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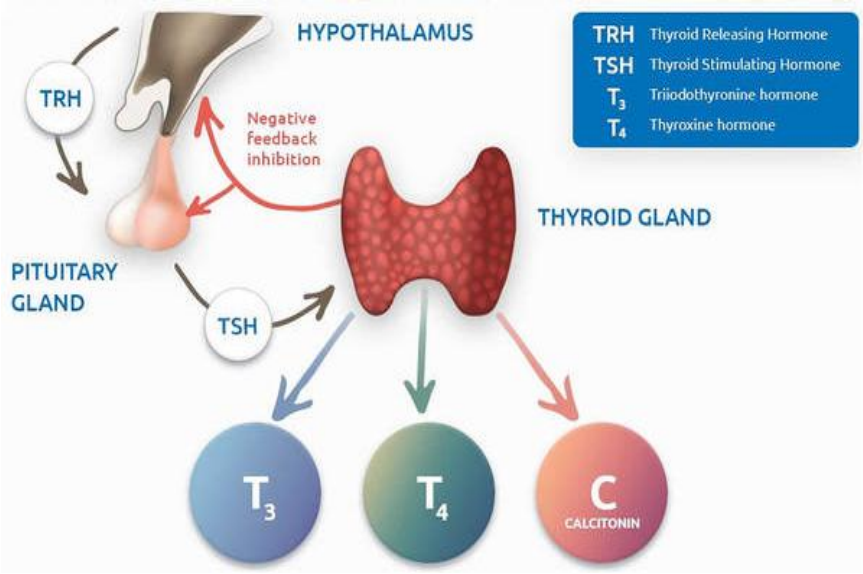
Biochemistry of the Thyroid Glands

The Thyroid Gland

The thyroid gland (Greek *thyros* "shield") is shaped like a shield and lies just below the Adam's apple in the front of the neck. Thyroid gland produces thyroxin (T4), triiodothyronine (T3) and calcitonin. T4 and T3 are products of the follicular cells and influence the rate of oxidative respiration in most cells in the body and, in so doing, help set the body's basal metabolic rate. Calcitonin a peptide hormone is produced by the C-cells and influences calcium metabolism. But this production is not possible without stimulation from the pituitary gland (TSH) which in turn is also regulated by the hypothalamus's TSH Releasing Hormone.



Structure

Thyroid contains large amounts of elemental iodine which is bound to a protein named iodothyroglobulin or simply thyroglobulin. It is a glycoprotein with a molecular weight of about 650,000 and iodine content from 0.5 to 1.0%. This protein represents the storage form of the hormone in the gland. Evidences available at present indicate that thyroglobulin is hydrolyzed, in the presence of thyrotropin (TSH), to release thyroxine (= 3, 5, 3′,5′-tetraiodothyronine) in the blood. The release of thyrotropin is, in turn, controlled by the level

of thyroxine in the blood. Thyroxine is one of the earliest recognized hormones. It is iodine containing aromatic amino acid and closely resembles tyrosine in structure. Diiodotyrosine is believed to be the precursor of thyroxine. Besides thyroxine, 3, 5, 3′-triodothyronine is also produced from enzymatic hydrolysis of thyroglobulin. It is 5 to 10 times more potent in biologic activity than thyroxine. This may, possibly, be due to the fact that triiodothyronine is bound loosely by serum proteins and hence diffuses much more rapidly into the tissues. It is present in the blood in much smaller quantities and persists for a much shorter time than thyroxine.

Thyroid hormone synthesis

Thyroid hormones are basically two tyrosines linked together with the critical addition of iodine at three or four positions on the aromatic rings. The number and position of the iodines is important.

Iodine Metabolism

Daily requirement of iodine is 150–200 mg/day. Its sources are drinking water, fish, cereals, vegetables and iodinated salt. Total body contains 25–30 mg of iodine. All cells do contain iodine; but 80% of the total is stored in the thyroid gland. Iodine level in blood is 5–10 μg/dL. In most parts of the world, iodine is a scarce component of the soil. Upper regions of mountains generally contain less iodine. Such areas are called **goitrous belts**, e.g. Himalayan region. Commercial source of iodine is seaweeds. Ingredients in foodstuffs, which prevent utilization of iodine, are called **goitrogens**. Goitrogens are seen in cassava, maize, millet, bamboo shoots, sweet potatoes and beans. Cabbage and tapioca contain **thiocyanate**, which inhibits iodine uptake by thyroid. Mustard seed contains **thiourea**, which inhibits iodination of thyroglobulin. The only biological role of iodine is in formation of thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3).

Tyrosines are provided from a large glycoprotein scaffold called **thyroglobulin.** A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.

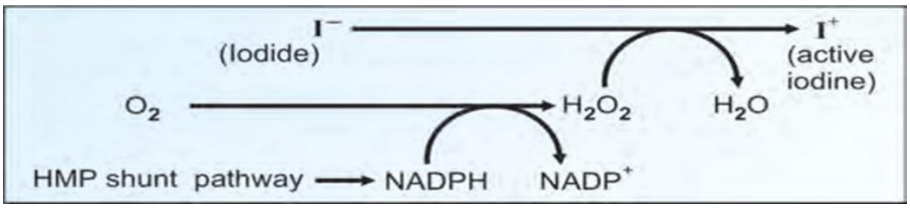
Synthesis and Secretion of Thyroxine

Step 1: Uptake of Iodine:

Thyroid gland takes up and concentrates iodine (20-100x blood plasma levels). Trapping of iodide from plasma is by a sodium iodine symporter in the thyroid. This step is stimulated by TSH.

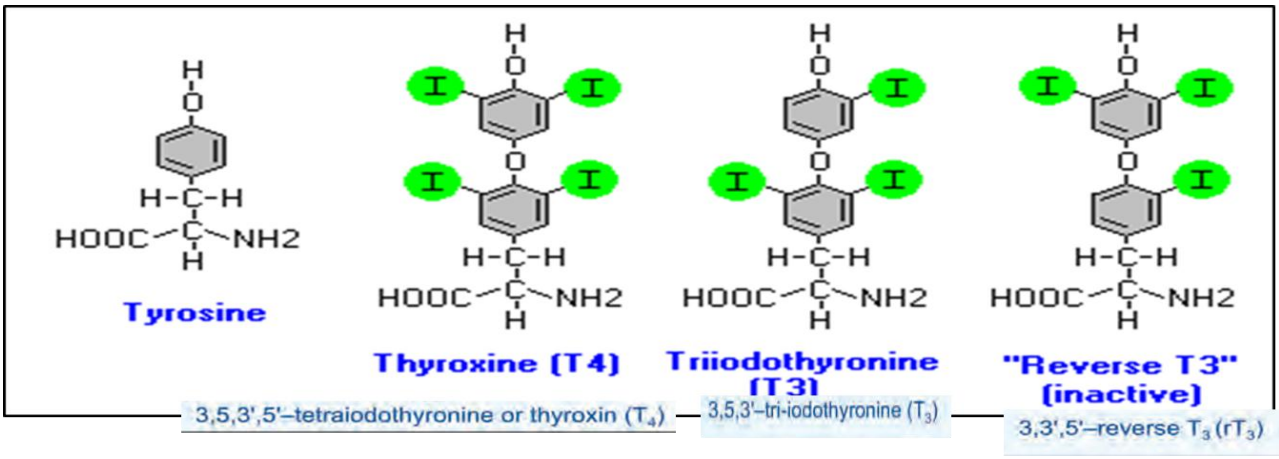
Step 2: Oxidation of Iodine

The iodide taken up by the thyroid cell is oxidized to active iodine. The thyroid is the only organ which can perform this oxidation step. This is catalyzed by the enzyme **thyroperoxidase**. The reaction needs hydrogen peroxide, which is produced by an NADPH-dependent reaction. This second step is stimulated by TSH and inhibited by **antithyroid drugs** such as thiourea, thiouracil and methimazole.



Step 3: Iodination

Then thyroglobulin (Tgb) is iodinated. **Thyroglobulin** is synthesized by the thyroid follicular cells. It is a large protein with about 5000 amino acids (660 kD). It contains about 10% carbohydrates. There are 115 tyrosine residues in the Tgb, out of which 35 residues can be iodinated. Iodination of the tyrosine is taking place on the intact Tgb molecule in the follicular space. Thus 3-monoiodotyrosine (MIT) and 3, 5-di-iodotyrosine (DIT) are produced.



Step 4: Coupling

Some of the tyrosine residues in the thyroglobulin are aligned opposite each other, and are coupled. When two DIT molecules coupled, one molecule of tetraiodothyronine (T4) is formed. Tri-iodothyronine (T3) may be formed by de-iodination of outer ring of T4 by 5'-deiodinase. Under normal conditions, 99% of the hormone produced by the thyroid gland is

T4. The T4 residues are now attached to the thyroglobulin molecule. The iodination and coupling are taking place in the borders of the follicular cells.

Step 5: Storage

The thyroid gland is unique, in that it is the only endocrine gland to store appreciable amounts of the hormone. The thyroglobulin contains about 8 T4 residues per molecule. It is stored as colloid in the thyroid acini.

Step 6: Utilization

When necessity arises, thyroglobulin is taken up from the acinar colloid, into the cell by pinocytosis.

Step 7: Hydrolysis

The T4 is liberated by hydrolysis by specific proteases. This activity is markedly enhanced by TSH. This hydrolysis is depressed by **iodide** and therefore potassium iodide (KI) is used as an adjuvant in hyperthyroidism.

Step 8: Release

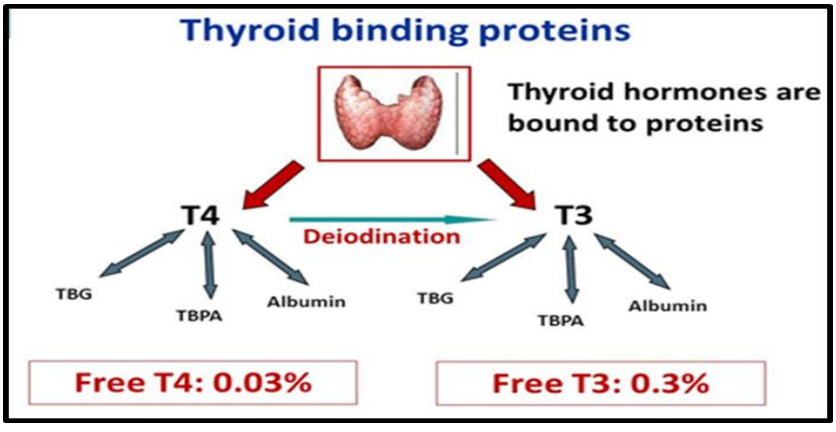
The T4 thus generated is released into the bloodstream. The T3 is produced by de-iodination at 5' position, either inside the thyroid cell or in the peripheral tissues. Reverse T3 (rT3) is formed by the inner ring de-iodination by 5-deiodinase. Its biological activity is negligible.

Step 9: Salvaging of Iodine

The MIT and DIT that are not utilized are de-iodinized and salvaged for re-utilization inside the cell itself.

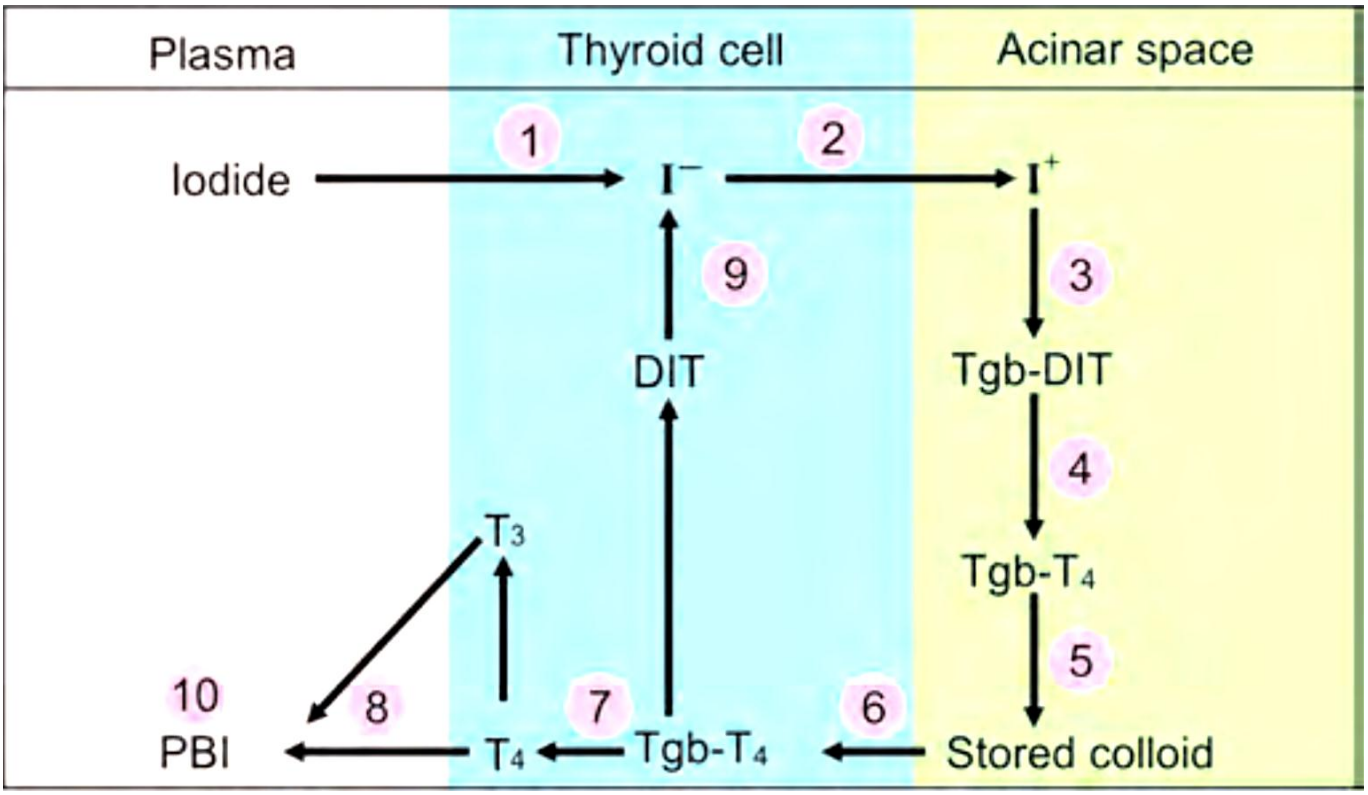
Step 10: Transport of Thyroid Hormones

Thyroid hormones are transported in plasma by proteins. The bound form is biologically inactive, but they can be rapidly released. The thyroxine binding globulin (TBG) (54 KD) carries about 80% of T4 and 60% of T3. The rest of thyroid hormones are loosely bound with Transthyretin (TTR) (prealbumin with 55 KD) and albumin (69 KD).



Step 11: Catabolism of Thyroid Hormones

T4 has a half-life of 4–7 days, while T3 has about 1 day. T3 is biologically more active. T4 is a prohormone which is de-iodinated to T3. In the peripheral tissues, de-iodination takes place. This is done by a de-iodinase, a selenium containing enzyme. Part of the T3 and T4 are conjugated with glucuronic acid and excreted through bile, and to a lesser extent, through urine. Deamination of T4 produces tetraiodothyroacetic acid (Tetrac); and T3 gives rise to tri-iodothyroacetic acid (Triac). These are only one-fourth as active as the parent compound.



Mechanism of Action of Thyroid Hormone

Only the free fractions can cross the cell membrane and affect intracellular metabolism. The hormone attaches to specific nuclear receptors. Then the receptor-hormone complex binds to the DNA. The T3 receptor complex binding sequence in the DNA or the thyroid responsive element (TRE) has been identified. The T3 binding results in increase in transcription rate.

Metabolic Effects of Thyroid Hormones

1- The hormone exerts action on every cell of the body. Calorigenic effect or **thermogenesis** is the major effect of thyroid hormone. This thermogenic effect is mediated by uncoupling of oxidative phosphorylation.
2- Basal metabolic rate (BMR) is increased. Thyroxine increases cellular metabolism.

3- Earliest effect of T4 is stimulation of RNA synthesis and consequent increase in protein synthesis. Higher concentration of T3 causes **protein catabolism** and negative nitrogen balance.
4- Loss of body weight is a prominent feature of hyperthyroidism.
5- **Gluconeogenesis** and carbohydrate oxidation are increased. Glucose tolerance test shows rapid absorption.
6- Fatty acid metabolism is increased. **Cholesterol** degradation is increased and hence cholesterol level in blood is decreased, which is another hallmark of hyperthyroidism.

- Additional activities:

- Increased cardiac output and systolic blood pressure
- Increased gastric motility
- Increased O2 consumption by muscles leading to muscular weakness
- TH increases sensitivity of target tissues to catecholamines, thereby elevating lipolysis, glycogenolysis, and gluconeogenesis.

Thyroid Function Tests

The plasma levels of T4and T3levels may be measured by any of the techniques of immunoassay like Radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA) or fluorescent immunoassay (FIA) for the diagnosis of thyroid diseases.

- **In hyperthyroidism**, thyroid hormone levels are increased. Both T3 and T4 levels are increased, while TSH is reduced due to feedback inhibition.
- **In hypothyroidism**, T3 and T4 are reduced; but TSH levels are increased due to lack of feedback effect.
- But when **hypothyroidism is due to hypothalamic or pituitary** defect, then TSH, T3 and T4, all are decreased.

Free T3 (fT3) and fT4

The free hormones are the really active molecules. The values of free hormones are not affected by the amount of carrier proteins in the blood. The free T4 constitutes only 0.03% of the total T4, whereas free T3 forms 0.3% of total T3. Variations in binding proteins do not affect the free hormone levels and therefore more reliable in diagnosing true hyper and hypofunction.

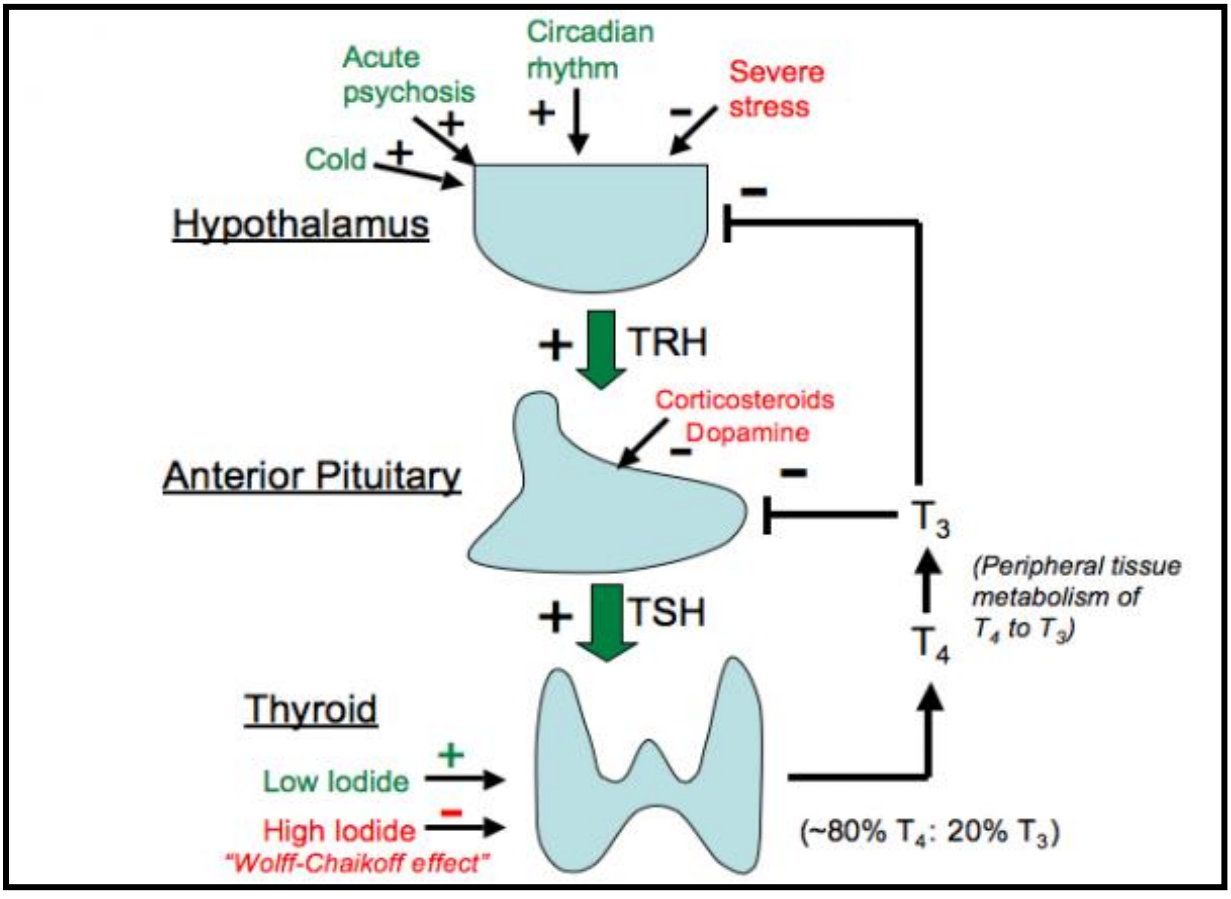
Plasma TSH

- In primary hypothyroidism, TSH level is elevated due to lack of feedback. But in secondary hypothyroidism, TSH, T3 and T4 levels are low; this could point to a pituitary or hypothalamic cause.
- Hyperthyroidism due to primary thyroid disease has high T3 and T4 levels, but suppressed TSH levels. Hyperthyroidism due to pituitary cause is indicated by high TSH, T3 and T4 levels.

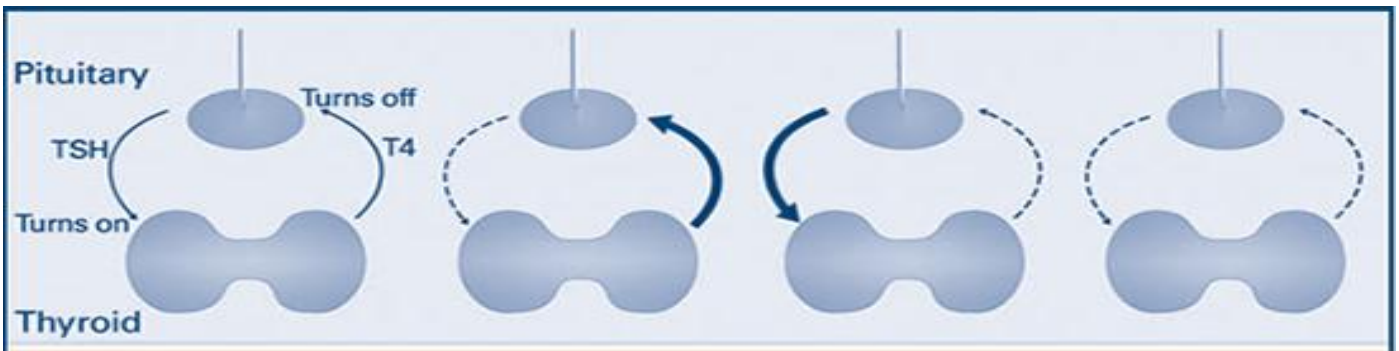
Control of Thyroid Hormone Synthesis and Secretion

TSH stimulates the synthesis and release of thyroid hormones from the thyroid gland. The secretion of TSH from the anterior pituitary gland is controlled by:-

- ❖ Circulating concentrations of thyroid hormones. Thyroid hormones reduce TSH secretion by negative feedback.
- ❖ Thyrotrophic-releasing hormone (TRH). TSH secretion is stimulated by TRH, produced in the hypothalamus.
- ❖ Dopamine, somatostatin and glucocorticoids also appear to be involved in inhibiting the release of TSH, and these agents together with the interleukins may be important modifiers of TSH release in nonthyroidal illness (NTI).



Thyroid diseases



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

Hypothyroidism

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland can't make enough thyroid hormone to keep the body running normally. Common causes are autoimmune disease, surgical removal of the thyroid, and radiation treatment.

- **Iodine deficiency**: Iodide is absolutely necessary for production of thyroid hormones; without adequate iodine intake, thyroid hormones cannot be synthesized. Historically, this problem was seen particularly in areas with iodine-deficient soils, and frank iodine deficiency has been virtually eliminated by iodine supplementation of salt.
- **Primary thyroid disease**: Inflammatory diseases of the thyroid that destroy parts of the gland are clearly an important cause of hypothyroidism.

Congenital hypothyroidism: May be due to absence of the thyroid gland (athyreosis) or may occur secondarily to defects of thyroid hormone synthesis. It occurs in approximately 1/2,000 to 1/4,000 newborns and is more common in Asian, Native American, and Hispanic infants. In children, hypothyroidism produces mental and physical retardation, known as **cretinism**. The clinical manifestations are often subtle or not present at birth, probably as a result of trans-placental passage of some maternal thyroid hormone and the fact that many infants have some thyroid production of their own. More specific symptoms often do not develop until several months of age. Common clinical features include decreased activity and increased sleep, feeding difficulty and constipation, prolonged jaundice, myxedematous facies, large fontanels (especially posterior), macroglossia, a distended abdomen with umbilical hernia, and hypotonia. Slow linear growth and developmental delay are usually apparent by 4-6 months of age. Without treatment CH results in severe intellectual deficit and short stature.

- **Secondary hypothyroidism**: Results from pituitary or hypothalamic disease that produce a deficiency of TSH.

Common symptoms of hypothyroidism arising after early childhood include lethargy, fatigue, cold-intolerance, weakness, hair loss and reproductive failure. If these signs are severe, the clinical condition is called myxedema. In the case of iodide deficiency, the thyroid becomes inordinately large and is called a goiter.

Laboratory Evaluation of Hypothyroidism

Hypothyroidism may be suspected by symptoms and signs, but the diagnosis needs to be confirmed biochemically.

- Free T4 levels are low, T3 levels may within normal limits. TSH is raised in primary hypothyroidism which is the most common cause of hypothyroidism. If TSH is not elevated, it is important to look for pituitary or hypothalamic disease.
- Thyroid autoantibodies suggest Hashimoto's thyroiditis
- LDL may be elevated

Hyperthyroidism

Hyperthyroidism is an overactive thyroid. The TSH is low, because there is already too much thyroid hormone circulating, so the thyroid stimulating hormone is turned OFF. Hyperthyroidism can significantly accelerate the body’s metabolism. While that may sound like a good thing, it can actually cause heart enlargement, heart dysrhythmias, and many other health problems. Patients have an increased rate of metabolism, weight loss,

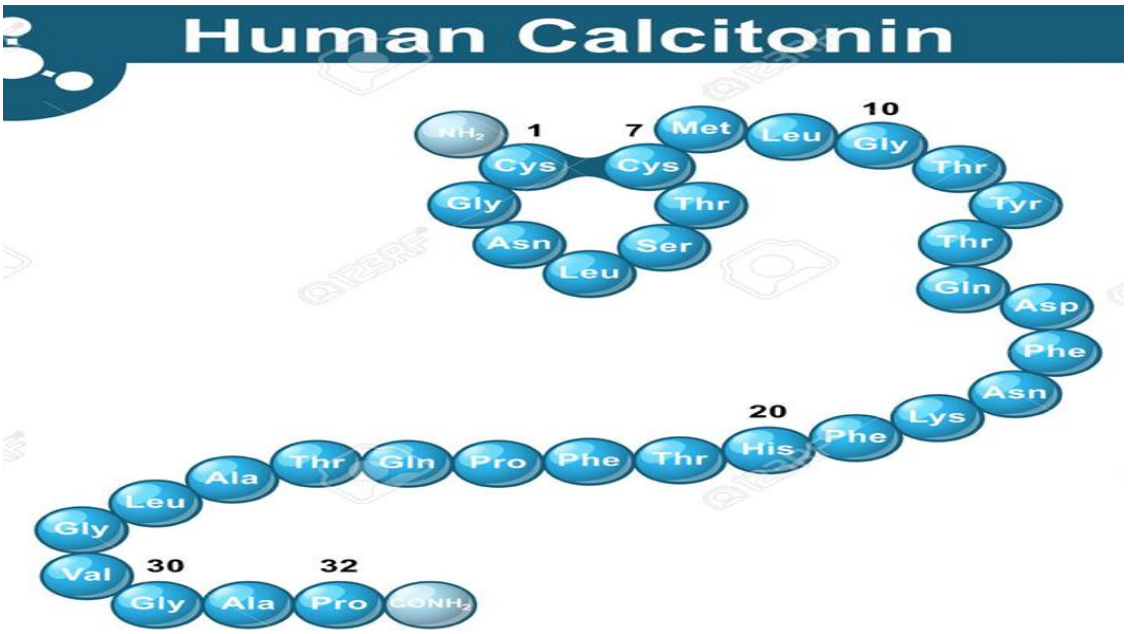
tachycardia, fine tremors, sweating, diarrhea, emotional disturbances, anxiety and sensitivity to heat.

Primary hyperthyroidism: It is due to diseases of thyroid gland. It is seen in Graves's disease, Toxic multinodular goiter, toxic adenoma, functioning metastatic thyroid carcinoma.

Secondary hyperthyroidism: It is due to diseases of pituitary or hypothalamus). It is seen in TSH secreting pituitary adenoma.

Calcitonin

Calcitonin is a hormone secreted from the parafolicular of C cells in the thyroid gland, known to participate in calcium and phosphorus metabolism. Calcitonin is a 32 amino acid peptide cleaved from a larger prohormone. It contains a single disulfide bond, which causes the amino terminus to assume the shape of a ring.



Physiologic Effects of Calcitonin

Calcitonin plays a role in calcium and phosphorus metabolism. In particular, **calcitonin has the ability to decrease blood calcium levels** at least in part by effects on two well-studied target organs:

- **Bone**: Calcitonin suppresses resorption of bone by inhibiting the activity of osteoclasts, a cell type that "digests" bone matrix, releasing calcium and phosphorus into blood.

- **Kidney**: Calcium and phosphorus are prevented from being lost in urine by reabsorption in the kidney tubules. Calcitonin inhibits tubular reabsorption of these two ions, leading to increased rates of their loss in urine.

Control of Calcitonin Secretion

The most prominent factor controlling calcitonin secretion is the **extracellular concentration of ionized calcium**. Elevated blood calcium levels strongly stimulate calcitonin secretion, and secretion is suppressed when calcium concentration falls below normal.

Disease States

A large number of diseases are associated with abnormally increased or decreased levels of calcitonin, but pathologic effects of abnormal calcitonin secretion *per se* are not generally recognized.