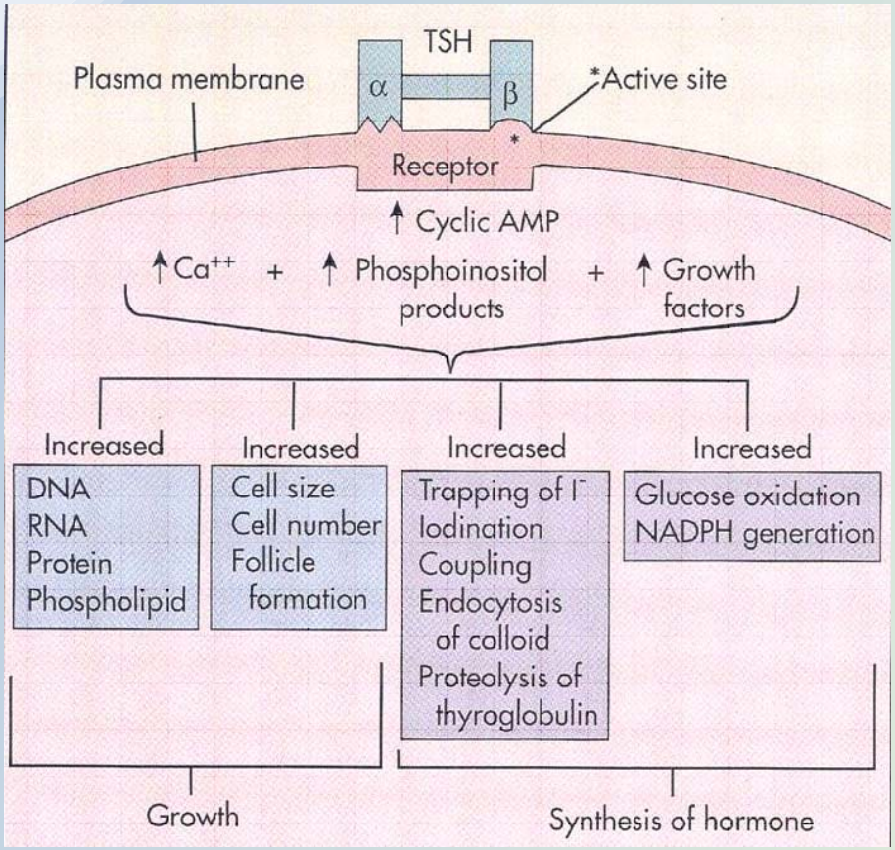
Synthesis of thyroid hormones



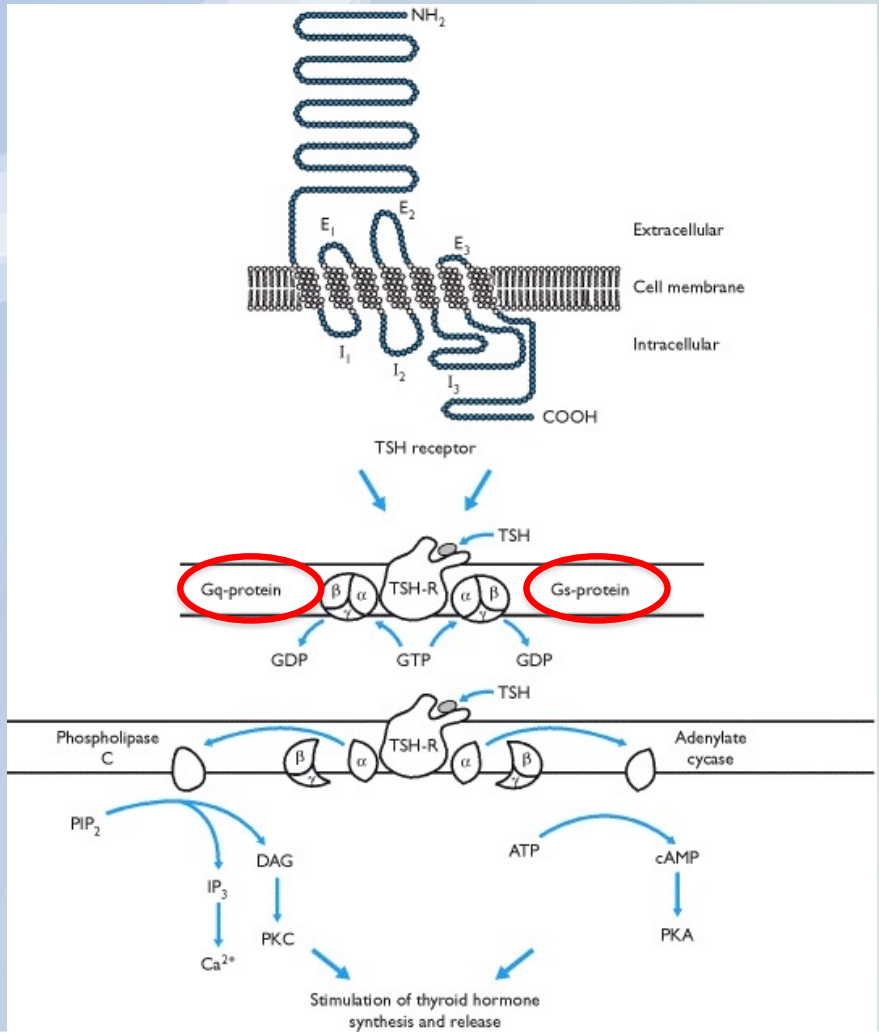
Synthesis of thyroid hormones



- **TSH regulates thyroid growth and the synthesis and secretion of thyroid hormones (all stages)**



TSH receptor signaling



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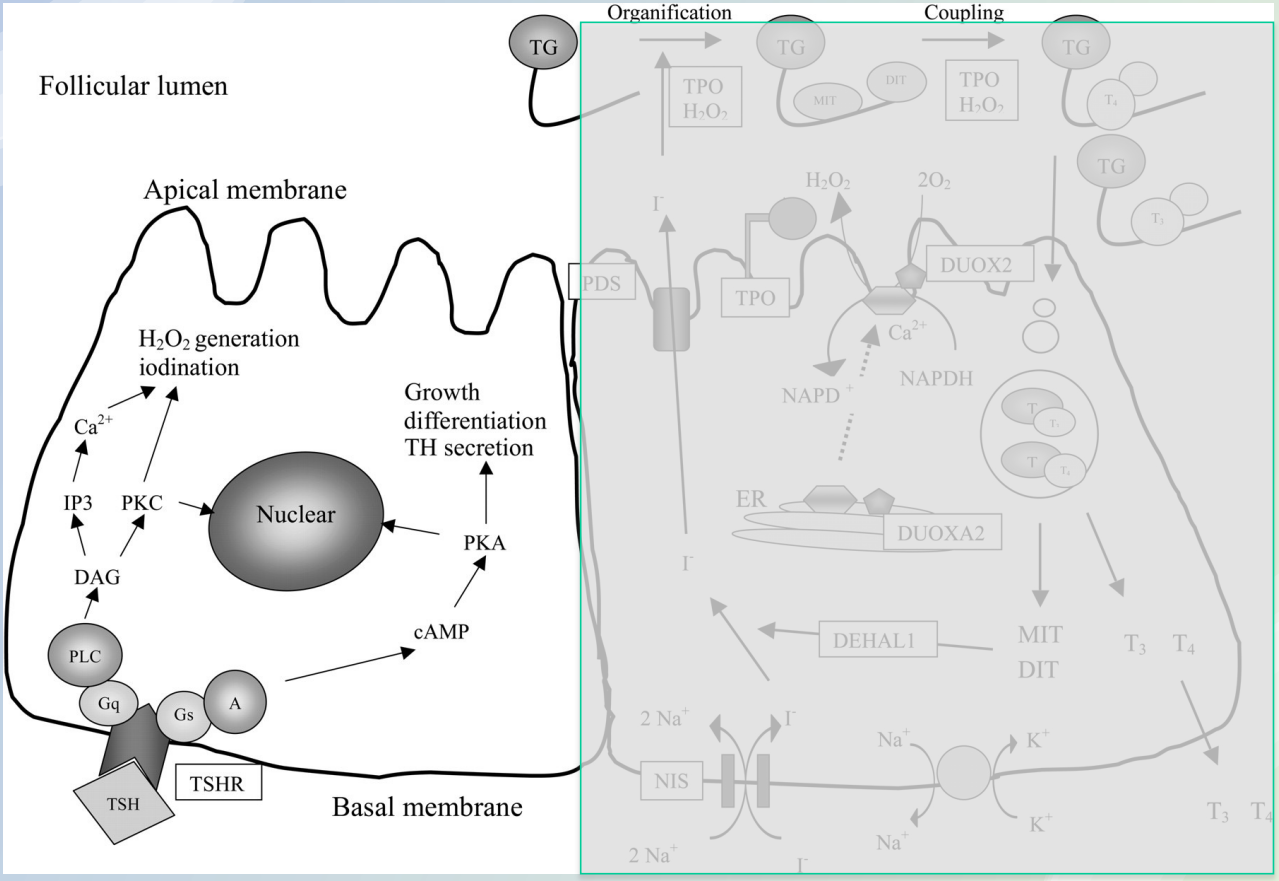
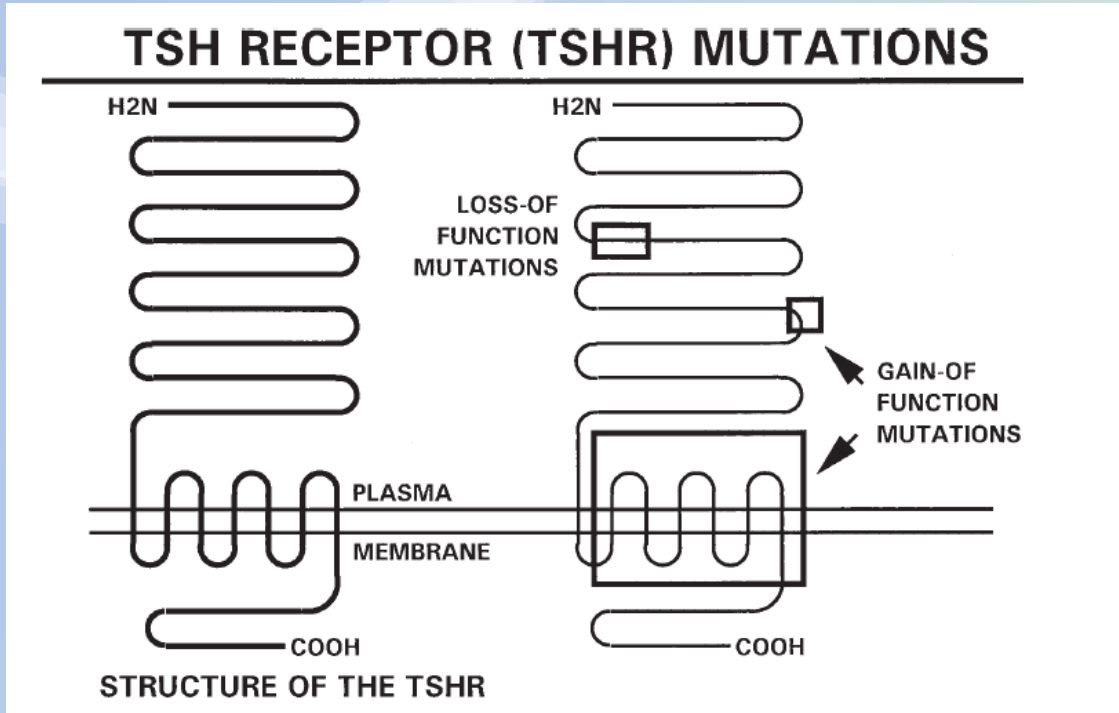


TSH receptor signaling



Extracellular part

seven membrane-spanning domains

Intracellular part

Gain of function mutations : that result in constitutive activation of a receptor (prevent clearance of protein from the cell surface via endocytosis)

Loss of function mutations : cause polypeptide chain termination during translation

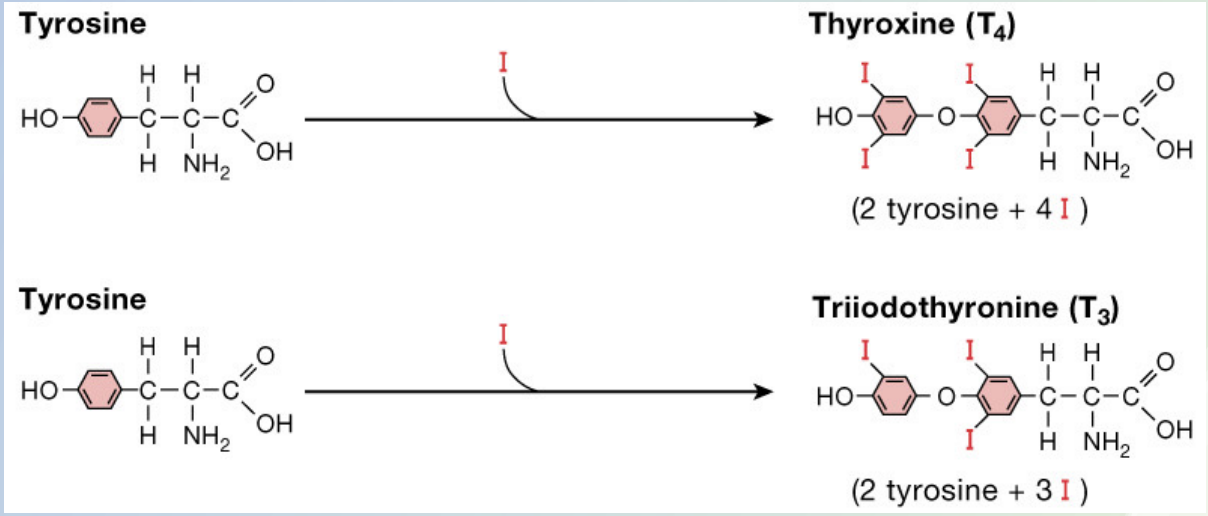
Thyroid hormone - structure

Two thyroid hormones

(T4, thyroxine)

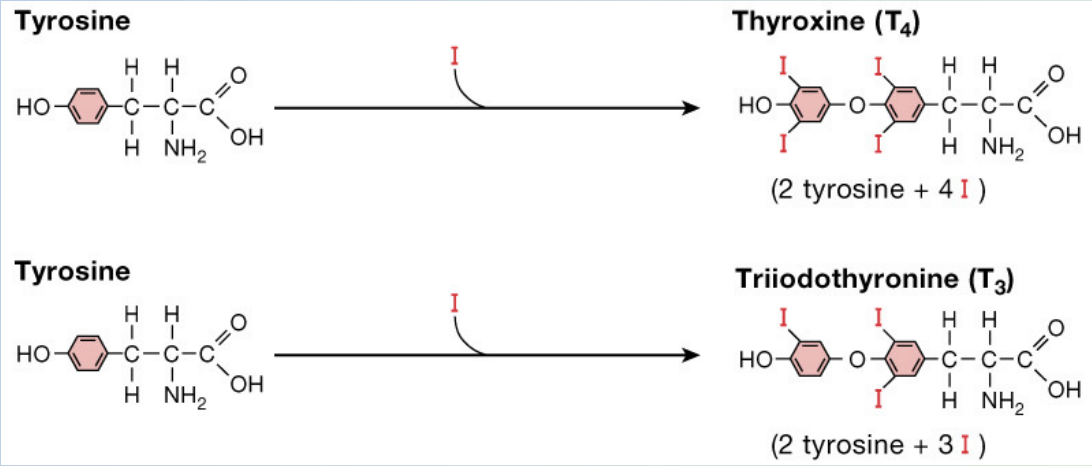
(T3, triiodothyronine)

Chemical structures of the coupled iodinated **tyrosine residues**.



Thyroid hormone - structure

- T4 is the primary secretory product of the thyroid gland, which is the only source of T4 (70-90 µg per day)
- T4 is biologically inactive in target tissues until converted to T3
- Activation occurs with 5' de-iodination of the outer ring of T4

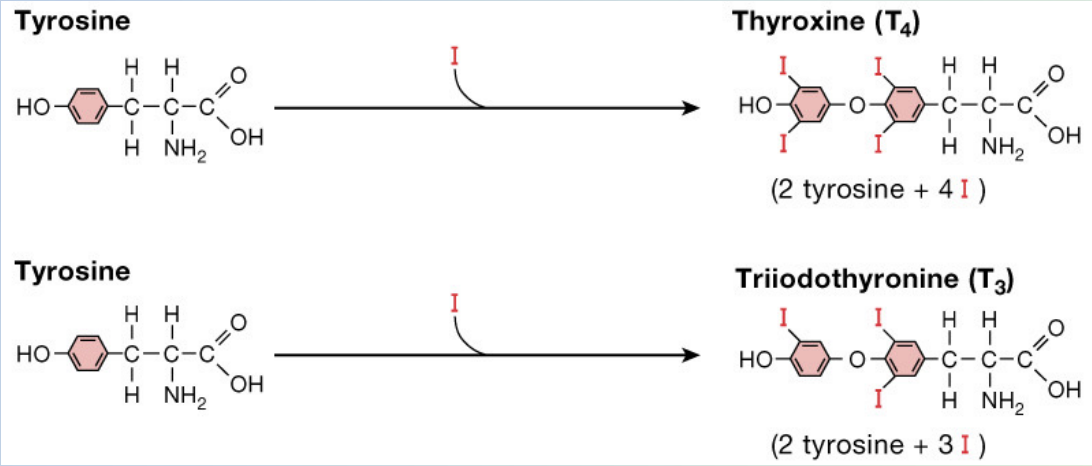


Thyroid hormone - structure

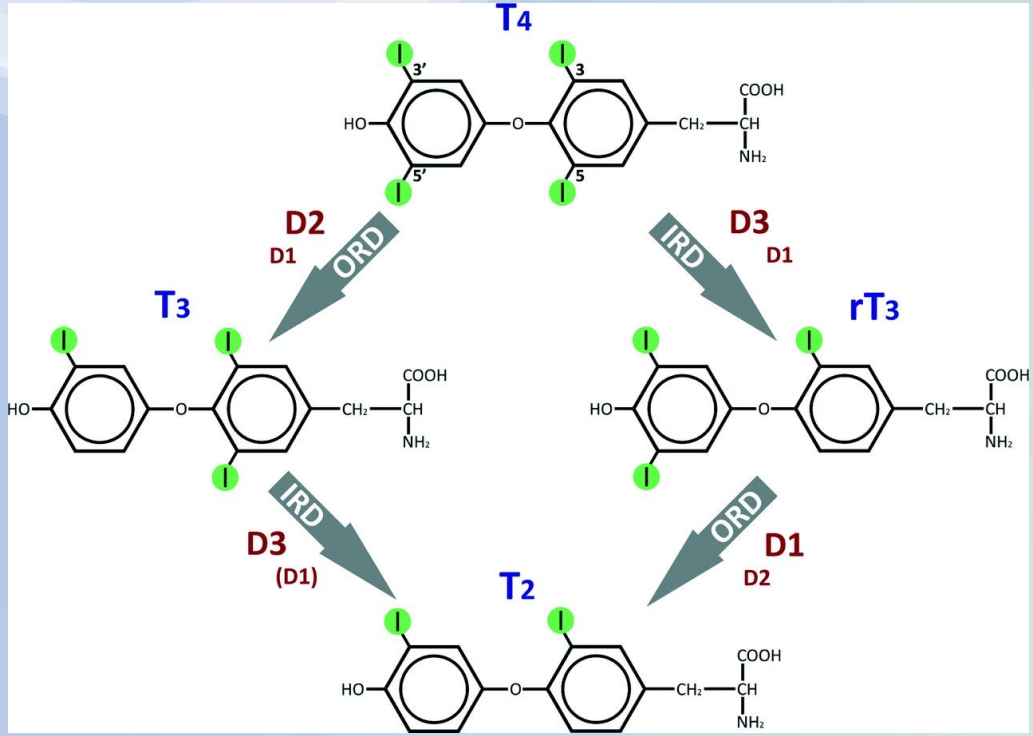
- T3 (15-30 µg per day) is derived from 2 processes:

- 20% comes from direct thyroid secretion

- 80% of circulating T3 comes from deiodination of T4 in peripheral tissues



Major pathways of thyroid hormone deiodination. D1, D2, D3, deiodinase types 1, 2 and 3.



Type 1: deiodinates at both the 5’ and 5 carbon atoms and is found in the liver, kidney, thyroid, pituitary gland and central nervous system. With a high K_m for T_4, it is the only isoenzyme inhibited by PTU. Its activity is increased in hyperthyroidism and reduced in hypothyroidism.

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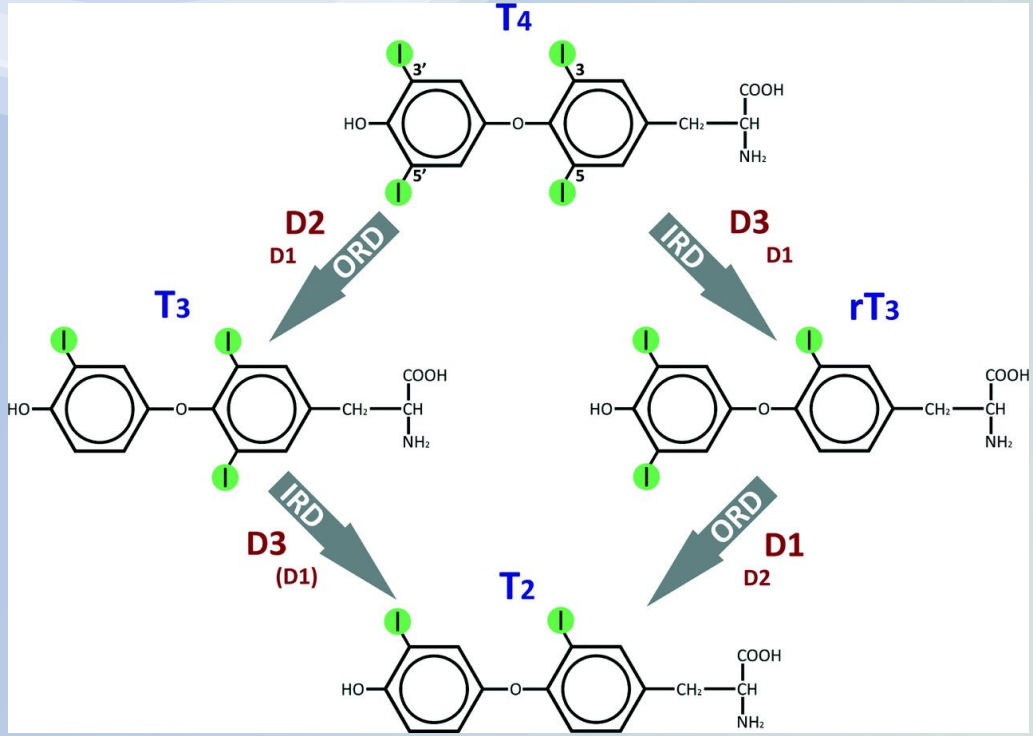
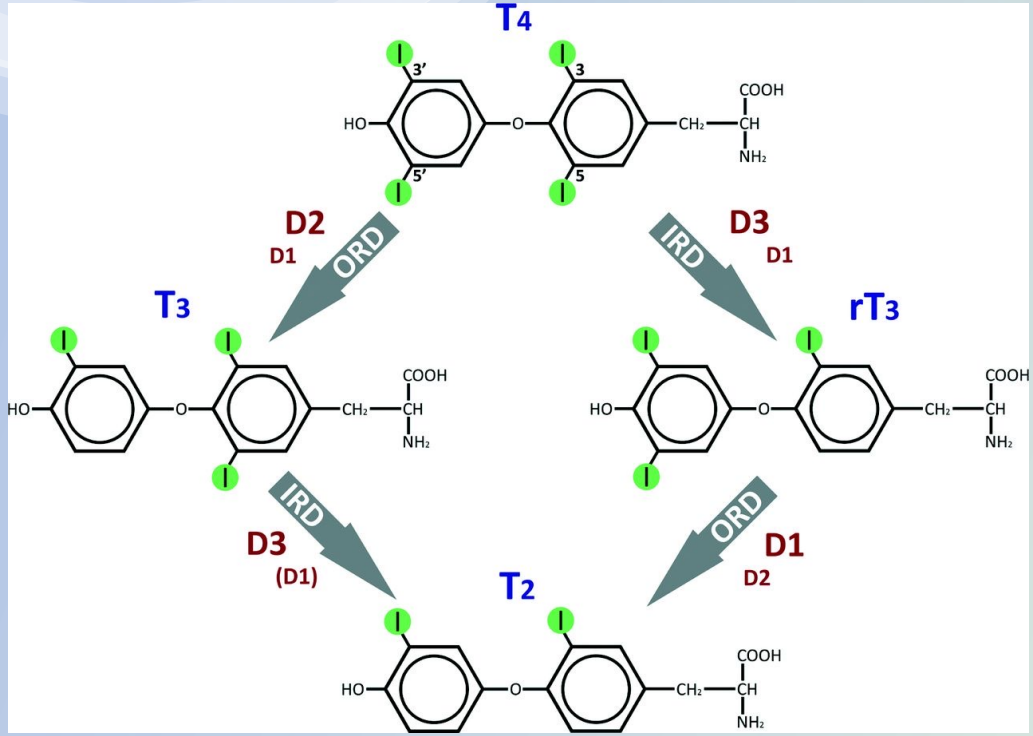


Type 2: deiodinates only at the 5′ position and is found in brain, brown fat, placenta and pituitary gland. With a lower K_m than Type 1, it is considered to maintain intracellular concentrations of T_3. This is important in the negative feedback actions of T_4 on the pituitary gland. Its activity is decreased in hyperthyroidism and increased in hypothyroidism.

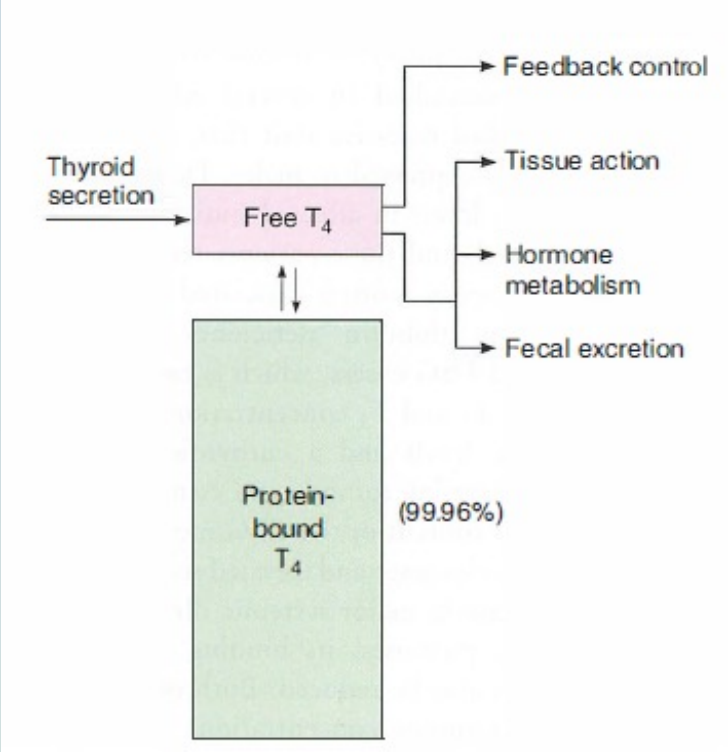
Major pathways of thyroid hormone deiodination. D1, D2, D3, deiodinase types 1, 2 and 3.



Type 3: deiodinates only at the 5 position and is found only in brain and placenta. As it is incapable of converting T_4 to the active T_3, it may protect the brain and fetus from excess active T_3.

Thyroid hormone transport

- Only 0.04% of T4 and 0.4% of T3 free.
- The rest is protein-bound.
- Major thyroid hormone transport proteins:
  - thyroxine-binding globulin (TBG)
  - transthyretin
  - albumin



Thyroid hormone transport

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- The half-life of T_4 is 5–8 days due to the high protein binding
- When TBG is abnormally high or low, measuring total thyroid hormone levels (TT_4, TT_3) can be misleading

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Paraalbumin	15–20%

Thyroid hormone transport (TBG)

Causes of abnormal plasma TBG concentrations

Increase
genetic
pregnancy
oestrogens, including oestrogen-containing oral contraceptives

Decrease
genetic
protein-losing states, e.g. nephrotic syndrome
malnutrition
malabsorption
acromegaly
Cushing's syndrome
corticosteroids (high dose)
severe illness
androgens

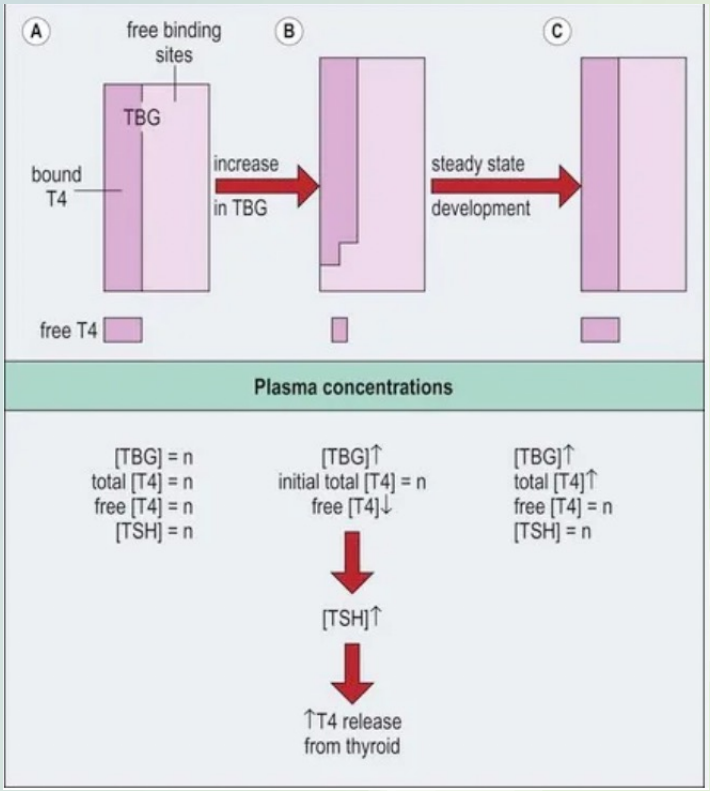
Thyroid hormone transport (TBG)

Increase in TBG

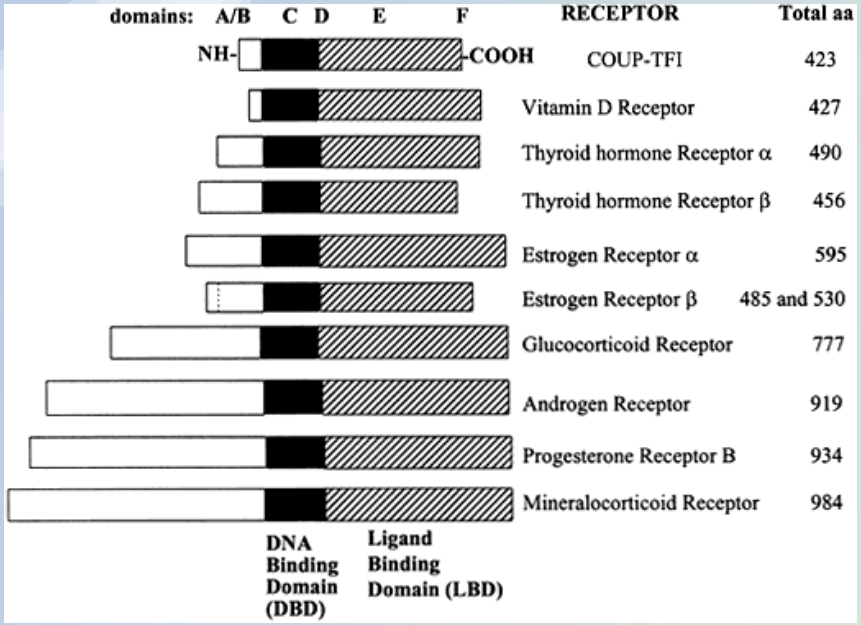
- the concentration of free thyroid hormones falls.
- decrease in the concentration of free thyroid hormones in the circulation stimulates TSH secretion,
- which in turn causes an increase in the production of free thyroid hormones.
- A new equilibrium is eventually reached at which the total quantity of thyroid hormones in the blood is elevated but the concentration of free hormones, the rate of their metabolism, and the rate of TSH secretion are normal.

Decrease in TBG

- Corresponding changes in the opposite direction occur when the concentration of thyroid-binding protein is reduced. Consequently, patients with elevated or decreased concentrations of binding proteins, particularly TBG, are typically neither hyper- nor hypothyroid; that is, they are **euthyroid**

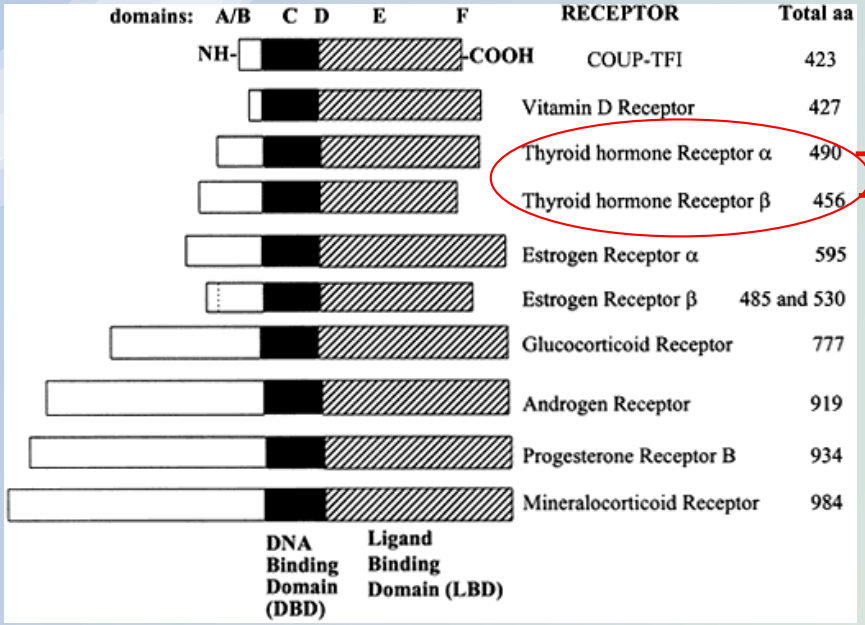


Thyroid hormone Receptors



- Thyroid hormone receptors (TRs) are members of the large nuclear receptor superfamily (NRs), along with other receptors such as RAR, VDR, PPAR
- TRs bind with 10- to 15-fold greater affinity to T3 than T4

Thyroid hormone Receptors

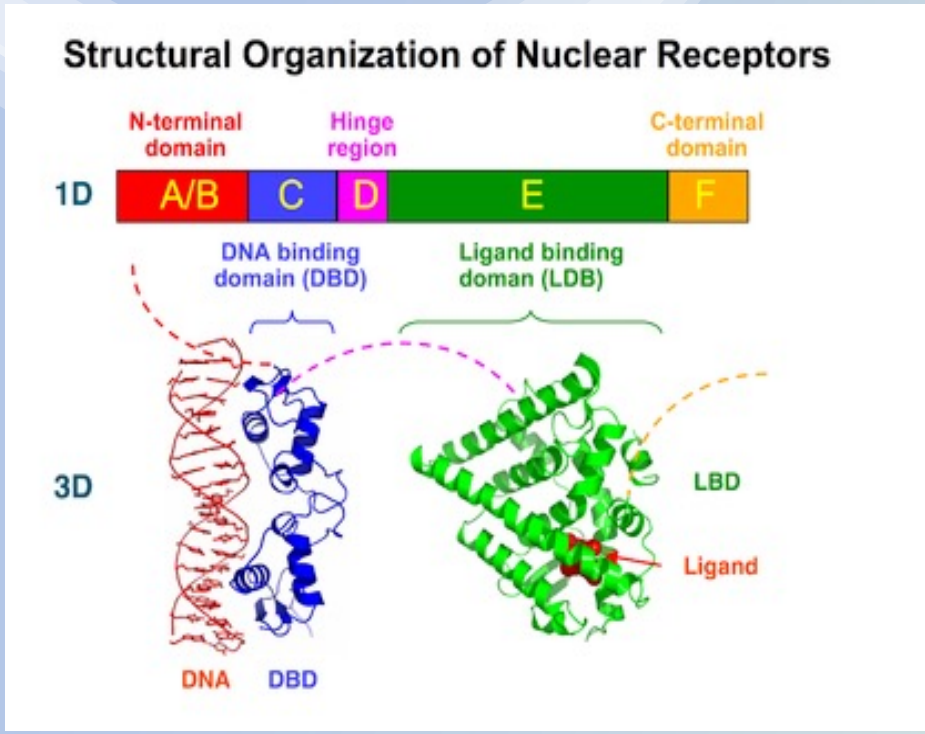


Chromosome 17

Chromosome 3

- The thyroid hormone receptors, TRα and TRβ, are ligand-dependent transcription factors that regulate gene expression by recruitment of coactivators and corepressors.
- The TRα and TRβ isoforms are the products of distinct genes residing on separate chromosomes

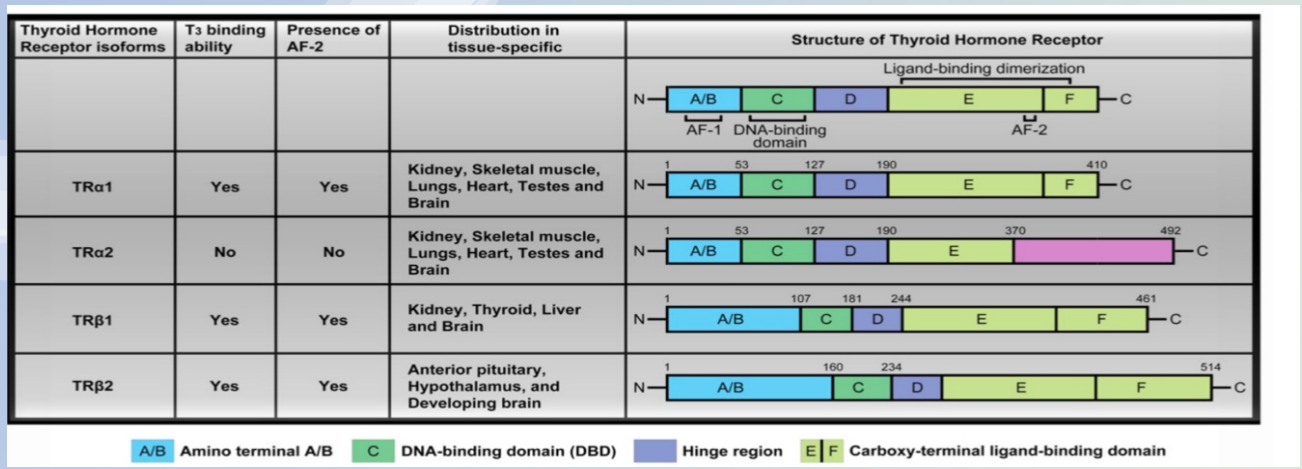
Thyroid hormone Receptors



- The NTD (N-terminal transactivation) domain varies among the different isoforms
- The DNA-binding domain (DBD) is highly conserved and contains two “zinc fingers” that interact with the thyroid hormone response elements (TREs) of DNA in the promoter of the target genes
- The hinge region containing the nuclear localization signal
- The ligand-binding domain (LBD, in C-terminal) is comprised of twelve amphipathic helices, some of which specifically interact with coactivators and corepressors.

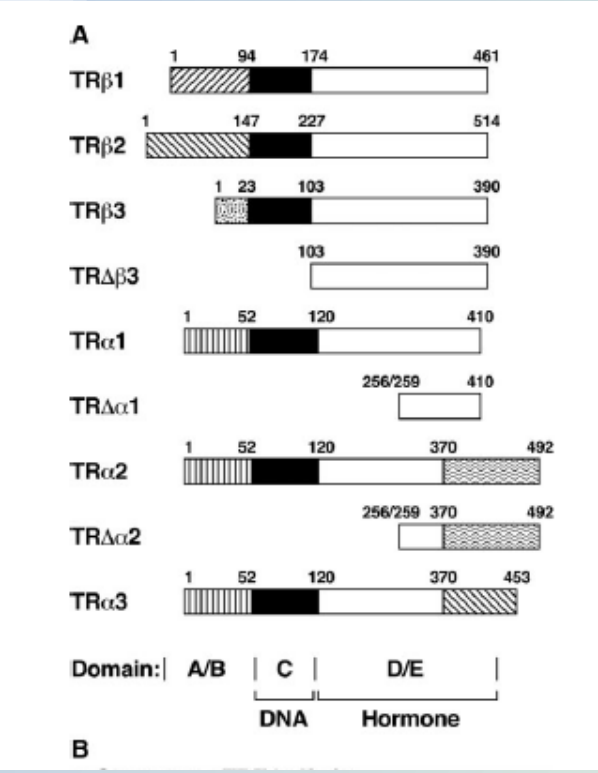
Thyroid hormone Receptors

Thyroid Hormone Receptor isoforms	T_3 binding ability	Presence of AF-2	Distribution in tissue-specific	Structure of Thyroid Hormone Receptor
TRα1	Yes	Yes	Kidney, Skeletal muscle, Lungs, Heart, Testes and Brain	
TRα2	No	No	Kidney, Skeletal muscle, Lungs, Heart, Testes and Brain	
TRβ1	Yes	Yes	Kidney, Thyroid, Liver and Brain	
TRβ2	Yes	Yes	Anterior pituitary, Hypothalamus, and Developing brain	



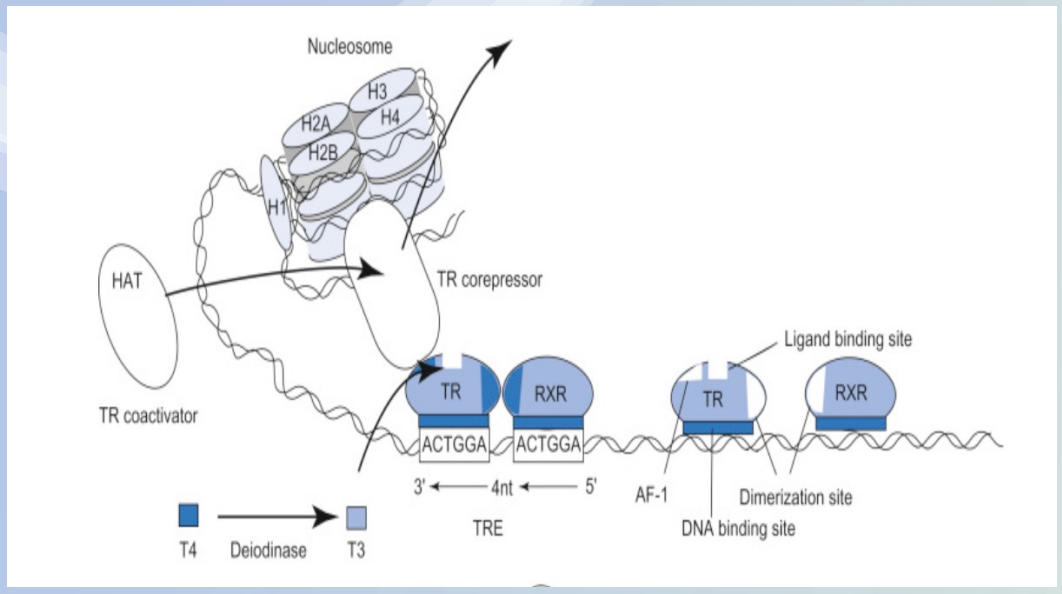
- THRα and THRβ are widely expressed in all tissues but exhibit differential expression in developmental and tissue-specific patterns and in distinct ratios in adult tissue.
- Regarding the tissue distribution of TRs, the predominant type of thyroid receptor in brain (except pituitary), heart and bone is TRα, while in kidney, thyroid and pituitary it is TRβ.
- Due to the high sequence homology, the isoforms of THRα and THRβ do share overlapping as well as distinct biological roles
- The distinct roles probably arise from the variants ability to bind ligands other than T_3 or recruit transcription factors into complexes with different transcriptional results.

Thyroid hormone Receptors



Thyroid hormone Receptors – Mechanism of action

➢ Genomic actions



B. **Consensue TRE sequence**

Half-site :	(A/G)GGT(C/A/G)A
Direct-repeat (DRs) :	5' AGGTCA NNNN AGGTCA 3'
Inverted-repeat arrangements (IPs) :	5' TGACCT NNNNNN AGGTCA 3'
Palindromic (Pal) :	5' AGGTCATGACCT 3'

The TR binds to a TRE, which consists of specific nucleotide sequences. The one shown is called a **direct repeat**, consisting of two sets of six nucleotides separated by four nucleotides of variable composition. The TR binds to one half-site in the TRE on its DNA-binding domain. The second half-site is occupied by a retinoid X receptor (RXR), which forms a heterodimer with the TR. This binding occurs in the absence of T3. In this case, the TR binds one of a variety of TR corepressors that inhibits transcription, probably through histone deacetylase activity.

Thyroid hormone Receptors – Mechanism of action

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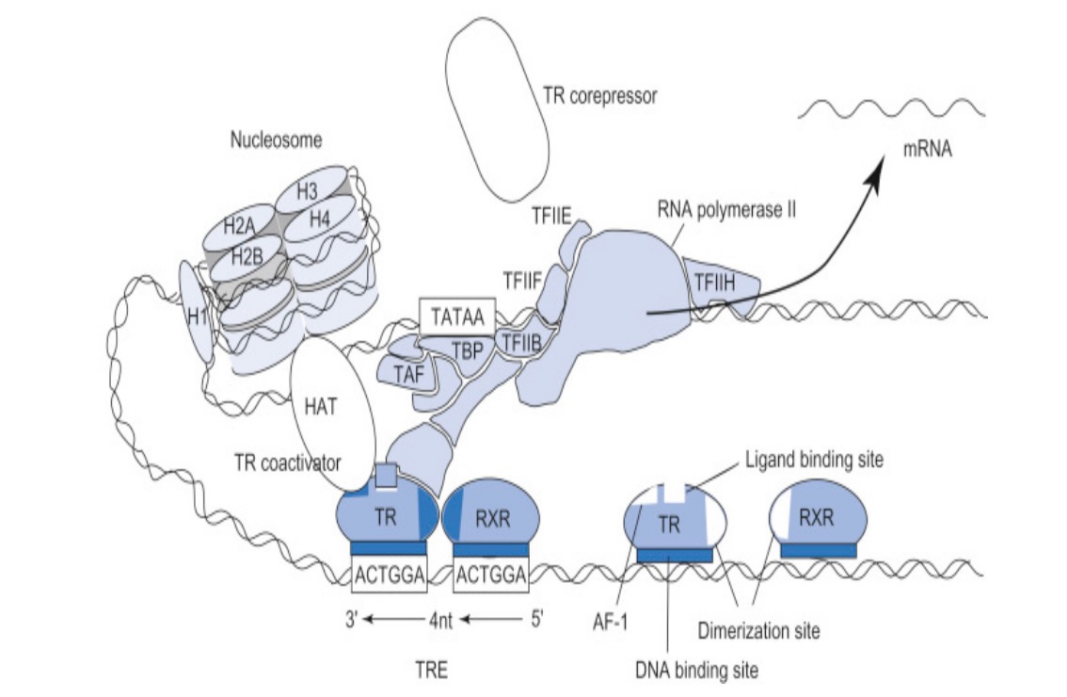
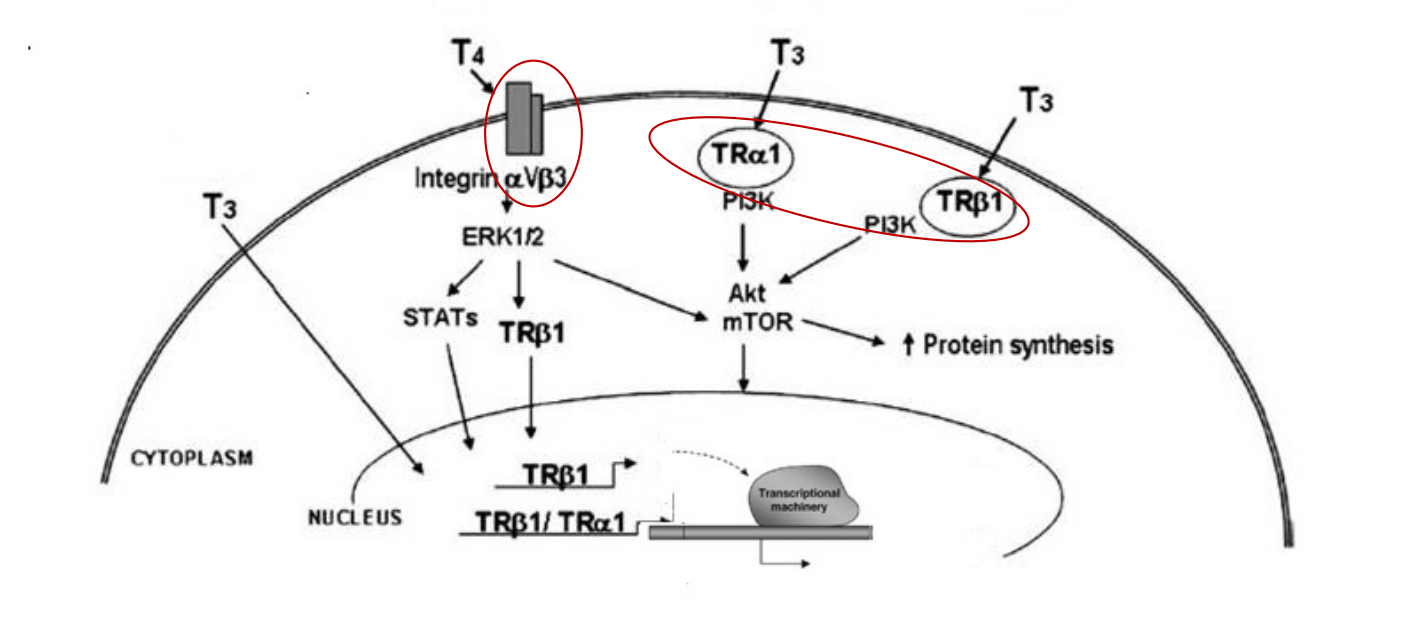


When T3 binds to the TR, a TR coactivator displaces the corepressor. There are several varieties of coactivator. Many of these activators have histone acetyl transferase activity (HAT). The unraveling of the DNA and exposure of the TATA box recruits a variety of proteins, culminating in the stabilization of the preinitiation complex and activation of RNA polymerase II to transcribe mRNA from the DNA template.

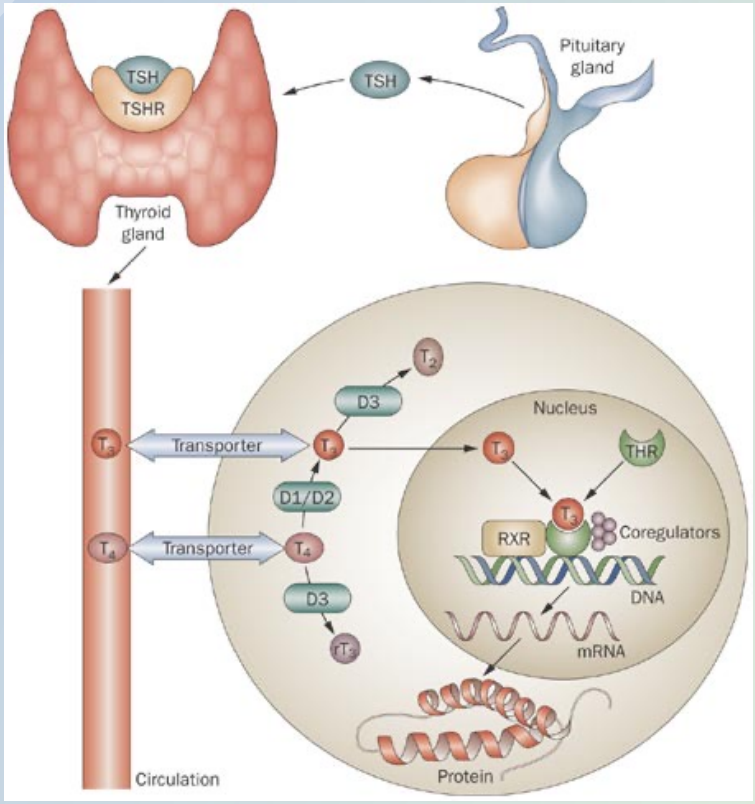
Thyroid hormone Receptors – Mechanism of action

➢ non Genomic actions



Nongenomic actions of thyroid hormones have been described at the plasma membrane, in the cytoplasm and in mitochondria but their physiological importance is unclear. The αVβ3 integrin mediates cell surface responses to T4 acting, for example, via the MAPK pathway to stimulate cell proliferation and angiogenesis. TRβ also mediates rapid responses to T3, acting via the PI3K/AKT/mTOR/$p70^{S6K}$ and PI3K pathways

Thyroid hormone Receptors – Overview



The Thyroid: Driving Metabolism

The thyroid gland produces, stores and secretes thyroid hormones which affect

- Growth and development
- Energy metabolism and oxygen consumption
  - Responsible for the basal metabolic rate
    - Deficiency = 40-50% fall in metabolic rate
    - Excess = 60-100% increase in metabolic rate
- Protein and carbohydrate metabolism
- Lipid metabolism
- Bone metabolism
- Muscle function
- Fertility and pregnancy
- Cardiovascular system
- Brain, nervous system
- *Increase the sensitivity of heart and nervous system in catecholamines*

Main Blood Tests for Thyroid function

- TSH (0.4 to 4 µU/mL) (the most sensitive index of thyroid function)
- T4 and FT4 (prefer FT4) - is more reliable than T3 in assessing thyroid function in patients with hypothyroidism
- T3 and FT3 (prefer T3)
- anti-TPO
- anti-TG
- Calcitonin
- Thyroglobulin (in cases of thyroid cancer)

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Definitions of thyroid function

- **Euthyroidism**
  - TSH 0.4–4.0 (2.5) mU/L, fT_4 normal
- **subclinical hypothyroidism**
  - TSH ↑, fT_4 normal
- **Overt hypothyroidism**
  - TSH ↑↑, fT_4 ↓
- **Subclinical hyperthyroidism**
  - TSH ↓, fT_3 normal
- **Overt hyperthyroidism**
  - TSH ↓↓, fT_3/fT_4 ↑

Types of hypothyroidism

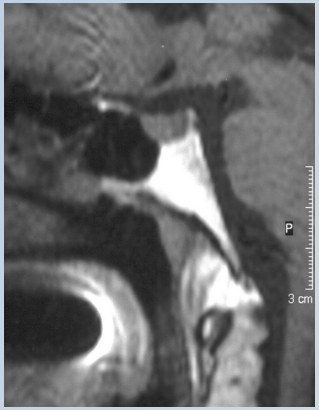
- **Classification by time of onset**
  - Congenital
  - Acquired
- **Classification by level of endocrine dysfunction responsible(aetiology)**
  - Primary
  - Secondary (central)
    - Primary hypothyroidism is much more common than secondary hypothyroidism (about 1000:1)
- **Classification by severity**
  - Overt (clinical)
  - Mild (subclinical)

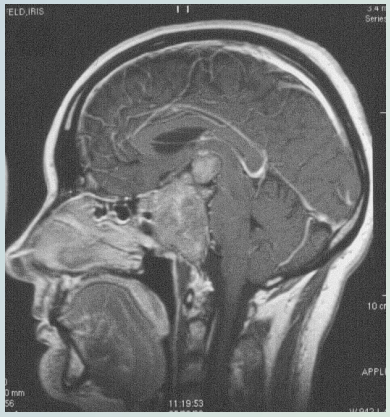
Causes of Hypothyroidism (1/2) – Primary Hypothyroidism

- **Thyroid dysgenesis or aplasia**
- **Destruction of thyroid tissue**
  - Chronic autoimmune thyroiditis
  - Infiltrative diseases of the thyroid (amyloidosis, scleroderma)
  - Radiation-^{131}I therapy for thyrotoxicosis, external radiotherapy to the head and neck for non-thyroid malignant disease
  - Subtotal and total thyroidectomy
- **Defective thyroid hormone biosynthesis**
  - Iodine deficiency
  - Drugs with antithyroid actions (lithium)
  - Congenital defects in thyroid hormone biosynthesis

Causes of Hypothyroidism (2/2) – Central or Secondary Hypothyroidism

- **Central hypothyroidism**
  - Pituitary disease
  - Hypothalamic disease





Hypothyroidism: thyroid fails to secrete an adequate amount of thyroid hormones

Tiredness

Forgetfulness/Slower Thinking

Moodiness/ Irritability

Depression

Inability to Concentrate

Thinning Hair/Hair Loss

Loss of Body Hair

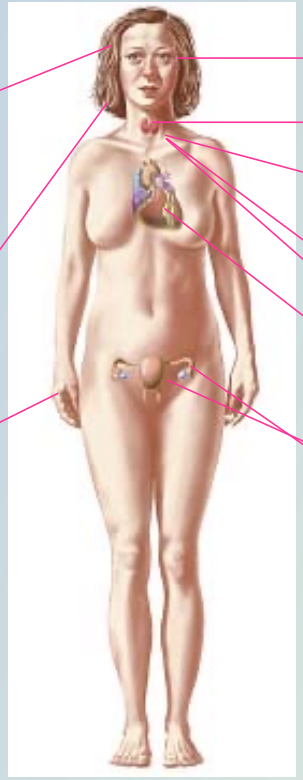
Dry, Patchy Skin

Weight Gain

Cold Intolerance

Elevated Cholesterol

Family History of Thyroid Disease or Diabetes



Puffy Eyes

Enlarged Thyroid (Goiter)

Hoarseness/ Deepening of Voice

Persistent Dry or Sore Throat

Difficulty Swallowing

Slower Heartbeat

Menstrual Irregularities/ Heavy Period

Infertility

Constipation

Muscle Weakness/ Cramps

Hashimoto's Thyroiditis

Autoimmune Disease: Auto-Ab against TPO or/and TG. Very common (>10%).

Manifestations:

- Goiter
- Atrophy
- Subclinical Hypothyroidism (TSH >4 with normal T3 and T4)
- Clinical Hypothyroidism (usually TSH >10, low T3 and T4)
- Myxedema coma (very rare, when hypothyroidism is untreated)

Hyperthyroidism: excess synthesis and secretion of thyroid hormones

Nervousness/Tremor

Mental Disturbances/ Irritability

Difficulty Sleeping

Bulging Eyes/Unblinking Stare/ Vision Changes

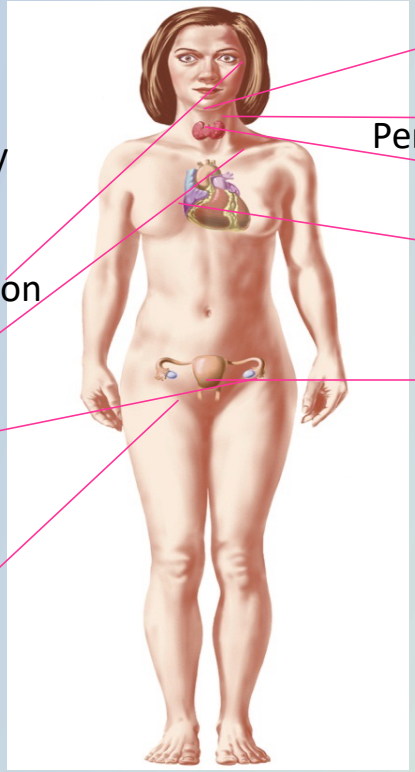
Enlarged Thyroid (Goiter)

Menstrual Irregularities/ Light Period

Frequent Bowel Movements

Warm, Moist Palms

First-Trimester Miscarriage/ Excessive Vomiting in Pregnancy



Hoarseness/ Deepening of Voice

Persistent Dry or Sore Throat

Difficulty Swallowing

Palpitations/ Tachycardia

Impaired Fertility

Weight Loss or Gain

Heat Intolerance
Increased Sweating

Sudden Paralysis

Family History of Thyroid Disease or Diabetes

Thyrotoxicosis vs Hyperthyroidism

- Thyrotoxicosis is the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormones. It results in a generalized acceleration of metabolic processes.

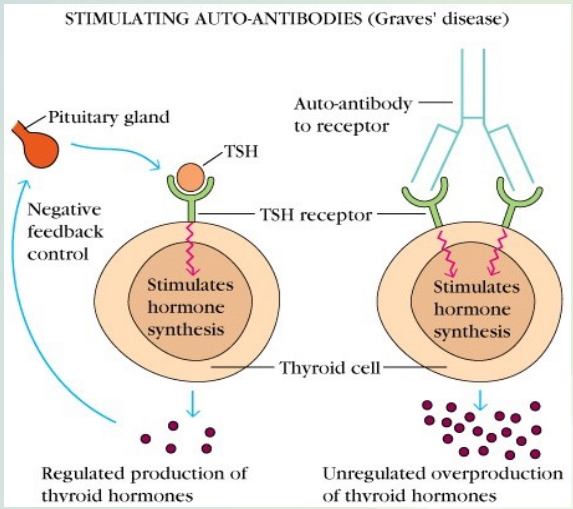
- In most instances, thyrotoxicosis is due to hyperactivity of the thyroid gland itself, known as hyperthyroidism.

Causes of Thyrotoxicosis

1. Diffuse toxic goiter (Graves disease)
2. Toxic adenoma (Plummer disease)
3. Toxic multinodular goiter
4. Subacute thyroiditis
5. "Silent" thyroiditis
6. Thyrotoxicosis factitia
7. Rare forms of thyrotoxicosis: ovarian struma, metastatic thyroid carcinoma (follicular), hydatidiform mole, hamburger thyrotoxicosis TSH-secreting pituitary tumor, pituitary resistance to T_3 and T_4

Graves' Disease

Autoimmune Disease: Auto-Ab activating the TSH Receptor (TRAb), known also as thyroid-stimulating antibody (TSAb) (pathognomonic for the disease).
In some cases, blocking TRAb.



Manifestations:

- Hyperthyroidism
- Goiter
- Ophthalmopathy (exophthalmos)
- Dermopathy (pretibial myxedema)

Spontaneous exacerbations and remissions of Graves' disease can occur. The environmental triggers are still not well characterised, but postpartum (after pregnancy) exacerbation is common.

Which is The (Most) Active Thyroid Hormone?

1. Free T_3 (fT_3)
2. Total T_4 (TT_4)
3. Reverse T_3 (rT_3)
4. Total T_3 (TT_3)
5. Free T_4 (fT_4)

Which is The (Most) Active Thyroid Hormone?

1. Free T_3 (fT_3)
2. Total T_4 (TT_4)
3. Reverse T_3 (rT_3)
4. Total T_3 (TT_3)
5. Free T_4 (fT_4)

Which is/are Correct?

- Thyroid hormones…

1. Are stored in the liver
2. Are big molecules (proteins)
3. Are produced in the thyroid gland
4. Contain iodine
5. Stimulate metabolism
6. 1 and 2
7. 3, 4 and 5

Which is/are Correct?

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1. Are stored in the liver
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What is not a typical clinical symptom of hypothyroidism?

1. Lethargy
2. Dry skin
3. Depression
4. Weight loss
5. Muscle weakness
6. Cold intolerance

What is not a typical clinical symptom of hypothyroidism?

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4. Weight loss
5. Muscle weakness
6. Cold intolerance

Correct answer: 4
Weight gain may be a clinical sign of hypothyroidism

What is the most reliable index of thyroid function?

1. T3
2. T4
3. fT4
4. TSH
5. Anti-TPO
6. Cold intolerance

What is the most reliable index of thyroid function?

1. T3
2. T4
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You are suspecting that your patient has hypothyroidism. What is the blood tests that you will order?

1. TSH and T3
2. TSH and T4
3. T3 and T4
4. TSH and anti-TPO
5. Anti-TPO and anti-Tg
6. TSH and anti-Tg

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6. TSH and anti-Tg

A female patient is pregnant and she presents with palpitations and tremor. The blood tests you will order are?

1. T3 and T4
2. FT3 and FT4
3. T3 and TSH
4. TSH and T4
5. TSH and fT4
6. TSH and anti-TPO

A female patient is pregnant and she presents with palpitations and tremor. The blood tests you will order are ?

1. T3 and T4
2. FT3 and FT4
3. T3 and TSH
4. TSH and T4
5. TSH and fT4
6. TSH and anti-TPO