Thyroid metabolism

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Thyroid hormones

Thyroid epithelial cells responsible for synthesis of thyroid hormones - are arranged in:

1- Thyroid follicles are epithelial cells responsible for synthesis of thyroid hormones – they are arranged in spheres single layer.

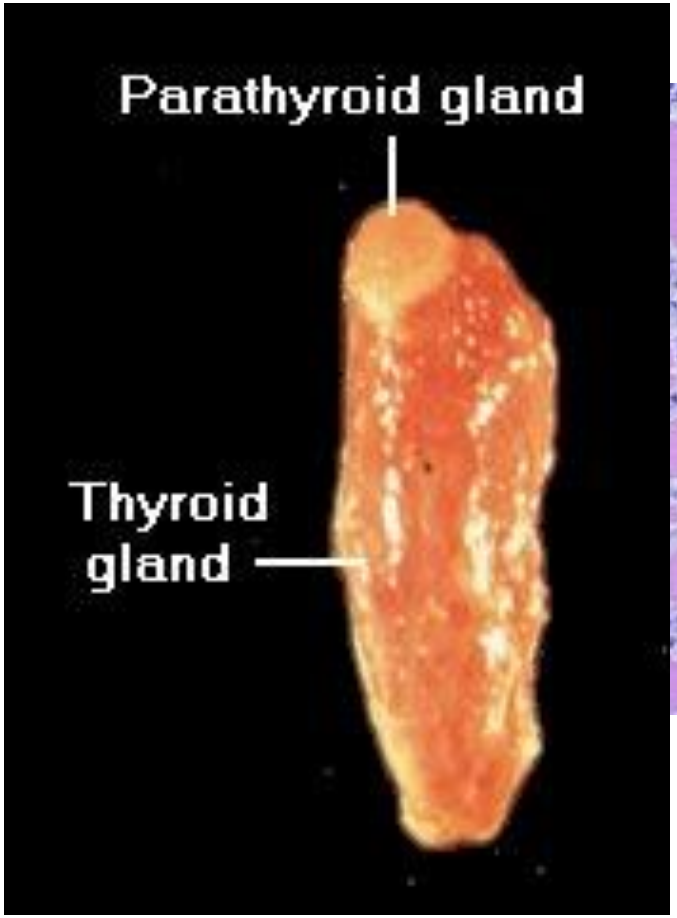
2- Colloid is the lumen which is filled with thyroglobulin.

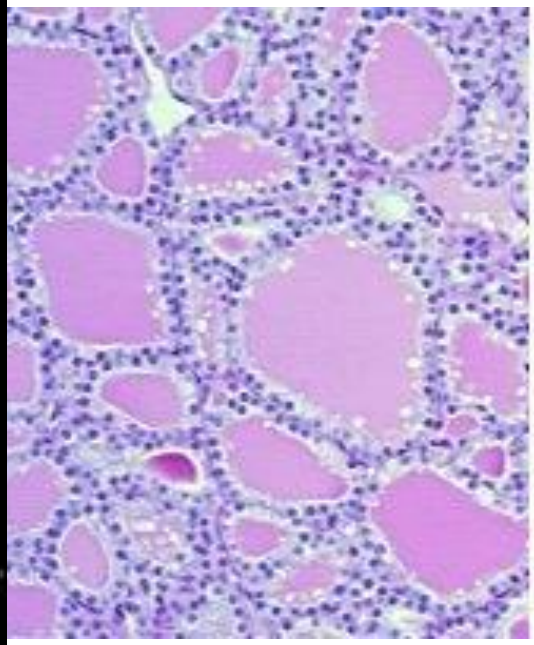
- Thyroid hormones include

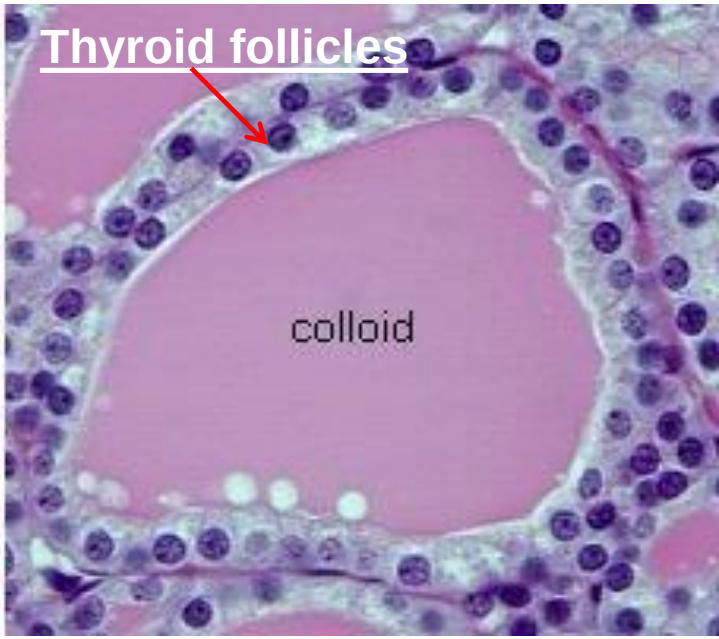
A- Thyroxine T4 is made up of two fused tyrosine rings and 4 iodine atoms at position 3 and 5 of each ring.

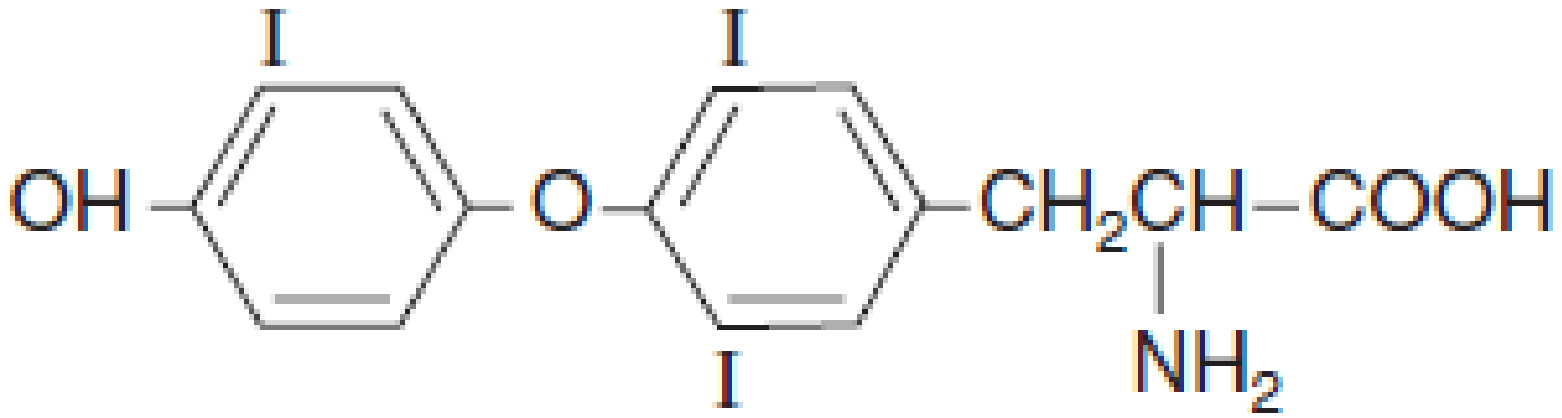
B- Triiodothyronine T3 is made up of two fused tyrosine rings and 3 iodine atoms at position 3,3',5 of the ring

- Triiodothyronine is the active form not T4
- The major secreted product of the thyroid gland is T4 while T3 is secreted only in small amounts
- The major source of circulating T3 is not from thyroid secretion, but from peripheral deiodination of T4

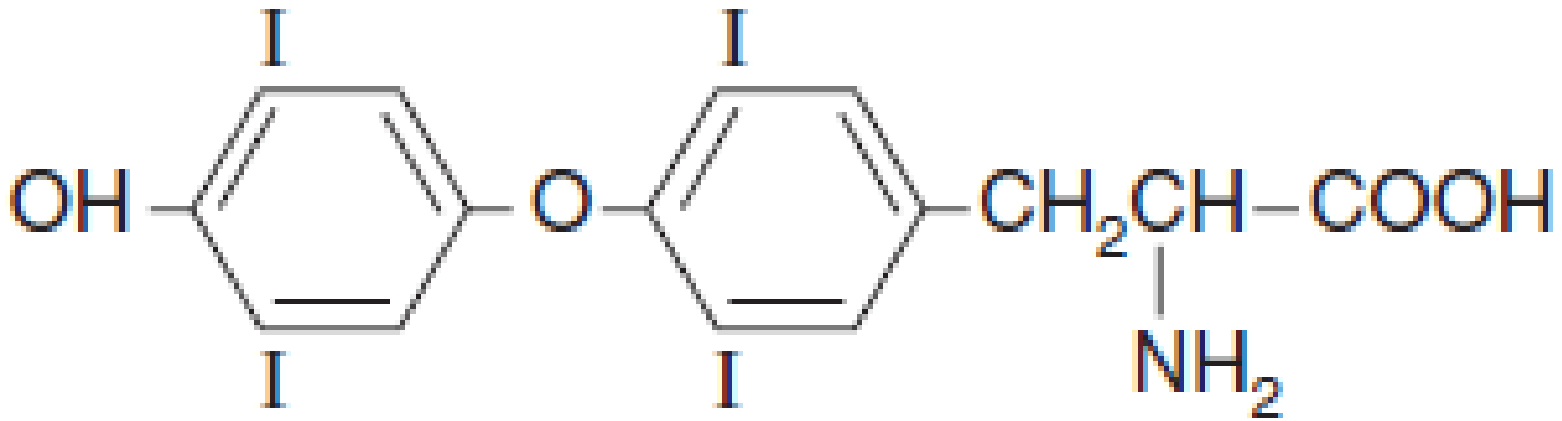

Parathyroid gland
Thyroid gland




Thyroid follicles
colloid



T^3



T^4

- **Thyroglobulin (**glycoprotein **)** is the precursor of T4 and T3.
- Thyroglobulin is synthesized in the rough endoplasmic reticulum of the follicle cells and secreted into the colloid by exocytosis.
- About 30% of thyroid gland is thyroglubulin and about 10% of thyroglubulin is carbohydrate and 0.5% is iodine
- Each molecule of thyroglobulin contains about 500 amino acid
- 123 monomers are of **tyrosine** at fixed places.
- Soon as the molecules of iodine and thyroglobulin come out of follicular cells, these interact in such a way that 15 tyrosine monomers of each thyroglobulin molecule at fixed places become iodinated.

- Certain tyrosine monomers bind with single atom of iodine, forming **monoiodotyrosine (MIT** or **T1).**
- Other tyrosine monomers bind with two atoms of iodine, forming **diiodotyrosine (DIT** or **T2).**
- About 70% of the iodide in thyroglobulin exists in the inactive precursors, **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT),** while 30% is in the **iodothyronyl residues,** T4 and T3.
- In cases of iodine deficiency, relatively more T3 and less T4 is synthesized and secreted.
- Within the colloid, molecules of iodothyroglobulin interact with each other that results in a coupling of most of the iodinated tyrosine monomers in pairs.
- When **monoiodotyrosine combine with diiodotyrosine the result is triiodothyronine (T3)**
- When two **diiodotyrosine joined the result is tetraiodothyronine (thyroxine—T4)**
- Obviously, the colloid acts as a reservoir of these hormones.
- When iodine supplies are sufficient, the T4:T3 ratio is about 7:1. In **iodine deficiency,** this ratio decreases, as does the DIT:MIT ratio. **Thyroglobulin is a reservoir for thyroid hormones and** several weeks' supply of these hormones exist in the normal thyroid.

- **Iodide Metabolism organification of I**
- The thyroid is able to concentrate iodide 30–50 times that of the circulating concentration using energy-dependent Na+-K+ ATPase-dependent thyroidal I– transporter.

1- Iodide (I-) inter **follicles** by Na+-K+ ATPase-dependent thyroidal Iodide (I-) transporter

2- Thyroperoxidase that uses H_2O_2 oxidize (I–) to Iodine (I) at the luminal surface of the follicular cell this step is called organification

3- The organified I is then linked to a tyrosine residue attached to thyroglobulin

4- Thyroid hormone synthesis occurs in the follicular space through a series of reactions

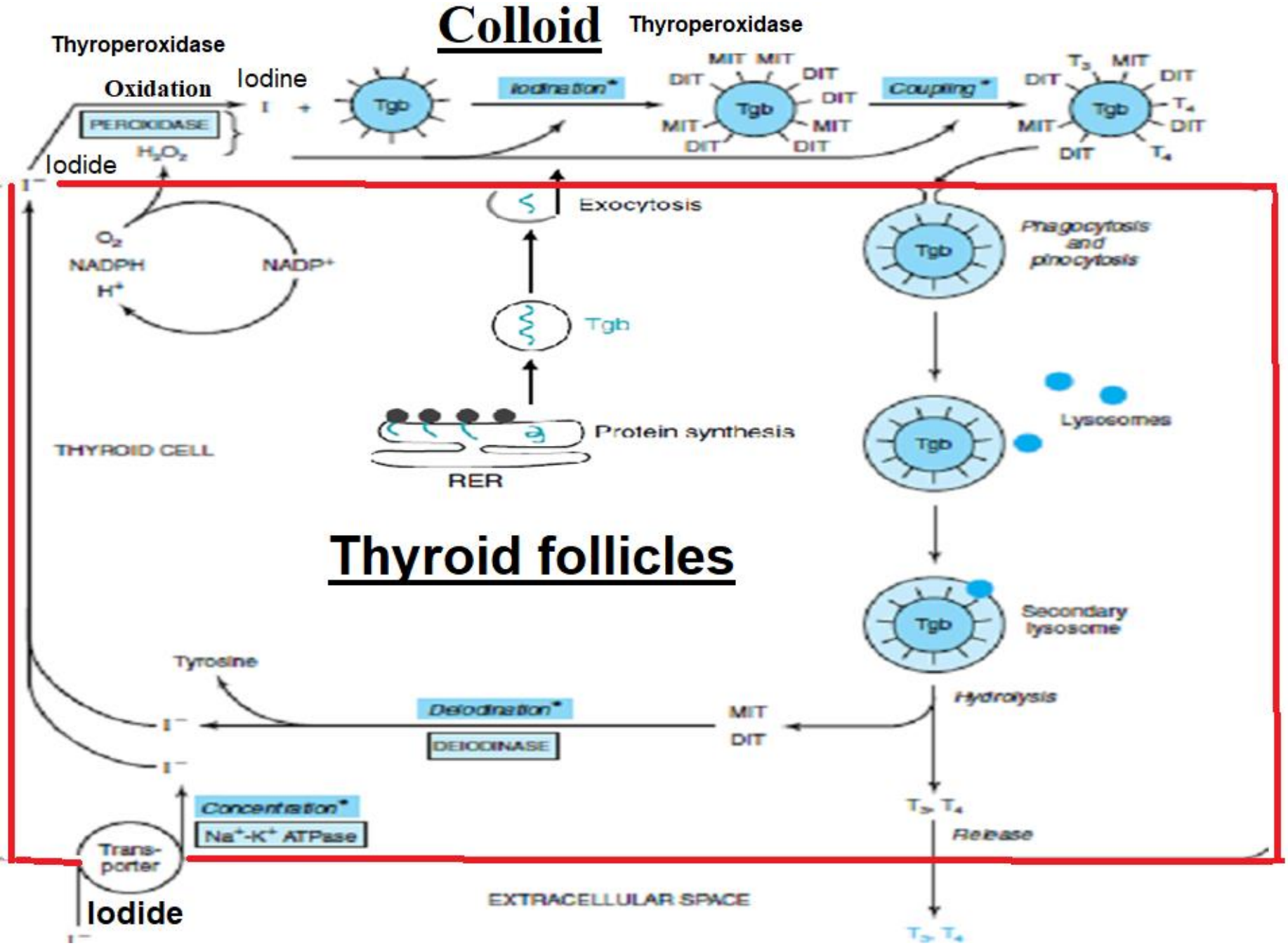
5- Thyroid hormones are then stored in the colloid in the follicular space.

6- Thyroperoxidase stimulate the coupling of two DIT molecules to form T4—or an MIT and DIT to form T3.

7- TSH stimulates the endocytosis of thyroglobulin to form endocytic vesicles within the thyroid cells.

8- Lysosomes fuse with these vesicles, and lysosomal proteases hydrolyse thyroglobulin, releasing free T4 and T3 into the blood.

9- In various tissues including pituitary, kidney, and liver T4 is deiodinated, forming T3, which is the active form of the hormone.


Colloid
Thyroperoxidase
Thyroperoxidase
Oxidation
Iodine
PEROXIDASE
H_2O_2
Iodide
Tgb
Iodination
Coupling
MIT
DIT
T_3
T_4
Exocytosis
Phagocytosis and pinocytosis
O_2
NADPH
H^+
$NADP^+$
Tgb
Protein synthesis
RER
THYROID CELL
Lysosomes
Thyroid follicles
Secondary lysosome
Tyrosine
Deiodination
DEIODINASE
Hydrolysis
Concentration
Na^+-K^+ ATPase
Trans-porter
Iodide
Release
EXTRACELLULAR SPACE

- **Thyroid Hormones Transport**
- More than 99% of T4 and T3 circulates bounded to a specific binding protein, **thyroxine-binding globulin (TBG) or thyroxine-binding prealbumin (TBPA).**
- TBG, a glycoprotein, binds non-covalently to T4 and T3.
- The plasma half-life of T4 is correspondingly four to five times that of T3.
- The small, unbound (free) fraction is responsible for the biologic activity. Most biologic activity is attributed to T3.
- T4 works as a reservoir for T3

Deiodinations of T4 to T3

Three enzymes catalyzing deiodinations have been identified, called type 1 (D1), type 2 (D2) and type 3 (D3) iodothyronine deiodinases.

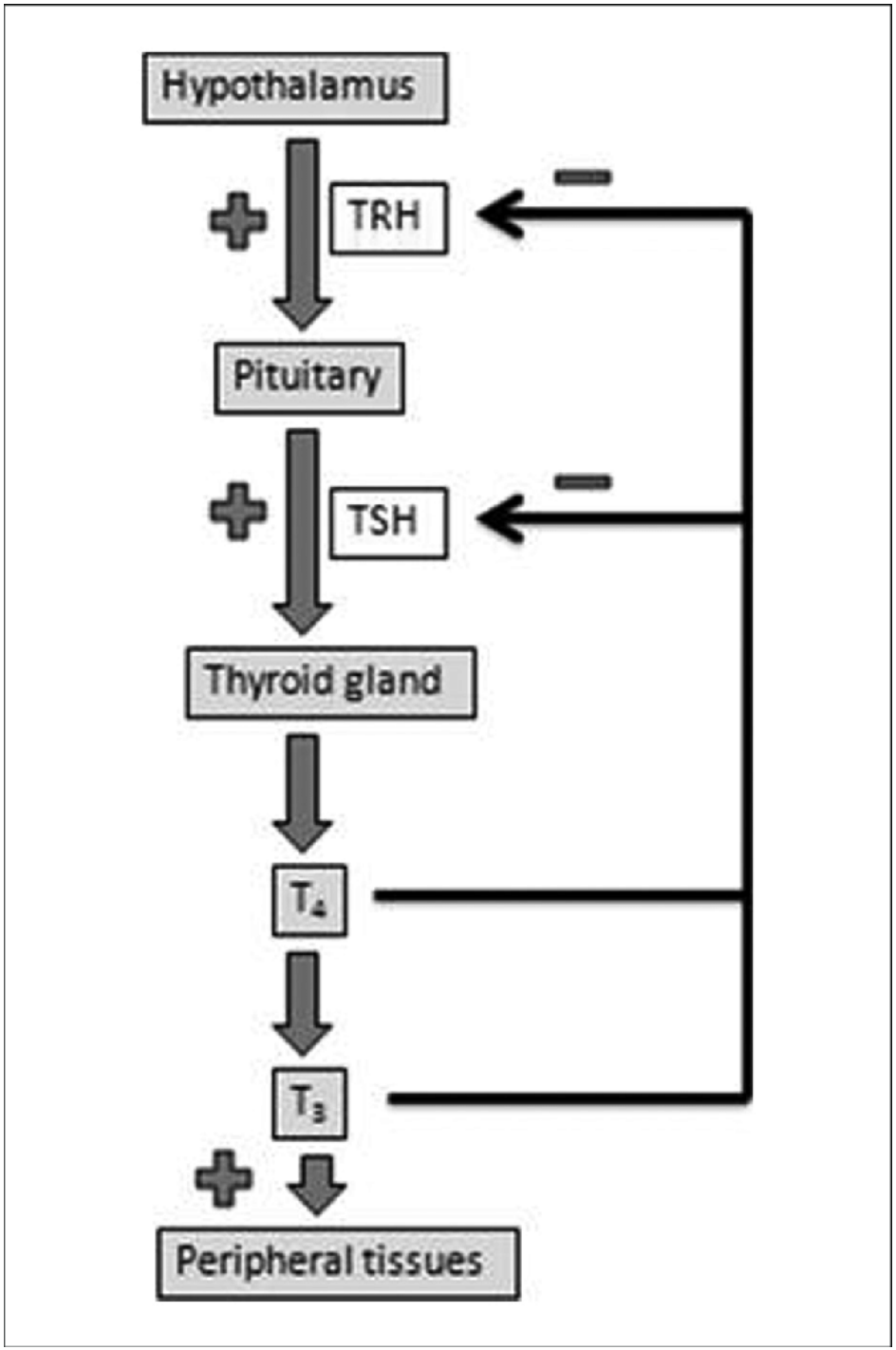
• D1 is expressed mainly in the liver, the kidneys and the thyroid.

• D2 expressed in the central nervous system, the pituitary, brown adipose tissue and skeletal muscle

• The brain is the predominant D3-expressing tissue in adult animals

Regulation of Thyroid Hormone Synthesis & secretion

- The release of T3 and T4 from thyroglobulin is controlled by thyroid-stimulating hormone (TSH)
- TSH is synthesized in the thyrotropic cells of the anterior pituitary.
- Its secretion is regulated by a balance between the stimulatory action of hypothalamic TRH and the inhibitory (negative feedback) influence of thyroid hormone (primarily T3)
- As the free T3 level in the blood bathing the thyrotrophs of the anterior pituitary gland rises, the feedback loop is closed. Secretion of TSH is inhibited until the free T3 levels in the systemic circulation fall just below a critical level, which once again signals the release of TSH.
- High levels of T3 also inhibit the release of TRH from the hypothalamus.
- TSH stimulates all phases of thyroid hormone synthesis by the thyroid gland, including iodide trapping from the plasma, organification of iodide, coupling of monoiodotyrosine and diiodotyrosine, endocytosis of thyroglobulin, and proteolysis of thyroglobulin to release triiodothyronine (T3) and tetraiodothyronine (T4).



<u>Feedback control</u> Example: Thyrotropin -<u>Releasing</u> Hormone (TRH) produced by hypothalamus stimulate pituitary gland to secrete Thyrotropin -<u>stimulating</u> hormone (TSH). That stimulate the thyroid gland to release T4 and T3

When T4 and T3 levels are high they block the release of TRH and TSH

- **Mechanism of action of TSH**

- TSH action is mediated by binding of TSH to its specific G-protein receptor of the thyroid cell, leading to an increase in the concentration of cAMP.

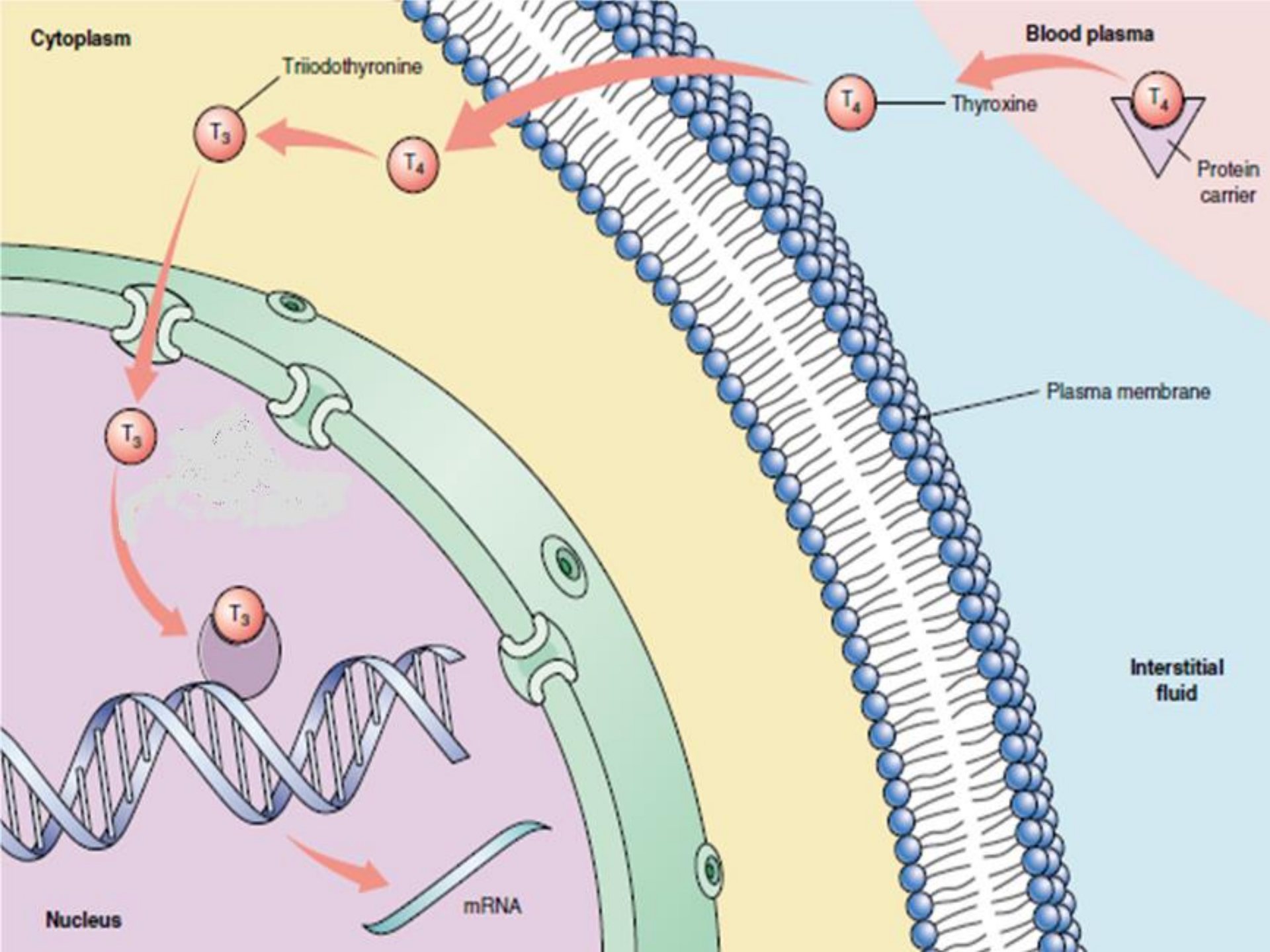
- These leads to activations of kinases which activate further signal transduction mechanisms that eventually stimulate several processes involved in thyroid hormone synthesis and release and thyroid growth.

- **Mechanism of Actions of thyroid hormones**
- T3 binds to its nuclear receptors
- Thyroid hormone receptors exist in the nucleus and remain bound to DNA in absence of hormone binding.
- Once inside the nucleus, T3 binds to its receptor that causes its activations.

Function of thyroid hormones:

- Thyroid hormones stimulate the metabolic rate by increasing the number and size of mitochondria, stimulating the synthesis of enzymes in the respiratory chain and increasing membrane Na+-K+ ATPase concentration

- T3 increases glucose uptake by muscle cells, stimulates protein synthesis, and, therefore, growth of muscle, through its stimulatory actions on gene expression.
- T3 increases the flow of fatty acids to the liver and thereby indirectly increases hepatic triacylglycerol synthesis.


Cytoplasm
Triiodothyronine
T_3
T_4
Blood plasma
T_4
Thyroxine
T_4
Protein carrier
Plasma membrane
T_3
T_3
Interstitial fluid
mRNA
Nucleus

- **Thyroid and Somatostatin**
- Somatostatin inhibitory hormone that inhibit the release of many hormones
- Somatostatin is produced in many places in the body including: digestive system**,** hypothalamus and delta cells of the pancreatic islets plus many areas of the central nervous system.
- Somatostatin binds to its G-protein plasma membrane receptors on target cells.
- These “activated” receptors interact with inhibitory αi in G proteins of adenylate cyclase. As a result, the production of cAMP is inhibited, and protein kinase A is not activated.
- This inhibitory effect suppresses secretion of growth hormone and thyroid-stimulating hormone (TSH) from the anterior pituitary gland as well as the secretion of insulin and glucagon from the pancreatic islets.
- Somatostatin inhibits the secretion of many other hormones.”

Hormone-induced activation and inhibition of adenylyl cyclase in adipose cells