HISTOLOGY AND PHYSIOLOGY OF THYROID GLAND IN MAMMALS

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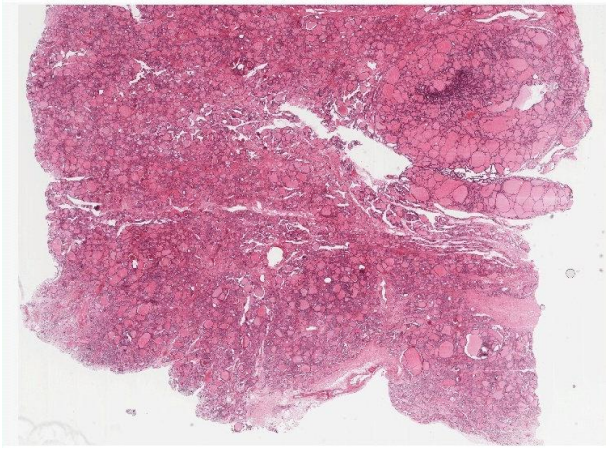
(B.Sc Part III PAPER V Zoology Hons)

The thyroid gland in mammal is a bilobular endocrine gland that is found in the neck, anterior and inferior to the larynx. Grossly, the gland appears brownish-red and the left and right lobes are connected by an isthmus.

The main purpose of this organ is to produce, store and secrete the iodine-based hormones triiodothyronine (T3) and thyroxine (T4). These hormones have various effects on fat, protein and carbohydrate metabolism, as well as on the development especially central nervous system and general growth.

The thyroid hormones are regulated by the Hypothalamus-Pituitary-Thyroid axis (HPT) via thyroid regulating hormones (TRH; from hypothalamus) and thyroid stimulating hormone (TSH; from pituitary gland).

HISTOLOGY



Thyroid gland: Histological slide

Cells of an endocrine gland have a cord-like arrangement and their products to be secreted are kept within the individual cells. The thyroid gland is an exception to this rule.

It is encased by a thin connective tissue capsule that enters the substance of the lobes to further subdivide the gland into irregular lobular units. Each lobule contains a cluster of follicles, which are the structural and functional units of the thyroid gland.

Thyroid follicles

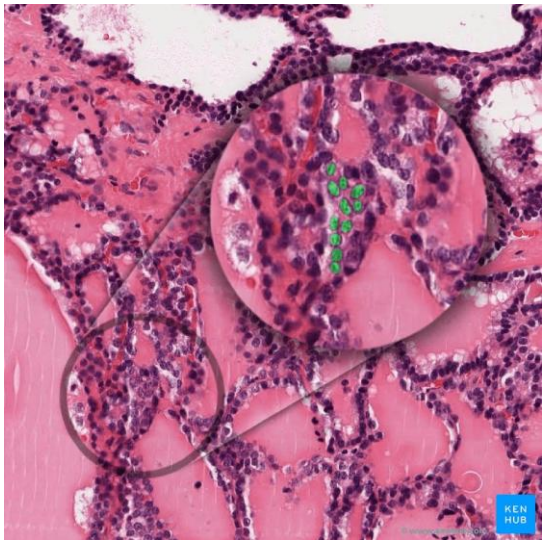
A follicle is surrounded by thin connective tissue stroma rich in fenestrated capillaries (along with the sympathetic nerves that innervate them) and lymphatics. Follicular epithelium is a simple epithelium consisting of low columnar, cuboidal or squamous cells depending on the level of activity of the follicle. When they are active, they appear cuboidal to low columnar, but when they are inactive the cells are squamous.

Colloid: Histological slide

These follicular (principal) cells take up the necessary amino acid precursors and iodine at its basolateral surface and release the final product into the blood stream at its basal end. Follicular cells are responsible for producing thyroglobulin (an

iodine rich, inactive form of the thyroid hormones), which is then stored as a semi-solid substance (colloid) in the lumen of the follicles.

The colloid stains pink with haematoxylin and eosin (H&E) staining, while the follicular cells have a purple appearance. The degree of activity of a follicle can also be assessed based on the amount and appearance of colloid it contains. Inactive follicular lumina are larger; colloid is abundant and appears solid. In contrast, active follicular lumina are smaller and there is little to no colloid present.



Parafollicular cells: Histological slide

Another cell type that can be identified on histological preparations of thyroid tissue is parafollicular cells, also known as C (clear) cells. C-cells appear clear due to the fact that they are lightly stained on H&E preparation. They can be found within the basal lamina of the thyroid follicles without extending into the follicular lumen or between thyroid follicles in the interfollicular space, either singly or in the form of groups.

Parafollicular cells are a subtype of neuroendocrine cells (amine precursor uptake and decarboxylation – AUPD – system) that produce thyrocalcitonin (calcitonin). This hormone aide in the regulation of blood calcium levels by downregulating bone resorption (breakdown of bone and subsequent release of minerals into the blood) and limiting calcium reuptake in the kidneys.

PHYSIOLOGY

The thyroid hormone is well known for controlling metabolism, growth, and many other body functions. The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis. The main hormones produced by the thyroid gland are thyroxine or

tetraiodothyronine (T4) and triiodothyronine (T3). Thyrotropin-releasing hormone (TRH) from hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland, and T4 work in synchronous harmony to maintain a proper feedback mechanism and homeostasis. Hypothyroidism, caused by an underactive thyroid gland, typically manifests as bradycardia, cold intolerance, constipation, fatigue, and weight gain. In contrast, hyperthyroidism caused by increased thyroid gland function manifests as weight loss, heat intolerance, diarrhea, fine tremor, and muscle weakness.

Iodine is an essential trace element absorbed in the small intestine. It is an integral part of T3 and T4. Sources of iodine include iodized table salt, seafood, seaweed, and vegetables. Decreased iodine intake can cause iodine deficiency and decreased thyroid hormone synthesis. Iodine deficiency can cause cretinism, goiter, myxedema coma, and hypothyroidism.

Regulation of thyroid hormone starts at the hypothalamus. The hypothalamus releases thyrotropin-releasing hormone (TRH) into the hypothalamic-hypophyseal portal system to the anterior pituitary gland. TRH stimulates thyrotropin cells in the anterior pituitary to the release of thyroid-stimulating hormone (TSH). TRH is a peptide hormone created by the cell bodies in the periventricular nucleus (PVN) of the hypothalamus. These cell bodies project their neurosecretory neurons down to the hypophyseal portal circulation, where TRH can concentrate before reaching anterior pituitary.

TRH is a tropic hormone, meaning that it indirectly affects cells by stimulating other endocrine glands first. It binds to the TRH receptors on the anterior pituitary gland, causing a signal cascade mediated by a G-protein coupled receptor. Activation of Gq protein leads to the activation of phosphoinositide-specific phospholipase C (PLC). PLC hydrolyzes phosphatidylinositol 4,5-P(PIP) into inositol 1,4,5-triphosphate (IP) and 1,2-diacylglycerol (DAG). These second messengers mobilize intracellular calcium stores and activate protein kinase C, leading to downstream gene activation and transcription of TSH. TRH also has a nontropic effect on the pituitary gland through the hypothalamic-pituitary-prolactin axis. As a nontropic hormone, TRH directly stimulates lactotropic cells in the anterior pituitary to produce prolactin. Other substances like serotonin, gonadotropin-releasing hormone, and estrogen can also stimulate prolactin release. Prolactin can cause breast tissue growth and lactation.

TSH is released into the blood and binds to the thyroid-releasing hormone receptor (TSH-R) on the basolateral aspect of the thyroid follicular cell. The TSH-R is a Gs-protein coupled receptor, and its activation leads to the activation of adenylyl cyclase and intracellular levels of cAMP. The increased cAMP activates protein

kinase A (PKA). PKA phosphorylates different proteins to modify their functions. The five steps of thyroid synthesis are below:

1. **Synthesis of Thyroglobulin**: Thyrocytes in the thyroid follicles produce a protein called thyroglobulin (TG). TG does not contain any iodine, and it is a precursor protein stored in the lumen of follicles. It is produced in the rough endoplasmic reticulum. Golgi apparatus pack it into the vesicles, and then it enters the follicular lumen through exocytosis.
2. **Iodide uptake**: Protein kinase A phosphorylation causes increased activity of basolateral Na+-I- symporters, driven by Na+-K+-ATPase, to bring iodide from the circulation into the thyrocytes. Iodide then diffuses from basolateral side to the apex of the cell, where it is transported into the colloid through Pendrin transporter.
3. **Iodination of thyroglobulin**: Protein kinase A also phosphorylates and activates the enzyme thyroid peroxidase (TPO). TPO has three functions: oxidation, organification, and coupling reaction.

    - Oxidation: TPO uses hydrogen peroxide to oxidize iodide (I-) to iodine (I2). NADPH-oxidase, apical enzyme, generates hydrogen peroxide for TPO.
    - Organification: TPO links tyrosine residues of thyroglobulin protein with I2. It generates monoiodotyrosine (MIT) and diiodotyrosine (DIT). MIT has a single tyrosine residue with iodine, and DIT has two tyrosine residues with iodine.
    - Coupling reaction: TPO combines iodinated tyrosine residues to make triiodothyronine (T3) and tetraiodothyronine (T4). MIT and DIT join to form T3, and two DIT molecules form T4.

4. **Storage**: thyroid hormones are bound to thyroglobulin for stored in the follicular lumen.

5. **Release**: thyroid hormones are released into the fenestrated capillary network by thyrocytes in the following steps:
    - Thyrocytes uptake iodinated thyroglobulin via endocytosis
    - Lysosome fuse with the endosome containing iodinated thyroglobulin
    - Proteolytic enzymes in the endolysosome cleave thyroglobulin into MIT, DIT, T3, and T4.
    - T3 (20%) and T4 (80%) are released into the fenestrated capillaries via MCT8 transporter.
    - Deiodinase enzymes remove iodine molecules from DIT and MIT. Iodine can be salvaged and redistributed to an intracellular iodide pool.