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THYROID GLAND

The butterfly-shaped thyroid gland is located just below the larynx (voice box). It is composed of right and left lobes, one on either side of the trachea and are linked by a thin transverse band or a connecting strip of glandular tissue across the midline, known as the isthmus. This connection provides an H- or U-shape to the gland . A median pyramidal lobe frequently extends upward from the isthmus and lies just in front of the larynx. The gland is covered by a capsule of fibrous connective tissue, which extends into the substance of the gland as septa or trabeculae. Septa extend from the capsule into the thyroid gland, subdivide the gland into lobules and carry blood vessels, lymphatics and nerves into the gland. Each lobule consists of follicles, the functional units of the thyroid gland. The follicles secrete two hormones thyroxine, T4, and its active derivative, T3. (Figure 1).

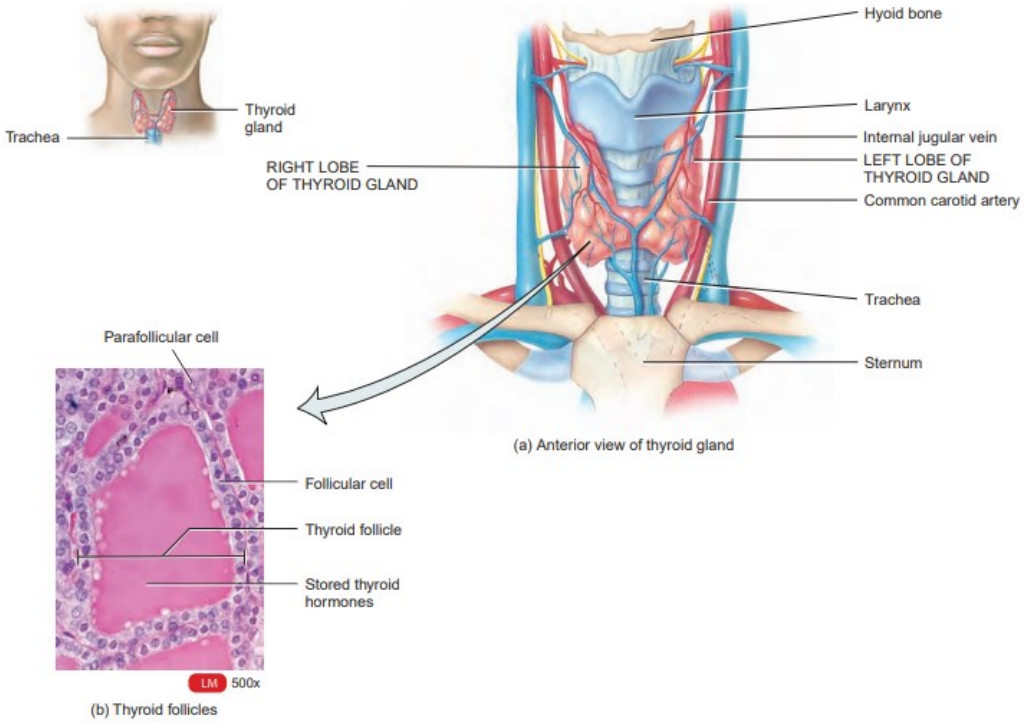

Figure 1: Location and histology of Thyroid gland

Each thyroid follicle, encased by a thin basement membrane is surrounded by a single layer of epithelial cells enclosing a lumen filled with colloid, a viscous proteinaceous solution. The colloid is clear in appearance and is composed of homogeneous granules that are secretory products of the follicle cell, principally the protein thyroglobulin, which is the storage form of the thyroid hormones. The wall of each thyroid follicle consists primarily of cells called follicular cells, which produce two hormones: thyroxine (thī-ROK-sēn), also called T_4 because it contains four atoms of iodine, and triiodothyronine (trī-ī'-ō-dō-TIII-rō-nēn) (T_3), which contains three atoms of iodine. T_3 and T_4 are also known as thyroid hormones. The central cavity of each thyroid follicle contains stored thyroid hormones. As T_4 circulates in the blood and enters cells throughout the body, most of it is converted to T_3 by removal of one iodine atom.

A smaller number of cells called parafollicular cells lie between the follicles (Figure 1b). They produce the hormone calcitonin.

Biosynthesis of Thyroid hormones

Thyroid hormones are derived from the amino acid tyrosine by a process which involves incorporation of iodine. The synthesis of these hormones begins as early as in the foetus at about third month of gestation and continues fairly constantly throughout life although there is a surge of thyroid gland activity at puberty and during pregnancy. The mammalian thyroid gland biosynthesizes, stores, and secretes two molecular species of thyroid hormone, thyroxine (T4; 3,5,3',5'- tetraiodothyronine) and triiodothyronine (T3; 3,5,3'-triiodothyronine). The synthesis of thyroxine is dependent on the incorporation of iodine atoms into the tyrosine residues of a protein called thyroglobulin (Tg). T3 is the biologically active form of the thyronines while thyroxine and reverse T3 are relatively inert. Each epithelial cell of the thyroid follicle, or thyrocyte, is specialized to carry out all the steps required for the synthesis and secretion of T4 and T3. These include:

1. Active transport of iodide into the thyroid gland follicular cells;

2. Oxidation of iodide and iodination of tyrosyl residues within the protein thyroglobulin;

3. Transfer and coupling of iodotyrosines within thyroglobulin to form T4 and T3;

4. Storage of thyroglobulin as the colloid in the lumen of the thyroid follicle;

5. Endocytosis of the colloid back into the thyroid epithelial cell

6. Proteolysis of thyroglobulin with concomitant release of T4 and T3 as well as free iodotyrosines and iodothyronines;

7. Secretion of T4 and T3 into the blood;

8. Deiodination of iodotyrosines within the thyroid follicular cells for reutilization of the liberated iodine.

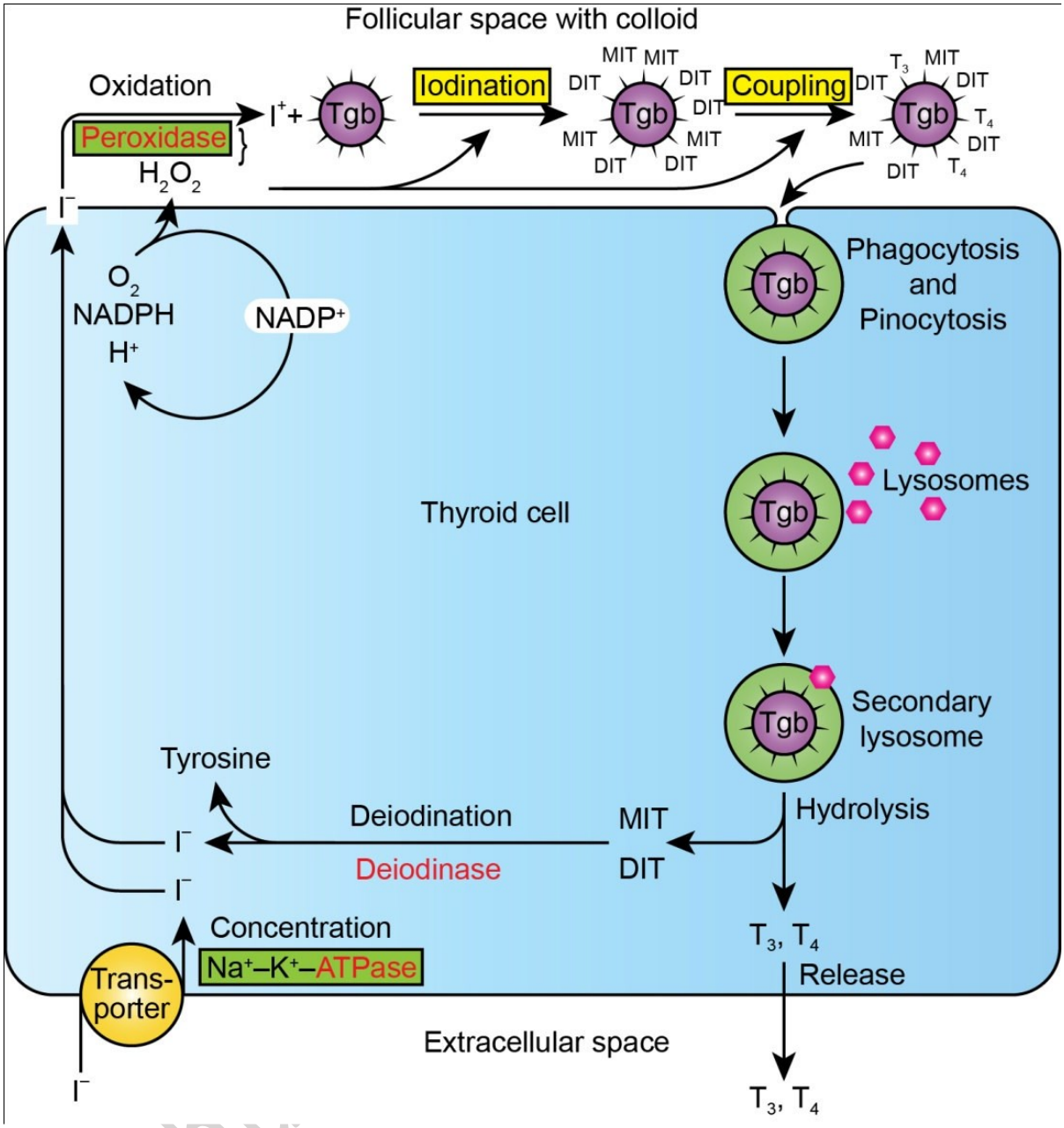

Figure 2: Graphical representation of iodide metabolism of in thyroid follicles

Transport of Thyroid Hormones

Thyroid hormones are insoluble in water, therefore in order for them to be transported within the blood, they must be bound to plasma proteins. Over 99 percent of the circulating thyroid hormones are protein bound, the majority (approximately 75 percent) of T4 binding is to thyronine binding globulin (TBG), while 15-20 percent being bound to thyroxine-binding prealbumin (TBPA) (also known as transthyretin, TTR) and 5-20 percent is bound to albumin. These proteins are synthesized in the liver. In the case of T3, there is extensive binding to TBG and albumin, with very little binding to TBPA. The total plasma protein binding of T4 is greater than that of T3, thus T3 accounts for approximately 20 percent of the free thyroid hormones. It should be remembered that only free, unbound hormone is biologically active, thus any factor which alters the extent of protein binding of these hormones can have profound effects on their apparent biological activity.

Actions of Thyroid Hormones

Because most body cells have receptors for thyroid hormones, T_3 and T_4 exert their effects throughout the body. Thyroid hormones increase basal metabolic rate (BMR), the rate of oxygen consumption under standard or basal conditions (awake, at rest, and fasting). The BMR rises due to increased synthesis and use of ATP. As cells use more oxygen to produce the ATP, more heat is given off, and body temperature rises. In this way, thyroid hormones play an important role in the maintenance of normal body temperature. The thyroid hormones also stimulate protein synthesis, increase the use of glucose and fatty acids for ATP production, increase the breakdown of triglycerides, and enhance cholesterol excretion, thus reducing blood cholesterol level. Together with human growth hormone and insulin, thyroid hormones stimulate body growth, particularly the growth of the nervous and skeletal systems.

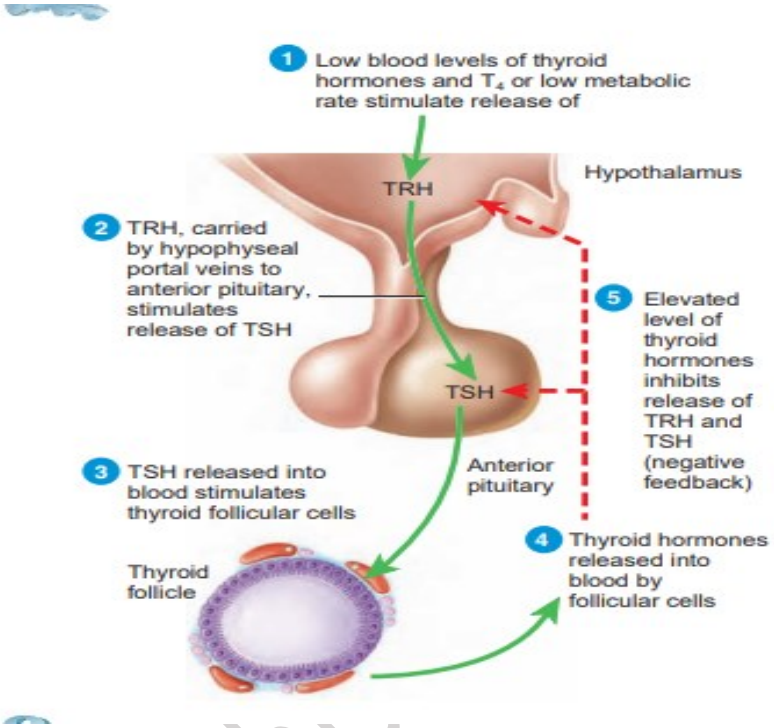

Figure 3: Regulation of secretion of thyroid hormones

What is the effect of thyroid hormones on metabolic rate?

Low blood level of thyroid hormones or low metabolic rate stimulate the hypothalamus to secrete TRH.

TRH is carried to the anterior pituitary, where it stimulates secretion of thyroid-stimulating hormone (TSH).

TSH stimulates thyroid follicular cell activity, including thyroid hormone synthesis and secretion, and growth of the follicular cells.

The thyroid follicular cells release thyroid hormones into the blood until the metabolic rate returns to normal.

An elevated level of thyroid hormones inhibits release of TRH and TSH (negative feedback).

Conditions that increase ATP demand—a cold environment, low blood glucose, high altitude, and pregnancy—also increase secretion of the thyroid hormones.

Calcitonin

The hormone produced by the parafollicular cells of the thyroid gland is calcitonin (CT) (kal-si-TŌ-nin). Calcitonin can decrease the level of calcium in the blood by inhibiting the action of osteoclasts, the cells that break down bone. The secretion of calcitonin is controlled by a negative feedback system (Figure 4). Calcitonin's importance in normal physiology is unclear because it can be present in excess or completely absent without causing clinical symptoms. Miacalcin, a calcitonin extract from salmon, is an effective treatment for osteoporosis, a disorder in which the pace of bone breakdown exceeds the pace of bone rebuilding. It inhibits breakdown of bone and accelerates uptake of calcium and phosphates into bone

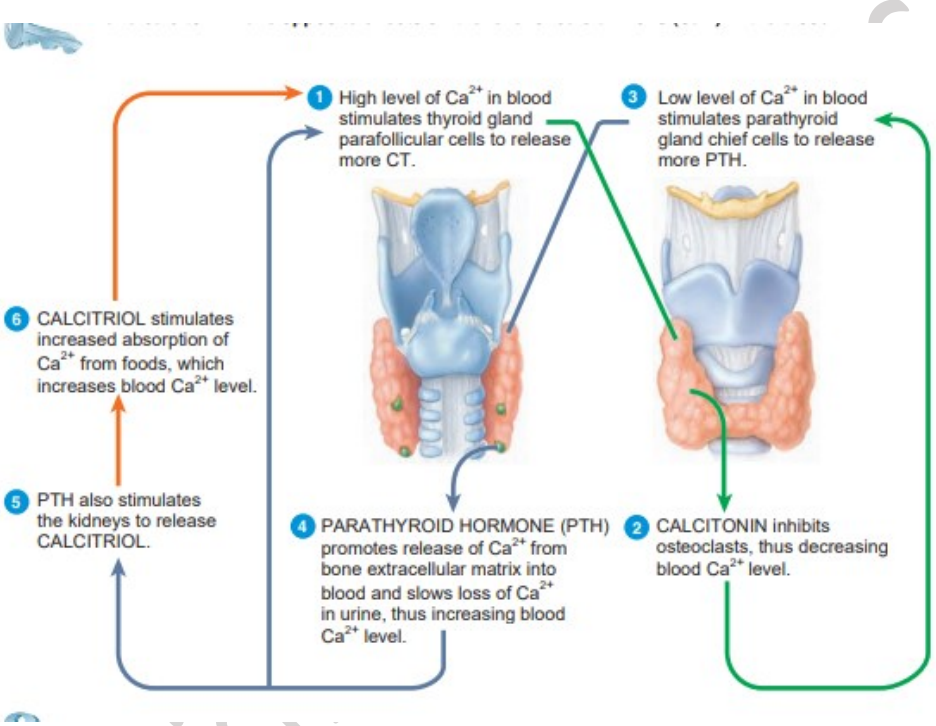

Figure 4: The role of calcitonin in in calcium homeostasis

Hypothyroidism:

Myxoedema:o Myxoedema is hypothyroidic condition in which there may be dry, flaky skin with hair loss and oedema. Oedema, which is typically widespread, is due to accumulation of skin proteins, polysaccharides and hyaluronic acid in the subcutaneous spaces. It is this oedema which resulted in the condition being named as Myxoedema. Another feature of this condition is a deepening of the voice, possibly as a consequence of oedema around the larynx. Because of the disruption of other endocrine systems, hypothyroidism also causes reproductive disorders, with menorrhagia or irregular menstruation in females and reduced fertility in both males and females. Cretinism If decreased thyroid activity occurs in utero, or in the neonate, there is the risk of severe mental retardation due to the failure of development of the central nervous system. This is the condition known as cretinism. Other features include short stature and oedema, coupled with a protruding tongue, which gives rise to coarse features and a hoarse cry. Cretinism occurs in about 1:4000 births and is usually due to a failure in the development of the thyroid gland. It is irreversible if untreated within a few weeks of birth, however, treatment is so successful if the condition is recognized rapidly that many countries routinely screen for the condition of assays of TSH in the newborn. In addition to the features of thyroid hypoactivity that are seen in adults, if the condition occurs in children there are also deficiencies in growth and maturation. Typically, there is delayed sexual maturation coupled with

diminishes linear growth and reduced limb length to trunk length ratio. Symptoms of hypoactivity of the thyroid gland may be a consequence of an inability of the thyroid gland to synthesize the thyroid hormones due to a deficiency of iodide or possibly due to a lack of the enzymes required for hormone synthesis. In some cases, it may be a dysfunction of secretion of TSH by the anterior pituitary gland or of TRH by the hypothalamus that is the cause of the problem. Alternatively, the target tissues may fail to respond to thyroid hormones due to a congenital defect in the expression of the thyroid hormone receptors.

Hashimoto's disease The most common cause of hypothyroidism, however, is Hashimoto's disease. This is an autoimmune disorder in which there is cell-mediated immune response resulting in the destruction of the follicular cells of the thyroid gland, or occasionally an immune response resulting in the production of an antibody capable of blocking the TSH receptor; circulating antithyroid antibodies are detected in 80 percent of cases of hypothyroidism. Hashimoto's disease affects approximately 1 percent of the population and it is ten times more common in females than in males. The treatment of thyroid hypoactivity is relatively straightforward if the condition is due to hormonal hyposecretion. In the case of iodine deficiencies, supplementation of iodine is effective, although administration of excessive doses of iodine paradoxically results in further decreases in thyroid hormone synthesis. The most common form of treatment is lifelong hormone replacement therapy with oral T4. T4 is favoured over T3, firstly on the grounds of cost, and secondly, because its longer plasma half-life means that stable plasma concentrations can be achieved after once-daily dosing. In most cases, the dose must be titrated against response and is therefore subject to constant monitoring. Administration of excessive replacement doses may cause cardiovascular problems and other symptoms of hyperthyroidism.

At present, there are no known treatments for hypothyroidism due to thyroid hormone receptor resistance.

Hyperthyroidism:

The symptoms of hyperthyroidism usually develop slowly and are those of increased metabolism. Excess secretion of thyroid hormones is known as hyperthyroidism. Symptoms of hyperthyroidism include increased heart rate and more forceful heartbeats, increased blood pressure, and increased nervousness.

There are tachycardia and possibly cardiac arrhythmias due partly to the increased metabolic demands of the tissue and partly due to the increased number of cardiac β-adrenoceptors; excessive sweating due to a combination of the increased body temperature and the increased activity of the sympathetic nervous system; agitation and anxiety, again possibly related to the increased β-adrenergic activity and weight loss despite increased appetite due to the catabolism of carbohydrates, lipid and proteins. Osteoporosis and amenorrhea may also occur and in nearly all cases there is a goitre.

Graves' Disease The most common cause of hyperthyroidism is Graves' disease which affects approximately 1 percent of the adult population (2 percent of the adult females and 0.2 percent of the adult males). Graves' disease is an autoimmune disease in which there is an antibody to TSH receptors on the thyroid gland. The action of this antibody is to stimulate the receptor and therefore to potentiate the synthesis and secretion of thyroid hormones; the antibody responsible for this effect has been labelled variously as the long-acting thyroid stimulating (LATS) antibody; thyroid stimulating immunoglobulin (TSI) and thyroid stimulating antibody (TSAB), although whether these names refer to the same immunoglobulin is unclear. Other antibodies produced as a consequence of Graves'

disease are responsible for the other features of the disorder, most notably the exophthalmos or proptosis induced by retro-orbital oedema and fat deposition and the pretibial myxedema due to subdermal mucinous deposits. It there follows that the ophthalmic and myxoedematmous symptoms of Graves' disease are due to the autoimmune component of the disorder rather than the hyperthyroidism. Together with toxic nodular goitre, which is overactivity of a single nodule of the thyroid gland, Graves' disease comprises 99 percent of cases of hyperthyroidism. The treatment of Graves' disease and other forms of hyperthyroidism is aimed at the reduction of circulating thyroid hormones although many of the symptoms of hyperthyroidism can be relieved by the use of β-adrenoceptor antagonists. The treatment options are surgical removal or reduction of the thyroid gland, destruction of thyroid tissue using radioactive iodine or reduction of the synthesis of thyroid hormones using antithyroid drugs. The other symptoms such as exophthalmos are sometimes treated by the use of immunosuppressant doses of corticosteroids.

Goitre A goitre is an enlargement of the thyroid gland to produce a swelling of the neck. Goitre may be a symptom of either an overactive or underactive thyroid gland. In the case of underactivity (eg. due to iodine deficiency), the anterior pituitary gland will secrete increased quantities of TSH in an attempt to boost thyroid hormone synthesis and secretion. The thyroid gland enlarges under the influence of the TSH. In the case of overactivity of the thyroid gland, the error may lie in the hypothalamus or anterior pituitary gland. Excessive production of either TRH Or TSH will lead to an enlargement of the thyroid gland (goitre) accompanied by excessive thyroid hormone secretion. A goitre may also be caused by a tumour or infection of the thyroid gland. In some areas, for example, New Guinea, the Andes and the Himalayas, there is a high incidence of endemic goitre due to the paucity of iodine in the diet. Prophylactic administration of iodine either by injection or by incorporation into table salt or flour has markedly reduced the incidence of endemic goitre worldwide, although it carries with it the risk of Jod-Basedow phenomenon in which iodine administration precipitates hyperthyroidism. There are also drugs which can induce goitre, most notably lithium which is used in the treatment of manic depression, and certain iodides which are contained in vitamin preparations and some cough remedies. These ions are selectively concentrated within the thyroid gland where they interfere with iodide incorporation and hormone release. Goitre is also common at puberty and during pregnancy due to the excessive hormonal flux at that time. Many goitres are self-limiting or respond to iodine supplementation or treatment of the underlying hypothyroidism. In cases that do not respond, surgical removal of the gland may be required although this invariably necessitates life-long hormone replacement therapy.

PARATHYROID GLANDS

The parathyroid glands (para- = beside) are small, round masses of glandular tissue that are partially embedded in the posterior surface of the thyroid gland (Figure 5). Usually, one superior and one inferior parathyroid gland are attached to each thyroid lobe. Within the parathyroid glands are secretory cells called chief cells that release parathyroid hormone (PTH).

PTH is the major regulator of the levels of calcium (Ca^{2+}), magnesium (Mg^{2+}), and phosphate (HPO_4^{2-}) ions in the blood. PTH increases the number and activity of osteoclasts, which break down bone extracellular matrix and release Ca^{2+} and HPO_4^{2-} into the blood. PTH also produces three changes in the kidneys. First, it slows the rate at which Ca^{2+} and Mg^{2+} are lost from blood into the urine. Second, it increases loss of HPO_4^{2-} from blood in urine. Because more is lost in the urine than is gained from the bones, PTH decreases blood HPO_4^{2-} level and increases blood Ca^{2+} and Mg^{2+} levels. Third, PTH promotes formation of the hormone calcitriol, the active form of vitamin D. Calcitriol acts on the gastrointestinal tract to increase the rate of Ca^{2+}, Mg^{2+}, and HPO_4^{2-} absorption from foods into the blood.

The blood calcium level directly controls the secretion of calcitonin and parathyroid hormone via negative feedback, and the two hormones have opposite effects on blood Ca^{2+} level (Figure 13.10).

A higher-than-normal level of calcium ions (Ca^{2+}) in the blood stimulates parafollicular cells of the thyroid gland to release more calcitonin.

CT inhibits the activity of osteoclasts, thereby decreasing blood Ca^{2+} level.

A lower-than-normal level of Ca^{2+} in the blood stimulates chief cells of the parathyroid gland to release more PTH.

PTH increases the number and activity of osteoclasts, which break down bone and release Ca^{2+} into the blood. PTH also slows loss of Ca^{2+} in the urine. Both actions of PTH raise the blood level of Ca^{2+}.

PTH also stimulates the kidneys to release calcitriol, the active form of vitamin D.

Calcitriol stimulates increased absorption of Ca^{2+} from foods in the gastrointestinal tract, which helps increase the blood level of Ca^{2+}.

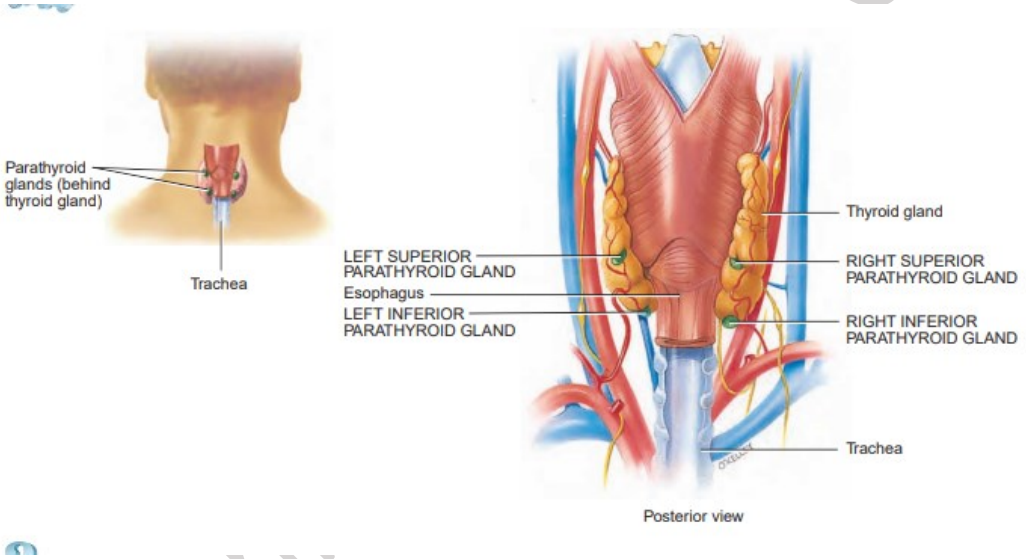

Figure 5: Location of Parathyroid gland

An imbalance in parathormone leads to the following conditions:

Hyposecretion: Results in low blood calcium (hypocalcemia), which can trigger muscle spasms, irritability, and convulsions in adults. Severe vitamin D and parathyroid deficiency in childhood can lead to rickets.

Hypersecretion: Results in excess parathormone, often caused by an adenoma. This can lead to hypercalcemia, which weakens bones and affects kidney function.