The Synthesis of triiodothyronine (T_3) & tetraiodothyronine (thyroxine; T_4)

- They are synthesized as part of a very large precursor molecule (**thyroglobulin**);
- They are stored in an intracellular reservoir (colloid) .
- There is peripheral conversion of T4 to T_3, which is a much more active hormone.

Thyroglobulin *(is the precursor of T4 and T_3)*

It is a large iodinated, glycosylated protein (5000 AA) with a molecular mass of 660 kDa.
- Carbohydrate accounts for → 8–10% of its weight
- Iodide for about → 0.2–1%, depending upon the iodine content in diet.

- Thyroglobulin is composed of two large subunits.
- It contains 115 tyrosine residues, each of which is a potential site of iodination.

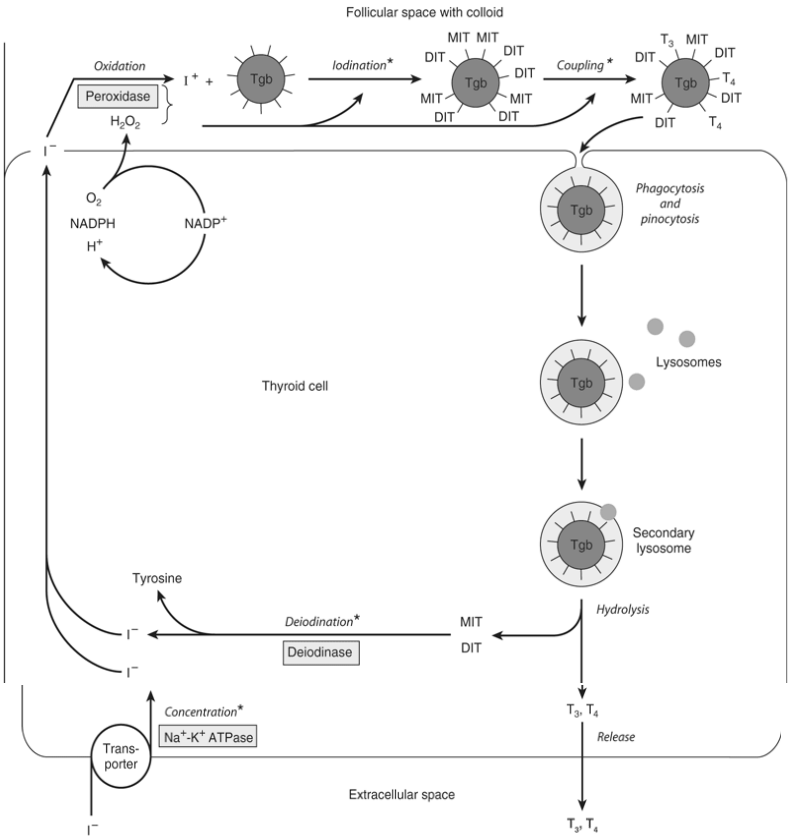
- About 70% of the iodide in thyroglobulin exists in the inactive precursors, **monoiodotyrosine (MIT)** and **diiodotyrosine (DIT)**
- While 30% is in the **iodothyronyl residues,** T_4 and T_3.

- When iodine supplies are sufficient, the T_4:T_3 ratio is about 7:1.
- In iodine deficiency, this ratio decreases, as does the DIT:MIT ratio.

Thyroglobulin, provides the conformation required for:
1- tyrosyl coupling &
2- iodide organification necessary in formation of the diaminoacid thyroid hormones.

It is synthesized in the rER of the thyroid epithelial cells and secreted into the lumen of the follicle, where it is a storage form of T_3 and T_4 in the colloid
(colloid is essentially a pool of thyroglobulin)

- Within minutes after stimulation of the thyroid by TSH, colloid reenters the cell and there is a marked increase of phagolysosome activity.
- Various acid **proteases** and **peptidases** hydrolyze the thyroglobulin into its constituent amino acids, including T_4 and T_3, which are discharged from the basal portion of the cell *(Thyroglobulin is thus a very large prohormone)*



- Iodine present in food as inorganic **iodide** (I-) which is taken from the blood by thyroid epithelium cells.
- Thyroid cells have on their outer plasma membrane a Sodium-Iodide symporter (or iodine trap), by which The thyroid is able to concentrate I^- against a strong electrochemical gradient *(This is an energy-dependent process requiring ATP)* .

N.B. *The ratio of iodide in thyroid to iodide in serum (T:S ratio) is a reflection of the activity of this transporter. The T:S ratio in humans on a normal iodine diet is about 25:1.*

Synthesis is conducted by enzyme: **Thyroperoxidase**

- It is an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells
- Thyroperoxidase, a tetrameric protein with a molecular mass of 60 kDa, requires hydrogen peroxide (H_2O_2) as an oxidizing agent.
- The H_2O_2 is produced by an NADPH-dependent enzyme.

1- Organification of iodide (Iodination of tyrosines) : *(occurs at the luminal surface of the follicular cell.)*

- An inner membrane- associated **thyroid peroxides enzyme** uses locally generated H_2O_2 oxidize **iodide** (I-) to → **iodine** which then iodinates various Tyrosine residues of thyroglobulin to form **monoiodotyrosine (MIT) .**
- These MIT residues can then be iodinated a second time by the same thyroid peroxidase enzyme to form **diiodotyrosine (DIT)**
- NOTE → Both MIT & DIT are still part of the thyroglobin protein.

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2- Coupling : *(occurs within the thyroglobulin molecule)*

- Thyroid peroxidase then cleaves of the phenolic ring from a donor MIT or DIT → and **couples** it to an acceptor DIT residue.
  - The coupling of MIT & DIT molecule (MIT + DIT) to form → **T_3** (The most active form of TH)
  - The coupling of two DIT molecules (DIT + DIT) to form → **T_4** (The major product) **after secretion into the circulation, T4 is peripherally activated into T3**
- NOTE → A separate coupling enzyme has not been found, and since this is an oxidative process it is assumed that the same thyroperoxidase catalyzes this reaction by stimulating free radical formation of iodotyrosine .

3- Intracellular resorption & digestion :

- The formed thyroid hormones remain as integral parts of thyroglobulin, **BUT** Within minutes after stimulation of the thyroid by TSH, colloid reenters the cell and there is a marked increase of phagolysosome activity.
- Various acid **proteases** and **peptidases** hydrolyze the thyroglobulin into its constituent amino acids, including T_4 and T_3, which are discharged from the basal portion of the cell *(Thyroglobulin is thus a very large prohormone)*.
- The iodine from MIT and DIT reidues released by thyroglobulin digestion is recycled within the follicle epithelial cell following cleavage by a deiodinase.

- NOTE → A peripheral deiodinase in target tissues such as pituitary, kidney, and liver selectively removes I^- from the 5' position of T_4 to make T_3 which is a much more active molecule. (Thus , T_4 can be thought of as a prohormone, though it does have some intrinsic activity.)

4- Secretion :

- Free T4 & T3 are secreted into the circulation
- About 85 – 90 % of the secreted product is T4, **BUT** low iodide or hight TSH → increases the ratio of T3 & T4 secreted BY increasing the activity of the **local 5' - deiodinase enzyme .**