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Hypothalamo-Pituitary-Thyroid Axis

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THYROID GLAND

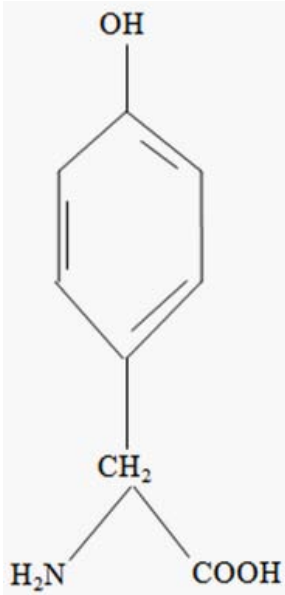
The thyroid gland is situated in the anterior portion of the neck. It consists of two lobes which are connected by a thin band of tissue called the isthmus; this gives the gland an 'H' or 'butterfly' shape. The entire gland weighs about 15-20 grams in an adult. The length and width of each lobe is about 4cm and 2.3cm respectively. The functional or secretory unit of the thyroid gland is called the thyroid follicle which comprises an outer layer of epithelial cells and an inner amorphous colloid. Within the colloid lie large glycoprotein molecules called thyroglobulin and small quantities of iodinated thyroalbumin. Iodine is a very essential element needed for the synthesis of thyroid hormone. Hormones by the thyroid gland are essentially 3, 5, 3′, 5′-L-tetraiodothyronine **(T_4)** which is also called thyroxine, and 3, 5, 3′-L-triiodothyronine **(T_3)**. These are the two major hormones that the gland secretes.

METABOLISM OF IODINE

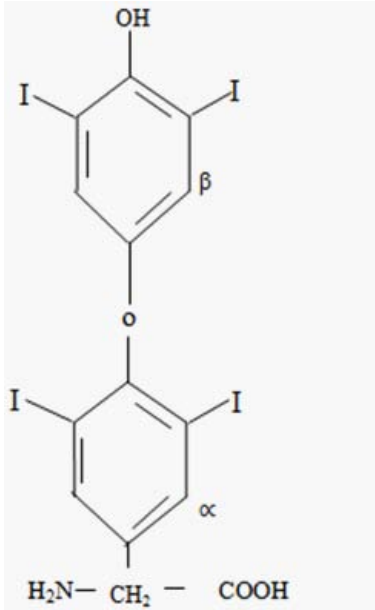
Iodine is a major raw material needed for synthesis of thyroid hormones. It is obtained naturally from sea foods especially fish and artificially in ionized salt. Ionization of salt has made deficiency goiters less prevalent. Iodine can also be gotten naturally from the soil. Iodine is taken in diet and absorbed in the upper small intestine in the form of iodide. After absorption from the small intestine, iodine is taken into secretory glands like the thyroid gland (which is the major gland that uses iodine), salivary gland and probably gastric mucosa. Excess iodine is excreted from the kidney. The liver is involved in peripheral deiodination of thyroid hormone. The liberated iodine is re-utilized by the thyroid gland.

BIOSYNTHESIS OF THYROID HORMONES

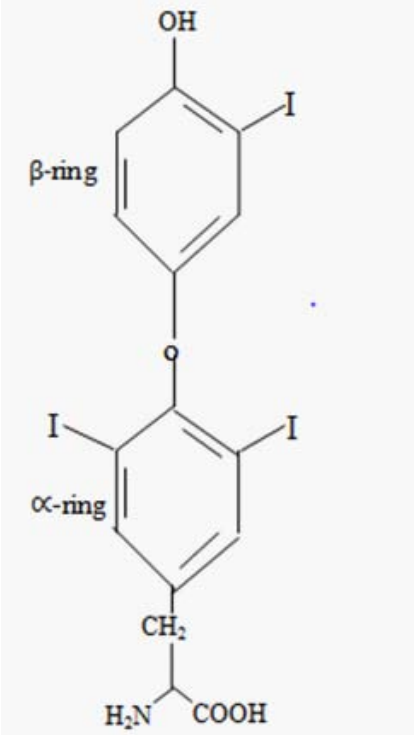
The synthesis of thyroid hormone (T_3 and T_4) is under the influence of the thyroid stimulating hormone (thyrotropin) from the anterior pituitary gland, which in itself is under the control of the thyrotropin releasing hormone from the hypothalamus. It is important to constantly bear in mind this hypothalamo-pituitary-thyroid relationship when discussing thyroid function because any abnormality anywhere along its axis will interfere with the normal synthesis of thyroid hormones. Synthesis of thyroid hormones takes place within the epithelial cells and colloid of the thyroid follicles. It involves 5 distinct stages which are mostly enzyme dependent. It is important to be familiar with these stages in other to understand the mechanism of action of the antithyroid drugs.



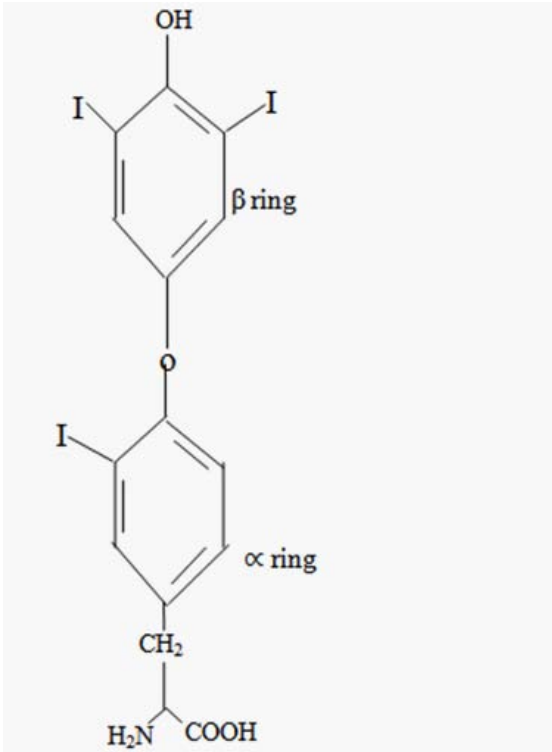
Tyrosine



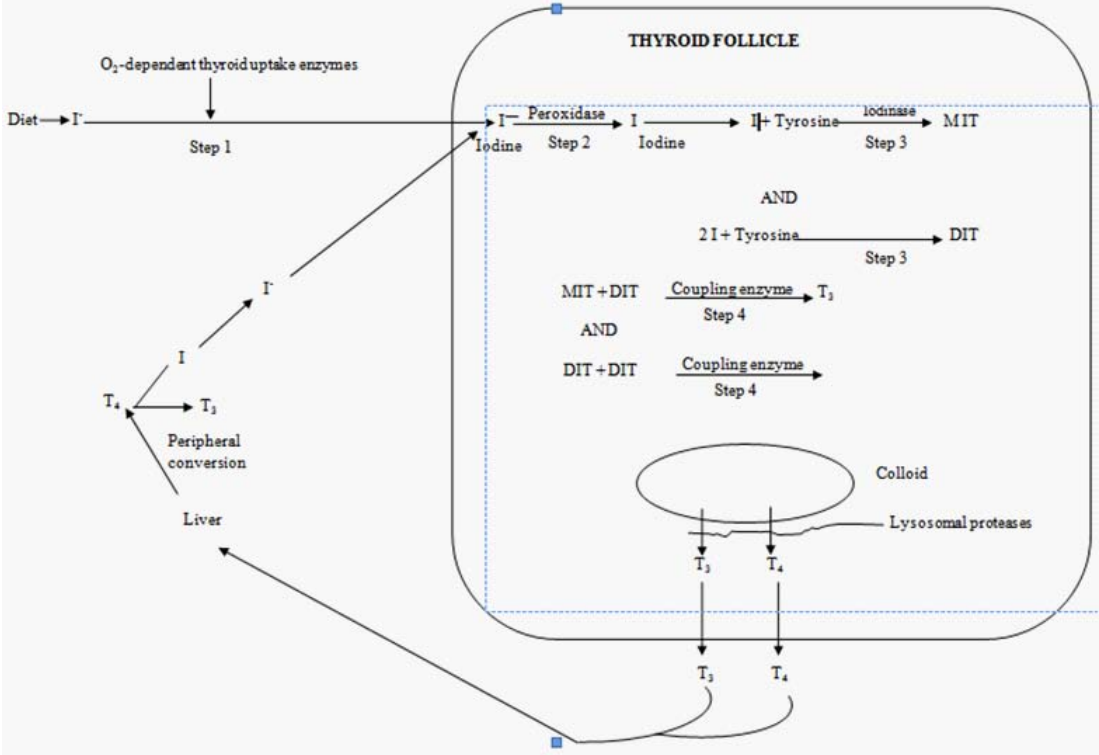
3,5,3151– Tetraiodothyronine (T_4)



3,5,31– Triiodothyronine (T_3)
(Most active form)



3,51,31– Triodothyronine (rT_3) (Inactive)



Figures: Structure of Tyrosine, Triiodothyronine, Tetraiodothyronine and Reverse T_3.

Within the thyroid follicle lie the colloids which contain large quantities of thyroid globulins. Each thyroid globulin unit within the colloid contains numerous tyrosine residues.

Biosynthetic Steps

Step I (uptake)

This involves the uptake of iodide derived from diet, from the blood into the thyroid follicle. This is the rate limiting step in thyroid hormone synthesis and it is catalyzed by O_2-dependent uptake enzymes. This step can be inhibited by thiocyanate and perchlorate.

Step II (Conversion)

It involves the conversion of iodide to iodine inside the thyroid follicle. This is catalyzed by peroxidase.

Step III (Iodination)

This involves the iodination of the tyrosine residues in the thyroglobulin of the colloid. This step is catalyzed by iodinase and can be inhibited by carbimazole and propylthiouracil. After the iodination, the products formed include monoiodotyrosine **(MIT)** and diiodotyrosine **(DIT)**.

Step IV (Coupling)

In this step, there is coupling of the iodotyrosines in the thyroglobulin. The major coupling reactions catalyzed by coupling enzymes include coupling of monoiodotyrosine with diodotyrosine to form triiodothyronine (T_3) and the coupling of two diiodotyrosines to form tetraiodothyronine (T_4). After the coupling reactions, these thyroid hormones are still attached to the thyroglobulin molecule awaiting release.

Step V (Release)

In this step; there is a proteolytic cleavage of the thyroid hormones (T_3 and T_4) from their attachment to thyroglobulin by splitting of the peptide bonds and hence release of the thyroid hormones into the circulation under the stimulation of the thyroid stimulating hormone **(TSH)**. Proteases present in lysosomes catalyze this reaction which can also be inhibited by large quantities of iodine. Once released, the thyroid hormones are bound to binding proteins. The major binding protein is thyroxine binding globulin **(TBG)**. Other binding proteins include albumin and thyroid binding prealbumin **(TBPA)**, also known as transthyretin. More T_4 than T_3 is produced and released by the thyroid. 99.7% of T_3 is protein bound while about 99.97% of T_4 is protein bound. The remainder exist as free unbound hormones. It is this unbound fraction for the thyroid hormones (T_3 and T_4) that are metabolically active. It is also this free fraction that is involved in the feedback coordination with the pituitary. In other words, TSH concentration is subject to changes in the levels of free (unbound) hormones.

T_3 is about 5 times more potent than T_4 even if T_4 is produced more in number than T_3 by the thyroid gland. About 85% of T_3 in circulation is produced by peripheral conversion of T_4 to T_3. In peripheral conversion, which occurs mainly in the liver there is deiodination of thyroxine by removal of one of the tyrosine residues in the outer ring (β-ring). The iodine produced in the process of deiodination is re-used by the thyroid gland. In certain circumstance, there could be defective peripheral deiodination such that instead of the iodine being removed from the outer ring it is removed from the inner ring. Under this circumstance, reverse T_3 (rT_3) is produced instead of the normal T3. (rT_3) is biologically inactive. Any severe chronic illness or severe malnutrition or starvation can lead to this type of defective deiodination.

Certain drugs have been known to block the peripheral conversion of T_4 to T_3. Such drugs include amiodarone and propanalol. Peripheral conversion can also be increased by drugs that can induce hepatic enzymes such as phenytoin, carbamazepine. These two drugs can increase T_3 level.

Functions of Thyroid Hormones

Thyroid hormones are involved in the regulation of general body metabolism. They are very important for normal growth, development and sexual maturation. They regulate energy expenditure by the body. They increase metabolism of carbohydrate, protein synthesis, cholesterol and triglyceride synthesis and degradation. They regulate heart rate.

Thyroid Function Test

These are a group of tests that could be used either individually or in group to assess the functional status of the thyroid gland, monitor treatment and relapse of thyroid disorders and for specialized research purposes. This test includes the following;

1. T_4 and T_3
2. Free T_4 and T_4
3. Thyroid stimulating hormone **(TSH)**
4. Thyroid releasing hormone **(TRH)** stimulating test
5. T_3 uptake test (thyroid hormone binding ratio-THBR)
6. Free thyroxine index **(FT_4 index)**

T_4 and T_3

Assessment of the levels of T_4 and T_3 can give an indication of the functional status of the gland. With a hyper functioning gland, total T_4 and T_3 are elevated and with a hypo functioning gland T_4 and T_3 are reduced. Problem encountered with total hormone assay is the interference caused by the binding protein for example, an increase in the major binding protein TBG will give a picture of a hyper functioning gland even when the gland is functioning normally (euthyroid state). A reduction in the level of TBG will give an erroneous picture of thyroid hypofunction. These problems encountered with the binding proteins make total hormone assay less reliable in their assessment of thyroid function. Free hormone assays, where available, are preferred.

TBG and by implication, total T_4 are increased in the following condition:

a) Oestrogen therapy

b) Pregnancy

c) Oestrogen oral contraceptive

TBG and by extension total T_4 are decreased under the following conditions.

a) Androgen therapy

b) Nephrotic syndrome, etc.

Under these conditions mentioned above, you must be careful when making statements on thyroid function based on the total T_4 alone.

Free T_4 and T_3

These are the biologically functional hormones. An increase in their levels will denote hyper functioning of the gland while decreased levels suggests hypo functioning of the glands. Free T_3 is

most useful in assessing hyperthyroid function while T_4 is more useful in assessing hypothyroid function. The utility of the free hormones in assessing thyroid function increases and their diagnostic value also increases when coupled with TSH assay results.

TSH

This is a very useful test in the assessment of thyroid function. It reflects the reservation or otherwise of the feedback mechanism involved in normal hypothalamo-pituitary axis. A low level of TSH when T_4 is high confirms primary hyperthyroidism and a high level of TSH when T_4 is very low confirms primary hypothyroidism. Recently, the ultra sensitive TSH assay has been introduced which can detect the minutest level of TSH. With this test, the TRH stimulation test for the diagnosis of hyperthyroidism is no more necessary. In primary hyperthyroidism (Graves' disease), TSH level will be undetectable using the ultra sensitive method and in primary hypothyroidism as in Hashimoto's thyroiditis, TSH level will be very high.

TRH Stimulation Test

This test is mostly used to confirm or exclude secondary hypothyroidism. 200µg of synthetic TRH is given intravenously after collecting sample from basal TSH estimation. After 30mins, 60mins, 90mins and 120mins of injection of synthetic TRH, samples are collected for estimation of TSH. High level of TSH much higher than the basal level denotes adequate response and rules out secondary cause of hypothyroidism. Low or insignificant response of TSH to TRH stimulation will occur in pituitary cause of hypothyroidism and in primary hyperthyroidism.

T_3 Uptake Test (Thyroid Hormone Binding Ratio-THBR)

This test is used to assess the uptake of a radioactively labeled T_3. In this test, serum of a patient containing TBG and T_4 is incubated with a radioactively labeled T_3 (^{125}I-T_3) and a resin. The amount of the radioactively labeled T_3 bound to the resin is directly proportional to the amount of thyroid hormone in the patient's serum. In other words, more radioactive T_3 bound to resin implies saturation of binding sites on TBG and a hyperthyroid state while less radioactive T_3 bound to resin denotes low binding of thyroid hormone to TBG or excess of TBG. In a hypothyroid state, less of radioactive T_3 will bind to resin.

Free Thyroxine Index (FT_4 index)

This test of thyroid function tries to cancel out or correct the erroneous picture created by the changes in the concentration of TBG. It is an alternative way of measuring free thyroid hormones. High level of FT_4 index denotes hyperthyroidism whereas low level denotes hypothyroidism. FT_4 index is calculated by the formula: **FT_4 index = T_4 X THBR**.

Other non-biochemical thyroid function tests

1. Thyroid scan: this could be used to assess 'hot' and 'cold' nodules
2. Magnetic resonance imaging **(MRI)**
3. CT scan

Specialized biochemical tests for thyroid antibodies

1. Thyroid stimulating immunoglobulin- this is found in Grave's disease
2. Thyroid peroxidase antibodies- This is found in autoimmune thyroiditis of the Hashimoto's type.

DISORDERS OF THE THYROID GLAND

Hyperthyroidism

This is a condition where the thyroid gland secretes more hormones than normal resulting in an exaggerated hormonal stimulation. Patients will present with features of hyper metabolism including tachycardia, sweating, feeling hot when others around are feeling cold, agitation, fine tremors. In Grave's disease, patients may present with exophthalmos and eye signs. Hyperthyroidism (thyrotoxicosis) could be caused by a thyroid gland disorder (primary hyperthyroidism) or a pituitary/hypothalamic disorder (secondary hyperthyroidism)

Causes of Hyperthyroidism

A. Primary

1. Thyroid tumor secreting thyroid hormone
2. Thyroid stimulating antibodies as in Grave's disease
3. Multi-nodular toxic goiter

In all these cases, there is autonomous secretion of the thyroid hormones by the thyroid gland and the gland in this case defies every feedback control.

B. Secondary

1. TSH-secreting pituitary adenoma
2. Ectopic secretion of TSH from tumors e.g. Hydatidiform mole or choriocarcinoma

In Grave's disease, the patient presents with enlargement of the thyroid gland (goiter) due to hyper stimulation of the gland and hyper functioning by the thyroid stimulating immunoglobulins.

C. Treatment

1. Antithyroid drugs
2. In cases of large goiter, do a surgical excision of the gland (total/subtotal thyroidectomy).

Note

Before thyroidectomy is carried out, the patient must be made euthyroid by using radioactive iodine and/or antithyroid drugs. It is risky to operate on a patient with hyper functioning active thyroid gland.

Hypothyroidism

This is a situation or condition where the thyroid gland is not secreting enough quantity of hormones to carry out its metabolic function. It may be due to a defect in the gland itself (primary hypothyroidism) or a defect in the pituitary/hypothalamus (secondary hypothyroidism). Patients with hypothyroidism show a generalized metabolic sluggishness, bradycardia, they feel cold when others are hot and they may be obese.

A. Primary causes

1. Autoimmune thyroiditis
    a) Hashimoto
    b) Atrophic
2. Malignant destruction of the thyroid gland
3. Thyroid agenesis
4. Iatrogenic cause: surgical removal of the thyroid gland following thyrotoxicosis

B. Secondary

1. Malignant infiltration/destruction of the pituitary or hypothalamus
2. Post partum pituitary necrosis-Sheehan's syndrome

C. Infilterative conditions affecting the gland

a) Amyloidosis
b) Sarcoidosis
c) Cystinosis
d) Haemochromatosis
e) Riedel's Thyroiditis

D. Investigation

1. Measure T_4 and TSH: In primary hypothyroidism, T_4 is decreased and TSH is increased while in secondary hypothyroidism both will be low.
2. TRH stimulation test will produce a normal response in secondary hypothyroidism caused by

hypothalamic disorder but will fail to produce a normal response in secondary hypothyroidism caused by pituitary disorder.

E. Treatment

Where possible, treat the underlying cause and commence thyroid replacement therapy. Sometimes this can continue for life.

EUTHYROID SICK SYNDROME (ESS)

Certain patients with chronic non-thyroidal illness or condition present with features suggestive of impaired thyroid function even when the patient has no thyroid disorder. This phenomenon is called euthyroid sick syndrome **(ESS)**. Because of this, it is advised that all thyroid function tests in this group of patients be suspended until they recover from their illness in other to avoid mis-interpretation of thyroid function.

Diseased states or conditions in which ESS will manifest will include

1. Prolonged starvation
2. Protein energy malnutrition
3. Prolonged fasting
4. Chronic renal failure
5. AIDS
6. Diabetic ketoacidosis
7. Cirrhosis
8. Any other prolonged severe systemic illness.

Biochemical features in this syndrome will include

1. Slightly decreased T_4 and T_3 levels
2. Increased rT_3 levels
3. Normal TSH levels