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Review Article

Thyroid Hormones in the Human Body: A review

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Abstract

Thyroid gland is an essential endocrine gland that is present in the human body. This review highlights the production, regulation and disease conditions of the thyroid hormones. The thyroid gland is controlled with the help of hypothalamus and the pituitary gland that is present in the brain. The production of thyroid hormones involves five main steps such synthesis of thyroglobulin (TG), iodide uptake, iodination of thyroglobulin, storage and release. The two important hormones produced by the thyroid gland are Thyroxine (T4) and Triiodothyronine(T3). These two hormones are iodine containing derivatives. Deficiency of iodine in the body results in the reduction of T3 and T4 production. Excess and deficiency of these two hormones result in the major diseases like Hyper and Hypothyroidism. The synthetic forms of Thyroxine(T4) and Triiodothyronine(T3) used in the Pharmaceutical field are Levothyroxine and Liothyronine. Women are most commonly prone to these thyroid diseases comparatively to men. Undiagnosed disease conditions may become fatal. Levothyroxine therapy is commonly used for thyroidism which is a similar synthetic thyroid hormone. Also natural thyroid hormones that are obtained from the dried thyroid glands of animals are available. Thyroid function test and the measurement of T3, T4 plasma level becomes essential for the identification and regular maintenance of thyroid hormones in the body and human well-being.

Keywords: Thyroid gland, Thyroxine(T4), Triiodothyronine(T3), Levothyroxine, Liothyronine

Introduction:

Thyroid is an endocrine gland situated on the either side of trachea at the root of the neck. It is a butterfly shaped organ responsible for metabolism, growth, internal temperature and many other body functions.[1] Thyroid hormones are stored in the thyroid gland and released when needed in the body.[2]

Thyroid hormones have a key role in the human metabolism.[3,4] The two essential hormones synthesized in the body by thyroid gland is Triiodothyronine (T3) and Thyroxine(T4). The biosynthetic pathways of the thyroid hormone starts with the iodine metabolism.[5]

In the production of thyroid hormones, triiodothyronine (T3) is synthesized to a lesser degree than the thyroxine (T4).[6] But triiodothyronine (T3) is more active than thyroxine (T4).[7] Thyroxine (T4) covers about 90% of the secretion and Ttriiodothyronine(T3) is about 9 % of the secretion from the gland. Reverse T3 (rT3) is the third minor hormone secreted by the thyroid gland that covers 1% of the secretion which is not biologically active.[8]

Production of Thyroid Hormones in the Human Body:

Thyroid gland is controlled by the hypothalamus and the pituitary gland, which are located in the brain. The hypothalamus releases thyrotropin-releasing hormone (TRH) that stimulates the pituitary gland to release Thyroid-Stimulating Hormone (TSH)[9]. Under the normal conditions of hypothalamus and pituitary gland, they sense when the thyroid hormone levels are low, and they secrete more TRH and TSH that stimulates to make more thyroid hormones and vice versa. More hormones are produced in the body when it is needed.[10]

This whole network of thyroid hormone production is referred as the hypothalamic-pituitary-thyroid axis(HPT), it also adapts to the metabolic changes and body's needs.[11]

Secretion of Thyroid Hormones:

Steps involved in the synthesis of thyroid hormone in the Human Body:

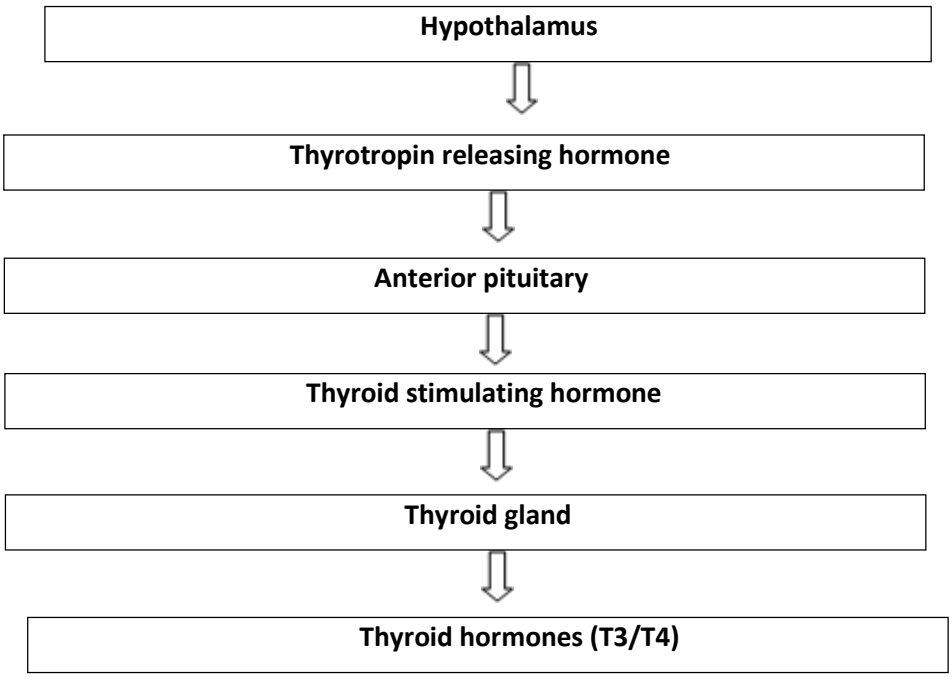
1. **Synthesis of Thyroglobulin (TG):** Thyroglobulin is a protein produced by thyrocytes in the thyroid follicles. TG does not contain any iodine on its own, it is a precursor protein stored in the lumen of follicles and it is produced in the rough endoplasmic reticulum. Golgi apparatus packs it into the vesicles and then it enters the follicular lumen through exocytosis.
2. **Iodide Uptake :**Protein Kinase A phosphorylation causes increase in the activity of basolateral Na+-I- symporters, which are powered by Na+-K+-ATPase, brings iodide from the circulation into the thyrocytes. Iodide then diffuses from basolateral side to the apex of the cell and transported into the colloid through Pendrin

transporter.[12]

3. **Iodination of thyroglobulin: Protein** kinase A phosphorylates and activates the enzyme thyroid peroxidase (TPO). TPO undergoes three reactions: oxidation, organification, and coupling reaction.

1. **Oxidation:** TPO oxidizes iodide (I-) to iodine (I2) using hydrogen peroxide. NADPH- oxidase, apical enzyme, generates hydrogen peroxide for TPO.
2. **Organification:** TPO links tyrosine residues of thyroglobulin protein with Iodine. It produces monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT is made of a single tyrosine residue with iodine, and DIT is of two tyrosine residues with iodine.
3. **Coupling reaction:** TPO combines iodinated tyrosine residues to form triiodothyronine (T3) and tetraiodothyronine (T4). T3 is formed by joining MIT and DIT , and two DIT molecules formT4.[13]
4. **Storage:** Thyroid hormones are bound to thyroglobulin for storage in the follicular lumen.
5. **Release:** Thyrocytes help in the release of thyroid hormones into the fenestrated capillary network.[14]

- Tyrosine + I2 = MIT (Monoiodotyrosine)
- MIT+I = DIT (Di iodotyrosine)
- DIT+MIT = T3 (Triiodotyrosine)
- MIT+DIT = ReverseT3
- DIT+DIT = T4 (Tetraiodotyrosine)[2]



Mechanism of action of Thyroid Hormones:

Thyroxine (T4) is the pro hormone that gets converted to triiodothyronine (T3) which is biologically more potent. This conversion is done by three iodothyronine deiodinases . They are type 1 deiodinase (D1), type 2 deiodinase (D2), and type 3 deiodinase (D3) enzymes. Type 1 and type 2 enzymes catalyse the removal of a 5' - iodine atom for the conversion of thyroxine(T4) to triiodthyronine (T3). Type 3 enzyme irreversibly removes a 5 - iodine atom to form reverse T3.[15,16]

Thyroid gland produces thyroid hormone, which consists of follicles where thyroid hormone is synthesized through iodination of tyrosine residues in the glycoprotein thyroglobulin.[17,18]

Thyroid stimulating hormone (TSH), that is secreted by the anterior pituitary acts directly on the TSH receptor (TSH-R) on the thyroid follicular cell. TSH regulates the sodium iodide symporter and it is followed by the steps that are necessary for thyroid hormone synthesis takes place.[19] When T3 and T4 enters into the blood from thyroid gland they bind to the protein called Thyroid Binding Protein (TBP) and travel in the blood stream. From the blood stream they reach the target cells.

What is Thyroxine (T4):

Thyroid gland produces thyroxine (T4) in the body by the regulation of hypothalamus and the pituiary gland. Thyroxine (T4) must be converted to triiodothyronine (T3) to become active by either type 1 (D1) or type 2 (D2) deiodinase enzyme.[20] Iodine is the major constituent that is required for the formation of thyroxine. To synthesize normal amount of thyroxine iodide is needed from the ingested iodine.[21]

What is triiodothyronine (T3):

Thyroid gland produces triiodothyronine (T3) which is the active thyroid hormone. It is involved in most of the physiological processes in the body like growth, metabolism and heart rate.[22]

Triiodothyronine (T3) is four times more potent than thyroxine (T4) and when comes to the duration of action, thyroxine (T4) has more duration when compared to

tiiodothyronine (T3). T3 is released quickly due to its lesser affinity for plasma proteins and its effect is faster than thyroxine(T4).

Effects of metabolically active form of triiodothyronine (T3):

- Potentiates basal metabolic rate
- Increases cardiac output
- Increases heart rate
- Positive impact in the effects of catecholamines
- Improves the brain action
- Thickens the endometrium in females
- Increases catabolism of proteins [23]

Treatment with Thyroxine (T4) and Triiodothyronine (T3):[24]

Thyroid hormone deficiency (hypothyroidism) is treated by T3 and T4 administration. As they are stable and well absorbed in the stomach, oral route is preferred. The synthetic version of Thyroxine (T4) is levothyroxine and Triiodothyronine (T3) is Liothyronine. T4 has longer biological half-life than T3, so once daily admininstration of T4 is recommended.

Levothyroxine contains only thyroxine (T4) and it is found to be ineffective for many patients due to the lack of deiodinases (Type 1 and 2) which converts T4 to T3. For such patients either a combination of synthetic T3 and T4 or a natural thyroid hormone which contains a mixture of both T3 and T4 is preferred. The source of natural thyroid hormone is pork thyroid gland.

They are given orally as they are well absorbed by the stomach. The Pharmaceutical name of manufactured version of T4 is Levothyroxine but it is metabolised slowly than T3 and hence once-daily administration will be enough. Some patients feel natural thyroid hormone works better over the biosynthetic forms and this is based on the evidence of clinical trials.[25]

Problems associated with T3 and T4 levels:

Excess and deficiency of thyroid hormone in the bloodstream results in various problems in the body. Improper functioning of the thyroid gland may result in many thyroid disorders.[26] The two main types of thyroid disorders are hypothyroidism and hyperthyroidisms.[27] Too much of T3 in the blood is referred to as thyrotoxicosis. This condition happens due to the over activity of thyroid gland, it is also called as hyperthyroidism. Hyperthyroidism occurs in various conditions such as Grave's disease, inflammation of the thyroid or a benign tumor. Hyperthyroidism occurs when more T3 supplements are ingested. or conversion of more T4 to T3 hormone by deiodinase enzyme.[28]

Signs of Thyrotoxicosis/Hyperthyroidism:

- Weight loss
- Irregular menstrual cycle
- Palpitations
- Increased appetite
- Tiredness and irritability
- Hair fall and hair thinning [29]

Hypothyroidism is the condition that results if the deficiency of thyroid hormone takes place in the body. This may be due to auto immune conditions and certain medications like amiodarone, methimazole, potassium iodide, interleukin 2 . Pituitary dysfunction such as pituitary tumors or inflammation also result in Hypothyroidism.[30]

Signs of Hypothyroidism:

- Weight gain
- Feeling cold
- Tiredness
- Mental depression
- Constipation
- Menstrual irregularities [31]

Some of the Most Common Thyroid Diseases:

Thyroid diseases are one of the most common endocrine disorders in the world.[32]

Goiters: It is the condition where the neck area is bulged. It is of toxic goiter and non- toxic goiter. Toxic goiter is associated with hyperthyroidism and non-toxic goiter is also known as a simple or endemic goiter and it is caused by iodine deficiency. [33,34]

Thyroid cancer: All age groups of people can be affected by thyroid cancer and the symptoms are neck pain, enlarged lymph nodes.[35]

Thyroiditis: It is an inflamed condition of thyroid gland that is associated with the abnormal thyroid function (mainly hyperthyroidism). Inflammation results in the death of thyroid cells, which makes the thyroid gland unable to produce enough hormones. Therefore, body's normal metabolism is affected. There are five types of thyroiditis; they are Hashimoto's thyroiditis, sub-acute thyroiditis, silent thyroiditis, post-partum thyroiditis and drug/radiation induced. Treatments for these types are specific to each type.

Hyperthyroidism: This condition occurs when too much thyroid hormone is secreted in human body. Hyperthyroid patients are often sensitive to heat, they eat excessively, hyperactive. One of the side effects of hyperthyroidism is goiter. This is due to the inflamed tissues and over-stimulated thyroid. Symptoms of hyperthyroidism are nervousness, tremor, abnormal heart rate, fatigue, increased sweating, increase in bowel movements, unintentional weight loss.

Some of the most common causes of hyperthyroidism are: [36,37]

- Excessive iodine consumption
- Thyroid nodules (Known as hot nodules)
- Grave's disease
- Toxic goiter

Hypothyroidism: This condition occurs when thyroid hormone is secreted in human body is too low. This condition is known as Cretinism and it often appears in infants. Cretinism may result in abnormal bone development and mental retardation. In case of adults, hypothyroidism may show symptoms like little appetite, sluggishness. Hypothyroidism is often unnoticed for years before diagnosed. Symptoms of hypothyroidism are dry skin, fluid

retention, depression, poor concentration, muscle and joint aches.[38]

Impact of thyroid disease in humans:

Thyroid diseases have become common worldwide.[39] Women are more affected to these thyroid diseases. Nearly 12% of the population in the world develops thyroid diseases in their lifetime. Around 20 million people get affected by some form of thyroid diseases. But 60% of the people are not aware of their disease condition. One woman in five will develop thyroid disorder in her lifetime. Thyroid disease that remains undiagnosed may result in serious stages for the patients. More than 60% of the thyroid diseases remains life long.[40,41]

Thyroid function test:

It is the blood test that is done to check the function of thyroid gland.[42] They are identified by many symptoms and after diagnosing, it needs to be regularly monitored for treatment.[43] Excess and deficiency of thyroid hormone occur at many condition, so adequate laboratory assessments are vital. Thyroid testing can provide details about the level of thyroid hormones in the body. Treatments like ablative therapy such as surgery, long term or life-long (anti-thyroid drugs and thyroid hormone replacement) medications. In these conditions frequent monitoring of patients is required.[44]

Measurement of Plasma level of T3 and T4:

1. T3, T4, and TSH hormone levels are measured by radioimmunoassay. In hyper thyroidism, serum T3 and T4 increase and serum TSH levels are decreased. In hypothyroidsm, the serum T3 and T4 decrease and serum TSH levels are increased. [45]
2. The direct measurement of concentration of free thyroid hormones (T3, T4) in the plasma is the diagnosis for hyper and hypothyroidism.
3. Basal metabolic rate is measured in thyroid condition. In hyperthyroid condition, it is increased about 30% to 60%. In hypothyroid condition it is decreased by about 20% to 40%.[2]

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