Thyroid hormones and clinical disorders

The thyroid gland is responsible for making thyroid hormones by concentrating iodine and utilizing the amino acid tyrosine. The hormones play major metabolic roles, affecting many different cell types in the body. Clinical conditions affecting the thyroid gland are common. Therefore, a thorough understanding is important.

Anatomy and vasculature

The adult thyroid weighs 10–20 g, is bigger in women than men and is also larger in areas of the world with iodine deficiency. It enlarges during puberty, pregnancy and lactation. The right lobe is usually slightly larger than the left. Its outer capsule is not well-defined, but attaches the thyroid posteriorly to the trachea. The parathyroid glands are situated between this and the inner capsule, from which trabeculae of collagen pervade the gland carrying nerves and a rich vascular supply (Figure 1). The thyroid receives ~1% of cardiac output from superior and inferior thyroid arteries, which are branches of the external carotid and subclavian arteries respectively. Per gram of tissue, this blood supply is almost twice that of the kidney. Blood flow through fenestrated capillaries is controlled by post-ganglionic sympathetic nerves from the middle and superior cervical ganglia.

The functional unit of the thyroid is the follicle, comprised of cuboidal epithelial (‘follicular’) cells around a central lumen of colloid. Colloid is composed almost entirely of the iodinated glycoprotein thyroglobulin (pink on periodic acid-Schiff (PAS) staining). There are many thousands of follicles 20–900 μm in diameter, interspersed with blood vessels, an extensive network of lymphatic vessels, connective tissue and the parafollicular calcitonin secreting C-cells. When the gland is quiescent (e.g. in hypothyroidism from iodine deficiency), follicles are distended with colloid and the epithelial cells are flattened with little cytoplasm. Conversely, in an overactive gland, follicular cells are columnar and there is less stored colloid

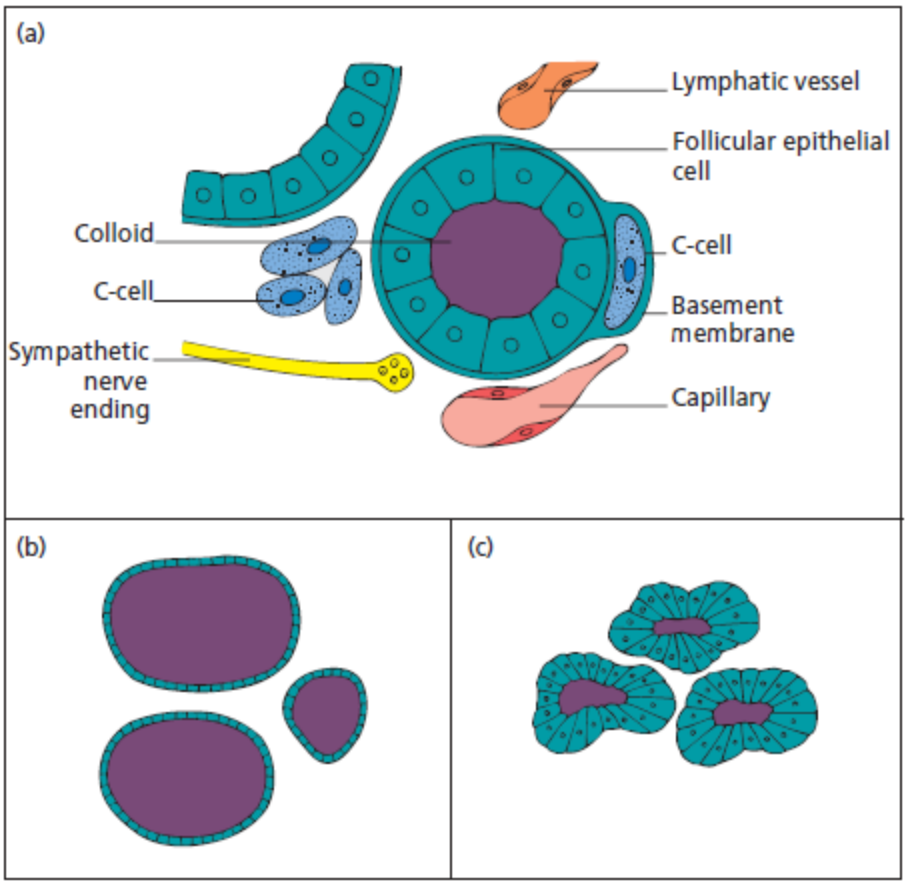

Figure 1 Histology of the human thyroid gland. (a) Euthyroid follicles are shown lined with cuboidal epithelium and lumens filled with gelatinous colloid that contains stored thyroid hormone. Surrounding each follicle is a basement membrane enclosing parafollicular C-cells within stroma containing fenestrated capillaries, lymphatic vessels and sympathetic nerve endings. (b) Underactive follicles with flattened epithelial cells and increased colloid. (c) Overactive follicles with tall, columnar epithelial cells and reduced colloid.

Thyroid hormone biosynthesis

There are two active thyroid hormones: thyroxine (3,3′,5,5′-tetra-iodothyronine; abbreviated to T4) and 3,5,3′-tri-iodothyronine (T3); the subscripts 4 and 3 represent the number of iodine atoms incorporated on each thyronine residue (Figure 2). These hormones are generated from the sequential iodination and coupling of the amino acid tyrosine and inactivated by de iodination and modification to 3,3′,5′-tri-iodothyronine [reverse T3 (rT3)] and diiodothyronine (T2). The equilibrium between these different molecules determines overall thyroid hormone activity. Synthesis of thyroid hormone can be broken down into several key steps (Figure 3).

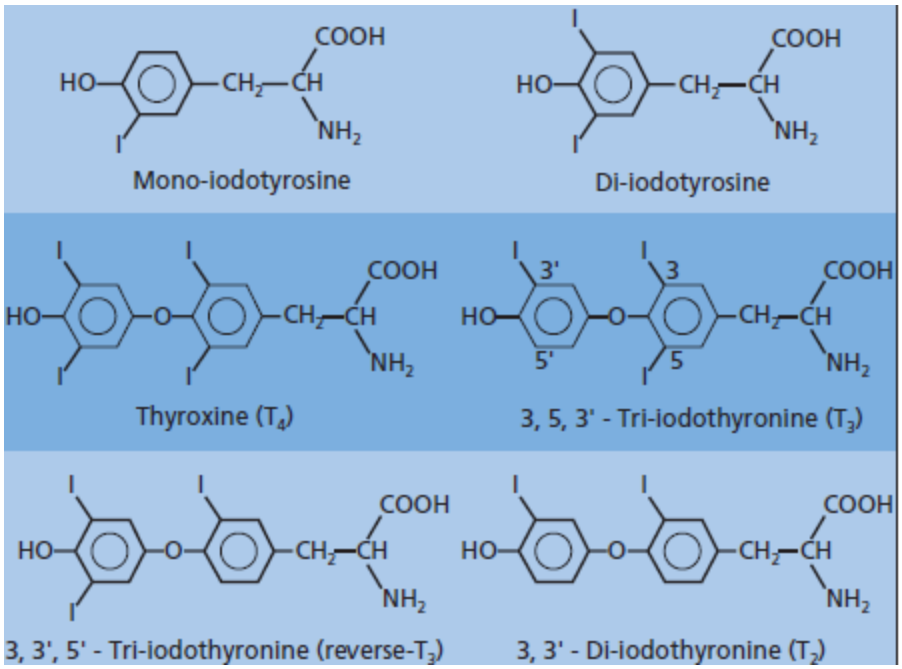

Figure2: The structures of active and inactive thyroid hormones and their precursors. Monoiodotyrosine and di-iodotyrosine are precursors. Thyroxine (T4) and tri-iodothyronine (T3) are the two thyroid hormones, of which T3 is the biologically more active. Reverse T3 and T2 are inactive metabolites formed by de-iodination of T4 and T3 respectively.

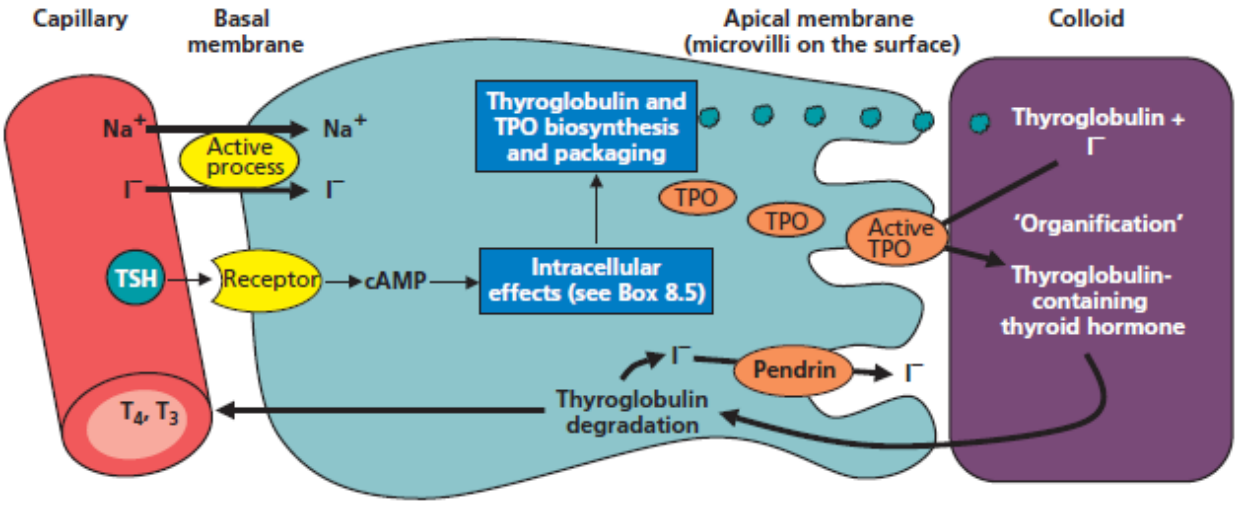

Figure 3: Thyroid hormone biosynthesis within the follicular cell. Active iodide (I^-) import is linked to the Na^+/K^+-ATPase pump. Thyroglobulin is synthesized on the rough endoplasmic reticulum, packaged in the Golgi complex and released from small, Golgi-derived vesicles into the follicular lumen. Its iodination is also known as 'organification'. Cytoplasmic microfilaments and microtubules organize the return of iodinated thyroglobulin into the cell as endocytotic vesicles of colloid, which is broken down to release thyroid hormone. TSH, thyroid-stimulating hormone; TPO, thyroid peroxidase; T4, thyroxine; T3, tri-iodothyronine.

Uptake of iodide from the blood

Synthesis of thyroid hormone relies on a constant supply of dietary iodine as the monovalent anion iodide (I^-). When the element is scarce the thyroid enlarges to form a goiter. Circulating iodide enters the follicular cell by active transport through the basal cell membrane. The sodium (Na^+)/I^- pump is linked to an adenosine triphosphate (ATP)-driven Na^+/potassium (K^+) pump. This process concentrates I^- within the thyroid gland to 20–100-fold that of the remainder of the body. Several structurally related anions can competitively inhibit the I^- pump. For instance, large doses of perchlorate ($ClO4^-$) can block I^- uptake in the short term (e.g. to treat accidental ingestion of radioiodine). The pertechnetate ion incorporating a γ-emitting radioisotope of technetium is also taken up by the I^- pump, allowing the thyroid to be imaged diagnostically.

The synthesis of thyroglobulin

Thyroglobulin (Tg) is the tyrosine-rich protein that is iodinated within the colloid to yield stored in thyroid hormone. It is synthesized exclusively by the follicular cell, such that the small amount in the circulation can serve as a tumour marker for thyroid cancer. Tg contains ~10% carbohydrate, including sialic acid responsible for the pink PAS staining of colloid. Tg is transcribed, translated, modified in the Golgi apparatus and then packaged into vesicles that undergo exocytosis at the apical membrane to release Tg into the follicular lumen (Figure 3)

Iodination of thyroglobulin

Thyroid peroxidase (TPO) catalyzes the iodination of Tg (mature Tg is ~1% iodine by weight). The enzyme is synthesized and packaged alongside Tg into vesicles at the Golgi apparatus (Figure 3). TPO becomes activated at the apical membrane where it binds I^- and Tg (at different sites), oxidizes I^-, and transfers it to an exposed Tg tyrosine residue. The enzyme is particularly efficient at iodinating fresh Tg; as the reaction proceeds, the efficiency of adding further I^- decreases. Drugs inhibiting TPO and iodination are used to treat hyperthyroidism. Some naturally-occurring chemicals [e.g. milk from cows fed on certain green fodder or from brassicae vegetables (cabbages, sprouts)] may also inhibit Tg iodination. This leads to diminished negative feedback at the anterior pituitary causing TSH secretion to rise (Figure 4), which chronically can stimulate a goitre; hence the chemicals are known as ‘goitrogens’.

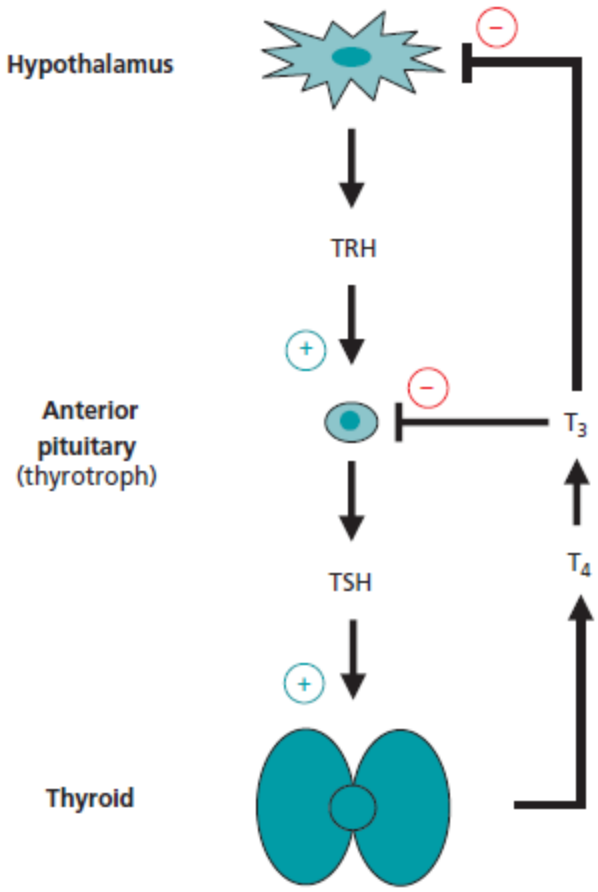

Figure 4: The hypothalamic–anterior pituitary– thyroid axis. The more active hormone, T3, provides the majority of negative feedback. TRH, thyrotrophinreleasing hormone; TSH, thyroid–stimulating hormone.

The production of thyroid hormone

Iodination of Tg initiates thyroid hormone formation (Figures 2 and 3). Within the Tg structure, di-iodotyrosine couples to either mono-iodotyrosine or another di-iodotyrosine to generate T3 or T4 respectively. This coupling occurs during the TPO mediated iodination, yielding thyroid hormone stored as colloid in the lumen of the thyroid follicle.

The secretion of thyroid hormone

To secrete thyroid hormone, colloid is first enveloped by microvilli on the cell surface (endocytosis) to form colloid vesicles within the cells that fuse with lysosomes (Figure 3). The enzymes from the lysosomes break down the iodinated Tg, releasing thyroid hormones. Other degradation products are recycled; for instance, the transporter, Pendrin, moves I^- back into the follicular lumen. Lossof- function mutations in the *PENDRIN* gene cause a congenital form of

hypothyroidism. The thyroid hormones move across the basal cell membrane and enter the circulation, ~80% as T4 and 20% as T3.

Regulation

The thyroid is controlled by TSH from the anterior pituitary, which in turn is regulated by thyrotrophin releasing hormone (TRH) from the hypothalamus. Thyroid hormone, predominantly T3 (the more active), completes the negative feedback loop by suppressing the production of TRH and TSH (Figure 4). TSH binds to its specific G-protein–coupled receptor on the surface of the thyroid follicular cell and activates both adenylate cyclase and phospholipase C. The former predominates and cAMP mediates most of the actions of TSH . This increases fresh thyroid hormone stores and, within ~1 h, increases hormone release. The most recently synthesized Tg is the first to be resorbed as it is nearest to the microvilli. This Tg has also had less time to be iodinated than the mature, central colloid, such that it releases thyroid hormone with a relatively higher T3:T4 ratio and, consequently, greater activity.