COMPARATIVE STUDY OF PROSTAGLANDINS IN SOME THYROID DISORDERS

THESIS

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(General Medicine)

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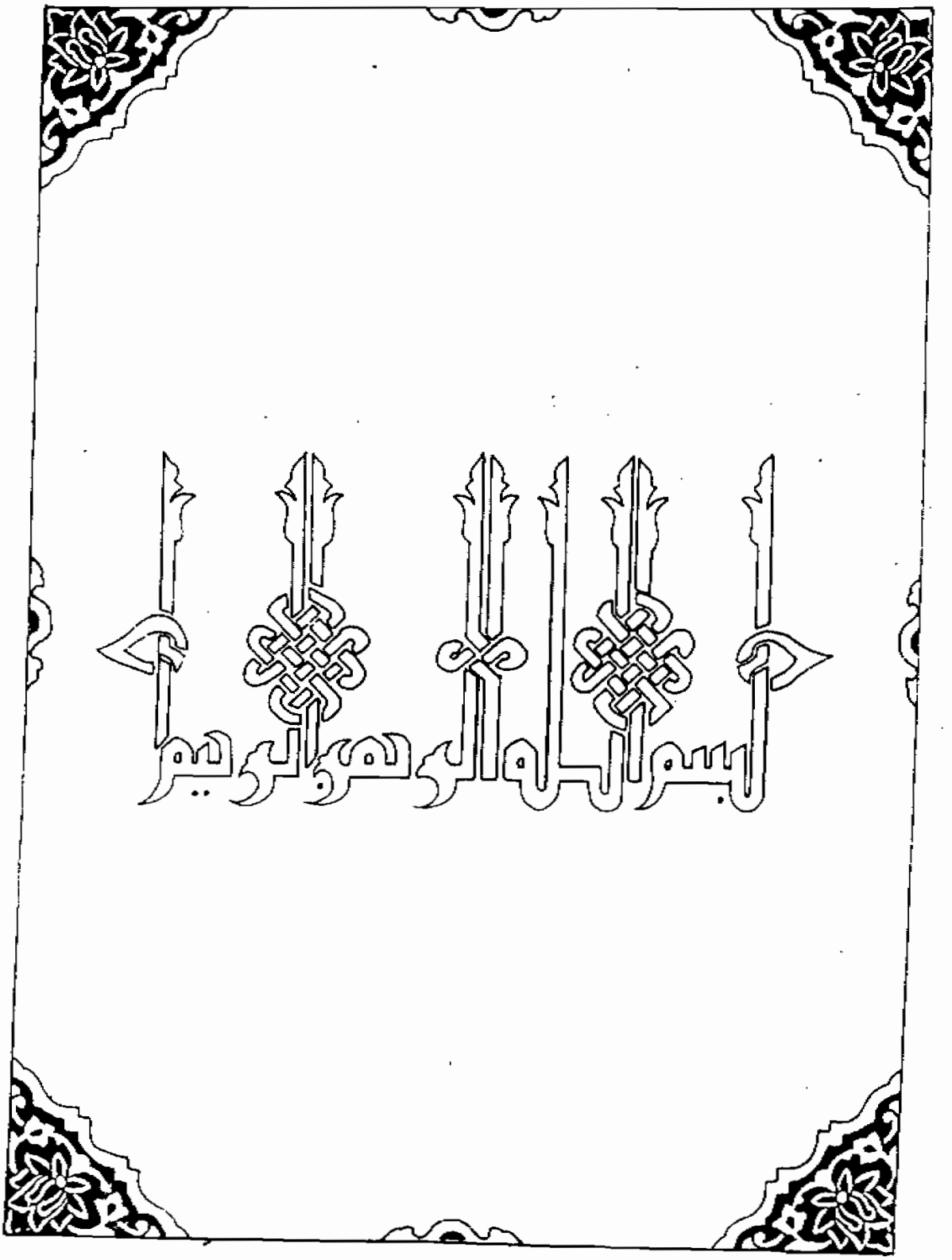
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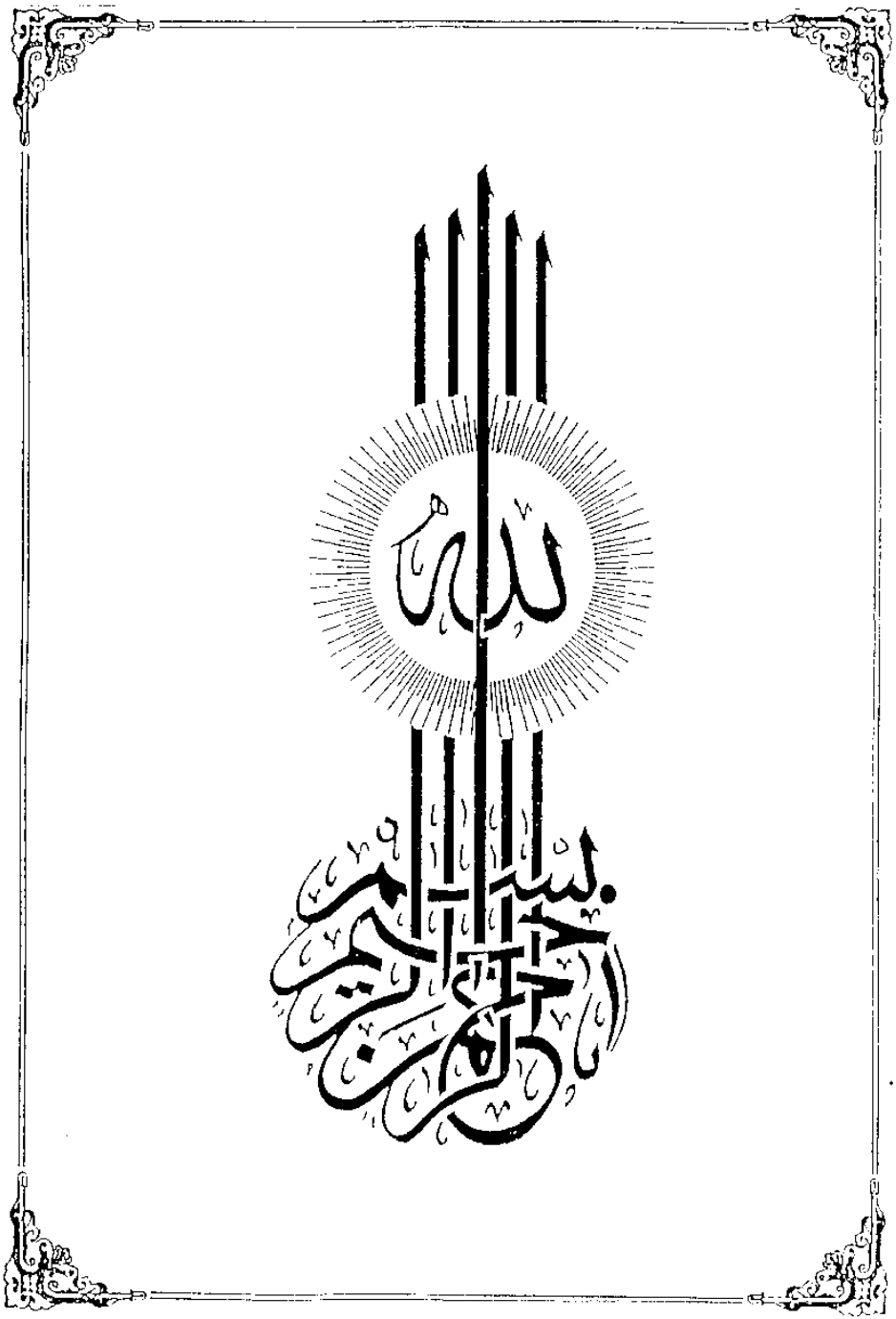

A C K N O W L E D G E M E N T

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Abbreviations

- ACTH : adrenocorticotrophic hormone.
- ADP : adenosine diphosphate.
- CAMP : cyclic 3, 5 adenosine monophosphate.
- CGMP : cyclic 3, 5 guanosine monophosphate.
- db-CAMP: dibutyryl cyclic 3, 5 adenosine monophosphate.
- dl : diciliter .
- GH : growth hormone
- HLA : histocompatibility leucoeytic antigen.
- Ig : immunoglobulin.
- LH : lutenizing hormone.
- μg : microgram.
- ng : nanogram.
- Pg : picogram.
- PGI : prostacyclin
- PG : prostaglandins.
- RNA : ribonucleic acid.
- T_4 : tetra iodothyronine (Thyroxine)
- TX : thromboxane.
- Tg : thyroglobulin.
- TSH : thyroid stimulating hormone.
- T_3 : tri iodothyronine

C O N T E N T S

INTRODUCTION

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The role of prostaglandins in normal thyroid physiology and metabolism and their changes in some thyroid disorders has been a point of great interest to study and to clarify.

Many investigators demonstrated the effects of prostaglandins in thyroid function. Thompson et al, (1977) found that in contrast to the inhibiting effect of prostaglandin E_1 on adipose tissues adenyl cyclase, PGE_1 stimulates adenyl cyclase in slices of dog thyroid, resulting in increase in cyclic AMP. As many of the effects of PGE_1 mimic those of TSH, hormonogenesis with the accompanying adenylate cyclase are inhibited by prostaglandin antagonists (Thompson et al, 1977).

Burke and coworkers, (1972, 1973) reported that TSH, and dibutryl cyclic AMP increase the level of various prostaglandins in isolated bovine thyroid cells and mouse thyroid.

The aim of this work is to correlate between prostaglandins changes and some thyroid disorders.

REVIEW OF LITERATURE

Thyroid Gland

Human thyroid is first recognizable at 1 month after conception when the embryo is 3.5–4.0 m.m. in length (Boyd, 1964).

The throid is one of the largest of the endocrine organs, weighting about 20 gm. It is made up of two lobes joined by a thin band of tissue, the isthmus.

The thyroid is closely affixed to the anterior and lateral aspects of the trachea by loose connective tissue. The upper margin of isthmus generally lies just below the cricoid cartilage. The lobes lie along the lower half of the lateral margins of the thyroid cartilage. Lying between the thyroid gland and the subcutanous tissue are the carotid sheaths and sternomastaid muscles, while the recurrent laryngeal nerves lie in the grooves between the lateral lobes and the trachea. The thyroid is supplied by 2 main arteries, superior and inferior thyroid arteries and the blood flow range from 4 to 6 ml./ min./ gm.

The adrenergic nervous system can influence thyroid function driectly as well as by changing glandular blood flow (Fawcett et. al., 1969).

Thyroid Hormones:

Formation of normal quantities of thyroid hormone ultimately depends upon the availability of adequate quantities of exogenous iodine. In the body, iodide is largly confined

to the extra cellular fluid, also found within the red blood cell and is concentrated in the intraluminal fluids of the gastrointestinal tract, notably the saliva and gastric juice.

In addition, untill bound to organic compounds, iodide brought into the thyroid by active transport is in essence a portion of extracellular iodide. The concentration of iodide in extracellular fluid is normally quite low about 1-1.5 μ g/ 100 ml. and the content of the peripheral pool about 250 μ g. Small amounts of iodid are lost in expired air and through the skin, but the major part cleared through the thyroid and the kidneys. Thyroid contains about 8000 μ g. of body iodine and this pool turns over quite slowly (about 1% day). (Ingbar, 1978).

Iodide enters the thyroid from the extracellular fluid by an active transport mechanism which is energy requiring process, highly dependent upon continued generation of phosphate bond and closely related to the function of Na^+, K^+ dependent ATP ase system. (Bastomsky, 1974). Iodide transport is enhanced by TSH and very important is the internal autoregulatory system by which the activity of iodide transport and its responsiveness to TSH stimiulation vary inversely with the glandular content of the organic iodine (Ingbar, 1978).

Iodide then enters into a series of reactions leading to the synthesis of the active thyroid hormones, firstly is oxidation of iodide mediated by a peroxidase, then iodinations occur leading to formation of hormonally inactive

iodotyrosines, monoiodotyrosin (M.I.T.) and diiodotyrosin (D.I.T) occuring within a performed thyroprotein mollecule, rather than in free amino acids that are then incorporated into protein (Taurog, 1974).

Then synthesis of hormonally active iodothyronines, T_4 and T_3 occur.

Nevertheless, the manner in which T_4 is synthesized remains uncertain but 2 general hypothesis have received major consideration, the first is that T_4 and T_3 are formed by the interaction of a peptide-bound D.I.T. with an oxidation product of D.I.T. or M.I.T., respectively. The second is that coupling of two iodotyrosines, both of which are initially held in peptide bond within the thyroglobulin mollecule (Taurog, 1974).

The thyroid is unique among the endocrine glands by virtue of the large store of the hormone and the slow overall rate at which the hormone normally turns over (Chopra et. al., 1973).

T_4 and T_3 enter the blood directly after liberation from thyroglobulin by proteolytic cleavage within the follicular cell, few minutes after stimulation by T.S.H. (Greer and Haibach, 1974).

The thyroid is capable of deiodinating both T_4 and T_3 and generating the latter from the former, but under normal conditions is probably small. Some thyroglobulin can be detected by radioimmunoassay in the blood of most normal

individuals (Stanbury, 1978). Thyroglobulin is the principal iodoprotein of the thyroid gland and form the major component of thyroid mass (Ui, 1974).

Very important now, are the non thyroglobulin proteins of the thyroid especially the soluble proteins with a sedimentation coefficient of approximately 4(4 S or S-1 iodoprotein). small quantities of this protein are found in normal thyroid and larger quantities detected in a wide variety of thyroid hyperfunction disorders, irrespective of the rate of T_4 and T_3 synthesis. A similar protein is also found in some thyroid neoplasms. (Otten et. al, 1971).

In the plasma, there is a wide variety of iodothyronines and their metabolic derivatives, of these T_4 is of highest concentration and it is the only one arises solely by direct secretion from thyroid gland.

Most of plasma T_3 is derived from the peripheral tissues by monodeiodination from T_4 and to a slight extent is secreted from the thyroid.

Also from T_4 and T_3 in the peripheral tissues, other iodothyronines are generated, principally are Reversal T_3 (r T_3) and 3, 3' di iodo L. thyronine (3, 3' - T_2), and trace concentrations of other diiodothyronines, monoiodothyronines and conjugates there of with glucouronic or sulfuric acid (woeber and Ingbar, 1974).

T_4 is mainly associated with a T_4-binding interα-globulin (T.B.G.) and a T_4 binding prealbumin (TBPA) and to limited

extent albumin. T_3 is bound mainly by TBG and to small extent albumin (Nicoloff, 1978).

About 80% of the metaboliom of thyroid hormones is derived by enzymatic monodeiodination at a time. T_4 is acted upon by two monodeiodinated enzymes, one of them is a $5'$ monodeiodenase which yield T_3, the other, a 5 monodeiodinase yields r T_3.

T_3 and r T_3 by the action of $5'$, 5 monodeiodinases yield all of three possible forms of diiodo-L-thyronine (T_2) and these in turn are monodeiodinated to yield the two possible types of monoiodo-L-thyronine (T_1).

At least 80% of normal T_3 and all of r T_3 production are formed by peripheral generation from T_4. (Burman, 1978).

T_3 is several times more active than T_4 is, while r T_3 is inactive, so the choice between $5'$ monodeiodination and 5 monodeiodination of T_4 is a choice between hormone activation and hormone inactivation (Larsen et al 1979).

The pituitary gland has an extremely active $5'$ monodeiodinase and T_3 generated here from T_4 is an important determinant of TSH secretion, while the brain has converse pattern, and the liver and kidney have equal activities of the two enzymes. (Ingbar and Borges, 1979).

Regulation of the thyroid, however, seems more complex and more extensive than that of other endocrine organs. The thyroid participates with the hypothalamus and pituitary in classic type of feed back control in which thyrotropin

releasing hormone (TRH) stimulates first the release and later the synthesis of TSH, while thyroid hormones inhibit indirectly these functions. Inaddition, there is intrinsic regulatory mechanism that creat an inverse relationship between glandular organic iodine and the activity of hormonogenetic mechanisms. Furthermore, relative to other metabolic hormones like insulin, the effects of thyroid hormones, although less dramatic, are much longer lasting (Florsheim, 1974 and Reichlin, 1978).

Organic iodine inhibits adenyl cyclase response to T.S.H (Ingbar 1978 a).

Thyroid hormones have a primary and independent actions at several sites including the nucleus, the mitochondrion and the plasma membrane of the cells. At the nuclear level, there is saturable, high affinity binding sites or receptors for T_3 which resemble each other substantially in being acidic (non histone) chromatin proteins and whose affinity for T_3 is 10 times that for T_4. A variety of nuclear events occur like the increase in the activity of RNA polymerases I and II, an increase in nuclear globulins and non histone proteins, nuclear phosphokinase activity is increased. T_3 enhances the concentration of specific m RNA for growth hormone and for α_2 globulin (De Groat, 1979).

At the mitochondrial level, there is high affinity, limited capcity binding of T_3 specific mitochondrial components or receptors which are lipoprotein derived from the inner mitochondrial membrane, the site of oxidative phosphorylation and the