Biosynthesis and chemistry of Thyroid Hormones

CHEMISTRY :-

Thyroid gland contain an iodized glycoprotein Thyroglobin, which apparently constitutes the storage form of the thyroid hormones. On the hydrolysis this protein yield several iodine containing derivatives of tyrosine (mono and di-iodotyrosin) and thyronine (di, tri, and tetra iodothyronines). Among there the tetra-iodothyronine (Thyroxine) and 3,5,3 tri iodothyronine are the most important in addition to there iodene containing compounds thyroid gland also produces a non iodinated compound known as Calciferon or Thyrocalcitonin a polypeptide which lowers serum calcium concentration.

SYNTHESIS OF THYROID HORMONES:-

The steps involve in biosynthesis of thyroid hormones are given below.

(a) SYNTHESIS OF T.G.
(b) IODENE ACCUMULATION BY THYROID.
(c) OXIDATION OF IODIDE.
(d) FORMATION OF ORGANICALLY BOUND IODINE COMPOUND
(e) PROTEOLYSIS OF THYROGLOBULIN.

(a) SYNTHESIS OF THYROGLOBULIN:-

T.G is a large globular glycoprotein constituting about 75% of the protein content of mammalian Thyroid. Each molecule consist of two identical subunit and contain carbohydrates which is about 10% by weight. There are three type of polysacchrides which are covalentaly linked to as per gene. Serine and Threonine residues. ~~There are 140 tyrosine residues.~~

~~25% of these residue are iodinated~~ T.G. contain 123 tyrosine residue but only four to eight of there one. incorporated into thyroid hormone.

Thyroglobulin is synthesized by epithilial cells thyroid follicles. The T.G is secreted into central cavity of follicle and constitutes the major protein component of colloid. Thyroglobin subunit are synthesized by polyribosomes of the rough endoplasmic reticulum (RER). They assemble and are discharged through E.R to golge apparatus. During this trasfer the molecule is glycosylated by specific glycosyl trasfesases. The completed molecule as packed into vesicles are secreted by the apical membrane into the lumen of the follicle.

Note- Thyroid cells thus have three function. They collect and trasport iodine, they synthesise TG and ~~thyroid~~ and secrete it into the colloid and they remove thyroid hormones from thyroglobulin and them into circulation.

(b) IODINE ACCUMULATION BY THYROID :-

(1) Bio synthesis of iodinated hormones in the thyroid gland start with the entry of iodine ion from the blood. This entry take place against the concentration gradient, the follicle cells of the thyroid is able to trap iodine enormasly higher amount (several hundred time) than that in circulation. The trasport of iodine from the blood and its accumulation in the thyroid are accelerated by TSH while Thiocynate and ~~pre~~ perchlora's produce revese effect.

(2) The thyroid follicular cells are able to trap iodide at the base of the cell and trasport against an electrical gradicent across the cell. Accumulation of iodine by the thyroid is an energy requiriory mechanism. Its Na^+ dependance was soon recognized and a $Na^+ - I^-$ cantransport system was demonstrated. The $Na^+ - I^-$ contrasport is inserted into the base lateral membrane of thyroid cell (thyrocytes) its activity is dependent on the Na^+ gradicent across the membrane and therfore on Na^+/K^+-ATPase. Therefor iodine is accumulated in gland. The gland contain iodide of 25 to 40 times its concentration in plasma and rapidlly converts it to organically bound iodine within about 10 sec. Normally the thyroid contain approximatelly 10 mg of exchangiable iodine compared with 5000 – 7000 mg organically bound iodine.

© OXIDATION OF IODIDE :-

The iodide (I^-) entering the thyroid promptly undergoes oxidation to an active ~~to an active~~ form probably the iodinium ion (I^+) or Hypoiodite (HIO) or both in the presence of H_2O_2 and enzyme iodide peroxidase. The thyroidal peroxidase may be present within the golgi derived vesicle containing newly synthesized T.G..

(d)→ Formation of organically bound IODINE COMPOUND:-

Conversion of iodine to active iodide and organification of iodide into ~~active~~ tyrosine residue of Thyroglobulin may occurs as T.G. is secreted into the follicular lumen. The oxidized iodide is then incorporated into tyrosyl group of thyroglobulin the synthesis of Thyroxin in T.G involves as -

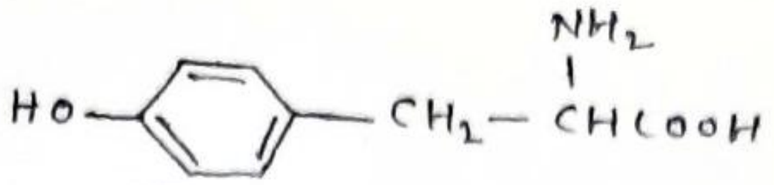
1. The active iodide react with tyrosine molecule of TG incorporated of single active iodide into the phenolic ring of thyrosine yield 3 monoiodotyrosine(MIT)
2. A second iodide may be incorporated into the 5th position to yield 3,5 diiodotyrosine (DIT).
3. Two molecule of the latter DIT undergo oxidative coupling to form tetra iodothyronine (Thyroxine) with the elemination of one alanine side chain.
4. Simuntaniously, one molecule each of Mono and di-iodotyrosines may couple to form triiodothyronine. Two molecule of monoiodotyrosine form diiodothyronine.

These iodothyronines is peptide linkage with the globulin constitute the thyroglobulin molecule which is stored in the colloid material within the lumen of the thyroid follicles. The iodienation and coupling reaction are accelerated by TSH and inhibited by certain antithyroid agents (eg. thiocarbamides, aminobenzenes etc)

(e) PROTEOLYSIS OF THYROGLOBULIN :-

In accordance with demand, the thyroglobolin undergoes hydrolysis by a proteolytic enzyme (proteinases) to release the iodinated compound which then exhibit the hormonal activity. This process again accelerate by TSH.

Colloid is engulfed by follicular cell (Pseudopods) and transported into the cell as colloid droplets. These colloid containing vasicle then fuse with lysosome and are refemed to as secondary lysosome. Much of the T.G. within there vesicle is degraded by lysosomal proteolytic enzymes. the thyroid hormones are then released (presumbly by diffusion) into the cytoplasm and enter the extracellular space by diffusion, through the basal or lateral follicular membrane ~~through~~. Exocytosis of vesicular products, including T_3 and T_4 is not excluded the iodinated tyrosine Tyrosomal proteolysis are then diiodinated by di-iodinase and recycled for are within the cell. ~~Fig Please turn over~~

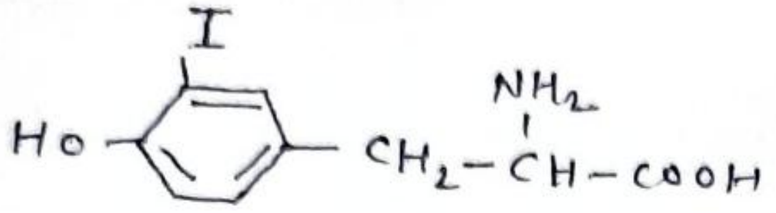


Tyrosin

Iodide in blood —— I^+ ← Iodide peroxidase

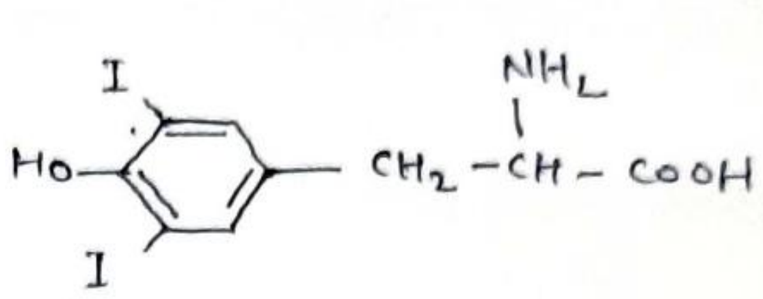
↓ Iodinase

I



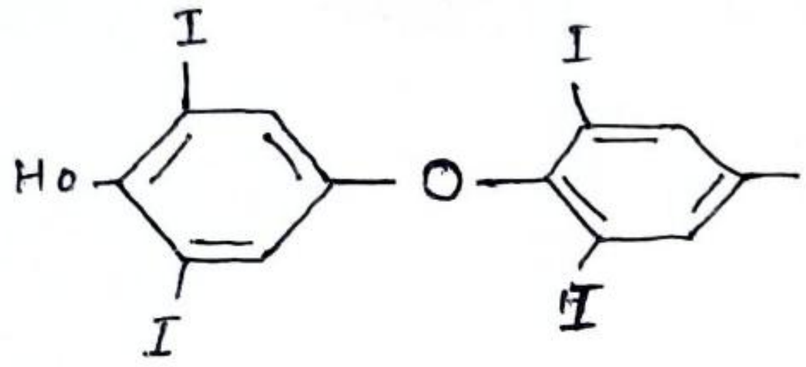
(3 Monoiodotyrosine)
[MIT]

+



(3,5 di-iodotyrosine)
[DIT]

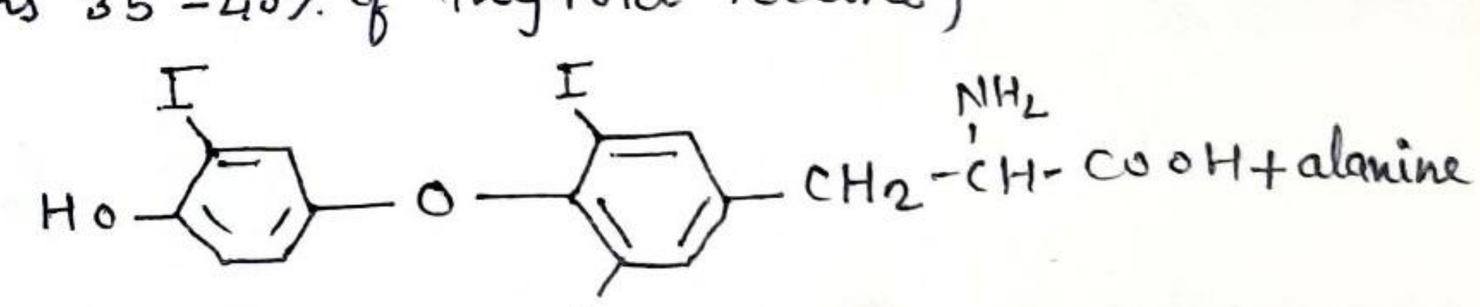
DIT + DIT →



+ Alanine

3,5-3's'-Tetraiodothyronine (Thyroxine)
(Contains 35-40% of thyroid iodine)

MIT + DIT →

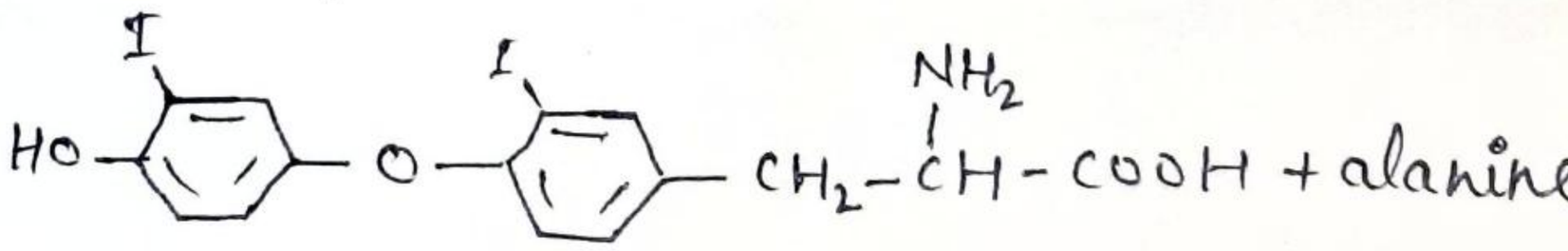


+ alanine

3,5,3'-tri-iodothyronine
(contain 5-8% of the thyroid iodine)

+

MIT + MIT →



+ alanine

3,3' di-iodothyronine
(contain than 1% thyroid hormones)

Fig Biosynthesis of Thyroid hormones