
Molecular Mechanisms of Thyroid Hormone Synthesis and Secretion

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Abstract

Thyroxine (T_4) and triiodothyronine (T_3), collectively called as thyroid hormones, are synthesized in the thyroid gland. Another molecule called reverse T_3 (rT_3), whose function is unknown, is also secreted from the thyroid gland. T_4 is the major molecule synthesized and secreted from the thyroid gland, whereas other molecules are mainly generated in extrathyroidal tissues by deiodination of T_4 . The thyroid hormone synthetic pathway comprises the following steps: (1) thyroglobulin synthesis and secretion into the follicular lumen; (2) iodine uptake into the follicular epithelial cells; (3) iodine transport and efflux into the follicular lumen; (4) oxidation of iodine, iodination of thyroglobulin tyrosine residues, and coupling of iodotyrosines; (5) endocytosis of the thyroglobulin-thyroid hormone complex into follicular epithelial cells; (6) hydrolysis of the complex; and (7) secretion of thyroid hormone. Thyroid-stimulating hormone (thyrotropin) stimulates thyroid hormone synthesis. In this chapter, the outline of the thyroid hormone synthetic pathway is discussed. The mechanisms regulating thyroid hormone synthesis is briefly described. Furthermore, the clinical aspects of altered thyroid hormone synthesis and secretion induced by immunological or genetic abnormalities are also discussed.

Keywords

Thyroxine • Triiodothyronine • Thyroid gland • Follicle • Iodine • Na^+/I^- symporter • Thyroglobulin • Thyroid peroxidase • Dual oxidase

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Chemical Structure of Thyroid Hormones

Thyroid hormones play a major role in development and functional maintenance of many organs (Koibuchi and Chin 2000). They are a group of hormones synthesized and secreted from the thyroid gland, which is located in front of the trachea, below the thyroid cartilage. In general, two compounds, thyroxine (3,5,3',5'-tetra-iodo-L-thyronine, T₄) and triiodothyronine (3,5,3'-tri-iodo-L-thyronine, T₃), are considered thyroid hormones. In addition, another compound called reverse T₃ (3,3',5'-tri-iodo-L-thyronine, rT₃) is secreted from the thyroid gland. Their chemical structures are shown in Fig. 1. The essential molecular structure comprises two iodinated benzene rings connected by ether linkage. T₄ is the major hormone secreted from the thyroid gland, whereas the other hormones are mainly generated by the deiodination of T₄ in extrathyroidal tissues. The ratio of the secretion of T₄:T₃:rT₃ from the thyroid gland is approximately 100:5:2.5. T₃, a bioactive thyroid hormone, is mainly produced by the deiodination of T₄ in thyroid hormone target tissues.

Synthesis and Secretion of Thyroglobulin into the Follicular Lumen

In the thyroid gland, thyroid hormone is synthesized within the unique structure called the thyroid follicle, which comprises a layer of follicular epithelial cells (also known as thyroid follicular cells or thyrocytes) surrounding a follicular lumen. Notably, the unique feature of the thyroid hormone synthetic pathway is that thyroid hormone is produced in the follicular lumen and not inside the follicular epithelial cells. No other hormone is produced outside the cell. The outline of the thyroid hormone synthetic pathway is shown in Fig. 2.

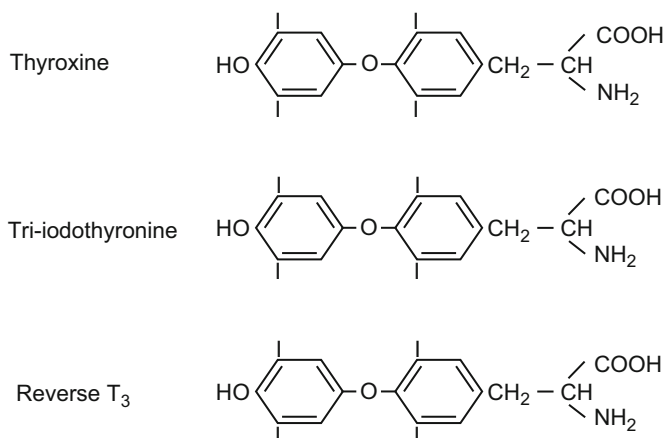


Fig. 1 Chemical structure of thyroid hormones

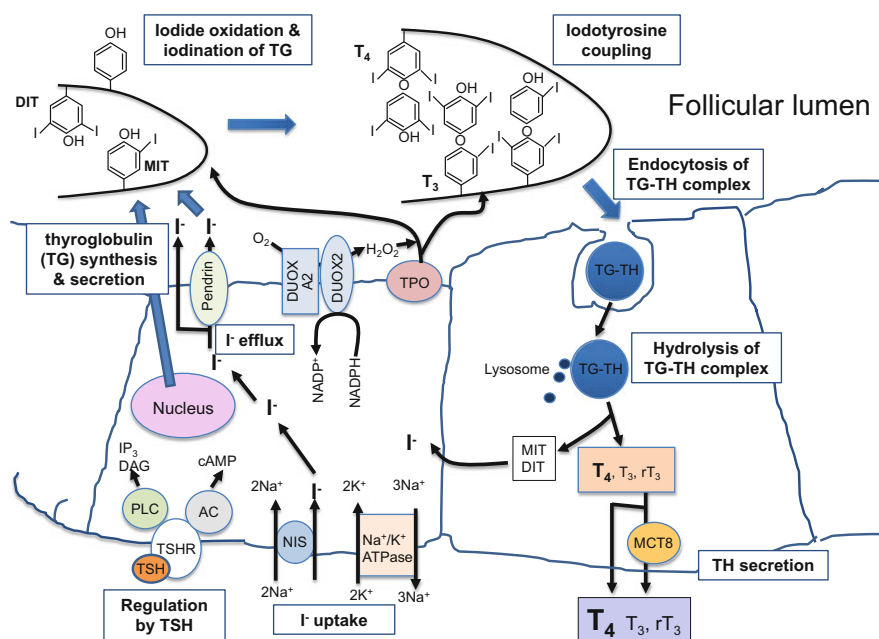


Fig. 2 Thyroid hormone (TH) synthetic pathway. AC, adeny cyclase; DIT, diiodotyrosine; DUOX, dual oxidase; MCT8, monocarboxylate transporter; MIT, monoiodotyrosine; NIS, Na⁺/I⁻ symporter; PLC, phospholipase C; TPO, thyroid peroxidase; TSH, thyrotropin; TSHR, thyrotropin receptor

The follicular lumen is filled with a glycoprotein called thyroglobulin (TG) that is specific to the thyroid gland. Human TG is a large glycoprotein containing 2,748 amino acids. It is synthesized within follicular epithelial cells and secreted by exocytosis into the lumen, where it forms a homodimer. TG contains 123 tyrosine residues. Among these residues, those located close to the N- and C-termini are utilized to synthesize thyroid hormones. Although these residues play a major role in thyroid hormone synthesis, other residues may also be important to form an appropriate secondary structure for effective hormone synthesis. Only a missense mutation (G2320R) in the TG gene induces severe hypothyroidism (Shimokawa et al. 2014).

Iodine Uptake into Follicular Epithelial Cells

The iodine concentration in follicular epithelial cells is 40-fold higher than that in plasma. Thus, iodine in plasma must be transported against a high concentration gradient. Iodine is transported as iodide (I^-) by secondary active transport. The transporter called Na^+/I^- symporter (NIS) is located on the basal membrane of thyroid epithelial cells (Portulano et al. 2014). Human NIS comprises 643 amino acids and has 13 transmembrane domains. NIS cotransports a single I^- molecule with two Na^+ molecules using a Na^+ electrochemical gradient generated by Na^+/K^+ ATPase. Thyroid-stimulating hormone (TSH, thyrotropin) stimulates iodine uptake mainly by stimulating NIS transcription. In contrast, high dose of intracellular I^- transiently inhibits thyroid hormone synthesis through the inhibition of iodine organification (Wolff-Chaikoff effect).

Iodine Transport and Efflux into the Follicular Lumen

After uptake by NIS, I^- is transported toward the apical membrane. I^- secretion into the follicular lumen is not mediated by NIS but by other transporters. Previous studies have shown that a transporter called pendrin, an anion exchange protein, plays a major role in transporting I^- into the lumen (Kopp et al. 2008). Pendrin is a highly hydrophobic membrane protein comprising 780 amino acids and contains 12 transmembrane domains. In addition to I^- , it transports other anions, such as Cl^- and HCO_3^- . However, although pendrin plays a major role in I^- efflux into the lumen, several other proteins may also be involved in I^- transport (Bizhanova and Kopp 2011).

Iodine Oxidization and Organification and Coupling of TG Iodotyrosine Residues

After efflux into the follicular lumen, I^- is oxidized to I, which is then linked to TG tyrosine residues by covalent bonds. Next, two mono- or di-iodinated tyrosine (iodotyrosine) residues are coupled to form ether bonds to generate iodothyronines.

The coupling of two diiodotyrosines forms T_4 , whereas, with lesser degree, that of monoiodotyrosine and diiodotyrosine forms either T_3 or rT_3 . Both synthesis steps are catalyzed by thyroid peroxidase (TPO) (Ruf and Carayon 2006), which belongs to the heme peroxidase family. Human TPO comprises 933 amino acids and is anchored at the apical membrane of follicular epithelial cells via a C-terminal transmembrane domain. Being a heme peroxidase, TPO requires hydrogen peroxide (H_2O_2) as the final electron acceptor. H_2O_2 is produced at the apical membrane by a membrane-bound NADPH-dependent flavoprotein called dual oxidase (DUOX) (Grasberger 2010). Two paralogs, DUOX1 and 2 (1,551 and 1,548 amino acids in humans, respectively), are located in the apical membrane. To localize in the apical membrane, they form heterodimers with another group of transmembrane proteins called DUOX maturation factors (DUOXA). Two human thyroid-specific DUOXA paralogs, DUOXA1 and 2 (483 and 320 amino acids, respectively), have been identified. Because TPO is not activated by phosphorylation, H_2O_2 production by DUOX is critical for both tyrosine residue iodination and coupling. Thus, failure to produce H_2O_2 causes severe hypothyroidism (Amano et al. 2016). DUOX is activated by increased intracellular calcium. TSH, upon binding to the TSH receptor, activates DUOX by intracellular calcium mobilization through the $G_{q/11}$ -phospholipase C pathway.

Uptake of TG-Thyroid Hormone Complex by Endocytosis

After iodotyrosine coupling, thyroid hormone does not dissociate from the TG molecule in the follicular lumen. TG-thyroid hormone complexes are endocytosed by follicular epithelial cells by endocytosis. This process is also activated by TSH.

Thyroid Hormone Production by TG Molecule Hydrolysis

Internalized vesicles containing TG-thyroid hormone complex fuse with lysosomes, resulting in complex breakdown and thyroid hormone release. This also produces iodotyrosines (monoiodotyrosine and diiodotyrosine). TG is further degraded to produce amino acids. Iodotyrosines are deiodinated by iodotyrosine dehalogenase to produce free iodine and are recycled in the follicular epithelial cells.

Secretion of Thyroid Hormone

After TG degradation, thyroid hormone (mainly T_4) is secreted into the bloodstream at the basal membrane. Although the precise mechanisms of thyroid hormone secretion have not yet been completely clarified, thyroid hormone transporters, particularly monocarboxylate transporter (MCT) 8, may play a major role in secretion (Di Cosmo et al. 2010). MCT8 comprises 539 amino acids in humans and

contains 12 transmembrane domains. It promotes the uptake and secretion of thyroid hormone. However, MCT8 disruption cannot completely inhibit thyroid hormone secretion, indicating that additional mechanisms may be involved.

Effect of TSH on Thyroid Hormone Synthesis

TSH, a glycoprotein hormone, is secreted from the anterior pituitary. It comprises an α -subunit, which is common to other glycoprotein hormones such as luteinizing hormone and follicle-stimulating hormone, and a β -subunit, which is unique to TSH. It binds to the TSH receptor (TSHR), a G-protein-coupled receptor. It is translated into a protein comprising 764 amino acids, followed by cleavage of a 352–366-amino acid peptide, resulting in the formation of extracellular A and B subunits containing seven transmembrane domains (Rapoport and McLachlan 2016).

The effects of TSH on the thyroid hormone synthetic pathway are shown in Table 1. TSHR activates both the G_s -adenyl cyclase-cAMP and $G_{q/11}$ -phospholipase C- β signaling pathways (Kleinau et al. 2013). The cAMP pathway regulates many steps in the synthesis and secretion of thyroid hormone, such as the expression of NIS, TG, and TPO, iodide uptake, and hormone secretion, whereas $G_{q/11}$ -phospholipase C- β pathway activates iodine organification (activation of H_2O_2 production, see above) by stimulating intracellular calcium mobilization and iodide efflux from the apical membrane. TSH also stimulates follicular epithelial cell proliferation.

Defects of Thyroid Hormone Synthesis and Secretion in Adults (Clinical Aspects)

Clinical disorders of thyroid hormone synthesis and secretion are commonly observed in adults. In the United States, hyperthyroidism has a prevalence of 1.3% of the population, whereas hypothyroidism has a prevalence of 4.6% (Hollowell et al. 2002). The prevalence is higher in East Asia such as Japan (hyperthyroidism, 2.9%; hypothyroidism, 6.5%) (Kasagi et al. 2009). In both hyper- and hypothyroid cases, the prevalence is higher in females. The most common cause of these disorders is an autoimmune thyroid disease. Autoimmune disease affects the thyroid gland more than any other organ (McLeod and Cooper 2012). Hyperthyroidism is mainly caused by Graves' disease, which is caused by a unique autoantibody to TSHR acting as a TSHR agonist. On the other hand, more than 90% of adult-onset hypothyroidism in countries with iodine sufficiency is caused by Hashimoto disease, which is caused by T-cell-mediated follicular epithelial cell injury, causing decreased secretion of the thyroid hormone. Autoantibodies against TG, TPO, and TSHR (blocking antibody) are found in patients. The mechanism causing autoimmune thyroid disease has not yet been fully clarified. In particular, the mechanism generating TSH receptor stimulating autoantibody needs to be clarified. Trials to clarify such mechanisms are currently underway by many researchers.

Table 1 Effects of TSH on the thyroid hormone synthetic pathway

Function	G-protein	Action
Iodine mobilization	G _s	Iodine uptake (induction of NIS expression and its translocation to basal membrane)
	G _{q/11} , G _s	Iodine efflux to follicular lumen
Hormone synthesis	G _s	TG and TPO expression
	G _{q/11}	H ₂ O ₂ production
	G _{q/11}	TG iodination
Hormone secretion	G _s	Iodinated TG uptake into follicular epithelial cells
	G _s	Thyroid hormone secretion
Other	G _s , G _{q/11}	Follicular epithelial cell proliferation

Another important cause of decreased synthesis and secretion of thyroid hormone is iodine deficiency. Because iodine is an essential component of the thyroid hormone, its deficiency results in impairment of the thyroid hormone synthesis (Zimmermann 2013). Although programs to control iodine deficiency, such as providing iodized salt, have been effective, it is still a major concern to the human health, particularly among children and pregnant women in many countries (de Benoist et al. 2008).

The signs and symptoms caused by hyper- and hypothyroidism are described in another chapter (Cheng, S. ► Chap.9, “Thyroid Hormone Nuclear Receptors and Molecular Actions” Part III).

Congenital Defects in Thyroid Hormone Synthesis and Secretion

Because the thyroid hormone is essential for normal growth, development, and functional maintenance of many organs, deficiency of the thyroid hormone induced by thyroid gland dysgenesis or thyroid dysmorphogenesis results in various abnormalities in many organs known as cretinism in humans. The role of thyroid hormone during development has been discussed in more detail in another chapter (Cheng, S. Part III) and a previous article (Koibuchi and Chin 2000). Most congenital thyroid dysgenesis and thyroid dysmorphogenesis are caused by mutation of genes that regulate thyroid development or thyroid hormone synthesis (Park and Chatterjee 2005). Another important factor that may cause congenital thyroid dysmorphogenesis is iodine deficiency (see above).

Various genes are involved in inducing congenital hypothyroidism. In particular, thyroid agenesis or dysgenesis is caused by mutations in thyroid transcription factors (TTFs) such as NKX2-1, FOXE1, and PAX 8 (Fernández et al. 2015). A homeobox protein, NKX2-1, which was previously called TTF-1, is expressed in multiple tissues in addition to the thyroid gland, e.g., lung, pituitary, and hypothalamus. In the thyroid gland, NKX2-1 may play an important role in maintaining thyroid follicular structure and follicular epithelial cell survival. Mutation of this gene in

humans results in thyroid agenesis or hypoplasia and respiratory distress. Forkhead box protein, FOXE1, which was previously called TTF-2, is expressed in the thyroid gland as well as in other tissues that are derived from the pharyngeal arches and wall, e.g., tongue, palate, and esophagus. It may regulate migration of thyroid precursor cells. Mutation of FOXE1 in humans results in ectopy, agenesis or hypoplasia of the thyroid gland, and cleft palate. Paired box protein, PAX8, is expressed in the developing thyroid gland, kidney, and brain. This protein may be essential for thyroid precursor cell survival possibly by inhibiting apoptosis. Mutation of PAX8 in humans results in ectopy, agenesis, or hypoplasia of the thyroid gland, problems in the urogenital tract, and, rarely, unilateral kidney. In addition to mutation of these transcription factors, mutation of TSH receptor sometimes results in hypoplasia of the thyroid gland, because TSH regulates the proliferation of thyroid follicular cells (Kleinau et al. 2013).

Thyroid dysmorphogenesis is caused by the mutations in genes that play critical roles in thyroid hormone synthetic pathway. Such genes include TG (Targovnik et al. 2010), TPO (Ruf and Carayon 2006), and DUOX (Grasberger 2010). The role of these factors on thyroid hormone synthesis has been discussed above.

Summary

The thyroid hormone synthetic pathway is quite unique, in that, although it is a relatively small molecule comprising two iodinated phenol rings, it is synthesized by the breakdown of a large protein, TG. Furthermore, most synthetic process occurs in the extracellular space (follicular lumen).

The research on thyroid hormone synthesis began early compared with that on other hormones. In addition, many genes that induce congenital hypothyroidism have been reported. Nevertheless, many questions remain to be answered. In particular, the mechanisms generating TSHR-stimulating autoantibody and the role of TTFs on the thyroid gland development remain unclarified. Additional novel approaches may be required to solve such questions.

Cross-References

- ▶ [The Thyroid](#)
- ▶ [Thyroid Hormone Nuclear Receptors and Molecular Actions](#)

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Further Reading

- Koibuchi N, Yen PM, editors. *Thyroid hormone disruption and neurodevelopment contemporary clinical neuroscience series*. New York: Springer-Verlag; 2016. ISBN 978-1-4939-3737-0.