Thyroid Gland: Anatomy and Physiology

Chapter · January 2018
DOI: 10.1016/B978-0-12-801238-3.96022-7

CITATIONS
0
READS
1,811

4 authors, including:

Prof. Dr. Giovanni Tuccari
Azienda Ospedaliera Universitaria “G. Martino”
219 PUBLICATIONS 2,228 CITATIONS

Antonio Ieni
Università degli Studi di Messina
116 PUBLICATIONS 689 CITATIONS

Roberto Vita
Università degli Studi di Messina
54 PUBLICATIONS 498 CITATIONS

Some of the authors of this publication are also working on these related projects:

Prognostic markers in triple negative breast carcinomas

All content following this page was uploaded by Antonio Ieni on 09 April 2018.

The user has requested enhancement of the downloaded file.
The thyroid gland is the first endocrine gland to develop in humans. The thyroid gland originates from a diverticulum located in the floor of the primitive pharynx between the first and second branchial pouches, dorsal to the aortic sac. 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 floor of the mouth. The thyroid tissue migrates downward, it passes just in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck. As the thyroid tissue migrates downward, it passes just in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck. As the thyroid tissue migrates downward, it passes just in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck. As the thyroid tissue migrates downward, it passes just in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck. As the thyroid tissue migrates downward, it passes just in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck.

Concerning pituitary organogenesis, 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.

Concerning pituitary organogenesis, suffice it to say that it is dictated by the orderly expression of cell-specific transcription factors, including Tif1/Nkx2.1, Bmp/Hex, Pax-6, Sox-3, Hox-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).

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 in front of the hyoid bone and laryngeal cartilages in order to reach the lower neck.
anteriory 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).

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).

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**

The thyroid gland is a highly vascularized organ located anteriorly in the neck between the C5 and T1 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.

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 (Braun et al., 2007).
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**

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).

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).

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.

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).

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).

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.

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.
Hormogenesis 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**

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, iodothyronines, and iodothyronines, the latter including thyroid hormones (T4 and T3) (Nilsson and Fagman, 2017).

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 mg 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).

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.

**Fig. 3** Evident thyroid follicles in the adult (green arrow) lined by a single epithelium filled with colloid (‘

**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\(^{\bullet}\) and iodination of tyrosine residues in thyroglobulin (T\(_g\)), and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to thyroid (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 T\(_g\), inhibited by I\(^{-}\); (e) deiodination of MIT and DIT; and (f) deiodination of T\(_4\), inhibited by propylthiouracil.
Second Step: Iodide Oxidation and Organification

Upon its entry into the cytoplasm of the polarized thyrocyte, iodide moves apically, where it is oxidized and covalently bound to TPO. TPO is a 100 kDa heme-containing protein that belongs to the same family of human peroxidase, together with lactoperoxidase, myeloperoxidase, and eosinophil peroxidase (Godlewski et al., 2017). Posttranslational modifications, including glycosylation, heme fixation, proteolytic trimming, and dimerization are essential to obtain the mature protein (Godlewski et al., 2017).

TPO acts as an H_{2}O_{2} donor and oxidizes iodide. The resulting compound may be I_{2} or OI^{-} (hypiodotyrosine); both are capable of interacting with Tg (Kopp, 2013). H_{2}O_{2} is generated by a NADPH oxidase system including DuOX (for thyroid H_{2}O_{2}-generating enzyme, THOX).

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; Benvena et al., 1997).

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 also occurs 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 125 (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).

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'-triiodothyronine 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.

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 MIT 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 synthesized 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.

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).
thyronamines (3-T₄AM and T₀AM) 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).

Third Step: Secretion of Iodothyronines

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).

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

Fig. 5 Structures of the main iodothyrosines, iodothyronines, and thyronamines. Concerning thyronamines, only two (3-T₄AM and T₀AM) have been detected in vivo so far.
Regulation of Thyroid Hormones Biosynthesis

- Thyroid hormones biosynthesis and metabolism is regulated by at least three factors: TSH-induced stimulation, iodine availability, and deiodinases activity.
- 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 under-supply (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 kiteshaped 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).
- 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 H2O2 production and Tg iodination (the Wolff-Chaikoff effect) (Wolff and Chaikoff, 1948).
- 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).

Thyroid Hormones Circulation in the Bloodstream and Biological Actions

- 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).
- 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 x1 and x2 at zone electrophoresis (Benvenga, 2013). Other minor serpins that bind to thyroid hormones are x1-antitripsin, x2-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). x2-acid glycoprotein and sex hormone binding globulin are nonserpin proteins demonstrated to be minor T4 carriers (Benvenga, 2013).
- 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 Ks of the second site (Neumann et al., 2001).
- 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 x2-fetoprotein, are capable of binding thyroid hormones (Benvenga, 2013).
- All classes of lipoproteins can bind T4, T3, and rT3. Particularly, thyroid hormones interact with apoA, apoB100, apoC, and apoE, and this interaction is inhibited by lipids (Benvenga and Robbins, 1996).
- 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 (Mayeul et al., 2014).
- 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 (x and b), encoded by different genes located in different chromosomes (chromosomes 17 and 3, respectively) (Cheng et al., 2010). Each isoform has three variants (x1, x2, x3 and b1, b2, b3). Of note, TRx2 and TRx3 are splicing variants of TRx1 that do not retain T3-binding activity. TR expression is spatially and temporally specific, as TRx is expressed mainly in the brain from the early stages of embryonic development, while TRb is expressed mainly in the brain, liver, kidney, thyroid, heart, and retina (TRb2) at a later stage of development (Cheng, 2000).
- 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 b-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).
- For the purpose of this article, suffice it to say that mutations may occur in genes encoding either TRx or TRb. Mutations of the TRb gene lead to resistance to the thyroid hormone, which is a syndrome characterized by signs of various degree, including goiter,
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 inductible proton leak; the latter is regulated by the uncoupling proteins, whose synthesis is stimulated by the thyroid hormone (Brand and Curtis, 2002).

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 synthesized (Yehuda-Shnaidman et al., 2014). The main strategies to obtain stable thymorimimetic 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).

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 αvβ3 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).

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).

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).

References


These proofs may contain colour figures. Those figures may print black and white in the final printed book if a colour print product has not been planned. The colour figures will appear in colour in all electronic versions of this book.

NDO2: 96022

Thyroid Gland: Anatomy and Physiology

9


Delage F (1996) Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and of its control. Thyroid 8: 1185–1192.


To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter SPI. It is not allowed to publish this proof in any form or by any means without the permission of the publisher. If you have received this proof in error, please return it to the publisher immediately. Any unauthorized reproduction or distribution of this Proof Copy constitutes a violation of the indemnification agreement and is subject to legal action.


Yehuda-Shnaidman E, Kaidar-B, and Bar-Tana J (2014) Thyroid hormone, thyromimetics, and metabolic efficiency. Endocrine Reviews 35: 35–58.

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