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CHAPTER 1

THYROID PHYSIOLOGY

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Thyroid Physiology

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The thyroid gland contains two separate physiologic endocrine systems: one responsible for the production of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3), and the other responsible for the production of the hormone calcitonin.

The functional unit for thyroid hormone production is the thyroid follicle. This is composed of a single layer of cuboidal follicular cells surrounding a central space filled with colloid. The average size of a follicle varies from 100 to 300 μm, each of which is surrounded by a network of capillaries. The primary function of the thyroid follicle is to make and store thyroid hormones.

Calcitonin is produced by C cells within the thyroid. These cells, of neural crest origin, are in a parafollicular position in direct contact with the follicular basement membrane.

THYROID EMBRYOGENESIS

Thyroid primordial cells develop from pharyngeal ectoderm, forming a visible medial anlage by human gestational days 16–17.[1] The thyroid diverticulum then migrates caudally to reach its final position in the thyroid primordial body anterior to the cricoid cartilage (Fig. 1.1). Subsequently, these cells begin to express markers of mature thyrocyte differentiation, including proteins that are intrinsic to thyroid secretory function [thyroglobulin, thyroperoxidase, and the sodium iodide symporter (NIS)], and the thyroid-stimulating hormone (TSH) receptor that controls both thyroid growth and secretory function. The foramen cecum, at the junction between the anterior two thirds and posterior third of the tongue base, remains as an embryologic reminder of thyroid origin. Thyrocytes form thyroid follicles, while intervening cells derived from the ultimobranchial body within the fourth pharyngeal pouch develop into calcitonin-secreting C cells (*see* Fig. 1.1). The parathyroid glands develop from the third and fourth pharyngeal pouches and migrate to the posterior surface of the thyroid gland. The thyroid gland begins to trap iodide between gestational weeks 10 and 12.[1]

Several transcription factors involved in the development of the thyroid gland have been identified. NKX2-1 (previously known as thyroid transcription factor (TTF)-1),[2,3] FOXE1 (formerly TTF-2),[4] and the paired homeodomain factor PAX8[5,6] were all identified and isolated by their binding to specific regulatory elements within the promoters of thyroid-specific genes (e.g. thyroperoxidase and thyroglobulin). These factors are cotemporally expressed during the descent of the thyroid primordium from its pharyngeal origin. Mutations in *NKX-2.1*, *FOXE1*, or *PAX8* are associated with thyroid dysplasia and congenital hypothyroidism, together with other phenotypic features specific to each transcription factor (NKX2-1, pulmonary disease and choreoathetosis; FOXE1, cleft palate; PAX8, renal hemiagenesis).[7–9] Mutation in another homeobox transcription factor *NKX-2.5* is also rarely associated with congenital hypothyroidism.[10] These and several additional transcription factors (e.g. *Hhex, Hoxa3, and Pax3*) have also been shown to be relevant to thyroid development in mouse models.[11]

Distinct transcription factors control parathyroid gland development. Hypoparathyroidism is associated with mutations in GATA3 (as part of HDR syndrome—hypoparathyroidism, sensorineural deafness, and renal

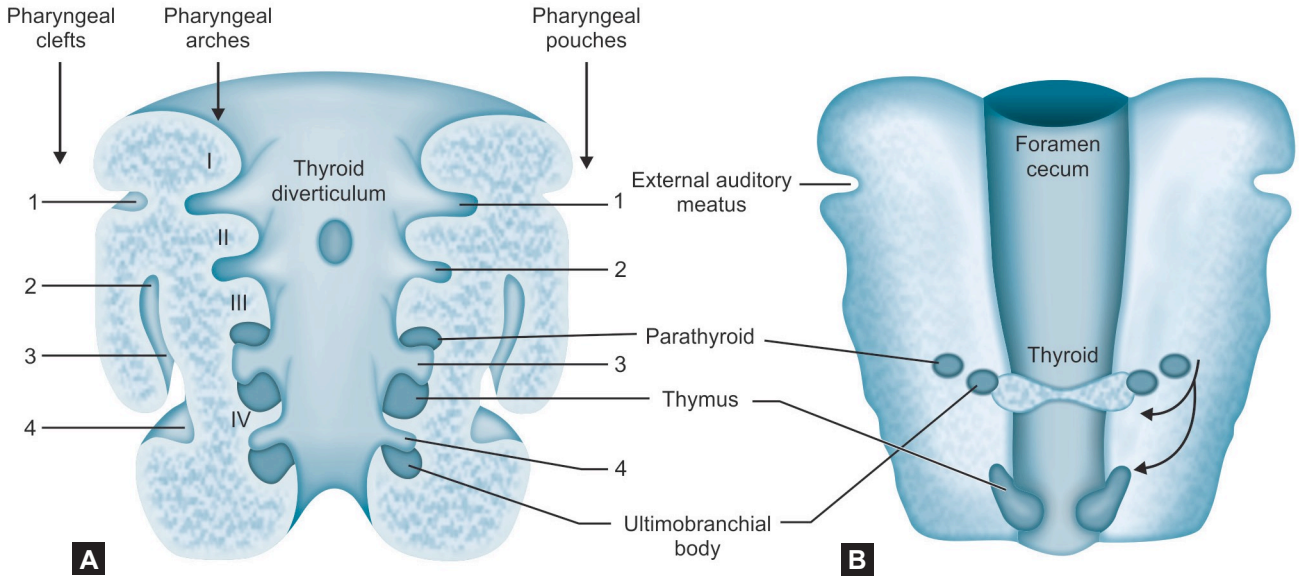

Fig. 1.1: Thyroid embryogenesis. (A) Coronal section through the pharyngeal arch region in a late-somite embryo. The thyroid diverticulum forms from a thickening in the midline of the anterior pharyngeal floor. The two lateral anlagen (ultimobranchial bodies) are derived from the fourth or fifth pharyngeal pouch; the thymus and inferior parathyroids are derived from the third pouch, whereas the superior parathyroid glands form from the fourth pharyngeal pouch (not shown). (B) Ventral view of the pharyngeal organ derivatives following migration toward their ultimate positions. The thyroid diverticulum has caudally migrated anterior to the cricoid cartilage, where it is infiltrated by cells from the ultimobranchial bodies that will form parafollicular C cells. The superior and inferior parathyroid glands are positioned on the posterolateral surface of the thyroid gland. The two thymic primordia will fuse to become a single gland anterior to the trachea. Adapted from Manley NR, Capecchi MR. The role of *Hoxa-3* in mouse thymus and thyroid development. Development. 1995;121:1989.

aplasia),[12] tubulin-specific chaperone E (TBCE, in hypoparathyroidism-retardation-dysmorphism syndrome),[13] and GCM2 (familial isolated hypoparathyroidism).[14] Failure of parathyroid gland development is also a feature of DiGeorge syndrome, in which parathyroid and thymic aplasia are variably accompanied by cardiac defects and facial malformations owing to microdeletion or rearrangement of the short arm of chromosome 22.[15]

THYROID HORMONE PHYSIOLOGY

Iodide Metabolism and Uptake

Iodine usually enters the body as the result of dietary and water uptake, but it can also be found in various drugs, such as cough medicines, and in diagnostic agents. Dietary iodine intake varies widely throughout various parts of the world. The relationship between iodine intake and thyroid disease was first demonstrated by Chatin in 1852, but the practice of iodine supplementation of food and water, which he recommended, fell into disrepute and was not revived until the large-scale experiments of Marine and Kimball in Ohio in 1917.[16] Even in areas where endemic goiter is not a problem, iodine intake and excretion vary considerably with urinary excretion, ranging from as little as 40 µg/day up to 400 µg/day.[17] Iodine deficiency is associated with nodular goiter, hypothyroidism, and cretinism[18] as well as the development of follicular thyroid carcinoma.[19] In areas of the world where iodine deficiency is still a problem, a variety of measures are being introduced to increase iodine intake, such as iodination of salt, bread, and water to treat entire population groups and injections of iodized oil for target groups such as pregnant women.[20] Iodine excess, on the other hand, is associated with an increased incidence of autoimmune thyroid disease such as Graves' disease and Hashimoto's thyroiditis[17,20] as well as papillary thyroid carcinoma.[19]

Iodine, in the form of inorganic iodide, is rapidly and efficiently absorbed from the gastrointestinal tract and enters the extracellular iodide pool, where it is joined by iodide derived from the breakdown of previously formed thyroid hormone. Less than 10% of total body iodide is contained in the extracellular pool; the remaining 90% is stored in the thyroid gland as either preformed thyroid hormone or iodinated amino acids.[21]

Iodide is taken up from the extracellular space into the follicular cells by an active transport process. The major source of loss of iodide from the extracellular space, in addition to uptake by the thyroid gland, is renal excretion. Small quantities of iodide are also lost through the skin, through the saliva, or in expired air. The active transport of iodide into the cells results in a significant intrathyroidal iodide gradient. The NIS is part of a family of membrane-associated transport glycoproteins that probably contain 12 membrane-spanning domains.[22,23] Iodide is actively transported using energy from the coupled inward sodium transport. Mutations in the *NIS* gene are associated with goitrous congenital hypothyroidism.[24] Iodide transport into the follicular cells is influenced by TSH levels as well as by the glandular content of iodide.

Synthesis of Thyroid Hormone

After uptake into the follicular cells through the basal membrane (Fig. 1.2), inorganic iodide is rapidly oxidized. Thyroid hormones are then synthesized by the combination of iodine with tyrosyl residues within the protein thyroglobulin. This reaction is catalyzed by thyroperoxidase in two principal steps. In the first reaction, iodide reacts with tyrosyl residues in thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). In the second reaction, MIT and DIT condense to form 3,5,3'-triiodothyronine (T_3) or the inactive 3,3',5'-triiodothyronine (rT_3), whereas two molecules of DIT condense to form T_4. T_3 and rT_3 are also formed by intrathyroidal deiodination of thyroxine, catalyzed by deiodinase enzymes.[25] In conditions of iodine-sufficient intake, the predominant iodothyronine synthesized by the thyroid gland is T_4.[26] Once formed, the thyroid hormones, covalently bound to thyroglobulin, are stored in colloid within the center of the follicle. The thyroid gland contains a very large store of thyroid hormone, which lasts for several weeks in the absence of the formation of new hormone.[21]

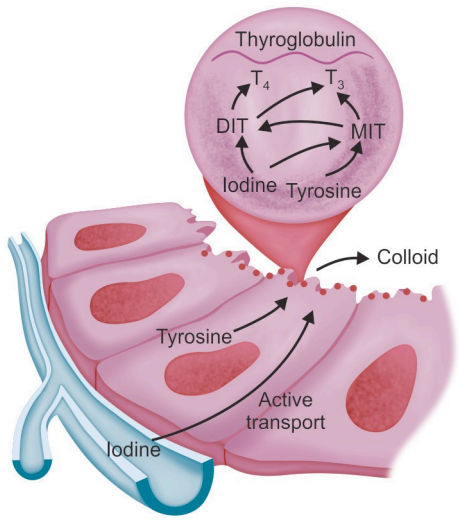

Fig. 1.2: Uptake of iodide into the follicular cell by active transport, with subsequent iodide oxidation, tyrosine iodination, and iodotyrosine coupling occurring at the apical membrane, catalyzed by thyroid peroxidase. DIT, diiodotyrosine; MIT, monoiodotyrosine; T_3, triiodothyronine; T , thyroxine.

Thyroid peroxidase (TPO) is a membrane-bound glycoprotein that is localized to the apical membrane of the follicular cell; the peroxidase reactions occur at the cell–colloid interface.[26] TPO has now been cloned and has been shown to have a hydrophobic signal peptide at its aminoterminus and a hydrophobic region with the characteristics of a transmembrane domain near the carboxylterminus.[25] This structure is consistent with TPO being a membrane-associated protein. The synthesis of thyroglobulin occurs exclusively in the thyroid gland, where homodimers are formed in the endoplasmic reticulum before being transported into the apical lumen of thyroid follicles.[27] Defects in thyroglobulin synthesis usually cause moderate-to-severe hypothyroidism in association with low-circulating thyroglobulin levels.[27] A partial organification defect and goiter (with or without overt hypothyroidism) is associated with sensorineural deafness in Pendred's syndrome. Mutations in a putative sulfate transporter gene (*PDS*) have recently been associated with this disorder.[28] Although the precise mechanisms by which the pendrin protein causes the phenotype is unclear, it is proposed that defective sulfation of thyroglobulin impairs its subsequent iodination.[28]

Release of thyroid hormone into the peripheral blood occurs as the result of lysosomal hydrolysis within the follicular cells (Fig. 1.3). Pseudopodia form at the apical membrane of the thyroid cell, and multiple vesicles containing thyroglobulin are incorporated into the follicular cell by endocytosis. Lysosomal hydrolysis of the thyroglobulin, with reduction of disulfide bonds, leads to release of both T_3 and T_4 through the basement membrane into the circulation. The ratio of the levels of these two hormones released into the peripheral blood approximates their levels in stored thyroglobulin (T_3:$T_4 \approx 1{:}13$). Very little thyroglobulin reaches the peripheral circulation; however, when sensitive immunoassay procedures are used, small quantities can be detected in normal individuals.[25] Iodotyrosines released from thyroglobulin undergo deiodination and are recycled, with the iodide so released available for new thyroid hormone synthesis.

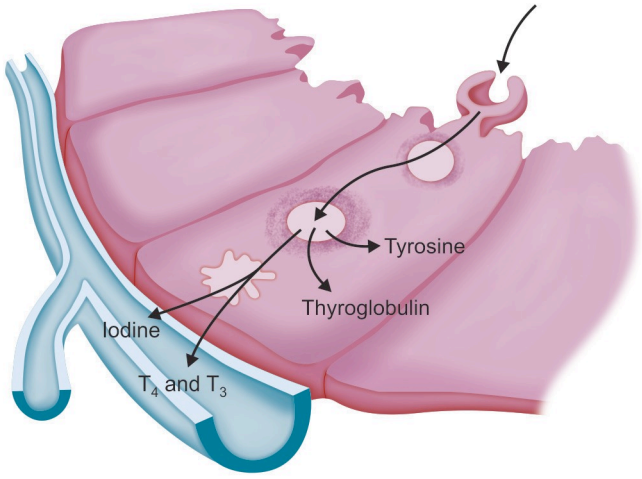

Fig. 1.3: Lysosomal hydrolysis of pinocytotic vesicles containing stored colloid, with subsequent release of thyroid hormone into the peripheral circulation. T_3, triiodothyronine; T , thyroxine.

Peripheral Transport and Metabolism of Thyroid Hormones

More than 99% of circulating thyroid hormones are bound to serum proteins, including thyroxine-binding globulin (TBG), transthyretin, and albumin.[29] TBG is a glycoprotein that contains only one binding site per molecule. TBG is responsible for the transport of more than three fourths of thyroid hormone in the blood, and its levels are significantly increased by elevated levels of estrogens, as occurs in pregnancy. Dissociation of the free hormone from its binding proteins is rapid and efficient. Thyroid hormones are lipophilic and are capable of passive diffusion into cells, although specific transporters may also regulate intracellular thyroid hormone content.[30]

T_3 synthesized directly by the thyroid forms a relatively small proportion of the effective T_3 concentration in tissues, which is mainly derived from peripheral deiodination of T_4. This reaction is catalyzed by two deiodinases with characteristic tissue distributions. Type I deiodinase (5'DI) is predominant in liver, kidney, and thyroid, whereas type II deiodinase (5'DII) is present in the central nervous system, pituitary, placenta, brown adipose tissue, cardiac and skeletal muscle, and thyroid.[29] A type III deiodinase (5'DIII) catalyzes deiodination of T_4 to rT_3 or T_3 to diiodothyronine (T_2) and is found in the placenta and central nervous system.[27] These differences in distribution and regulation may explain some tissue-specific variation in thyroid hormone action. Peripheral conversion of T_4 to T_3 may be impaired in a number of situations, including systemic illness, malnutrition, and trauma or by various drugs.

The thyroid hormones generally have slow turnover times in the peripheral circulation. In adults, the half-life of T_4 is about 7 days, presumably because of the high degree of binding of T_4 to its carrier proteins, whereas the half-life of T_3 is approximately 8–12 hours.

Peripheral Action of Thyroid Hormones

The major effects of thyroid hormone action occur through the intranuclear action of T_3, with T_4 being largely a prohormone.[31] It remains controversial as to whether T_4 might also regulate nonnuclear biologic responses in some contexts, for instance, the activation of certain mitochondrial or cell-membrane enzymes.[31] In the 1960s, Tata and associates observed that T_3 treatment resulted in the rapid synthesis of nuclear RNA, which preceded increases in protein synthesis and mitochondrial oxygen consumption.[32] Subsequently, subcellular fractionation demonstrated specific nuclear binding sites for T_3 and identified the anterior pituitary, liver, brain, and heart as having high binding capacity for T_3.[33] Thus, the current concept of thyroid hormone action is that its nuclear receptor binds to specific regulatory regions in target genes and regulates gene transcription in response to T_3.[34–36]

Thyroid hormone receptors (TRs) are members of the steroid hormone receptor superfamily. There are two TR genes, α and β, located on chromosomes 17 and 3, respectively, and differential splicing of both these genes yields a total of four isoforms, denoted as TRα1, TRα2, TRβ1, and TRβ2 (Fig. 1.4).[34] The expression of the various TR isoforms is both developmentally regulated and tissue specific, such that TRα is widely expressed at all stages of development, preceding the appearance of endogenous thyroid hormone, whereas TRβ begins to be expressed as thyroid hormone-dependent processes occur.[31] An aminoterminal splice variant of the TRβ receptor, TRβ2, is specifically expressed in the hypothalamus and pituitary and may therefore be the critical subtype involved in negative-feedback effects of T_3.[34] In the adult, TRα1 may be the predominant isoform in myocardium, skeletal muscle, and fat, whereas TRβ1 and TRβ2 predominate in the pituitary and liver.[34] TRα2 does not bind ligand and its function is poorly understood, although it may function as an inhibitor of thyroid hormone action in some contexts.[34]

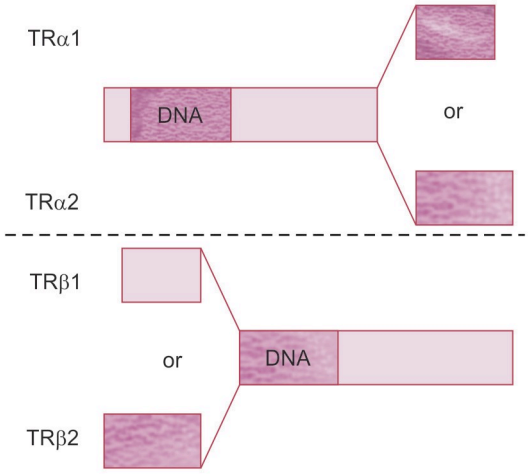

Fig. 1.4: Multiple human thyroid hormone receptor (TR) isoforms. TRα and TRβ receptors are transcribed from different genes on chromosomes 17 and 3, respectively. Different isoforms are then generated from differential splicing of the primary messenger RNA transcripts in each case, such that TRα1 and TRα2 isoforms differ in their carboxytermini, whereas TRβ1 and TRβ2 isoforms differ in their aminotermini, as shown. Adapted from Lazar.[34] The clinical manifestations of thyroid hormone action are the net result of the actions of the products of the various genes whose expression is regulated by T_3. For example, thyroid hormones affect cardiac contractility by affecting the transcription of, and subsequent relative proportions of, the various myosin heavy chains in cardiac muscle.[37,38] In the pituitary, T_3 regulates the transcription of the genes for both a and β subunits of TSH, thus affecting the level of TSH secretion.[39]

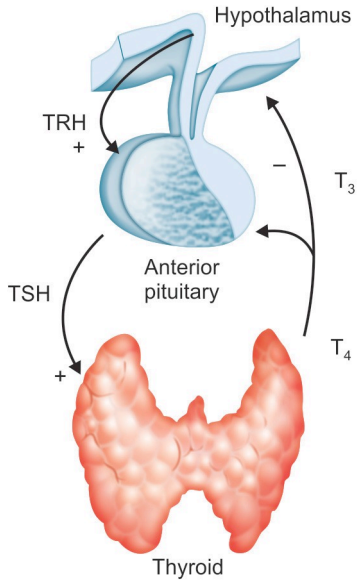

Fig. 1.5: Negative-feedback regulation of thyroid hormone production. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

These tissue-specific actions of TRα and β are exemplified by the syndromes of thyroid hormone resistance. The classic syndrome of resistance to thyroid hormones (RTH) was discovered in 1988 to be associated with mutations in *THRB* (encoding TRβ) that diminish negative feedback in pituitary thyrotrophs leading to elevated serum thyroid hormone levels and nonsuppressed TSH, together with variable T_3 responsiveness (via normal TRα) in peripheral tissues that can present with tachycardia, attention-deficient disorder, and osteopenia.[35] More recently, a distinct syndrome termed RTHα due to mutation in *THRA* has been described in which hypothyroid features develop in TRα-regulated tissues (i.e. short stature, bradycardia, severe constipation, intellectual disability, and impaired bone maturation) but with normal hypothalamic-pituitary-thyroid axis (via normal TRβ); an unusual thyroid hormone profile of low normal serum T_4, high normal serum T_3, and normal TSH exists in these patients due to alterations in peripheral thyroid hormone metabolism.[36]

TRs bind to specific regulatory DNA sequences usually within gene promoters.[37] A consensus regulatory binding site, termed the *thyroid hormone response element* (TRE), consists of a pair of hexanucleotide half-sites. Natural TREs present in gene promoters are commonly degenerate variations of these consensus sequences. Biochemical evidence suggests that on many TREs, the receptor complex is most active when bound to DNA as a heterodimer with the retinoid X receptor.[38]

Thyroid Hormone Regulation

Thyroid hormone production and release are under the control of the hypothalamic-pituitary-thyroid axis (Fig. 1.5), acting in a negative-feedback cycle.[40] TSH is the major regulator of thyroid gland activity. Increased levels of TSH lead to hypertrophy and increased vascularity of the gland, whereas decreased levels of TSH lead to gland atrophy. A glycoprotein secreted by the anterior pituitary, TSH is composed of an α subunit and a β subunit. The α subunit is common to a family of glycoprotein hormones, including follicle-stimulating hormone, luteinizing hormone, and human chorionic gonadotropin (hCG).

TSH binds to a specific receptor on the surface of the thyroid cell. The TSH receptor is a G protein-coupled receptor. After activation by TSH, the receptor interacts with a

guanine nucleotide-binding protein (G protein), which induces the production of cyclic adenosine monophosphate (cAMP).[41] This cAMP then stimulates the synthesis and secretion of thyroid hormones. Receptors that are linked to G proteins are characterized by the presence of seven transmembrane-spanning domains linked by cytoplasmic and extracellular loops. The first cytoplasmic loop, as well as the carboxylterminal residues in the second and third cytoplasmic loops, is important in mediating a TSH-dependent increase in intracellular cAMP production.[42] The TSH receptor has been cloned,[43] and specific mutations have been identified in association with congenital nonautoimmune diffuse hyperthyroidism (when germ line)[44] and also with hyperfunctioning follicular thyroid neoplasms (when somatic).[45,46]

TSH is secreted from the anterior pituitary in response to thyrotropin-releasing hormone (TRH) and to reduced pituitary levels of T_3. TRH acts to directly stimulate the thyrotropic cells to increase both the synthesis and the release of TSH. TRH is a tripeptide synthesized in the paraventricular nucleus of the hypothalamus, and, after synthesis, it passes to the median eminence and down the pituitary stalk in the hypophysial portal system. It is thought that the principal function of TRH is to set the ambient level of regulatory control whereby thyroid hormone levels are mediated by negative feedback. TRH secretion itself is also under negative-feedback control in response to peripheral thyroid hormone levels.

T_3, on the other hand, derived principally from the local deiodination of peripheral T_4 in the pituitary, directly inhibits the release and synthesis of TSH. It is also thought that peripheral thyroid hormone levels may regulate TRH receptor numbers on the surface of the pituitary thyrotropic cells, thus decreasing their responsiveness to TRH.

A number of other factors affect thyroid hormone synthesis in addition to the hypothalamic-pituitary feedback cycle. Other hormones can have a direct effect on the thyroid gland. Catecholamines are thought to have a direct stimulatory effect on thyroid hormone release. hCG also stimulates thyroid hormone production, with free levels of thyroid hormone increasing during pregnancy and in the presence of hydatidiform moles.[47] Glucocorticoids, on the other hand, act to reduce thyroid hormone production by suppressing pituitary TSH secretion. The thyroid also obtains direct adrenergic innervation, and there is some evidence that sympathetic stimulation can increase thyroid hormone synthesis.

Other external factors that can affect thyroid regulation include nonthyroidal illness, starvation, and temperature changes. A variety of disorders, especially severe illness, lead to reduced levels of peripheral thyroid hormone in the absence of a compensatory rise in TSH (the so-called sick euthyroid syndrome). Starvation also leads to markedly reduced levels of both T_4 and T_3, as does exposure to high temperatures.

Autoregulatory Mechanisms

The thyroid can also control its own stores of thyroid hormone by intrinsic autoregulatory mechanisms. These mechanisms are principally seen in response to alterations in iodide availability. For example, an excess of dietary iodide leads to autoregulated inhibition of iodide uptake into the follicular cells, whereas iodide deficiency results in increased iodide transport and uptake. Large doses of iodide have more complex effects, including an initial increase followed by a decrease in organification, the so-called Wolff–Chaikoff effect.[48] Excess iodide also inhibits, at least initially, the release of stored thyroid hormone from the thyroid follicle.

CALCITONIN PHYSIOLOGY

Calcitonin Secretion

Calcitonin is secreted by the parafollicular C cells located in the lateral lobes of the thyroid. This hormone is a 32-amino acid polypeptide with an NH-terminal seven-member disulfide ring.[49] Calcitonin acts to lower serum calcium concentration, principally by inhibition of bone resorption. Secretion of the hormone is increased in the presence of elevated levels of serum calcium. In the clinical context, calcitonin secretion can be stimulated by a number of techniques, including calcium infusion, pentagastrin infusion, and alcohol.[50]

Peripheral Action of Calcitonin

Calcitonin acts via specific cell surface receptors located predominantly on the surface of osteoclasts.[51] These receptors have also been found in renal tubular epithelium, neural tissue, and lymphocytes.[52] The predominant action of calcitonin is to inhibit osteoclast action, although in the physiologic situation calcitonin does not actually cause a lowering of serum calcium levels. Indeed, in patients with medullary carcinoma of the thyroid, in which calcitonin levels may be many thousands of times the normal level, hypocalcemia is not seen. Similarly, patients who have had a total thyroidectomy, with removal of all known C cells, maintain normal calcium metabolism.

SUMMARY

In summary, the thyroid gland contains two separate functioning units. The follicular cells produce T_4 and T_3, which regulate growth and metabolism, whereas the parafollicular cells produce the antihypercalcemia hormone calcitonin. Iodine is required for the synthesis of thyroid hormone, and iodine deficiency can result in endemic goiter and cretinism. Circulating levels of thyroid hormone depend on a negative feedback between T_3 and T_4 and TSH secretion as well as a positive action of TSH. Thus, medications and other factors can influence ambient thyroid hormone levels and, consequently, the metabolic state.

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