UG CBCS Semester-IV (MJC-7: Endocrinology)

The Mammalian Thyroid

The thyroid gland (Figure 6-1) is unique among vertebrate endocrine glands in that it stores its secretory products (thyroid hormones) extracellularly. It is possibly the most highly vascularized endocrine gland in mammals and appears to be one of the oldest vertebrate endocrine glands phylogenetically. Thyroid function is regulated by the hypothalamus-pituitary-thyroid (HPT) axis. Thyrotropin (TSH) from the pituitary stimulates the synthesis of tetraiodothyronine or thyroxine (T4). To synthesize T4, the amino acid tyrosine is incorporated into a glycoprotein called thyroglobulin (Tgb). Tyrosine is iodinated and then two iodinated tyrosines are enzymatically linked together to form T4. Some T4 is partially deiodinated to form the more active thyroid hormone triiodothyronine (T3) prior to release from the thyroid gland.

Thyroid hormones influence many aspects of reproduction, growth, differentiation, and metabolism. Many of these actions occur cooperatively with other hormones, and the thyroid hormones enhance their effectiveness. This cooperative role for thyroid hormones is referred to as a permissive action whereby thyroid hormones produce changes in target tissues that "allow" these tissues to be more responsive to another hormone, to neural stimulation, or possibly to certain environmental stimuli such as light. Thyroid hormones may maintain maximal sensitivity to other regulating agents in many types of tissues. The importance of thyroid hormones is reflected in the observation that the incidence of thyroid disease in humans is exceeded only by the incidence of metabolic syndrome and diabetes mellitus.

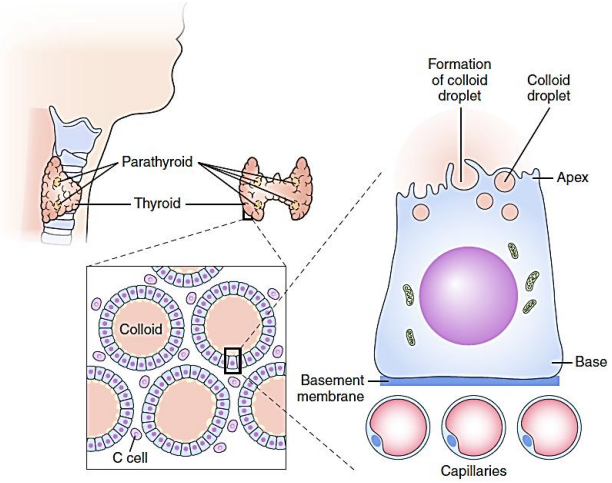

FIGURE 6-1 **The mammalian thyroid.** The thyroid gland is located in the neck region. It consists of many hollow follicles, each of which is filled with a proteinaceous fluid called colloid which is secreted by the follicle cells. Thyroxine synthesized by the follicle cells is stored in the colloid. The C-cells or parafollicular cells are of ultimobranchial origin and secrete the calcium-regulating hormone, calcitonin (see Chapter 14). *(Adapted with permission from McNabb, F.M.A., "Thyroid Hormones," Prentice Hall, Upper Saddle River, NJ, 1993.)*

Although rarely lethal, thyroid disorders have widespread effects in humans due to their many actions with other hormones. Of the more than 13 million thyroid disorders diagnosed in the United States, 11 million occur in women. This difference in incidence between males and females is not understood, although many cases are linked to pregnancy. Thyroid deficiencies that occur during pregnancy can have devastating effects on the development of the nervous system of the fetus, leading to extensive mental deficiencies. Thyroid deficiencies develop so gradually that they often are not recognizable, even by physicians.

SOME HISTORICAL ASPECTS OF THYROID PHYSIOLOGY

Either deficient or excessive production of thyroid hormones may lead to serious pathological states with overt symptoms (Table 6-1). The first description of thyroid disease was of abnormal enlargement of the thyroid in humans recognized by Chinese physicians about 3000 BC. As a remedy, they recommended ingestion of seaweed and burned sponge or desiccated deer thyroids. The first two substances contained therapeutic quantities of iodide and the last

sufficient thyroid hormones to alleviate the pathological symptoms in most cases. Hypothyroid deficiencies of this sort were not recognized in Western culture as clinical disorders until many centuries later. The cretinism syndrome was described clinically in Europe in 1526. Cretinism is manifest very early in life as a consequence of severe thyroid deficiency. This syndrome is characterized by dwarfism and a number of other physical abnormalities in addition to severe mental retardation, slow mental and physical activity, bradycardia (slowing of heart beat), and hypothermia (decreased body temperature). From 1880 to 1890, another clinical disorder in adults, myxedema, was linked to hypothyroid function. Myxedematous symptoms in adults are related to abnormal accumulation of water and protein throughout the body as well as to other disturbances in general metabolism. Accumulations of protein and fluid in the skin alter facial features, causing the patient to appear expressionless. In later stages of the disorder, the sufferer becomes less interested in both self and environment and, if untreated, would eventually enter a coma and die. Juvenile myxedema is similar to cretinism except that early growth and development are normal but severe retardation develops in later childhood. All of these clinical syndromes have the same basic cause: hypo-functioning of the thyroid gland.

Bauman discovered in 1896 that an organic iodine containing compound could be extracted from thyroid glands. Subsequently, it was demonstrated that this "thyroidin" substance could reverse the adverse effects of iodide deficiency. In the early 1900s, the thyroid gland and its hormones were implicated in elevating basal metabolic rate, primarily through effects on certain tissues (e.g., liver, kidney, muscle). This observation has strongly influenced the direction of thyroid research in mammals as well as in many non-mammalian vertebrates.

TABLE 6-1 Symptoms of Thyroid Deficiency and Hyperactivity in Humans

Type of Symptom	Hypothyroid	Hyperthyroid
Appearance	Myxedema; deficient growth	Exophthalmos
Behavior	Mental retardation; mentally and physically sluggish; somnolent; sensitive to cold	Often quick mentally; restless, irritable, anxious, hyperkinetic; wakeful; sensitive to heat
Metabolism	Hypophagia; low basal metabolic rate; reduced QO_2[a] of liver, kidney, and muscle *in vitro*; decrease in oxidative enzymes; constipation	Hyperphagia; high basal metabolic rate; increased QO_2 of liver, kidney, and muscle *in vitro*; increased oxidative enzymes; diarrhea
Muscle function	Weakness; hypotonia	Weakness; fibrillary twitchings, tremors

[a] *QO_2, respiratory quotient.*

The action of thyroid hormones on metabolism is reflected in clinical thyroid states (Table 6-1). The iodine-containing hormone T4 was isolated, crystallized, and reported by Edward C. Kendall in 1915. This event marked a significant milestone, not only in thyroid research but also in endocrinology as a whole, for T4 was the first hormone to be isolated in pure form. It was not until 1952, however, that the second thyroid hormone, T3, was identified by J. Gross and R. Pitt-Rivers. This second thyroid hormone was soon found to be more potent than T4 as a thyroid hormone and is considered by many to be the active form of thyroid hormone. It was the discovery of anti-thyroid drugs in the early 1940s, as well as the ready availability of radioactive isotopes of iodide (radioiodide) following developments in nuclear physics, that provided diagnostic tools for assessing thyroid function (radioiodide) and chemicals (anti-thyroid drugs) suitable for blocking thyroid function. Radioiodide proved useful for clinical and laboratory work and provided a label for thyroid molecules that made it possible to elucidate the details of thyroid hormone synthesis, metabolism, and mechanisms of action.

II. DEVELOPMENT AND ORGANIZATION OF THE MAMMALIAN THYROID GLAND

The mammalian thyroid gland consists of many epithelial follicles encapsulated by a connective tissue sheath. The gland is highly vascularized, with a dense capillary network surrounding each follicle. The thyroid vasculature receives cholinergic innervation, and the follicle cells receive adrenergic (norepinephrine and dopamine) and peptidergic (e.g.,

neuropeptide Y, NPY; vasoactive inhibitory peptide, VIP) innervation. Direct innervation of the follicle cells may play an important role in overall thyroid regulation.

Development of the thyroid gland begins by formation of a ventral bud in the floor of the embryonic pharynx (endoderm) between the first and second pharyngeal pouches. The gland initially differentiates as cellular cords that later separate into clusters of cells destined to become thyroid follicles. The cells of a cluster secrete a protein rich fluid termed colloid that accumulates extracellularly in the center of the cluster. This secretory activity eventually leads to formation of a colloid-filled space, the lumen of the follicle, surrounded by a single layer of epithelial cells, the thyroid epithelium (Figure 6-1). The portion of the follicular cell that borders on the lumen of the follicle is known as the apex or apical portion. The apical portion of each thyroid follicle cell is linked to the adjacent cell by occluding or tight junctions, thus forming an impenetrable barrier between the cells. The nucleus is generally found in the basal portion of the cell that is farthest from the lumen and closest to the capillaries that surround each follicle.

TABLE 6-2 Comparison of Characteristics of Thyroid Follicular and Parafollicular Cells

Thyroid Follicular Cell	Thyroid Parafollicular Cell
Absence of secretion granules	Large number of eosinophilic granules, 0.2-μm diameter; stain with silver nitrate
Endoplasmic reticulum cisternae of larger diameter, containing flocculent precipitate like that found in albumin-secreting cells	Many mitochondria and high level of the mitochondrial enzyme α-glycerophosphate dehydrogenase
Carbohydrate added at Golgi apparatus, which is rather inconspicuous in these cells	No lumenal surface present
	Nucleus more irregular in outline than those of follicular cells
Enlargement of Golgi apparatus from TSH treatment	Golgi apparatus prominent
Binds antibody to thyroglobulin but not to calcitonin	Binds antibody to calcitonin
Cytology not altered by high blood calcium level	Degranulation due to high blood calcium level
Readily accumulates iodide	

In addition to capillaries and follicles, parafollicular or C cells occur in the regions between or adjacent to the follicles. Parafollicular cells may occur within the follicular epithelium or may even form separate follicular structures in some species. These cells are derived from another pharyngeal derivative, the ultimobranchial body, and secrete a hypocalcemic hormone, calcitonin, that influences calcium metabolism. A comparison of parafollicular cells and follicular cells (Table 6-2) emphasizes their different structural and functional features. In some mammals, the parathyroid glands also may be embedded within the mass of the thyroid (Figures 6-1 and 6-2). The parathyroids, like the parafollicular cells, have their origin nearby from the embryonic pharynx and in some species become embedded in the mass of thyroid follicles during development. The parathyroid glands secrete the hypercalcemic hormone parathyroid hormone (PTH). Unlike the thyroid follicular cells that appear to be of endodermal origin, the parafollicular cells and the secretory cells of the parathyroid glands actually are of neural crest origin and migrate into the embryonic glands.

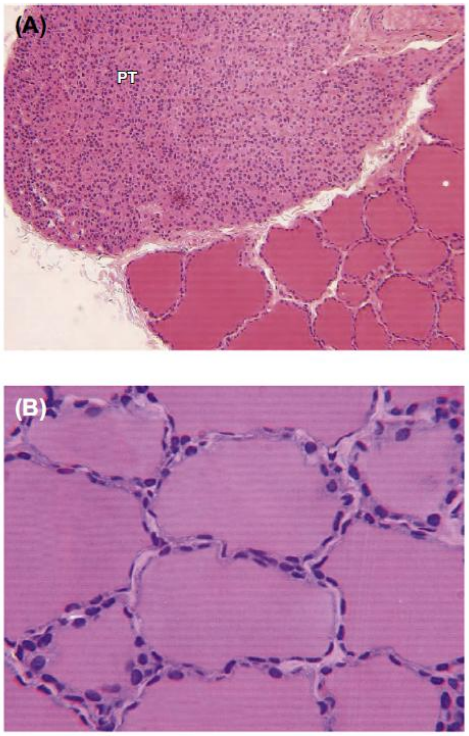

FIGURE 6-2 Thyroid and parathyroid glands. (A) Low magnification of compact parathyroid gland (above) embedded in the thyroid gland consisting of colloid-filled follicles (below). (B) High magnification of thyroid follicles with squamous epithelium surrounding colloid.

References

- Norris DO & James AC (2013). Vertebrate Endocrinology (5th edition). Academic Press, USA. http://dx.doi.org/10.1016/B978-0-12-394815-1.00001-X.