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Thyroid gland: An anatomical perspective

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Abstract

The thyroid is an endocrine gland lies in the neck, in front of the upper part of the trachea. The thyroid term is derived from Greek word 'thyreos' and 'eidos'. 'Thyreos' means an oblong shield and 'eidos' means form, because its shape is like a shield. The gland is enclosed in a connective tissue capsule that is continuous with the surrounding cervical fascia. Gland is composed of large number of follicles of various sizes. The follicles are spherical in shape and lined by a single layer of epithelium. These cells are simple cuboidal or short columnar depending upon their size and content i.e. colloidal substance called thyroglobulin. The small sized follicles are lined by high simple cuboidal, medium sized follicles are lined by very low simple cuboidal, while the large sized follicles have low simple cuboidal and even squamous epithelium in some very large follicles. The thyroid gland is the first glandular structure to form. Initially it develops as an exocrine gland.

Keywords: Endocrine, Parafollicular cells, Parafollicular cells, thyroid gland, thyroglobulin

1. Introduction

Endocrinology is the science that studies the internal secretions produced by endocrine glands. The endocrine system is the system of glands, each of which secretes a type of hormone into the bloodstream to regulate a body function. Hormones are chemical messengers that have many different functions.



Endocrine glands are distributed throughout the body and secrete chemical messenger (hormones), in response to an internal or external stimulus. These hormones are released directly into the bloodstream in contrast to exocrine glands, which use a ductal system to release their secretions in locations to the site of action. Hormones are transported through the bloodstream to target organs, where they exert a physiological control, even in low concentration, coordinating a multiplicity of organ functions and maintaining homeostasis (Vala *et al.*, 2013)^[33].

The thyroid term is derived from Greek word 'thyreos' and 'eidos'. 'Thyreos' means an oblong shield and 'eidos' means form, because its shape is like a shield. The thyroid is an endocrine gland lies in the neck, in front of the upper part of the trachea (Leeson and Leeson, 1970)^[17]. Two types of hormones are produced, which are the iodine containing hormones, triiodothyroxin and thyroxin (Banks, 1993)^[2].

Thyroid hormone regulate the basal metabolic rate and important in the regulation of growth of tissues. The release of hormone is stimulated by thyroid stimulating hormone (TSH) released from the pituitary gland. The second type of hormone produced from the thyroid gland is calcitonin which regulates blood calcium level along with parathyroid hormone and acts to reduce blood calcium by inhibiting its removal from bone. The most outstanding feature of the vertebrate thyroid gland is its ability to concentrate large amount of iodine for the synthesis of thyroxin (Turner, 1966)^[32].

The thyroid gland shows a marked variation in structural components according to the functional status of the gland, during development and in response to environmental influence. It differs among animal species. This alteration is related to the number of cells, morphology and hormone storage in the cells (Kameda *et al.*, 1984) ^[14]. The gland is unique among vertebrate endocrine organs in that, it stores secretory product (Thyroid hormones) extracellularly (Braverman and Cooper, 2012) ^[5].

2. Gross Anatomy

2.1 Topographic position

In ox glands are situated at the ventrolateral aspect of the junction of larynx and trachea. Glands of each side are connected ventrally by isthmus which traverses the ventral aspect of the trachea at the level of 2^{nd} ring. Median surface is related to cricoid cartilage and first one or two tracheal ring. Laterally it is related to carotid artery, internal jugular vein, vagus nerve and esophagus (Bloom and Fawcett, 1978; Peksa *et al.*, 2011 and Ghosh, 2015)^[4, 25, 10].

In horse the glands are situated on either side of trachea and just behind the larynx. The deep surface of each lobe is related to the first three or four tracheal rings. In Dogs they are situated at the lateral aspect of first six or seven tracheal cartilages. Accessory or extra thyroidal tissue is seen in the dog particularly near the thoracic inlet. In fowl two widely separated lobes are present at the level of the clavicle and two reddish dark colored round small bodies situated at the ventral aspect of the common carotid artery close to the thoracic inlet (Balasundarum and Mookkappan, 2000)^[1].

2.2 Morphologyss

The gland is reddish- brown in colour in the adult and darkred in the calf. The shape and colour of the gland varies as per the species (Getty, 1975)^[9].



S.N.	Species	Shape	Colour
1.	Ox	Triangular	Dark red
2.	Horse	Oval in shape	Red brown
3.	Dog	Flattened and Ellipsoidal	Dark red
4.	Goat	Elliptical	Dark red
5.	Sheep	Elliptical	Dark red
6.	Pig	Irregularly triangular	Red brown
7.	Fowl	Elliptical	Red or pinkish red

The isthmus, connecting the two lobes of the thyroid, it is the region that varies most markedly between species. Human and pig have a large discrete isthmus that forms a pyramidal lobe connecting the two lobes. The cow has a fairly wide band of glandular tissue that forms the connecting isthmus. In the horse, sheep, goat, cat and dog the isthmus is a narrow remnant of tissue and may be nonexistent. In pig lobes are connected by an isthmus with a small, central pyramidal lobe as part of that structure. In fowl isthmus is absent and widely separated pair of thyroid lobes are present on each side of the trachea (Getty, 1975; Singh and Beigh, 2013)^[9, 29].

The gland is enclosed in a connective tissue capsule that is continuous with the surrounding cervical fascia. This outer capsule is loosely connected on its deep surface to another layer of moderately dense connective tissue that is intimately adherent to the gland. This separation of the capsule into two layers creates plane of cleavage between the two, which facilitates surgical removal of the gland (Bloom and Fawcett, 1978)^[4].

2.3 Blood Supply and Nerve Supply

The gland is supplied by the cranial thyroid artery, which arises from the common carotid artery and arches around the cranial pole. A subsidiary supply is occasionally provided by a caudal thyroid artery, which takes a more proximal origin. In the dog the two vessels are connected by a substantial anastomosis along the dorsal margin. The venous drainage is to the internal jugular vein. The glandular tissue receives both sympathetic and parasympathetic fibers, sympathetic through the cranial cervical ganglia, the parasympathetic through the recurrent laryngeal nerve of the vagus nerves. The fibers are predominantly vasomotor and denervation has little effect on secretory activity (Raghvan, 1964 and Dyce *et al.*, 1996)^[26, 7].

3. Histology

3.1 Capsule

In general the thyroid gland consist of a connective tissue capsule composed of coarse and fine collagenous fibers (Mathur, 1971; Kauser and Shahid, 2006) ^[18, 15]. The outer layer is continuous with and is part of the pretracheal fascia, which in turn is part of the deep cervical fascia. The inner layer is regarded as the true capsule of the gland. It consists of fibroelastic connective tissue and sends septae in to the gland, providing internal support and carrying blood vessels, lymphatic and nerves in to its substance. The septae divide the gland in to lobules.

In fowl the capsule is comprised of three layers. The outer "capsule serosa", middle "capsule adiposa" and the inner most "capsule fibrosa" (Singh and Bharadwaj, 1982) ^[30]. According to Balasundarum and Mookkappan (2000) ^[1], the external layer is a mesothelial layer lined with simple squamous epithelium, the middle layer is rich in fat cells, blood vessels and nerves and the inner layer is closely adherent to the gland.

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3.2 Lobules

The parenchyma of the thyroid is encased externally by a capsule of dense irregular connective tissue that internally branches in to very narrow septae. These septae which consist of a capillary network surrounded by sparsely populated fibrocytes and their thinly developed extracellular matrix (E.C.M.), separate most of parenchyma into thyroid follicles (Samuelson, 2007) ^[28]. The septa do not join with one another so as to delimit entirely separate lobules of tissue; hence the thyroid is not truly lobulated but pseudolobulated (Ham and Cormack, 1972) ^[11].

3.3 Thyroid follicles

The gland is composed of large number of follicles of various sizes. In between the follicles there are Parafollicular cells. The follicles are spherical in shape and lined by a single layer of epithelium. These cells are simple cuboidal or short columnar depending upon their content i.e. colloidal substance called thyroglobulin. The Parafollicular cells are single or arranged in cluster form present in the basement membrane but outside the follicular cells (Ghosh, 2015)^[10]. The follicles are categorized as small, medium and large follicles. The size of follicles varies from a few to several hundred micrometers (0.02-0.9 mm) in diameter. In man there is great variability in the size of the follicles, but the small predominate over the large. In animals the follicles are of more uniform size. In the rat and guinea pig, those at the periphery of the gland are larger than those more centrally situated (Bloom and Fawcett, 1978)^[4]. The size of follicles increases with advancement of age and body size with a percentage corresponding decrease in parenchyma (Samuelson, 2007)^[28]. In old age the follicles are distended and irregular (Mathur, 1971, Balasundarum and Mookkappan, 2000) [18, 1]. According to KratochviI and Krabacova (2011) ^[16]. the average follicle size in cow ranges between 130 and 150 µm and the thyrocyte height is 7-11 µm.

The small sized follicles are lined by high simple cuboidal epithelium (even low columnar in some follicles), the medium sized follicles are lined by very low simple cuboidal epithelium with flattened nuclei, while the large sized follicles have low simple cuboidal and even squamous epithelium in some very large follicles. The stroma of thyroid gland is also consisted of a thin network of inter follicular connective tissue made up of reticular fibers and capillaries (Igbokwe and Ezeasor, 2010)^[13].

The colloid represents the stored product of secretory activity by the epithelium lining the follicles. The quantity of colloid varies according to the activity of the thyroid gland. In the inactive follicles it is more and thicker due to accumulation of large amount of colloid, whereas in active follicles it is lesser and thinner. This might be due to regular production and consumption of the colloid. Stein and Miller (1940) [31] reported that the freshly secreted colloid in human thyroid assumed a blue colour and later on aging it become pink. Beresford (1983)^[3]. recorded that the thyroid colloid was acidophilic when dense and basophilic when dilute and the colloid content of active follicles is basophilic whereas that of inactive follicles is acidophilic in fowl. The thyroid follicles are filled with a homogenous colloidal mass. In the follicles which are lined with simple cuboidal low columnar epithelium the colloid predominantly basophilic while those follicles lined by simple squamous epithelium have acidophilic colloid (Balasundarum and Mookkappan, 2000) ^[1]. The large and medium sized follicles showed a small number of inconspicuous peripheral vacuoles, while the small

follicles are filled with many peripheral colloid vacuoles that are visible in the colloid material (Igbokwe and Ezeasor, 2010)^[13].

4. Histochemistry

The colloid mass in some of the follicles stained with trichrome showed different staining properties. It is aniline blue positive at the periphery and fuchsin positive in the center. This may be due to the fact that the peripheral colloid is iodinated and showed aniline positive reaction while in the center, the colloid was non-iodinated and is fuchsin positive. The colloid is amphoteric because it exhibits varying colour reactions by different staining procedures (Firdous *et al.*, 2013)^[8].

4.1 Parafollicular cells(C cells)

The Parafollicular (C) cells usually occur as single cell enclosed within the basal lamina of the follicles but may also form groups in the same location or outside the follicles especially in dog. They do not border directly the lumen but are separated from it by overarching processes of neighbouring follicular cells (Bloom and Fawcett, 1978; Hullinger and Andrisani, 2006)^[4, 12]. The Parafollicular cells often are positioned in the basolateral compartment between follicular epithelial cells and within the basal lamina, while others form clusters between the follicles. These large epithelioid cells (prominent in the dog) synthesize calcitonin and are APUD cells (Hullinger and Andrisani, 2006)^[12].



Parafollicular cells in the dog thyroid gland occur as single cells (arrow head) but frequently form relatively large cluster (arrow) Trichome stain



Silver nitrate method of Cajals showing brown pigments in Parafollicular cytoplasmic granules in dog thyroid

The cells are also referred as C cells or clear cells because of their pale staining cytoplasm which surrounds a comparable large round nucleus. The cells often measure twice the diameter to that of follicular cells. They represent only a small fraction of the total parenchyma of the thyroid (Samuelson, 2007)^[28]. The secretory granules are not easily preserved and extracted during preparation of specimens. They are adequately preserved by aldehyde fixatives and appear as membrane limited dense, spherical granules 0.1-0.4 μ m in diameter. They can be selectively stained by the silver nitrate method of Cajals which reveals the presence of brown or black cytoplasmic granules. The granules exhibit an affinity for aniline blue in Trichome stain (Bloom and Fawcett, 1978)^[4].

5. Ultrastructure

5.1 Follicular cells

Pantic (1974) ^[21] described five types of follicular epithelial cells in the thyroid gland of mammals. These are follicular (including parafollicular) cells, colloid, ciliated, AR and U cells.

In contrast to other endocrine tissue, the follicular epithelium display polarity. The polarized follicular epithelial cells (thyrocytes) vary in height (columnar, cuboidal, squamous), depending upon their synthetic activity. The columnar cells indicate highly secretory follicles, whereas squamous cells are linked to follicles in a resting state. The cells have microvilli and pinocytic vesicles on the luminal surface. The microvilli are more numerous in columnar cells than on its lower relatively inactive cells. In active cells a basally positioned round nucleus that is surrounded by acidophilic cytoplasm. Follicular cells display an elaborate granular endoplasmic reticulum, free ribosomes, Golgi complex and secretory vesicles, characteristic of cells activity in the synthesis of protein. The mitochondria are oval shaped. The mitochondria and rough endoplasmic reticulm occupy the subnuclear region of the follicular cells, where as the Golgi complex, free ribosomes and colloid droplets are found in the apical cytoplasm. At light or electron microscopic levels, there is no sex difference in morphological characteristic of the thyroid glands (Parchami and Dehkordi, 2012) [22]. The thyroid follicle is delineated by a simple epithelium; the follicular cells are joined by junctional complex near the lumen. Thyroglobulin is a glycoprotein, and is exocytosed at the apical surface of the follicular epithelial cell, this iodinated glycoprotein, accumulating in the follicular lumen, it is also called colloid.



Transmission electron micrograph of Parafollicular cells in the thyroid of cat (X 8800)

5.2 Parafollicular cells

Most salient ultrastructural feature of the Parafollicular cell is the numerous granules that fill extensive area of the cell cytoplasm. In glutaraldehyde fixed tissue the secretory granules are found to contain a homogenous or finely granular electron-dense core, sometimes separated by a light rim of the smooth membrane limiting the granules. Secretory granules are from 100-200 nm in the rabbit and pig from 100-300 nm in the dog and sheep (Rost et al., 1975)^[27]. The granules tend to concentrate in the cytoplasmic areas closest to the follicular basement membrane, however, inspite of very close opposition of mature secretory granules to the plasma membrane signs of exocytosis have rarely seen in adult cells. This may indicate that adult cells are not very active in secretion. In the adult thyroid gland Parafollicular cells filled with secretory granules predominately. These are considered to be in a storage phase of the secretory cycle (Yong and Capen, 1971) ^[34]. These cells contain little rER, abundant Golgi complex and many mitochondria (Hullinger and Andrisani, 2006) [12].

6. Development

The thyroid gland is the first glandular structure to form (Noode and Lahunta, 1985) ^[19]. Parenchyma is derived from the pharyngeal endoderm as a ventral, tubular extension caudally along the midline, beginning at the root of the tongue. The diverticulum is seen at the level between the 1st and 2nd pharyngeal arches. Initially the thyroid develops as an exocrine gland. The caudal end of the thyroid primodial structure extends ventrally and caudally into the underlying mesoderm. Initially, it remains attached to the foregut, by the thyroglossal duct (Noode an Lahunta, 1985) ^[19]. Later on duct is lost and the parenchyma develops as many follicles supported by a delicate interstitial stroma (mesodermal) of reticular or loose collagenous connecting tissue. The stroma bears a profuse plexus of blood sinusoids, lymph capillaries and adrenergic axons.

The cells of fifth pharyngeal pouch (which is often considered to be part of the fourth pouch) give rise to what is termed the ultimobranchial body. In fish, amphibian, reptiles and birds, the ultimobranchial bodies are separate glands. But in mammals the cells that grow out from the fifth pharyngeal pouch become intimately associated with the developing thyroid gland. It was suggested many years ago that these cells were the forerunners of the light cells of the thyroid gland. That this is indeed the origin of C cells was confirmed by Pearse and Carvalheira (1967)^[24]. However, further studies revealed that in mammals this body advances to fuse with the developing thyroid, it is colonized by migrating neural crest cells. These neural crest cells differentiate in the thyroid as Parafollicular (calcitonin producing, C) cells (Hullinger and Andrisani, 2006)^[12].

So attention has been paid to obtaining ultimobranchial glands from birds and fish, in which they are separate from the thyroid and extracting calcitonin from them. There are indications that substantial amount of calcitonin can be obtained by this way.

These cells appear in small groups or a solitary cell between the follicular cells and the capillary wall. In early development they can be easily recognized as light cells localized among the follicular cells never reaching the follicular lumen. The number of Parafollicular cells increases with age of animals and the increase is particularly pronounced in the early postnatal period (Nuzez and Gershan, 1976; Zebel and Biela-Jacek, 1987)^[20, 35].

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Parafollicular cells develop and accumulate characteristic secretory granules prior to birth, at birth and during neonatal period but not in adult thyroids. The cells release their content by exocytosis, this indicates that the cells are more active at this time prior to birth, at birth and neonatal than in early foetal and later adult life (Getty, 1975)^[9].



Neural crest cells migrating into the developing thyroid gland

7. Function

7.1 Secretion and storage of T_3 and T_4

Thyroglobin, a glycoprotein, is exocytosed at the apical surface of the follicular epithelial cell; this iodinated glycoprotein, accumulating in the follicular lumen, is also called colloid. Furthermore, these follicular epithelial cells are simultaneously active in the endocytosis of the colloid from the follicular lumen via apical cell processes and the proteolysis of thyroglobulin, as evidenced also by the presence of lysosomes and phagolysosomes (secondary lysosomes).

The release of stored thyroglobulin is affected by endocytosis of colloid via the extension of microvilli and lamellipodia of the follicular cells. Endocytotic vesicles containing colloid fuse with lysosomes, and proteolysis of the thyroglobulin release T_1 , T_2 , T_3 , or T_4 . Only T_3 and T_4 are released into the blood from the basolateral cell surface, by diffusion through the membrane.

The synthesis, iodination, and proteolysis of thyroglobulin occur simultaneously in the same cell, and are regulated by TSH. Gap junctions between the cells provide synchronized activity of all the cells lining a given follicle (Hullinger and Andrisani, 2006)^[12].

7.2 Secretion of calcitonin

These large epitheliod cells (prominent in the dog) synthesize calcitonin and are APUD (amino precursor uptake and decarboxylation) cells. Synthesis and release of calcitonin is regulated, not by the pars distalis, but by the concentration of calcium in intercellular fluid. When the intercellular calcium concentration rises, the calcium- sensing GPCRs on the Parafollicular cell detect the calcium increase and trigger calcitonin release. Gastrin also promotes calcitonin release. Calcitonin binds to its GPCR on osteoclasts and kidney epithelium, lowering calcium concentration in blood and interstitial fluid by inhibiting osteoclast activity and lowering tubular resorption of calcium, respectively.

8. Conclusion

The thyroid is an endocrine gland lies in the neck, in front of the upper part of the trachea. Two types of hormones are produced, which are the iodine containing hormones, triiodothyroxin and thyroxin. The gland is composed of large number of follicles of various sizes. In between the follicles there are Parafollicular cells. The follicles are spherical in shape and lined by a single layer of epithelium. The size of follicles increases with advancement of age and body size with a corresponding decrease in parenchyma percentage.

The thyroid gland is an important endocrine gland shows slight variation in its topographic position and morphology in different species of animals. The important features of this gland its ability to concentrate large amount of iodine and extracellular storage of material i.e. colloid. Two hormones secreted by the glands are maintain the metabolic activity of the body and blood calcium level respectively, Therefore the anatomical knowledge of the gland is essential to know its clinical manifestation and disorder.

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