TDC 5TH SEM MAJOR : PAPER 5.3

SYNTHESIS OF THYROXIN

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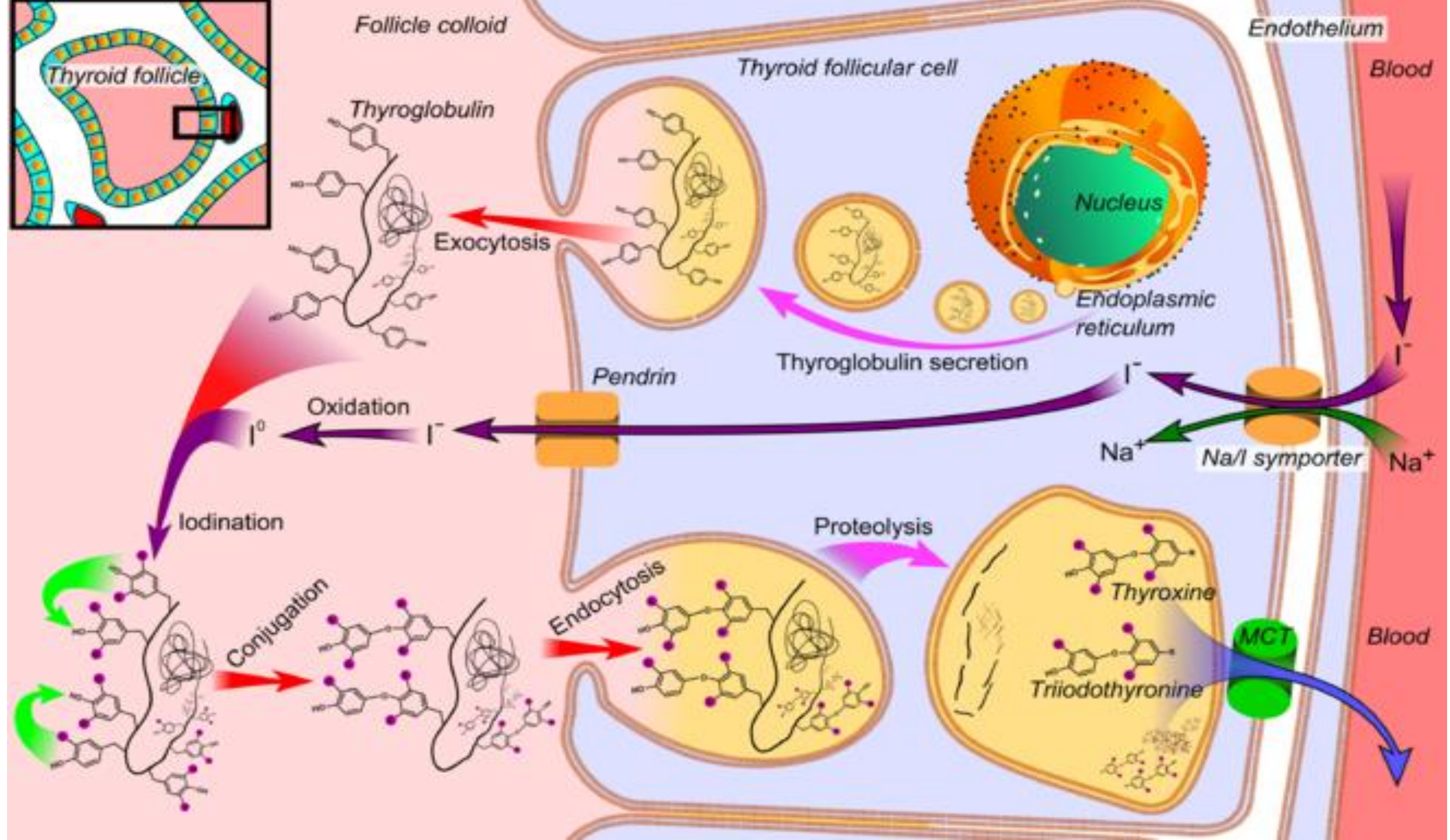
Thyroid hormones are two hormones produced and released by the thyroid gland, namely triiodothyronine (T_3) and thyroxine (T_4). They are tyrosine-based hormones that are primarily responsible for regulation of metabolism. T_3 and T_4 are partially composed of iodine. A deficiency of iodine leads to decreased production of T_3 and T_4.

Thyroid hormones (T_4 and T_3) are produced by the follicular cells of the thyroid gland and are regulated by TSH made by the thyrotropes of the anterior pituitary gland. The effects of T_4 in vivo are mediated via T_3 (T_4 is converted to T_3 in target tissues). T_3 is three to five times as active than T_4.


Thyroid follicle
Follicle colloid
Endothelium
Blood
Thyroid follicular cell
Thyroglobulin
Exocytosis
Nucleus
Endoplasmic reticulum
Thyroglobulin secretion
Pendrin
Oxidation
I^0
I^-
I^-
I^-
Na^+
Na/I symporter
Na^+
Iodination
Conjugation
Endocytosis
Proteolysis
Thyroxine
Triiodothyronine
MCT
Blood

(FIG:Synthesis of the thyroid hormones, as seen on an individual thyroid follicular cell .Thyroglobulin is synthesized in the rough endoplasmic reticulum and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis.

Thyroglobulin is synthesized in the rough endoplasmic reticulum and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis.

Meanwhile, a sodium-iodide (Na/I) symporter pumps iodide (I–) actively into the cell, which previously has crossed the endothelium by largely unknown mechanisms.

- This iodide enters the follicular lumen from the cytoplasm by the transporter pendrin, in a purportedly passive manner.

In the colloid, iodide (I^-) is oxidized to iodine (I^0) by an enzyme called thyroid peroxidase.

- Iodine (I^0) is very reactive and iodinates the thyroglobulin at tyrosyl residues in its protein chain (in total containing approximately 120 tyrosyl residues).
- In conjugation, adjacent tyrosyl residues are paired together.
- Thyroglobulin re-enters the follicular cell by endocytosis.
- Proteolysis by various proteases liberates thyroxine and triiodothyronine molecules
- Efflux of thyroxine and triiodothyronine from follicular cells, which appears to be largely through monocarboxylate transporter (MCT) 8 and 10, and entry into the blood.fig)

Thyroxine (3,5,3′,5′-tetraiodothyronine) is produced by follicular cells of the thyroid gland. It is produced as the precursor thyroglobulin (this is not the same as thyroxine-binding globulin (TBG)), which is cleaved by enzymes to produce active T4.

The steps in this process are as follows:

1.The Na+/I− symporter transports two sodium ions across the basement membrane of the follicular cells along with an iodide ion. This is a secondary active transporter that utilises the concentration gradient of Na+ to move I− against its concentration gradient.

2.I− is moved across the apical membrane into the colloid of the follicle by pendrin .

3.Thyroperoxidase oxidizes two I− to form I2. Iodide is non-reactive, and only the more reactive iodine is required for the next step.

4.The thyroperoxidase iodinates the tyrosyl residues of the thyroglobulin within the colloid. The thyroglobulin was synthesised in the ER of the follicular cell and secreted into the colloid.

5.Iodinated Thyroglobulin binds megalin for endocytosis back into cell.

6.Thyroid-stimulating hormone (TSH) released from the anterior pituitary (also known as the adenohypophysis) binds the TSH receptor (a Gs protein-coupled receptor) on the basolateral membrane of the cell and stimulates the endocytosis of the colloid.

7.The endocytosed vesicles fuse with the lysosomes of the follicular cell. The lysosomal enzymes cleave the T4 from the iodinated thyroglobulin.

8.The thyroid hormones cross the follicular cell membrane towards the blood vessels by an unknown mechanism. In recent studies indicate that monocarboxylate transporter (MCT) 8 and 10 play major roles in the efflux of the thyroid hormones from the thyroid cells

Thyroglobulin (Tg) is a 660 kDa, dimeric protein produced by the follicular cells of the thyroid and used entirely within the thyroid gland. Thyroxine is produced by attaching iodine atoms to the ring structures of this protein's tyrosine residues; thyroxine (T_4) contains four iodine atoms, while triiodothyronine (T_3), otherwise identical to T_4, has one less iodine atom per molecule. The thyroglobulin protein accounts for approximately half of the protein content of the thyroid gland.[citation needed]

Each thyroglobulin molecule contains approximately 100–120 tyrosine residues, a small number of which (<20) are subject to iodination catalysed by thyroperoxidase. The same enzyme then catalyses "coupling" of one modified tyrosine with another, via a free-radical-mediated reaction, and when these iodinated bicyclic molecules are released by hydrolysis of the protein, T3 and T4 are the result.[citation needed] Therefore, each thyroglobulin protein molecule ultimately yields very small amounts of thyroid hormone (experimentally observed to be on the order of 5–6 molecules of either T_4 or T_3 per original molecule of thyroglobulin)

Thank you