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PHYSIOLOGY OF THYROID GLAND

After studying this lecture, you should be able to:

1. Describe the structure of the thyroid gland and how it relates to its function.
2. Define the chemical nature of the thyroid hormones and how they are synthesized.
3. Understand the critical role of iodine in the thyroid gland and how its transport is controlled.
4. Describe the role of protein binding in the transport of thyroid hormones and peripheral metabolism.
5. Identify the role of the hypothalamus and pituitary in regulating thyroid function.
6. Define the effects of the thyroid hormones in homeostasis and development.
7. Understand the basis of conditions where thyroid function is abnormal and how they can be treated.

THYROID GLAND:

Thyroid is an endocrine gland situated at the root of the neck on either side of the trachea (figure 1).It develops from an evagination of the floor of the pharynx, and a **thyroglossal duct** marking the path of the thyroid from the tongue to the neck sometimes persists in the adult.

It has two **lobes,** which are connected in the middle by an **isthmus.** It weighs about 20 to 40 g in adults. Thyroid is larger in females than in males. The structure and the function of the thyroid gland change in different stages of the sexual cycle in females. Its function increases slightly during pregnancy and lactation and decreases during menopause.

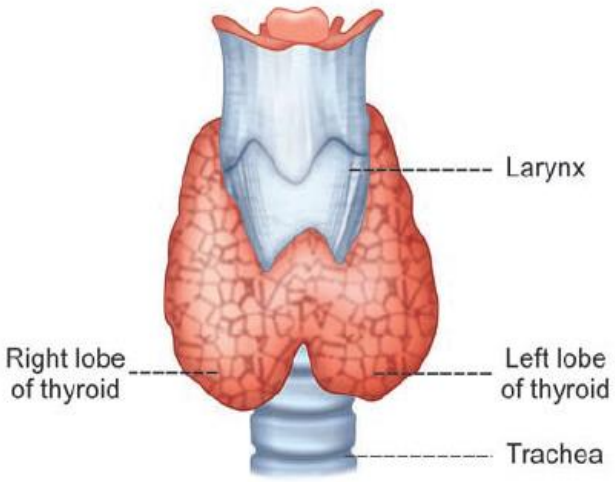

Figure (1): Demonstrating anatomy of thyroid gland.

HISTOLOGY OF THYROID GLAND:

Thyroid gland is composed of large number of closed **follicles.** These follicles are lined with cuboidal epithelial cells, which are called the **follicular cells.** Follicular cavity is filled with a colloidal substance which is secreted by the follicular cells. The major constituent of colloid is the large glycoprotein called *thyroglobulin*. Follicular cells also secrete tetraiodothyronine (T4 or thyroxin) and tri-iodothyronine (T3).Thyroid secretion is controlled primarily by *thyroid-stimulating hormone (TSH)* secreted by the anteriorpituitary gland. In between the follicles, the **parafollicular cells** are present .These cells secrete calcitonin (figure 2).Thyroid gland has very rich blood supply.

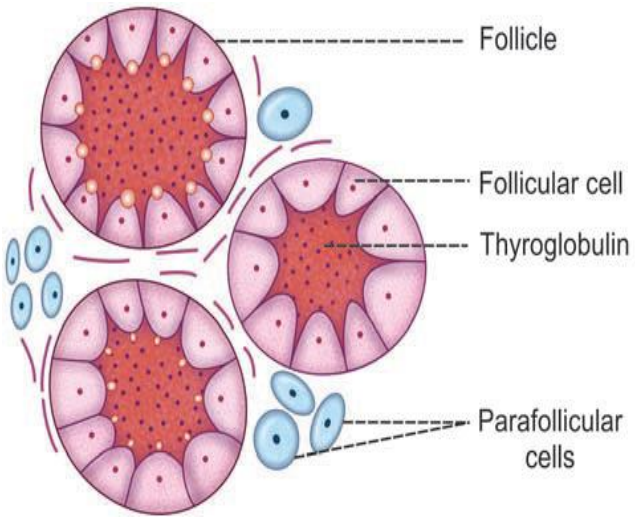

Figure2: Demonstrating histology of thyroid gland.

Chemistry

Both T4 and T3 are iodine-containing derivatives of amino acid **tyrosine.**

The potency of T3 is four times more than that of T4. Duration of T4 action is four times more than T3 action. This is because of the difference in the affinity of these hormones to plasma proteins. T3 has less affinity for plasma proteins and combines loosely with them, so that it is released quickly.T4 has more affinity and strongly binds with plasma proteins, so that it is released slowly. T4 has a long half-life of 7 days. Half-life of T3 is less than 24 hours.

Plasma Level

Total T3 = 0.12 µg/dL

Total T4 = 8 µg/dL.

HORMONES OF THYROID GLAND

Thyroid gland secretes three hormones:

1. Tetraiodothyronine or T4 (thyroxine) it forms about 93% of the total secretion

2. Tri-iodothyronine or T3 is only 7% to 10% of total secretion.

3. Calcitonin.

SYNTHESIS OF THYROID HORMONES

Synthesis of thyroid hormones takes place in thyroglobulin, present in follicular cavity. Iodine and tyrosine are essential for the formation of thyroid hormones. Iodine is consumed through diet. It is converted into iodide and absorbed from GI tract. Tyrosine is also consumed through diet and is absorbed from the GI tract. For the synthesis of normal quantities of thyroid hormones, approximately 1 mg of iodine is required per week or about 50 mg per year. To prevent iodine deficiency, common table salt is iodized with one part of sodium iodide to every 100,000 parts of sodium chloride. The principal organs that take up circulating Iodide are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in the urine.

STAGES OF SYNTHESIS OFTHYROID HORMONES

Synthesis of thyroid hormones occurs in six stages:

1. Thyroglobulin synthesis.

2. Iodide trapping.

3. Oxidation of iodide.

4. Transport of iodine into follicular cavity.

5. Iodination of tyrosine.

6. Coupling reactions.

1. *Thyroglobulin Synthesis*

Endoplasmic reticulum and Golgi apparatus in the follicular cells of thyroid gland synthesize and secrete thyroglobulin continuously. Thyroglobulin molecule is a large glycoprotein containing 140 molecules of amino acid tyrosine. After synthesis, thyroglobulin is stored in the follicle.

2. *Iodide Trapping*

Iodide is actively transported from blood into follicular cell, against electrochemical gradient. This process is called **iodide trapping** .The salivary glands, the gastric mucosa, the placenta, the ciliary body of the eye, the choroid plexus, the mammary glands, and certain cancers derived from these tissues also can transport iodide against a concentration gradient. Iodide is transported into the follicular cell along with sodium by sodium-iodide pump, which is also called iodide pump. Normally, iodide is 30 times more concentrated in the thyroid gland than in the blood. However, during hyperactivity of the thyroid gland, the concentration of iodide increases 200 times more.

3. *Oxidation of Iodide*

Iodide must be oxidized to elementary iodine. The oxidation occurs in the presence of thyroid peroxidase. Absence or inactivity of this enzyme stops the synthesis of thyroid hormones.

4. *Transport of Iodine into Follicular Cavity:* From the follicular cells, iodine is transported into the follicular cavity by an **iodide-chloride pump** called **pendrin.**

5. *Iodination of Tyrosine*

Combination of iodine with tyrosine is known as iodination. First, iodine is transported from follicular cells into the follicular cavity, where it binds with thyroglobulin. This process is called **organification** of thyroglobulin. Then, iodine (I) combines with tyrosine. Iodination process is accelerated by the enzyme iodinase, which is secreted by follicular cells.Iodination of tyrosine occurs in several stages.Tyrosine is iodized first into monoiodotyrosine (MIT) and later into di-iodotyrosine (DIT). MIT and DIT are called the iodotyrosine residues.

6. *Coupling Reactions*

Iodotyrosine residues get coupled with one another. The coupling occurs in different configurations, to give rise to different thyroid hormones. Coupling reactions are:

Tyrosine + I = Monoiodotyrosine (MIT)

MIT + I = Di-iodotyrosine (DIT)

DIT + MIT = Tri-iodothyronine (T3)

MIT + DIT = Reverse T3

DIT + DIT = Tetraiodothyronine or Thyroxine (T4). (Figure 3)

After synthesis, the thyroid hormones remain in the form of vesicles within thyroglobulin and are stored for long period. When there is a need for thyroid hormone secretion, colloid is internalized by the thyrocytes by endocytosis, and directed toward lysosomal degradation. Thus, the peptide bonds of thyroglobulin are hydrolyzed and free T4 and T3 are discharged into cytosol and thence to the capillaries .In combination with thyroglobulin, the thyroid hormones can be stored for **several months.** Thyroid gland is unique in this, as it is the only endocrine gland that can store its hormones for a long period of about 4 months. So, when the synthesis of thyroid hormone stops, the signs and symptoms of deficiency do not appear for about 4 months.

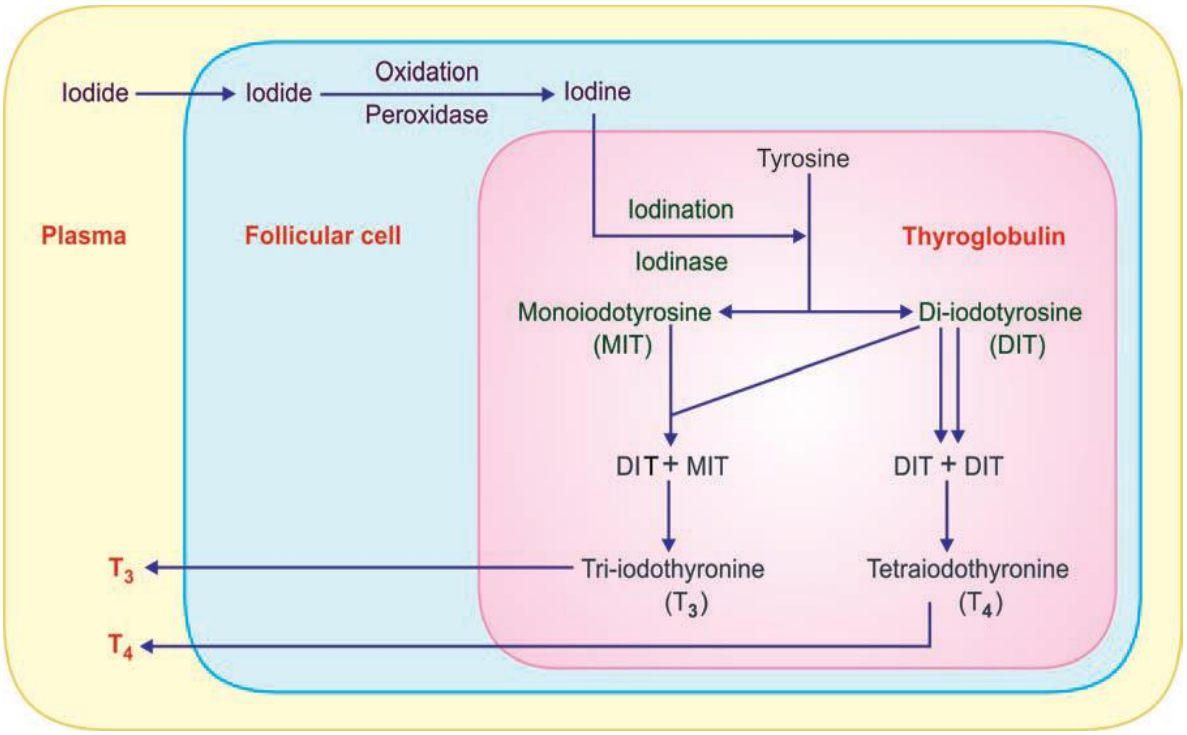

Figure3: Steps of Thyroid hormone synthesis.

Thyroid hormones are transported in the blood by three types of proteins:

1. Thyroxine-binding globulin (TBG), mainly T4

2. Thyroxine-binding prealbumin (TBPA)

3. Albumin. Mainly T3

Most of the Thyroxine Secreted by the Thyroid Is Converted to Triiodothyronine. Before acting on the genes to increase genetic transcription. Intracellular thyroid hormone receptors have a very high affinity for T3. Consequently, more than 90 per cent of the thyroid hormone molecules that bind with the receptors are T3.

Metabolism of Thyroid Hormones

Degradation of thyroid hormones occurs in muscles, liver and kidney by deiodination process.

FUNCTIONS OF THYROID HORMONES

The actions of thyroid hormones are:

1. ACTION ON BASAL METABOLIC RATE (BMR): Thyroxin increases the metabolic activities in most of the body tissues, except brain, retina, spleen, testes, uterus lymph nodes, anterior pituitary and lungs. It increases BMR by increasing the oxygen consumption of the tissues. The

action that increases the BMR is called calorigenic action.This action is brought about by increase mitochondrial and Na^{+}- k^{+} ATPase activities.

BMR: is the quantity of energy production at rest (physical and mental) during optimal temperature, measured 12 hours after last meal.

In hyperthyroidism, BMR increases by about 60%to 100% above the normal level and in hypothyroidism itfalls by 20% to 40% below the normal level.

2. ACTION ON PROTEIN METABOLISM:

Thyroid hormone increases the synthesis of proteins in the cells, by the following ways:

- Increasing the Translation of RNA.
- Increasing the Transcription of DNA to RNA.
- Increasing the Activity of Mitochondria and increase the production of ATP.
- Increasing the Activity of Cellular Enzymes.

This action is when thyroid hormone is within physiological limits .But if we have increase in the level of thyroid hormone this will be converted to catabolic action and causes protein break down especially in muscles and causes muscle weakness (thyrotoxic myopathy). Conversely, lack of Thyroid hormone causes muscles to become sluggish, and relax slowly after contraction.

3. **ACTION ON CARBOHYDRATE METABOLISM:**

Thyroxine:

- Increases the absorption of glucose from GI tract.
- Enhances the glucose uptake by the cells, by accelerating the transport of glucose through the cell membrane.
- Increases the breakdown of glycogen into glucose.
- Accelerates gluconeogenesis.

4. ACTION ON FAT METABOLISM

Thyroxine decreases the fat storage by mobilizing it from adipose tissues and fat depots. The mobilized fat is converted into free fatty acid and transported by blood. Thus, thyroxine increases the free fatty acid level in blood.

5. ACTION ON PLASMA AND LIVER FATS

Even though there is an increase in the blood level of free fatty acids, thyroxine specifically decreases the cholesterol, phospholipids and triglyceride levels in plasma. So, in hyposecretion

of thyroxine, the cholesterol level in plasma increases, resulting in **atherosclerosis.** Thyroxine also increases deposition of fats in the liver, leading to **fatty liver.** Thyroxine decreases plasma cholesterol level by increasing its excretion from liver cells into bile. Cholesterol enters the intestine through bile and then it is excreted through the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells.

6. ACTION ON VITAMIN METABOLISM

Thyroxine increases the formation of many enzymes. Since vitamins form essential parts of the enzymes, it's believed that the vitamins may be utilized during the formation of the enzymes. Hence, **vitamin deficiency** is possible during hypersecretion of thyroxine.

7. ACTION ON BODY TEMPERATURE

Thyroid hormone increases the heat production in the body, by accelerating various cellular metabolic processes and increasing BMR. It is called thyroid hormone induced thermogenesis. During hypersecretion of thyroxine, the body temperature increases greatly, resulting in excess sweating.

8. ACTION ON GROWTH:

In humans, the effect of thyroid hormone on growth is manifest mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so that the duration of growth and the eventual height of the adult may actually be shortened.

An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded, and the brain remains smaller than normal. Without specific thyroid therapy within days or weeks after birth, the child without a thyroid gland will remain mentally deficient throughout life.

9. ACTION ON BODY WEIGHT: Thyroxin is essential for maintaining the body weight. Increase in thyroxine secretion decreases the body weight and fat storage. Decrease in thyroxine secretion increases the body weight because of fat deposition.

10. ACTION ON BLOOD

Thyroxine accelerates erythropoietic activity and increases blood volume. It is one of the important general factors necessary for erythropoiesis. Polycythemia is common in hyperthyroidism.

11. ACTION ON CARDIOVASCULAR SYSTEM

Thyroxine increases the overall activity of cardiovascular system.

- *On Heart Rate*

Thyroxine acts directly on heart and increases the heart rate (β1 receptor stimulation). It is an important clinical investigation for diagnosis of hypothyroidism and hyperthyroidism.

- *On the Force of Contraction of the Heart* :
  Due to its effect on enzymatic activity, thyroxine generally increases the force of contraction of the heart. But in hyperthyroidism or in thyrotoxicosis, the heart may become weak due to excess activity and protein catabolism. So, the patient may die of cardiac decompensation. *Cardiac decompensation refers to failure of the heart to maintain adequate circulation associated with dyspnea, venous engorgement (veins overfilled with blood) and edema.*
- *On Blood Vessels:*

  Thyroxine causes vasodilatation by increasing the metabolic activities.

- *On Arterial Blood Pressure:* Because of increase in rate and force of contraction of the heart, increase in blood volume and blood flow by the influence of thyroxine, cardiac output increases. This in turn, increases the blood pressure. But, generally, the *mean* arterial pressure usually remains about normal after administration of thyroid hormone. Because of increased blood flow through the tissues between heart beats, the pulse pressure is often increased, with the systolic pressure elevated in hyperthyroidism 10 to 15 mm Hg and the diastolic pressure reduced in a corresponding amount.

  MAP = 1/3 (SBP – DBP) + DBP

12. ACTION ON RESPIRATION

Thyroxine increases the rate and force of respiration indirectly. The increased metabolic rate (caused by thyroxine) increases the demand for oxygen and formation of excess carbon dioxide. These two factors stimulate the respiratory centre to increase the rate and force of respiration.

13. ACTION ON GASTROINTESTINAL TRACT

Generally, thyroxine increases the appetite and food intake. It also increases the secretions and movements of GI tract. So, hypersecretion of thyroxine causes diarrhea and the lack of thyroxine causes constipation.

14. ACTION ON CENTRAL NERVOUS SYSTEM

Thyroxine is very essential for the development and maintenance of normal functioning of central nervous system (CNS).

- *On Development of Central Nervous System: Thyroxine* is important development of synapses and myelination of the axons.
- *On the Normal Function of Central Nervous System :*Thyroxine
  - *Increases the blood flow to brain.*
  - *It has Excitatory Effects on the Central Nervous System.*

  The hyperthyroid individual is likely to have extreme nervousness and many psychoneurotic tendencies, such asanxiety complexes, extreme worry, and paranoia.

15. ACTION ON SKELETAL MUSCLE

Thyroxine is essential for the normal activity of skeletal muscles. Slight increase in thyroxine level makes the muscles to work with more vigor. But, hypersecretion of thyroxine causes weakness of the muscles due to catabolism of proteins. This condition is called thyrotoxic myopathy. The muscles relax very slowly after the contraction. Hyperthyroidism also causes fine muscular tremor. Tremor occurs at the frequency of 10 to 15 times per second. It is due to the thyroxine-induced excess neuronal activity. The lack of thyroxine makes the muscles more sluggish.

16. ACTION ON SLEEP

Normal thyroxine level is necessary to maintain normal sleep pattern. Hypersecretion of thyroxine causes excessive stimulation of the muscles and central nervous system. So, the person feels tired, exhausted and feels like sleeping. But, the person cannot sleep because of the stimulatory effect of thyroxine on neurons. On the other hand, hyposecretion of thyroxine causes somnolenc, with sleep sometimes lasting 12 to 14 hours a day.

17. ACTION ON SEXUAL FUNCTION

Normal thyroxine level is essential for normal sexual function. In men, hypothyroidism leads to complete loss of libido (sexual drive) and hyperthyroidism leads to impotence.

In women, hypothyroidism causes menorrhagia and polymenorrhea . In some women, it causes irregular menstruation and occasionally amenorrhea.

Hyperthyroidism in women leads to oligomenorrhea and sometimes amenorrhea.

18. ACTION ON OTHER ENDOCRINE GLANDS: Because of its metabolic effects, thyroxine increases the demand for secretion by other endocrine glands.

Sequence of Events of thyroid hormone action:

Thyroid hormones enter the nucleus of cell and bind with thyroid hormone receptors (TR), and form the hormone-receptor complex. This complex activates the ribosomes to synthesize the new proteins. New proteins are involved in many activities including the enzymatic actions.

REGULATION OF SECRETION OF THYROID HORMONES

Secretion of thyroid hormones is controlled by anterior pituitary and hypothalamus through feedback mechanism. Many factors are involved in the regulationof thyroid secretion.

Thyroid-stimulating Hormone

Thyroid-stimulating hormone (TSH) secreted by anterior pituitary is the major factor regulating the synthesis and release of thyroid hormones. It is also necessary for the growth and the secretory activity of the thyroid gland. Thus, TSH influences every stage of formation and release of thyroid hormones.

Chemistry

Thyroid-stimulating hormone is a peptide hormone withone α-chain and one β-chain.Half-life of TSH is about 60 minutes. The normal plasmalevel of TSH is approximately 2 U/mL.

Actions of Thyroid-stimulating Hormone

Thyroid-stimulating hormone increases:

1. The number of follicular cells of thyroid.

2. The development of thyroid follicles.

3. Size and secretory activity of follicular cells.

4. Iodide pump and iodide trapping in follicular cells.

5. Thyroglobulin secretion into follicles.

6. Iodination of tyrosine and coupling to form the hormones.

7. Proteolysis of the thyroglobulin, by which release of hormone is enhanced and colloidal substance, is decreased.

Immediate effect of TSH is proteolysis of the thyroglobulin, by which thyroxine is released within 30 minutes. Effect of TSH on other stages in thyroxine synthesis takes place after some hours, days or weeks.

Mode of Action of TSH

TSH acts through cyclic AMP mechanism.

ROLE OF HYPOTHALAMUS

Hypothalamus regulates thyroid secretion by controlling TSH secretion through thyrotropic-releasing hormone (TRH). From hypothalamus, TRH is transported through the hypothalamo-hypophyseal portal vessels to the anterior pituitary. After reaching the pituitary gland, the TRH causes the release of TSH.

FEEDBACK CONTROL

Thyroid hormones regulate their own secretion through negative feedback control, by inhibiting the release of TRH from hypothalamus and TSH from anterior pituitary (figure 4).

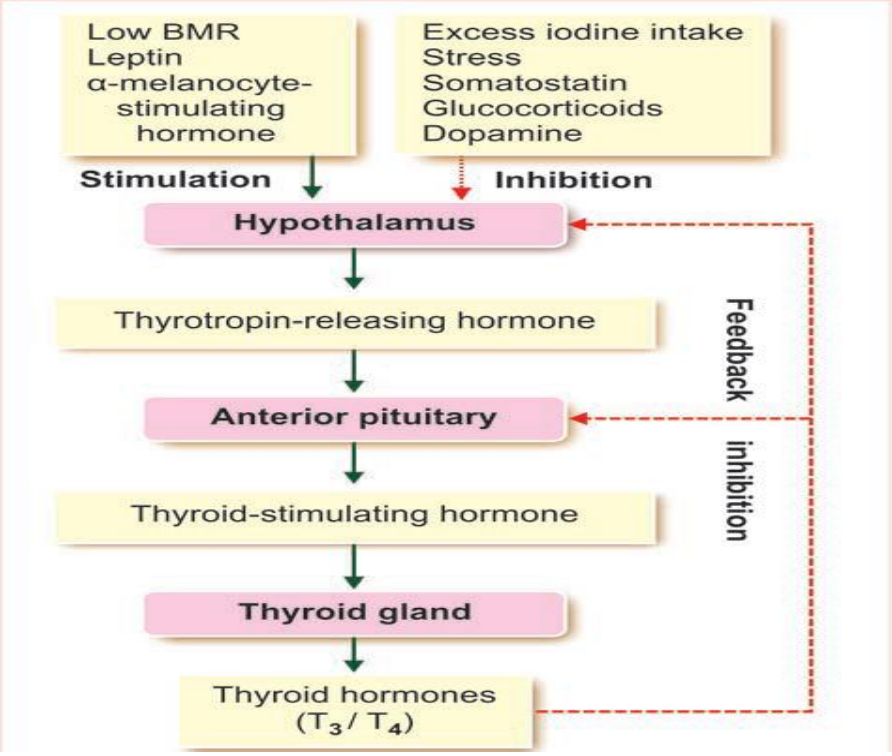

Figure (4):Factors regulating thyroid hormone secretion.

THYROID FUNCTION TESTS

Functional status of thyroid gland is assessed by the following tests:

1. Measurement of plasma level of T3 and T4.

2. Measurement of TRH and TSH: There is almost total absence of these two hormones in hyperthyroidism. It is because of negative feedback mechanism, by the increased level of thyroid hormones.

3. Measurement of basal metabolic rate: In hyperthyroidism, basal metabolic rate is increased by about 30% to 60%. Basal metabolic rate is decreased in hypothyroidism by 20% to 40%.