Molecular and Cellular Endocrinology xxx (2017) 1–10

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Thyroid hormone biosynthesis and release

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form
7 January 2017
Accepted 23 January 2017
Available online xxx

Keywords:
Thyroglobulin
TPO
NIS
DUOX
Pendrin
Anoctamin-1
ClC5

ABSTRACT

Thyroid hormones (TH) 3,5,3′,5'- tetraiodothyronine or thyroxine (T4) and 3,5,3'- triiodothyronine (T3) contain iodine atoms as part of their structure, and their synthesis occur in the unique structures called thyroid follicles. Iodide reaches thyroid cells through the bloodstream that supplies the basolateral plasma membrane of thyrocytes, where it is avidly taken up through the sodium/iodide symporter (NIS). Thyrocytes are also specialized in the secretion of the high molecular weight protein thyroglobulin (TG) in the follicular lumen. The iodination of the tyrosyl residues of TG preceeds TH biosynthesis, which depends on the interaction of iodide, TG, hydrogen peroxide (H_2O_2) and thyroid peroxidase (TPO) at the apical plasma membrane of thyrocytes. Thyroid hormone biosynthesis is under the tonic control of thyrotropin (TSH), while the iodide recycling ability is very important for normal thyroid function. We discuss herein the biochemical aspects of TH biosynthesis and release, highlighting the novel molecules involved in the process.

- Follicular thyroid cells are specialized in thyroid hormone (TH) biosynthesis.
- NIS, pendrin, ClC5 and anoctamin-1 are essential for thyroid iodide availability.
- Thyroglobulin iodination depends on thyroperoxidase and DUOX2.
- MCT8 is a transporter involved in thyroid hormone release.
- TSH, iodide, selenium, thyroglobulin and TH metabolites regulate thyroid function.

1. Introduction

Thyroid hormone biosynthesis comprises a series of specific biochemical reactions that are closely related to the histological organization of thyroid tissue. Thyroid follicles, which are considered the functional units of the thyroid, are formed by a monolayer of polarized follicular epithelial cells, the so-called thyrocytes that are organized in a tridimensional ovoid structure surrounding the follicle lumen (Fig. 1A). The interior of the follicle primarily contains iodinated thyroglobulin (TG) and is called the “colloid” due to the high content of proteins, which are in close contact with the apical plasma membrane of thyrocytes. The exterior of the follicle is delimited by the basolateral plasma membrane of thyrocytes and is in contact with a large network of blood capillaries where intense exchange with the blood occurs (Fig. 1). In follicular cells, the tight junctions form a strong barrier that impairs the diffusion of transmembrane proteins from the apical domain to the basolateral domain, and *vice versa*. As a result of this intercellular barrier, it is also believed that the follicular luminal content cannot reach the bloodstream through the intercellular spaces unless the barrier is disrupted, as occurs in some pathophysiological circumstances, such as thyroid inflammation.

Thyroid hormones contain iodine atoms as part of their molecular structure. However, the initiation of thyroid hormone biosynthetic pathways depends not only on the specificity of iodine metabolism but also on what occurs outside the cells in the follicular lumen at the outer surface of the apical plasma membranes of thyrocytes. This biosynthesis is accomplished thanks to a set of genes that encode transcription factors whose joint expression is characteristic of and specific to thyroid tissue. Altogether, these transcription factors are fundamental for the expression of thyroid differentiation markers, such as TG and other proteins whose

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http://dx.doi.org/10.1016/j.mce.2017.01.038
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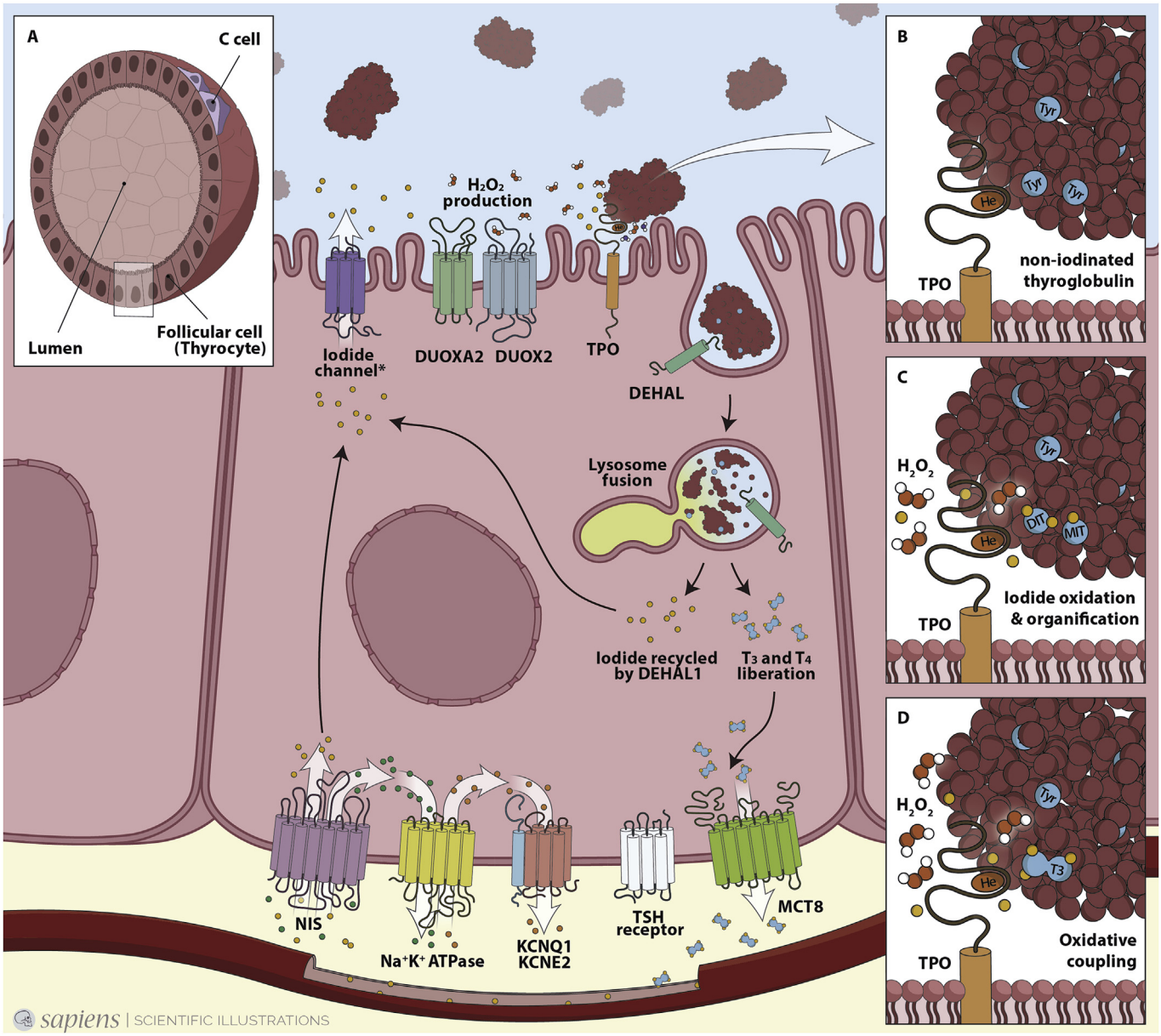

Fig. 1. Schematic Representation of Thyroid Hormone Biosynthesis and Release. The proteins involved in thyroid hormone biosynthesis and release are represented. NIS: sodium/iodide symporter; KCNQ1 and KCNE2: Voltage-gated K^+ channels; TSHR: thyrotropin receptor; MCT8: SLC16A2 monocarboxylate transporter 8, thyroid hormone transporter; DUOX2: dual oxidase 2; DUOXA2: maturation factor of dual oxidase 2; TPO: thyroperoxidase; DEHAL: iodotyrosine dehalogenase. A- Tridimensional structure of the thyroid follicles that is surrounded by epithelial follicular thyroid cells. C cells are parafollicular cells that produce calcitonin; B- TPO: thyroperoxidase, he: heme group of TPO, Tyr: tyrosine residues of thyroglobulin; C- iodide oxidation and its incorporation into thyroglobulin (organification) depends on the presence of TPO and hydrogen peroxide (H_2O_2) produced by DUOX2, DIT: diiodotyrosine, MIT: monoiodotyrosine; D- the oxidative coupling of iodotyrosines, MIT and DIT, depends on the presence of TPO and hydrogen peroxide (H_2O_2) and lead to the formation of T3 (and mainly T4) that remains bound to the thyroglobulin molecule.

localization at the apical plasma membrane allows the iodination of the tyrosyl residues of TG. Some of the iodotyrosine residues formed in the TG core are then coupled to form thyroxine or 3,5,3′,5’- tetraiodothyronine (T4), through the assembly of two diiodotyrosines (DITs), or 3,5,3'- triiodothyronine (T3), when one monoiodotyrosine (MIT) is coupled to DIT. There are at least four molecules that must interact at the apical plasma membrane of a thyrocyte for thyroid hormone biosynthesis to occur: iodide, TG, hydrogen peroxide (H_2O_2) and thyroid peroxidase (TPO). Iodide is absorbed in the gastrointestinal tract and reaches the basolateral plasma membranes of thyrocytes through the bloodstream. Although some other tissues are also able to take up iodide from the circulation, the thyroid gland is the only one that avidly concentrates iodide and accumulates it for a prolonged period of time, as a result of the histologic features of the thyroid follicles and the ability to organify iodine into tyrosyl residues of TG.

The biosynthesis of thyroid hormones occurs at the interface of the apical thyroid cell plasma membrane and the colloid, and TG molecules containing T4 and T3 are stored in the follicle lumen. The secretion of thyroid hormones depends on the reabsorption of iodinated TG, its proteolysis and the subsequent release of T4 and T3 into the blood, which occurs at least partially through transporters located in the basolateral plasma membrane of thyrocytes.

Please cite this article in press as: Carvalho, D.P., Dupuy, C., Thyroid hormone biosynthesis and release, Molecular and Cellular Endocrinology (2017), http://dx.doi.org/10.1016/j.mce.2017.01.038