STUDY OF THYROID FUNCTION AND CYCLIC ADENOSINE 3', 5' MONOPHOSPHATE (CYCLIC AMP) IN SOME CATABOLIC STATES

THESIS

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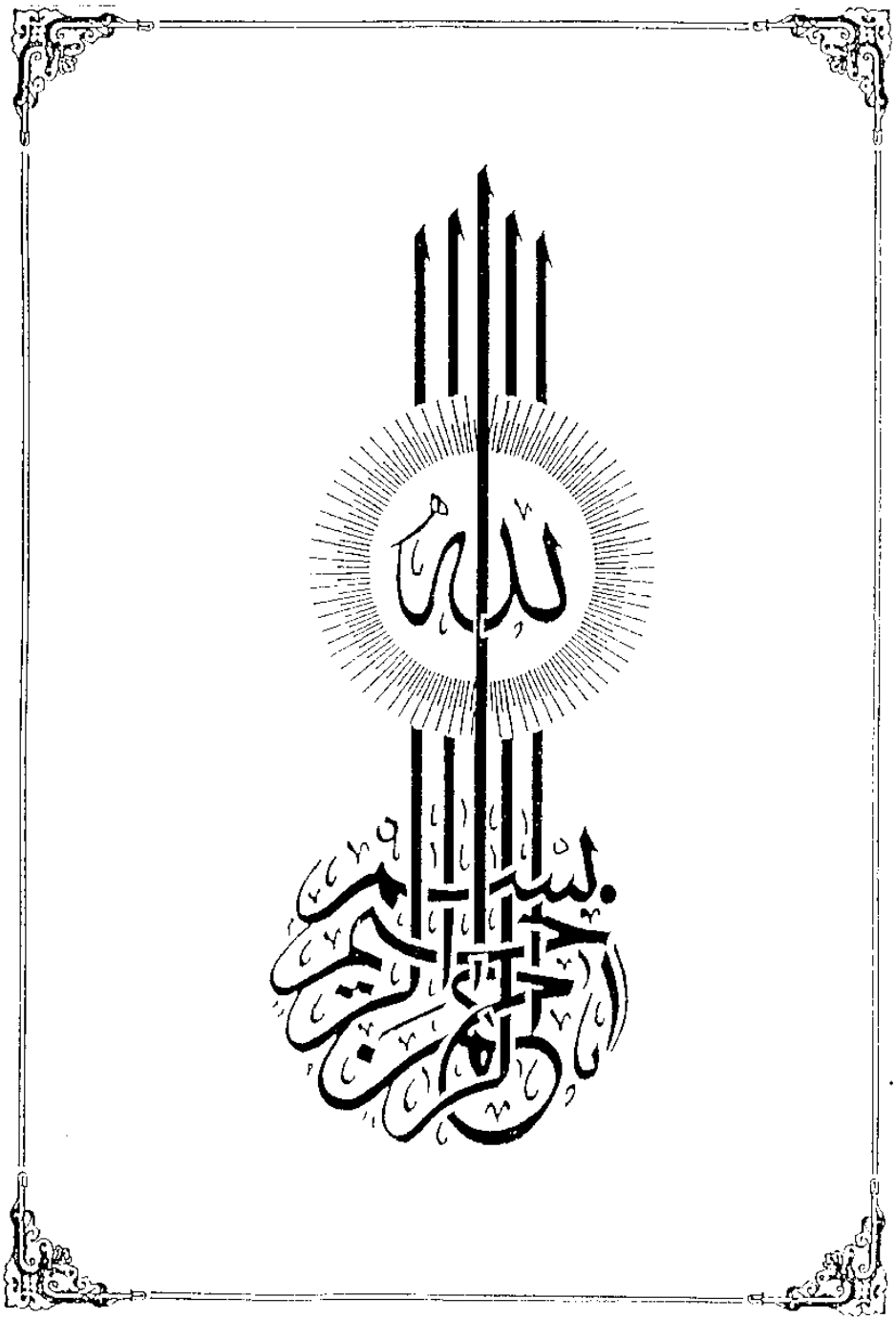

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INTRODUCTION

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Anabolism and Catabolism are two known metabolic states which occur in man and in animals. Although anabolic hormones are known to be accelerated during the first twenty years of human life, they are known to be decelerated after age 40. Thyroid hormones are one of the known anabolic hormones, their dynamics in the process of aging is the subject of another thesis in this unit.

However, it is of great interest to know which thyroid hormones is increased or decreased in diseases known to be catabolic in man viz diabetes mellitus, renal failure and malignancy.

Besides, since Sutherland described cyclic adenosine monophosphate to be the second messenger for any hormone to act, it is also of interest to us to measure and quote it as a biological marker in the above mentioned catabolic states.

R E V I E W

Anatomy of the Thyroid Gland

The thyroid gland is one of the largest endocrine organs, it weighs about 15 - 20 gms and extends from the fifth or the sixth tracheal ring inferiorly to the side of the thyroid cartilage superiorly. It is enclosed in a sheath of pre tracheal fascia.

The gland is made up of 2 lobes joined by an isthmus. Each lobe is conical in shape and measures about 2.5 cm in both thickness and width at its largest diameter and approximately 4 cm in length. Occasionally a pyramidal lobe is seen as a finger like projection extending from the isthmus upwards towards the hyoid bone to which it may be attached by a narrow slip of muscle, the levator glandulae thyroidae or a fibrous band. This strand is the remanant of the thyroglossal duct indicating the embryonic path along which the thyroid gland has developed. Two pairs of parathyroid glands are embeded in its posterior surface.

Blood supply

The thyroid gland receives ample blood supply from two main arteries, the external carotid and the subclavian. The superior thyroid arteries from the external carotid artery and the inferior thyroid arteries from

the subclavian arteries. An occasional small artery (thyroida ima) may arise from the brachiocephalic trunk or the left common carotid or the aortic arch.

The venous drainage is mainly through three pairs of veins: the superior and middle thyroid veins ending in the internal Jugular vein and the inferior thyroid veins ending in the innominate vein of the same side or both join the left innominate.

The thyroid gland is a highly vascular organ, the thyroid blood flow ranges from 4 to 6 ml/min/gm in comparison with the renal blood flow which is 3 ml/min/gm.

Lymph Drainage

The gland is drained by two sets of lymph vessels ascending and descending. Each consists of medial and lateral channels. The ascending vessels include medial channel draining into the prelaryngeal gland and lateral channel to the deep cervical glands. The descending vessels go medially to the pretracheal gland and laterally to the gland of the recurrent chain (Du Plessis, 1975).

Histology of the thyroid gland

With light microscope

The gland is composed of closely packed acini (follicles) filled with a proteinaceous material called colloid. The follicles are lined with a single layer of cells. When the gland is inactive, the colloid is abundant and the lining cells are flat. When the gland is active, the follicles are small and the cells become cuboidal or columnar. Connective tissue septa seperate the follicles from each other. From 20 to 40 follicles are packed together by connective tissue septa to form a lobule supplied by a single artery. In between the thyroid cells, lie the para follicular cells to which we will refer later.

With electron microscope

From the surface of the follicular cells microvilli extend into the colloid. The nucleus has no distinctive features. The cytoplasm contains an extensive endoplasmic reticulum composed of a network of wide irregular tubules that contain the precursor of thyroglobulin. The Golgi apparatus is located apically and probably adds the carbohydrate component to this precursor. Lysosomes and mitochondria are scattered

throughout the cytoplasm. Upon TSH stimulation, Golgi apparatus enlarges and forms pseudopodia at the apical surface where many droplets appear at the apical portion of the cell containing colloid taken up from follicular lumen (Fawcett et al, 1969).

The para follicular cells are another type of cells present in between the follicular cells but never reaching the lumen of the follicle. They are rich in both mitochondria and glycerophosphate dehydrogenase. The release a calcium lowering hormone called calcitonin or thyrocalcitonin.

Thus we can regard the thyroid gland as two endocrine glands in one organ. Besides, the parathyroid glands lie behind the thyroid gland secreting a calcium raising hormone.

Embryology of the thyroid gland

The thyroid gland begins to appear during the 3rd week as an endodermal thickening in the midline of the floor of the pharynx. Later this thickening becomes a diverticulum that grows inferiorly into the underlying mesenchyme and is called the thyroglossal duct. As development continues, the duct elongates and its distal

end becomes bilobed. Soon the duct becomes a solid cord of cells and as a result of epithelial proliferation the bilobed terminal swellings expand to form the thyroid gland. The thyroid gland now migrates inferiorly in the neck and passes either anterior to or through or posterior to the developing body of the hyoid bone. By the seventh week it reaches its final position in relation to the larynx and trachea. Mean while, the solid cord connecting the thyroid gland to the tongue fragments and disappears. The site of origin of the thyroglossal duct on the tongue remains as a pit called the foramen caecum. In the earliest stages, the thyroid gland consists of a solid mass of cells. Later, as a result of invasion by surrounding vascular mesenchymal tissue, the mass becomes broken into plates and cords and finally into small clusters of cells. By the third month, the gland starts to function and colloid starts to accumulate in the centre of each cluster so that follicles are formed.

The parafolliculer cells have different origin. They arise from the ultimobranchial bodies that in turn arise from the fifth pharyngeal arch and become incorporated into the thyroid gland (Snell, 1975). In goats they are quite seperated from the thyroid gland.

The anatomic and functional development of the thyroid is dependent upon TSH whose origin is necessarily fetal since placenta is impermeable to maternal TSH (Dillon, 1980).

PHYSIOLOGY

Biosynthesis of Thyroid Hormone

Thyroid hormone is made up of a halogen and an amino acid.

In the thyroid gland, iodine is actively pumped into the cells against an electrical gradient since the resting membrane potential is -50 mV (Ganong 1981). About 120 ug/d of iodide enter the thyroid gland at normal rates for thyroid hormone synthesis.

Iodide is oxidised to iodine and bound in a matter of seconds to the 3 position of tyrosine molecules attached to thyroglobulin so that thyroid iodine never exists as iodide at any time. The enzyme responsible for the oxidation and binding of iodide is thyroid peroxidase with hydrogen peroxide as a substrate to accept the electrons.

Mono iodo tyrosine is next iodinated in the 5 position to form diiodo tyrosine. A trace amount of iodo histidine is found in thyroglobulin (Wolff et al 1969).

Two diiodothyrosine molecules undergo oxidative condensation with the release of an alanine residue and the formation of thyroxine, still in peptide linkage to thyroglobulin.

3, 5, 3' triiodothyronine (T_3) is probably formed by condensation of monoiodotyrosine with diiodotyrosine. A small amount of 3, 3', 5' triiodothyronine (reverse T_3) is also formed probably by condensation of diiodotyrosine (DIT) and monoiodotyrosine (MIT). The condensation reaction is an aerobic, energy requiring reaction and like the oxidation and binding it appears to be catalysed by thyroid peroxidase (Ganong 1981). Binding of 2 molecules of DIT results in tetra iodothyronine (T_4).

Hormone Secretion

The human thyroid secrets about 80 ugm of free thyroxine and up to 8 ugm of triiodothyronine per day.

By endocytosis, thyroid cell ingest calloid at their apical margin to form colloid droplets. Inside the cells, colloid droplets fuse with thyroid lysosomes to form phagolysosomes then splitting of the hormones from their peptide linkage in thyroglobulin occurs and also deiodination of iodotyrosine.

Acid protease (Reinwein, 1964), glycosidases (Wollman, 1969) and iodotyrosine deiodinase (Stanbury, 1969) were demonstrated in thyroid lysosomes.

T_4, T_3, diiodotyrosine and monoiodotyrosine are liberated into cytoplasm and pass into circulation probably