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Thyroid Gland: Anatomy and Physiology ☆

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Glossary

dt0010   **Follicle**   A hollow sphere lined by a single layer of epithelial cells called thyrocytes, and filled with colloid.

dt0015   **Iodotyrosines**   Precursors of thyroid hormones resulting from iodination of tyrosyl residues of thyroglobulin. They include monoiodotyrosine and diiodotyrosine.

dt0020   **Iodothyronine**   Thyroid hormones resulting from coupling of two iodotyrosines.

dt0025   **Thyrocyte (follicular cell)**   The cell type that takes up iodide from the bloodstream and incorporates it in the thyroglobulin, the backbone of the colloid, thus producing iodotyrosines and iodothyronines.

dt0030   **Thyronamines**   Compounds with a chemical structure similar to thyroid hormones, in which the carboxylate group is replaced with the alanine side chain. Compared with thyroid hormones, their biological actions are either in the same or in the opposite direction.

s0010

Embryology

p0010   It is beyond the scope of this article to provide a detailed review of the embryological development of the hypothalamic thyrotropin-releasing hormone (TRH)-secreting neurons and the pituitary thyrotrophs. Concerning the hypothalamus, suffice it to say that, similarly to the releasing factors for other pituitary hormones, TRH is synthesized in parvocellular, not magnocellular, neurons of the paraventricular nucleus. On a historical note, the identification and characterization of TRH in 1970 and other releasing hormones by Roger Guillemin and Andrew Schally permitted these two scientists to share the Nobel Prize in Medicine 7 years later.

p0015   Concerning pituitary organogenesis, suffice it to say that it is dictated by the orderly expression of cell-specific transcription factors, including Titf1/Nkx2.1, Rpx/Hesx-1, Pax-6, Sox-3, Lhx-3, Prop-1, Pit-1, and TEF. Some of these genes are involved in the formation of other specific populations in the adenohypophysis. Accordingly, depending on the mutated gene, congenital secondary hypothyroidism may or may not be accompanied by other pituitary hormone deficiencies. Adenohypophysis anlage is recognizable at 4–5 weeks of gestation, but the hypothalamic-pituitary unit becomes mature only by 20 weeks. Within the anterior pituitary, the thyrotrophs are placed anteromedially and anterolaterally, and account for less than 10% of all the cell types (Aaron et al., 2007).

p0020   The thyroid gland is the first endocrine gland to develop in humans. The thyroid gland originates from a diverticulum located in the median ventral wall of the pharynx (called the thyroid diverticulum). During the fourth week of embryonal development, an endodermal thickening (thyroid placode) appears in the midline floor of the primitive pharynx between the first and second pharyngeal pouches, dorsal to the aortic sac (Fancy et al., 2010). This primitive thyroid tissue is hollow at first, but soon becomes solid (thyroid bud) and penetrates the underlying mesenchymal tissue, descending anteriorly through the thyroglossal duct to the hyoid bone and laryngeal cartilages in order to reach the lower neck. As the thyroid tissue migrates downward, it passes just

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anteriorly to the hyoid bone and laryngeal cartilages. The thyroid gland is initially spherical and then assumes a more bi-lobed configuration as it enlarges; a major increase regards its lateral portions (lobes) in comparison to the median connecting portion (isthmus) (Fancy et al., 2010). Whereas in mice thyroid organogenesis takes about 1 week, in humans it takes a much longer time, and thyroid hormones synthesis is not evident before the 11th week of gestation (Szinnai et al., 2007).

p0025   Whereas the epithelial cells, the most abundant cell type in thyroid, derive from endostyle, an endodermal area containing iodine-concentrating cells, C-cell precursors derive from the neural crest bilaterally to the fourth pharyngeal pouches and are located in the ultimobranchial bodies. Epithelial cells' differentiation is assumed to be the consequence of signals from the heart primordium, which is close to the ventral pharyngeal endoderm during the early embryogenesis. This hypothesis is supported by the frequent association of congenital cardiac malformations with congenital hypothyroidism. In addition, the close association of the thyroid and heart partly accounts for thyroid migration, which ends at day 45–50 (Santisteban, 2013). Differentiated follicular cells (thyrocytes) are polarized cells with a basolateral and an apical surface; the first faces the extrafollicular space, while the second faces the follicular lumen. This polarity is functionally paramount, as iodine uptake occurs at the basolateral side, whereas thyroid hormone secretion occurs at the apical side (Nilsson and Fagman, 2017).

p0030   During embryogenesis, thyroid development depends on the expression of a number of transcription factors, the most important being TTF-1 (thyroid transcription factor-1), PAX8 (paired box gene 8), FOXE-1 (forkhead box E1), and HHEX (hematopietically expressed homeobox). TTF-1 (also called NKX2–1) is a single polypeptide in humans and regulates the transcription of thyroglobulin, thyroid peroxidase (TPO), and thyrotropin (TSH) receptor genes in the follicular cells (Kratzsch and Pulzer, 2008). Moreover, TTF-1 promotes the expression of HHEX, FOXE1, and (weakly) PAX8. In turn, HHEX, PAX8, and FOXE1 regulate each other (Nilsson and Fagman, 2017). PAX8 plays a fundamental role in cell differentiation, in maintenance of the differentiated state, and in proliferation. FOXE-1 is essential in promoting migration of the follicular cells and seems to be involved in their survival and/or differentiation. HHEX is an early marker of thyroid cells with a putative effect in maintaining the expression of TTF-1 and PAX8 during thyroid organogenesis (Kratzsch and Pulzer, 2008). Hence, deletion of any one of the genes encoding HHEX, TTF-1, PAX8, or FOXE1 inevitably confers athyreosis or severe thyroid hypoplasia (Nilsson and Fagman, 2017). Currently available data indicate that gene expression undergoes significant changes during thyroid organogenesis and confirm the existence of unknown factors at least as critical as TTF-1, PAX8, FOXE-1, and HHEX (Kratzsch and Pulzer, 2008).

Anatomy

s0015

p0035 The thyroid gland is a highly vascularized organ located anteriorly in the neck between the C_5 and T_1 vertebrae, deep in the platysma, sternothyroid, and sternohyoid muscles. The thyroid weighs 15–20 g and weighs more in men than in women; the thyroid weighs approximately 1 g in a newborn and increases by about 1 g/year until age 15. It is an H-shaped, soft and reddish parenchymal organ, consisting of two lobes (left and right) and one isthmus that binds them together (Fig. 1). Each lobe is approximately 4 cm in length, 2 cm in width, and 2–3 cm in thickness. The isthmus measures about 2 cm in width, 2 cm in height, and 2–6 mm in thickness.

p0040   The superior extremity (called the superior horn) lies lateral to the inferior constrictor muscle and posterior to the sternothyroid muscle, while the inferior part (inferior horn) extends to the levels of the fifth or sixth tracheal ring. In the posterolateral section, the gland overlaps the carotid sheath and its components. About 50% of individuals present a pyramidal lobe (Morgagni's or Lalouette's pyramid), arising from either lobe or the superior portion of the isthmus and directed upward, usually to the left (Fig. 1) (Braun et al., 2007).
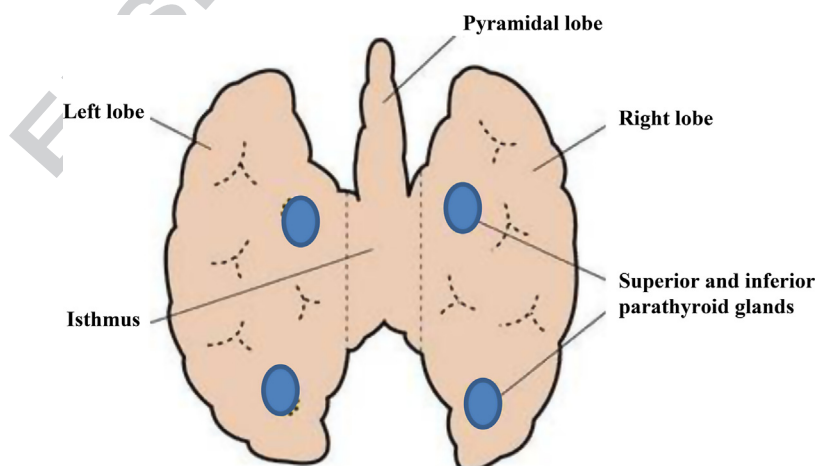
f0010   **Fig. 1**   Macroscopic posterior view of the thyroid.

p0045   The thyroid is enveloped by the layers of the deep cervical fascia and covered by the strap muscles anteriorly and the sternocleidomastoid muscle more laterally. The true thyroid capsule is firmly adherent to the gland, developing projections into the thyroid, forming septae and dividing it into lobes and lobules. The posterior layer of the thyroid capsule is thick. Posteriorly, the middle layer of the deep cervical fascia condenses to form the posterior suspensory ligament of Berry, connecting the thyroid lobes to the cricoid cartilage and the first two tracheal rings. In the posterior surface of the lateral lobes are located the parathyroid glands; normally there are four (two superior and two inferior), and these are roundish, and about the size of a grain of rice (Fig. 1).

Histology
s0020

p0050 Microscopically, thyroid is divided into lobules; each lobule consists of 20–40 round follicles that vary considerably in size, with a diameter ranging from 45 to 250 μm. In the newborn, follicles are small and grow slowly (Fig. 2).

p0055   Each follicle is lined by a single cuboidal layer of epithelium (9–13 μm) with a thin basement membrane filled with acidophilic colloid-core. Thyrocytes have a definite polarity, with their apices directed toward the lumen of the follicles and their basis toward the basement membrane. The apical surface of the epithelial cells has numerous microvilli extending to the colloid, while the spheroid nuclei are located at the same level in all cells, mainly near to their basis (Fig. 3). Thyroid is the only human gland in which the hormonal product is stored extracellularly (viz. in the colloid).

p0060   Mitoses are infrequent, being evident only in young people. Thyrocytes are characterized by a pale acidophilic or amphophilic cytoplasm in which lysosomal bodies, granules, and secretory vacuoles are evident. Immunohistochemistry shows that normal follicular epithelium contains thyroglobulin, low-molecular weight keratin, epithelial membrane antigen, and vimentin. Follicles are embedded in a small amount of a loose connective tissue that forms the gland stroma, in which blood vessels, nerves, and lymphatics are present.

p0065   C-cells are dispersed between follicles, mainly in the posterolateral portion of the lobes, or are located beyond the basement membrane within the follicles, close to thyrocytes (Nilsson and Fagman, 2017). As noted above, C-cell precursors derive from the neural crest. They constitute about 0.1% of thyroid cells, and their identification is possible only using immunohistochemical methods for calcitonin. Moreover, the numerous dense-core granules of C-cells show immunoreactivity for neuron-specific enolase (NSE), chromogranins A and B, synaptophysin, and carcinoembryonic antigen (CEA). The stromal compartment surrounding follicles consists of fibroblasts derived from the neural crest (Kameda et al., 2009), and includes also macrophages and mast cells, which recently were reported to have a role in thyroid cancer development (Visciano et al., 2015).

p0070   Vascular supply of the thyroid gland is conspicuous, bilaterally represented by the superior thyroidal artery (from the external carotid) and inferior thyroid artery (from the succlavia). Exceptionally, another artery, the thyroid IMA artery (also known as Neubauer's artery), originating from either the common carotid or the anonymous troncus, may be present (Mohebati and Shaha, 2012). The thyroid contains a rich network of capillaries surrounding follicles. Venous blood drains through two sets of vessels: superior and medial thyroidal veins realize a plexus, which drains into the external jugular vein, whereas inferior thyroidal veins realize a plexus in front of the trachea joining the brachiocephalic vein (Mohebati and Shaha, 2012).

p0075   A rich lymphatic network is present in the thyroid. Intraglandular and subcapsular lymphatics drain into the internal jugular lymph nodes. In particular, the superior lymph node group drains the upper gland and medial isthmus, while the inferior group drains the lower gland.

p0080   The thyroid nerves originate from the superior and middle cervical sympathetic ganglia. These fibers are vasomotor, indirectly influencing thyroid secretion (Mohebati and Shaha, 2012). Moreover, adrenergic fibers realize a network, which ends near the follicular basement membrane; adrenergic receptors are also present in follicular cells.
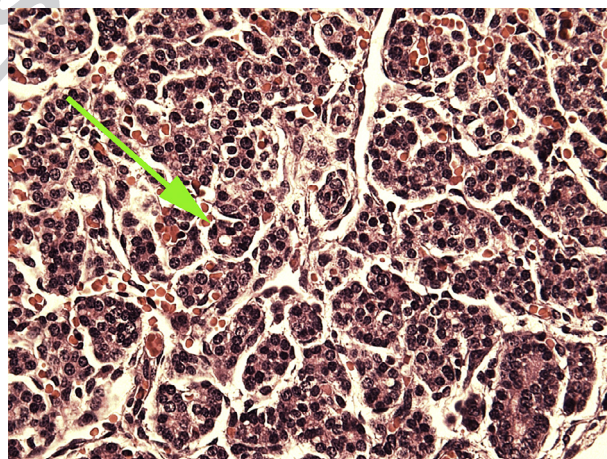
f0015   **Fig. 2**   Thyroid follicle of a newborn (*green arrow*), greatly different in size from that observed in adult ones (see Fig. 3).
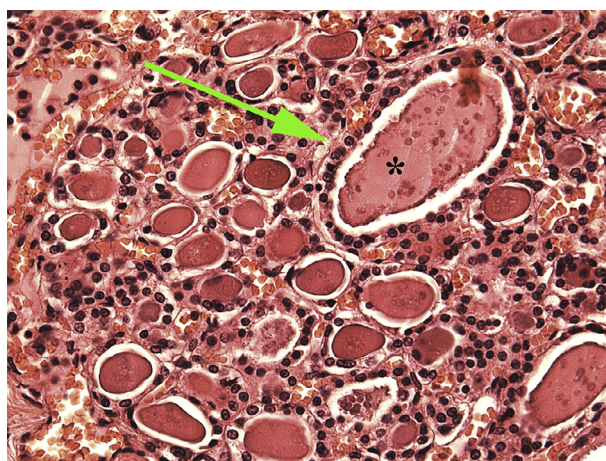
f0020 **Fig. 3** Evident thyroid follicles in the adult (*green arrow*) lined by a single epithelium filled with colloid (*).

Physiology
s0025

p0085 Hormonogenesis in the thyrocyte can be subdivided into three main steps: iodide uptake; iodide oxidation and organification; and secretion of thyroid hormones. These steps are summarized in Fig. 4.

First Step: Iodide Uptake
s0030

p0090 All living beings are capable of taking up iodine and incorporating it into proteins. Iodinated compounds are of the utmost importance in regulating diverse functions in invertebrates devoid of the thyroid gland (Nilsson and Fagman, 2017). In humans and most vertebrates, the thyroid gland has evolved to save and store iodine. The thyroid produces iodinated molecules, iodotyrosines, and iodothyronines, the latter including thyroid hormones (T4 and T3) (Nilsson and Fagman, 2017).

p0095   Iodine is ingested with a number of food including dairy products, grains, and meat. Upon ingestion, organic iodine is reduced to inorganic iodide (I^-), the chemical form needed for the biosynthesis of thyroid hormones. Approximately 150 µg iodide are required by the thyroid gland for its daily activity, but in certain conditions, such as pregnancy and breastfeeding, iodide requirements are greater (Pennington and Young, 1991).

p0100   The thyroid and kidney are the most iodine-hungry organs. Indeed, the thyroid actively takes up iodine from the bloodstream, where its concentration is approximately 30 times lower than in the thyroid (Eskandari et al., 1997). Particularly, the sodium/iodide symporter (NIS), located in the basolateral membrane of the follicular cell, entraps iodide from the circulation into cytoplasm
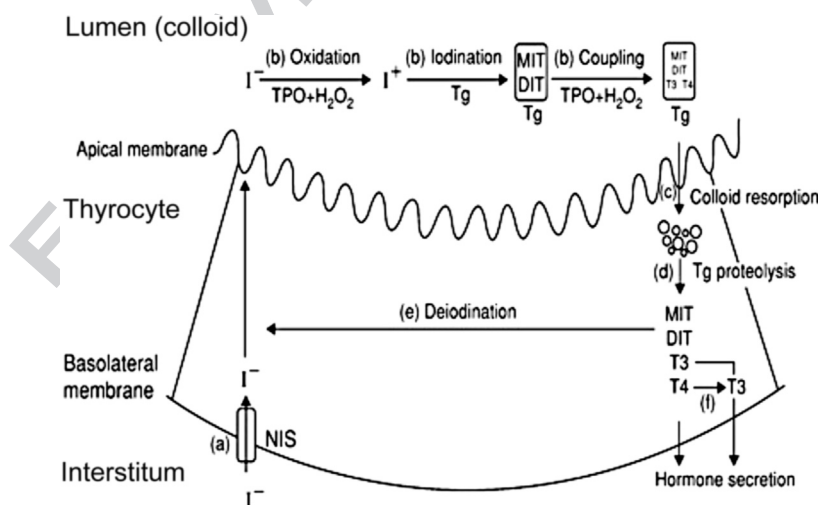
f0025 **Fig. 4** Schematic diagram of thyroid hormone biosynthesis in and release from the thyrocyte. Subsequent metabolic steps are: (a) iodide transport via the Na^+/I^- symporter (NIS) inhibited by ClO_4^- and SCN^-; (b) oxidation of I^- to I^+ and iodination of tyrosine residues in thyroglobulin (Tg), and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to thyroxine (T_4) or triiodothyronine (T_3), catalyzed by thyroid peroxidase (TPO) and inhibited by propylthiouracil and methimazole; (c) colloid resorption, inhibited by lithium and I^-; (d) proteolysis of Tg, inhibited by I^-; (e) deiodination of MIT and DIT; and (f) deiodination of T_4, inhibited by propylthiouracil.

against its electrochemical gradient, together with sodium ions. Unlike iodide, sodium entry into the cell is down its gradient, and results in energy production, which is required for the inward translocation of iodide. In turn, the sodium/potassium pump maintains the sodium gradient (Ferreira et al., 2005). The next step is iodide efflux, namely its passive (down its electrochemical gradient) translocation from the cytoplasm to the apical side of the polarized thyrocyte, and the subsequent transport through the apical membrane. Crossing of the apical membrane was previously assumed to depend on pendrin and a putative apical iodide transporter, but the latter was recently ruled out. Nevertheless, a chloride channel was shown to mediate iodide efflux together with pendrin (Twyffels et al., 2014; Rodriguez et al., 2002).

s0035 Second Step: Iodide Oxidation and Organification

p0105 Upon its entry into the cytoplasm of the polarized thyrocyte, iodide moves apically, where it is oxidized and covalently bound to thyroglobulin (Tg). This step requires TPO and H_2O_2.

p0110 TPO is a 100 kDa heme-containing protein that belongs to the same family of human peroxidase, together with lactoperoxidase, myeloperoxidase, and eosinophil peroxidase (Godlewska et al., 2017). Posttranslational modifications including glycosylation, heme fixation, proteolytic trimming, and dimerization are essential to obtain the mature protein (Godlewska et al., 2017).

p0115 TPO acts as an H_2O_2 donor and oxidizes iodide. The resulting compound may be I^+ or OI^- (hypoiodite); both are capable of interacting with Tg (Kopp, 2013). H_2O_2 is generated by a NADPH oxidase system including DuOX (or thyroid H_2O_2-generating enzyme, THOX).

p0120 Tg, the most abundant protein of the thyroid, is a large glycosylated protein with more than 2700 amino acids and molecular mass of 660 kDa, representing the largest 1% of proteins in the vertebrate proteome (Lee et al., 2008; Di Jeso and Arvan, 2016). Tg contains at least 66 tyrosyl residues, with slight differences between species. The number of tyrosines that are iodinated varies with iodine intake. Particularly, there is a hierarchy in iodination of tyrosines, so that tyrosine at position 5 is one of the most favored (see below) (Di Jeso and Arvan, 2016). There is evidence that Tg antigenicity depends on post-translational modifications, including iodination and glycosylation (Targovnik, 2013; Benvenga et al., 1997).

p0125 Glycosylation of 10% of the total Tg weight occurs in the rough endoplasmic reticulum and in the Golgi apparatus, where N-linked oligosaccharides are acquired. Glycosylation is essential for the tertiary structure and the normal folding of Tg, which occurs also by interaction of Tg with endoplasmic reticulum oxidoreductase and molecular chaperones, such as calnexin and calreticulin (Di Jeso and Arvan, 2016). Within the endoplasmic reticulum, but before intracellular transport to the Golgi complex, two 12S (330 kDa) monomers are dimerized into a stable 19S (660 kDa) molecule. Tg represents the scaffold of the colloid in the follicular lumen, and acts as a depot of thyroid hormones and iodine (Targovnik, 2013; Di Jeso and Arvan, 2016). From this point of view, thyrocytes are more similar to exocrine cells than to the other major endocrine glands (Nilsson and Fagman, 2017).

p0130 Iodination of Tg results in monoiodotyrosine (MIT) and diiodotyrosine (DIT), depending on the number of iodine ions incorporated in Tg. Subsequently, when a MIT (donor) is coupled to a neighboring DIT (acceptor), 3,5,3′-triiodothyronine (T3) is generated, whereas when a DIT (donor) is coupled to another neighboring DIT (acceptor), 3,5,3′,5′-tetraiodothyronine or thyroxine (T4) is generated. Coupling of noniodinated tyrosine donor to a DIT acceptor forms 3,5-diiodothyronine (T2), whose effects on adiposity and body weight are still a matter of debate (Lanni et al., 2005; Vatner et al., 2015). Finally, 3,3′,5′-triiodothyronine (reverse T3 or rT3) accounts for only 0.9% of thyroid hormones released in the circulation. This results from either unfavorable coupling of a donor DIT to an acceptor MIT, or deiodination of T4 by type 1 or type 3 deiodinases (Bianco et al., 2002). Structures of iodotyrosines and iodothyronines are shown in Fig. 5.

p0135 The major thyroid hormones forming sites are at the extreme N-terminus (T4) and C– terminus (T3 and T4) (Di Jeso and Arvan, 2016). Indeed, four main hormonogenic DIT-acceptor tyrosines were identified at position 5, 2554, 2747, and 1291, the first being the most efficient in T4 formation, while the third was the most efficient in T3 formation (Di Jeso and Arvan, 2016; Lamas et al., 1989). Furthermore, formation of DIT and T4 are favored over MIT and T3, respectively. In iodine-sufficient areas the ratio of DIT:MIT:T4:T3 per molecule of Tg is 5:5:2.5:0.7, whereas in iodine-deficient areas, DIT:MIT and T4:T3 ratios are increased. Even if three or four thyroid hormones are synthetized per molecule of Tg, this process is warranted at extremely low levels of iodination (even 4 mol I^-/mol Tg) (Di Jeso and Arvan, 2016). The thyroid produced T3 accounts for only 20% of total T3; the remainder was obtained peripherally by T4 deiodination.

p0140 The iodide pool of the follicular unit includes also that resulting from deiodination of MIT and DIT. This part of the pool is recycled or further organified, or alternatively moved to the bloodstream (Rosenberg et al., 1961). The daily turnover rate of the iodide pool is about 1% (Delange, 1998).

p0145 Although thyronamines were discovered in the 1950s, only in 2004 were they identified as ligands of a class of G protein-coupled receptors called trace-amine associated receptors. Thyronamines are structurally related to thyroid hormones as they have an identical carbon skeleton, but differ from the thyroid hormones in terms of the absence of the carboxylate group of the alanine side chain, which is replaced by an ethylamine chain (Fig. 5) (Chiellini et al., 2017). Thyronamines include nine compounds differing for either the number or the position of the iodine atoms, the most abundant being 3-T_1AM (Fig. 5) (Chiellini et al., 2017). These compounds were initially considered catabolites of thyroid hormones. However, recent observations suggest that thyronamines result from decarboxylation of thyroid hormones by ornithine decarboxylase, not by the aromatic amino acid decarboxylase as first reported (Hoefig et al., 2015). Biosynthesis of 3-T_1AM occurs also in the intestine via the intermediate metabolite 3,5-T2, as demonstrated in thyroid cancer patients after thyroidectomy or radioiodide treatment (Hoefig et al., 2011). So far, only two

Thyronamine	R1	R2	R3	R4
T_0AM	H	H	H	H
$3-T_1AM$	H	H	H	I
$3'-T_1AM$	I	H	H	H
$3,5-T_2AM$	H	H	I	I
$3,3'-T_2AM$	I	H	H	I
$3',5'-T_2AM$	I	I	H	H
T_3AM	I	H	I	I
rT_3AM	I	I	H	I
T_4AM	I	I	I	I

f0030 **Fig. 5**   Structures of the main iodotyrosines, iodothyronines, and thyronamines. Concerning thyronamines, only two ($3-T_1AM$ and T_0AM) have been detected in vivo so far.

thyronamines ($3-T_1AM$ and T_0AM) have been detected in vivo, particularly in the blood, heart, liver, adipose tissue, thyroid, and brain of rats and other animals. The other thyronamines are synthetically derived (Piehl et al., 2011).

s0040 **Third Step: Secretion of Iodothyronines**

p0150 Tg is internalized in the thyrocytes through the apical membrane via micropinocytosis, namely vesicle-mediated endocytosis. Thus, invaginations of the apical membrane by pseudopods formation form colloid droplets (Bernier-Valentin et al., 1991). These droplets release their content into endosomes, where Tg is sorted based on iodine content: whereas the highly iodinated molecules are fused with prelysosomes and then to lysosomes, those that are poorly iodinated are recycled and return back to the apical membrane, where they are secreted into the follicle lumen (Kostrouch et al., 1993). Lysosomal endopeptidases, such as cathepsins B, D, and L, cleave Tg, thus releasing T3 and T4 (Dunn et al., 1991). Direct cleavage within the follicle lumen has been also proposed (Tepel et al., 2000). Proteolytic cleavage of Tg occurs at four major cluster sites, called A, B, C, and D, which fall at around residue 500, 990, 1800, and 2515, respectively (Dunn et al., 1991). Three additional cleavage sites have been also found at residue 240, between residues 1142 and 1184, and at residue 597 (Gentile and Salvatore, 1993).

p0155 Upon their release into the cytoplasm, thyroid hormones reach the basolateral membrane with unknown mechanisms, and finally enter the circulation (Vickers et al., 2012).

s0045 **Regulation of Thyroid Hormones Biosynthesis**

p0160 Thyroid hormones biosynthesis and metabolism is regulated by at least three factors: TSH-induced stimulation, iodine availability, and deiodinases activity.

p0165 TSH stimulates most if not all steps of thyroid hormones biosynthesis, from the uptake of iodine (by enhancing NIS expression) to internalization of Tg from the follicular lumen and consequent secretion of thyroid hormones into the bloodstream. TSH secretion is stimulated by TRH, which is in turn produced by neurons of the paraventricular nucleus of the hypothalamus, and prevents thyroid undersupply (Hoermann et al., 2015). In order to prevent hyperstimulation by TSH, and to restore the individual set point of the hypothalamus–pituitary–thyroid axis, there are multiple negative feedback loops. Indeed, the thyroid hormone inhibits both TRH and TSH secretion (Hoermann et al., 2015). Concerning the inhibition of TRH release, it involves TRH-secreting neurons and tanycytes (Hoermann et al., 2015). Also, the homeostatic relationship between TSH and FT4 is defined by a kite-shaped curve (Dietrich et al., 2012). In addition, there is an ultrashort feedback loop by TSH on its own secretion by the thyreotrophs (Prummel et al., 2004).

p0170 Iodine availability regulates thyroid hormones biosynthesis and secretion (Song et al., 2010). When iodine availability is insufficient, T3 and T4 are inadequately synthetized, TSH increases, and goitrogenesis occurs. In addition, conversion of T4 to T3 is enhanced. In contrast, excessive iodine exposure leads to inhibition of thyroid hormones' biosynthesis by blocking H_2O_2 production and Tg iodination (the Wolff-Chaikoff effect) (Wolff and Chaikoff, 1948).

p0175 Thyroid hormone activation and inactivation are regulated by the deiodinases. Type 2 deiodinase (D2) acts on the outer ring of T4, converting it into T3; by contrast, type 3 deiodinase (D3) inactivates T4 and T3, deiodinating their inner ring and converting them into rT3 and T2, respectively. In addition, type 1 deiodinase (D1) acts both on the outer and inner ring. Thyroid contains especially D1 and D2 (Bianco, 2013).

s0050 **Thyroid Hormones Circulation in the Bloodstream and Biological Actions**

p0180 Similarly to steroid hormones, thyroid hormones are hydrophobic molecules, and therefore have to be carried in plasma by transporter proteins. Indeed, the free fraction of thyroid hormones is very low (0.03% of T4 and 0.3% of T3). The three major carriers are thyroxine binding globulin (TBG), transthyretin, and albumin. In addition, there are a number of minor carriers, such as lipoproteins, immunoglobulins, and serine protease inhibitors (serpins) (Benvenga, 2013).

p0185 TBG is the most important carrier of the thyroid hormone in blood in most mammals. It is a four-carbohydrate-chain glycoprotein that belongs to the serpin family, and peaks between α_1 and α_2 at zone electrophoresis (Benvenga, 2013). Other minor serpins that bind to thyroid hormones are α_1-antitripsin, α_1-chymotripsin, antithrombin III, and cortisol binding globulin. All the serpins have one thyroid hormone binding site with a relative higher affinity for T4 compared with T3 (Benvenga et al., 2002). α_1-acid glycoprotein and sex hormone binding globulin are nonserpin proteins demonstrated to be minor T4 carriers (Benvenga, 2013).

p0190 Transthyretin is a homotetramer forming a cylindrical channel, which carries thyroid hormones and vitamin A in distinct sites. There are two sites for thyroid hormones, but only one is available, due to the much lower K_a of the second site (Neumann et al., 2001).

p0195 From a phylogenetical point of view, serum albumin is the most ancient carrier. It has five binding sites for the thyroid hormones in its two subdomains (A and B). Albumin also binds sterol-derived hormones. Interestingly, other two homologues of albumin, vitamin D binding protein and α-fetoprotein, are capable of binding thyroid hormones (Benvenga, 2013).

p0200 All classes of lipoproteins can bind T4, T3, and rT. Particularly, thyroid hormones interact with apoA, apoB100, apoC, and apoE, and this interaction is inhibited by lipids (Benvenga and Robbins, 1996).

p0205 Transport of thyroid hormones into cells relies on monocarboxylate transporters (MCT) 8 and 10, which are responsible for both the influx and the efflux of the thyroid hormones, and are ubiquitous. Another transporter of the thyroid hormones is the organic anion transporting polypeptide 1C1 (OATP1C1), which is particularly expressed in the astrocytes, where it is involved in T4 uptake (Mayerl et al., 2014).

p0210 Upon its entry into the cell, T3, not T4, binds the thyroid hormone receptor (TR), which is a member of the nuclear receptor superfamily. There are two isoforms of TR (α and β), encoded by different genes located in different chromosomes (chromosomes 17 and 3, respectively) (Cheng et al., 2010). Each isoform has three variants (α1, α2, α3 and β1, β2, β3). Of note, TRα2 and TRα3 are splicing variants of TRα1 that do not retain T3-binding activity. TR expression is spatially and temporally specific, as TRα is expressed mainly in the brain from the early stages of embryonic development, while TRβ is expressed mainly in the brain, liver, kidney, thyroid, heart, and retina (TRβ2) at a later stage of development (Cheng, 2000).

p0215 TR is a single polypeptide with a carboxyl-terminal ligand-binding domain (LBD), which interacts with coregulators (either activators or repressors) and participates in homodimerization (dimerization between two TR) and heterodimerization (dimerization between TR and retinoid X receptor). The binding of T3 to TR induces structural changes that lead to displacement of corepressors, recruitment of coactivators, and transcription activation, which is also regulated by other molecules, such as p53 and β-catenin (Cheng et al., 2010). TR contains also a central, highly conserved domain, which interacts with the thyroid hormone response elements (TRE) (Wagner et al., 1995).

p0220 For the purpose of this article, suffice it to say that mutations may occur in genes encoding either TRα or TRβ. Mutations of the TRβ gene lead to resistance to the thyroid hormone, which is a syndrome characterized by signs of various degree, including goiter,

tachycardia, short stature, decreased IQ, and elevated thyroid hormone concentrations in serum together with nonsuppressible TSH (Weiss and Refetoff, 2000). Only a few cases of homozygosity for TRβ mutations have been reported so far (Ferrara et al., 2012). Mutations of the TRβ gene have been also found in thyroid cancer and TSH-secreting pituitary adenoma (Cheng et al., 2010). Concerning TRα, in mice, mutations in both alleles lead to death shortly after birth, while mutation of one allele results in dwarfism and abnormal lipid metabolism, and a phenotype different from that found in mutations of TRβ (Kaneshige et al., 2001). Indeed, no mutation of TRα1 has been found in patients with resistance to thyroid hormones, indicating that TRα1 and TRβ have distinct functions. The phenotype resulting from TRα1 mutations is variable according to the location and type of mutation. These differences in the resulting phenotype might stem from the different interaction of TRα1 with various corepressors, with variable repression of different target genes (Cheng et al., 2010).

p0225   In addition, thyroid hormones act directly in mitochondria stimulating cellular respiration. T3 or T2 binds a specific site in the mitochondrial inner membrane. Even if T2 is as potent as T3, it has a more rapid action (Horst et al., 1989), and therefore its therapeutic use has been recently proposed (Lanni et al., 2005). Thyroid hormones also induce mitochondrial heat generation, which depends on both basal proton leak and inducible proton leak; the latter is regulated by the uncoupling proteins, whose synthesis is stimulated by the thyroid hormone (Brand and Curtis, 2002).

p0230   The effect of the thyroid hormone in inducing thermogenesis had been used to treat obesity until 1978, when the US Food and Drug Administration issued a warning against it, due to severe heart and bone side effects. Subsequently, analogs of the thyroid hormone maintaining its thermogenic action, called thyromimetics, were synthetized (Yehuda-Shnaidman et al., 2014). The main strategies to obtain stable thyromimetic molecules are the introduction of a bulky group at 5′ position for antagonism for TR, the replacement of iodine atoms to achieve resistance to metabolic deactivation, the change of bridging oxygen, and the replacement of the polar amino acid group at position 1 to change binding to TR (Hirano and Kagechika, 2010). Thyromimetics are TRβ-selective compounds that do not bind to TRα, which mediates the cardiac activity of the thyroid hormones. Some of these thyromimetics were proven efficient in treating obesity and dyslipidemia (Yehuda-Shnaidman et al., 2014). However, despite TRβ selectivity, they can still interact with TRα, giving rise to heart and bone side effects (Unnikrishnan et al., 2012). Also, because TRβ mediates the hepatic effects of the thyroid hormone as well as the negative feedback of the thyroid hormone in the hypothalamus, thyromimetics may induce both hepatic hyperthyroidism and systemic hypothyroidism due to hypothalamus–pituitary–thyroid axis suppression (Yehuda-Shnaidman et al., 2014).

p0235   Except for direct action of the thyroid hormone in the mitochondrion, its effects have been long ascribed to genomic mechanisms. Only in the past decade the existence of a number of nongenomic effects of thyroid hormone has been demonstrated. These effects are, by definition, not mediated by the interaction of T3 with its nuclear receptor and protein synthesis, and therefore they have a much more rapid onset (minutes or hours) (Hammes and Davis, 2015). Furthermore, nongenomic actions are initiated by T3, T4, or rT3 binding to nontruncated TR, or truncated TR, or integrin αvβ at the level of cell membrane, cytoplasm, and cytoskeleton. Activation of certain kinases (protein kinase C, mitogen activated protein kinases) ensues, with gene transcription or activation of the Ca-ATPase (Davis et al., 2016). Nongenomic actions of the thyroid hormone might mimic the effects of estrogens in certain tumors by supporting cell proliferation and angiogenesis (Hammes and Davis, 2015).

p0240   Finally, recent investigations have highlighted a neural route of action of the thyroid hormone, originating in the hypothalamus at the level of T3-responsive nuclei, such as the paraventricular, ventromedial, and arcuate nucleus, and the preoptic and anterior areas. The activation of these areas, via the sympathetic and parasympathetic branch of the autonomic nervous system, regulates metabolism in liver and brown adipose tissue (Zhang et al., 2017).

p0245   Thyronamines in the blood bind with high affinity to apoB100, with consequent very low free concentrations in serum, and interact with a class of G protein-coupled receptors called trace-amine associated receptors, but also with adrenergic receptors (Chiellini et al., 2017). Biological effects of thyronamines are partly in the opposite direction of T3, since they reduce heart rate, cardiac output, metabolic rate, and body temperature. However, thyronamines also have actions that are synergic to T3, as they stimulate lipid metabolism over the carbohydrates one and neurological responses (Chiellini et al., 2017). Like monoamine neurotransmitters, thyronamines have an ethylamine chain, and may also act as neuromodulators (Ianculescu and Scanlan, 2010).

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Non-Print Items

Abstract:

This article starts with the description of gross and microscopic thyroid anatomy, and thyroid ontogenesis through gestation. We further analyze thyroid hormones biosynthesis through its steps, from iodide uptake by thyrocytes to secretion of T4 and T3 in circulation. We focus also on other iodinated and biologically active compounds, the thyronamines, which result from thyroidal or nonthyroidal decarboxylation of thyroid hormones. Finally, we outline thyroid hormone transport in blood and thyroid hormone actions, for which we refer to specific articles.

Keywords: Follicle; T3; T4; Thyrocyte; Thyroglobulin; Thyroglossal duct; Thyroid; Thyronamines; Thyronines; Thyroperoxidase; Tyrosines