Chapter 1

Thyroid anatomy and physiology

Anatomy

The thyroid gland consists of left and right *lobes* connected by a midline isthmus (Fig. 1.1). The isthmus lies below the cricoid cartilage, and the lobes extend upward over the lower half of the thyroid cartilage. The thyroid is covered by the strap muscles of the neck and overlapped by the sternocleidomastoids. The pretracheal fascia encloses the thyroid gland and attaches it to the larynx and the trachea. This accounts for the upward movement of the thyroid gland on swallowing.

The thyroid gland develops from the floor of the pharynx in the position of the foramen caecum of the adult tongue as a downgrowth that descends into the neck. During this descent, the thyroid gland remains connected to the tongue by the thyroglossal duct, which later disappears. However, aberrant thyroid tissue or thyroglossal cysts (cystic remnants of the thyroglossal duct) may occur anywhere along the course of the duct (Fig. 1.2). Such thyroid remnants move upward when the tongue is protruded.

The thyroid gland is composed of epithelial spheres called *follicles* (Fig 1.3), whose lumens are filled with a proteinaceous colloid containing *thyroglobulin*. Two basic cell types are present in the follicles. The follicular cells secrete thyroxine (T_4) and triiodothyronine (T_3) and originate from a downward growth of the endoderm of the floor of the pharynx (see above). The parafollicular or C cells secrete calcitonin and arise from neural crest cells that migrate into the developing thyroid gland. The follicles are surrounded by an extensive capillary network.

Physiology

Thyroid hormones act on many tissues. They regulate:

- organogenesis, growth and development (central nervous system, bone)
- energy expenditure
- protein, carbohydrate and fat metabolism
- gut motility
- bone turnover
- heart rate and contractility, and peripheral vascular resistance
- beta-adrenergic receptor expression
- muscle contraction and relaxation
- the menstrual cycle
- erythropoiesis.

Iodine is essential for normal thyroid function. It is obtained by the ingestion of foods such as seafood, seaweed, kelp, dairy products, some vegetables and iodized salt. The recommended iodine intake for adults is 150 µg per day (250 µg per day for pregnant and lactating women). Dietary iodine

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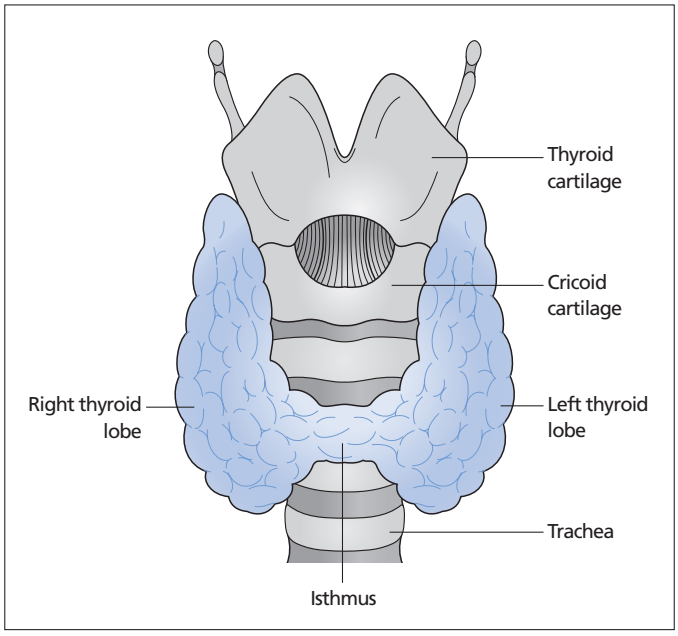


Figure 1.1 Thyroid gland.

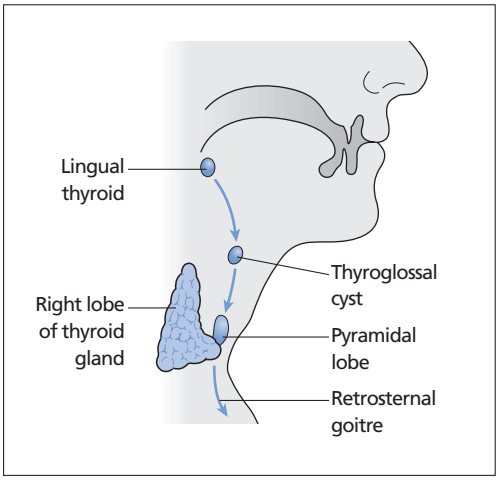


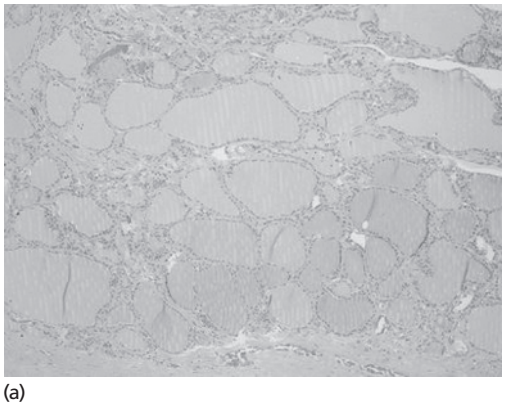
Figure 1.2 Possible sites of remnants of the thyroglossal duct.

is absorbed as iodide. Iodide is excreted in the urine.

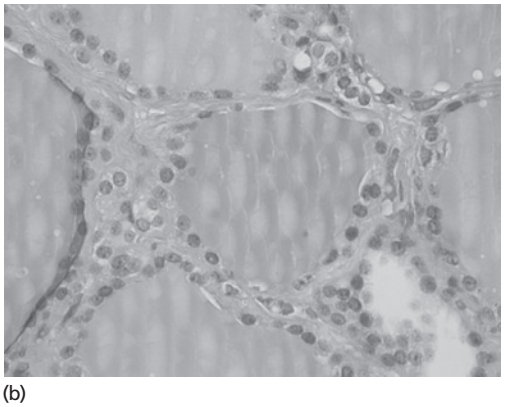
Thyroid hormone synthesis

Figure 1.4 illustrates different steps in thyroid hormone synthesis:

- *Thyroglobulin* is synthesized in the rough endoplasmic reticulum and is transported into the follicular lumen by exocytosis.
- Iodide is transported into the thyroid follicular cells via a sodium–iodide symporter on the basolateral membrane of the follicular cells. Iodide transport requires oxidative metabolism.
- Inside the follicular cells, iodide diffuses to the apical surface and is transported by pendrin (a membrane iodide–chloride transporter) into the follicular lumen.
- *Thyroid peroxidase* (TPO) enzyme catalyzes the process of oxidation of the iodide to iodine and its binding (organification) to the tyrosine residues of thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
- DIT and MIT molecules are linked by TPO to form *thyroxine* (T_4) and *triiodothyronine* (T_3) in a process known as coupling.
- Thyroglobulin containing T_4 and T_3 is resorbed into the follicular cells by endocytosis and is cleaved by lysosomal enzymes (proteases and peptidases) to release T_4 and T_3. T_4 and T_3 are then secreted into the circulation.
- Uncoupled MIT and DIT are deiodinated, and the free tyrosine and iodide are recycled.



(a)



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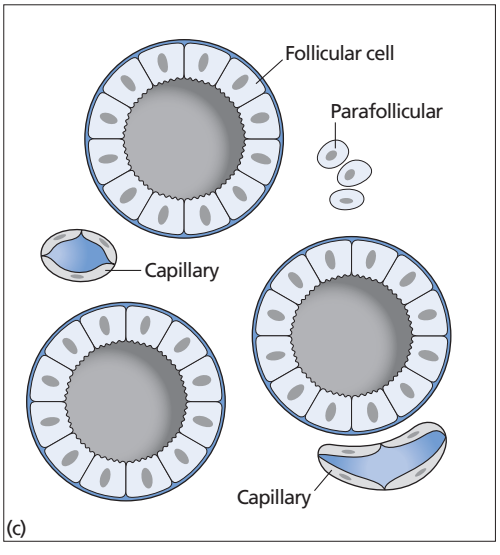

Figure 1.3 (a) A low-power histological image of thyroid tissue showing numerous follicles filled with colloid and lined by cuboidal epithelium. (b) A high-power view of follicles lined by cuboidal epithelium. (c) Thyroid follicles (lined by follicular cells), surrounding capillaries and parafollicular cells.

The thyroid gland stores T_4 and T_3 incorporated in thyroglobulin, and can therefore secrete T_4 and T_3 more quickly than if they had to be synthesized.

Extra-thyroidal T_3 production

T_4 is produced entirely by the thyroid gland. The production rate of T_4 is about 100 µg per day. However, only 20% of T_3 is produced directly by the thyroid gland (by coupling of MIT and DIT). Around 80% of T_3 is produced by the deiodination of T_4 in peripheral extra-thyroidal tissues (mainly liver and kidney). The total daily production rate of T_3 is about 35 µg.

T_4 is converted to T_3 (the biologically active metabolite) by *5′-deiodination* (outer-ring deiodination). 5′-Deiodination is mediated by deiodinases type 1 (D1) and type 2 (D2). D1 is the predominant deiodinating enzyme in the liver, kidney and thyroid. D2 is the predominant deiodinating enzyme in muscle, brain, pituitary, skin and placenta. Type 3 deiodinase (D3) catalyzes the conversion of T_3 to reverse T_3 (the inactive metabolite) by 5-deiodination (inner ring deiodination), as shown in Fig. 1.5.

Changes in T_3 concentration may indicate a change in the rate of peripheral conversion and may not be an accurate measure of the change in thyroid hormone production. For example, the rate of T_3 production (by 5′-deiodination of T_4) is reduced in acute illness and starvation.

Total and free T_4 and T_3

Approximately 99.97% of circulating T_4 and 99.7% of circulating T_3 are bound to plasma proteins: *thyroid-binding globulin* (TBG), *transthyretin* (also

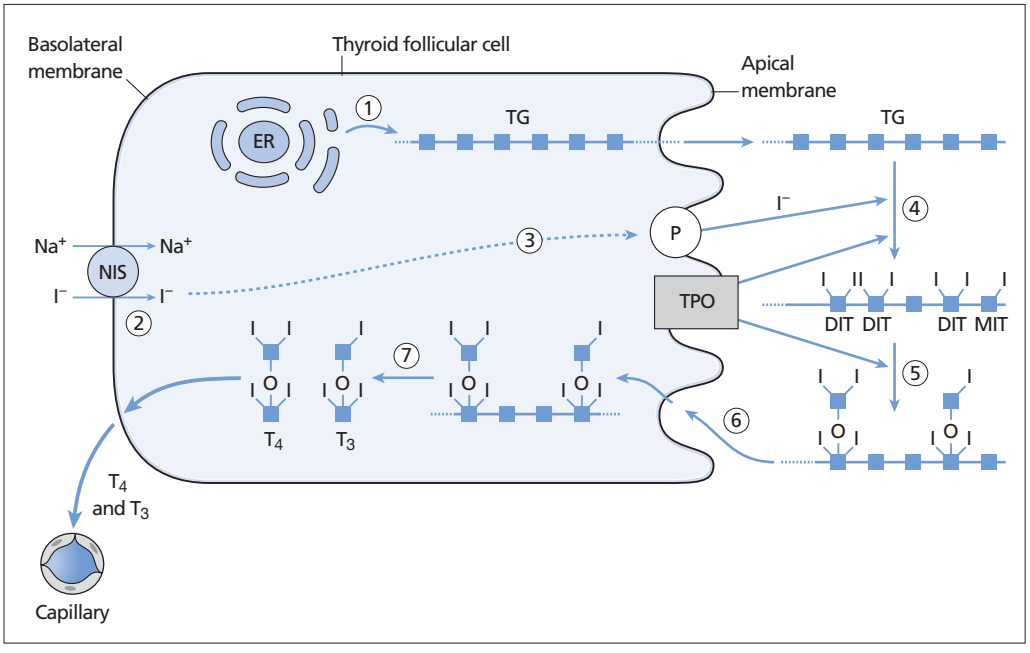

Figure 1.4 Steps in thyroid hormone synthesis. (1) Thyroglobulin (TG) is synthesized in the endoplasmic reticulum (ER) in the thyroid follicular cells and is transported into the follicular lumen. The small blue squares represent the amino acid residues comprising TG. (2) Iodide is transported into the follicular cell by the sodium–iodide (Na^+/I^-) symporter (NIS). (3) Iodide diffuses to the apical surface and is transported into the follicular lumen by pendrin (P). (4) Iodide is oxidized and linked to tyrosine residues in TG to form diiodotyrosine (DIT) and monoiodotyrosine (MIT) molecules. (5) Within the TG, T_4 is formed from two DIT molecules, and T_3 is formed from one DIT and one MIT molecule. (6) TG containing T_4 and T_3 is resorbed into the follicular cell by endocytosis. (7) TG is degraded by lysosomal enzymes to release T_4 and T_3 molecules, which move across the basolateral membrane of the follicular cell into the adjacent capillaries. TPO, thyroid peroxidase.

known as thyroid-binding pre-albumin), albumin and lipoproteins.

Only the unbound thyroid hormone is available to the tissues. T_3 is less strongly bound and therefore has a more rapid onset and offset of action. The binding proteins have both storage and buffer functions. They help to maintain the serum free T_4 and T_3 levels within narrow limits, and also ensure continuous and rapid availability of the hormones to the tissues.

Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels. This is because the level of bound hormone alters with changes in the levels of thyroid-binding proteins, even though free T_4 (and T_3) concentrations do not change and the patient remains euthyroid (Fig. 1.6). Box 1.1 summarizes factors that may alter TBG levels.

Box 1.1 Factors that may alter thyroid-binding globulin (TBG) levels

↑ TBG

Hereditary TBG excess (X-linked dominant)
Pregnancy
Drugs, e.g. oestrogen, tamoxifen, opiates, phenothiazines, 5-fluorouracil, clofibrate
Hepatitis
Acute intermittent porphyria

↓ TBG

Genetically determined
Malnutrition
Chronic liver disease
Nephrotic syndrome
Drugs, e.g. androgens, corticosteroids, phenytoin
Cushing's syndrome
Acromegaly

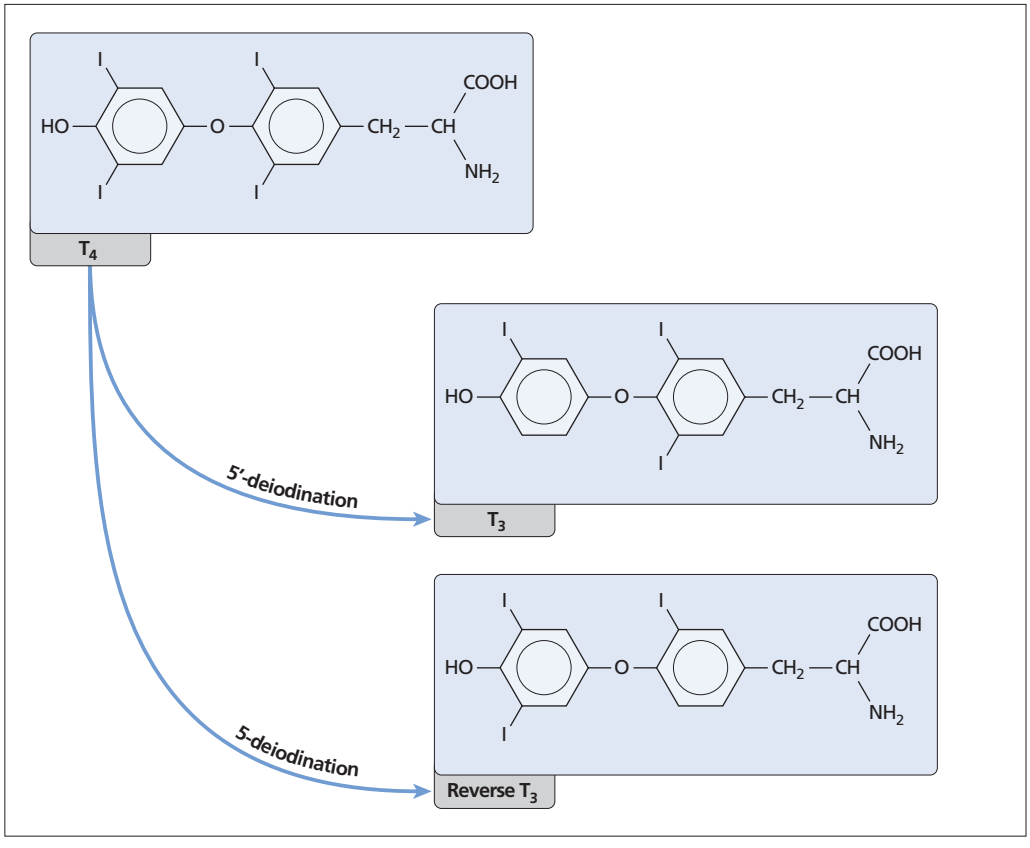

Figure 1.5 The conversion of T_4 to T_3 by 5′-deiodination and to reverse T_3 by 5-deiodination.

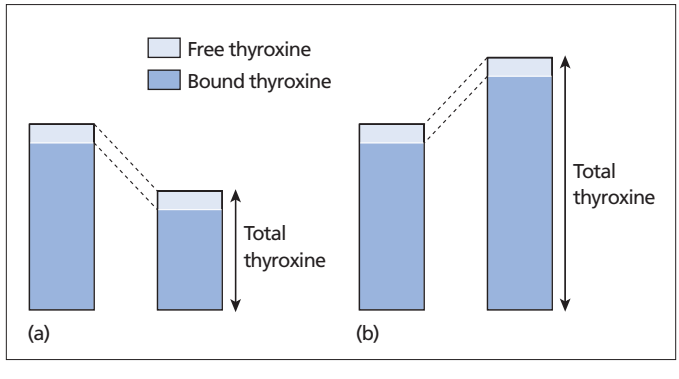

Figure 1.6 (a) If serum thyroid-binding globulin (TBG) levels are decreased, the level of thyroid hormone bound to TBG also decreases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free thyroid hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be lower. (b) If TBG levels are increased, the level of thyroid hormone bound to TBG also increases (the dark blue part of the bar). However, homeostatic mechanisms will maintain the free hormone levels (the light blue part of the bar). Note that although free hormone levels are unchanged, the 'total' hormone levels measured will be higher.

Other causes of increased serum total T_4 and T_3 levels include familial dysalbuminaemic hyperthyroxinaemia (due to the presence of an abnormal albumin with a higher affinity for T_4) and the presence of anti-T_4 antibodies. Patients with these conditions are euthyroid, have normal serum thyroid-stimulating hormone (TSH) levels, and usually have normal serum free T_4 and T_3 levels when measured by appropriate methods.

Thyroid hormone metabolism

T_4 is degraded at a rate of 10% per day. Around 40% of the T_4 is deiodinated to T_3 and 40% to reverse T_3. The remaining T_4 is conjugated with glucuronide and sulphate, deaminated and decarboxylated, or cleaved between the two rings.

T_3 is degraded (mostly by deiodination) at a rate of 75% per day. Reverse T_3 is degraded even more rapidly than T_3, mostly by deiodination.

Regulation of thyroid hormone production and release

T_3 and T_4 synthesis and secretion is stimulated by the *thyroid-stimulating hormone* (TSH) released from the anterior pituitary gland (Fig. 1.7). TSH production and release is increased by hypothalamic *thyrotrophin-releasing hormone* (TRH).

Thyrotrophin-releasing hormone

TRH is a tripeptide synthesized and released by the hypothalamus. TRH content is highest in the median eminence and paraventricular nuclei of the hypothalamus. TRH stimulates TSH secretion by activating a G-protein-coupled receptor and the phospholipase C-phosphoinositide pathway, resulting in mobilization of calcium from intracellular storage sites.

Chronic TRH stimulation also increases the synthesis and glycosylation of TSH, which increases its biological activity.

Thyroid-stimulating hormone

TSH is a glycoprotein secreted by the thyrotroph cells of the anterior pituitary. TSH is composed of alpha and beta subunits that are non-covalently bound. The alpha subunit is the same as that of luteinizing hormone, follicle-stimulating hormone and human chorionic gonadotrophin. However, the beta subunit is unique to TSH. TSH binds to specific plasma membrane receptors and activates adenylyl cyclase. TSH also stimulates phospholipase C activity.

TSH stimulates every step in thyroid hormone synthesis and secretion. It also stimulates the expression of many genes in thyroid tissue and causes thyroid hyperplasia and hypertrophy.

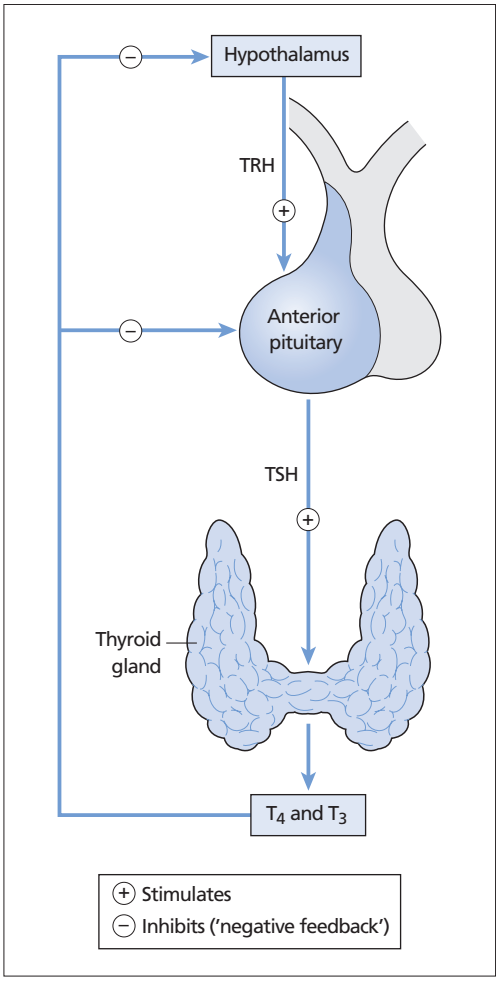

Figure 1.7 Hypothalamic–pituitary–thyroid axis. TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone.

Box 1.2 Causes of increased and decreased thyroid-stimulating hormone (TSH) concentration

Increased TSH secretion

Primary/subclinical hypothyroidism
Secondary hyperthyroidism
Recovery from non-thyroidal illness
Thyroid hormone resistance
Primary adrenal insufficiency
Drugs: dopamine antagonists (metoclopramide, domperidone), amiodarone
Patients with antibodies to the murine immunoglobulins used in the assay

Decreased TSH secretion

Primary/subclinical hyperthyroidism
Secondary hypothyroidism
Non-thyroidal illness
Drugs: dopamine agonists, octreotide, phenytoin, steroids
Increased human chorionic gonadotrophin, e.g. early pregnancy, molar pregnancy, choriocarcinoma

T_4 and T_3 inhibit TSH synthesis and release both directly (by inhibiting transcription of the TSH subunit genes) and indirectly (by inhibiting TRH release). T_4 and T_3 also decrease the glycosylation and hence bioactivity of TSH.

TSH secretion is regulated by very small changes in serum T_4 and T_3 concentrations. However, an important exception is that the reduced T_3 levels in patients with non-thyroidal illness have little effect on TSH secretion. This may be due to a greater contribution of serum T_4 to the nuclear T_3 content of the pituitary than other tissues.

Box 1.2 shows a list of the causes of increased and decreased TSH concentration.

Mechanism of action of thyroid hormones

Thyroid hormones enter cells via active membrane transporter proteins (e.g. MCT8). Inside the cells, T_3 formed from the deiodination of T_4 and T_3 that enters the cells from the serum is transferred to the nucleus. The thyroid hormone receptors (TRs) heterodimerize with the retinoid X receptor and act as nuclear transcription factors. TRs bind thyroid hormone response elements in the promoter region of thyroid hormone-responsive genes. In the absence of T_3, TRs bind co-repressor proteins that repress transcription. On T_3 binding, co-repressors are displaced and co-activator proteins bind the TRs, resulting in histone acetylation, generation of a permissive chromatin structure and induction of gene transcription.

There are two T_3 nuclear receptors—alpha and beta—encoded by separate genes located on chromosomes 17 and 3. Two forms of each TR are generated by alternative splicing. Only the beta-1, beta-2 and alpha-1 receptors bind T_3. Liver predominantly expresses beta receptors, whereas heart and bone express alpha receptors. The hypothalamus and pituitary express beta-2 receptors which mediate the negative feedback regulation.

Key points:

- Thyroid hormone synthesis involves the transport of iodide into follicular cells, iodide oxidation into iodine, binding of iodine to thyroglobulin tyrosine residues (organification) to form MIT and DIT, and coupling of DIT and MIT to form T_4 and T_3. The processes of iodide oxidation, organification and coupling are catalyzed by the thyroid peroxidase enzyme.
- Thyroid hormone synthesis and secretion is stimulated by the TSH released from the anterior pituitary gland. TSH production and release is increased by hypothalamic TRH.
- 80% of T_3 is produced by the 5′-deiodination of T_4 in peripheral extra-thyroidal tissues (mainly liver and kidney).
- Free thyroid hormone concentrations are easier to interpret than total thyroid hormone levels as the level of bound hormone alters with changes in the levels of thyroid-binding proteins.
- T_4 is largely a prohormone, and almost the entire nuclear-bound hormone is T_3.