SOME THYROID ASPECTS IN DIABETES MELLITUS

THESIS
FOR PARTIAL FULFILLMENT OF MASTER DEGREE
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Presented By

Kamal Rizkalla Saba

supervised by

PROF. DR. AHMED GHAREEB
Ass.Prof.Dr.Moghazi Ali Mahgoub Ass. Prof. Dr. Sayed Raafat

General Medicine
Ain Shams University

FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

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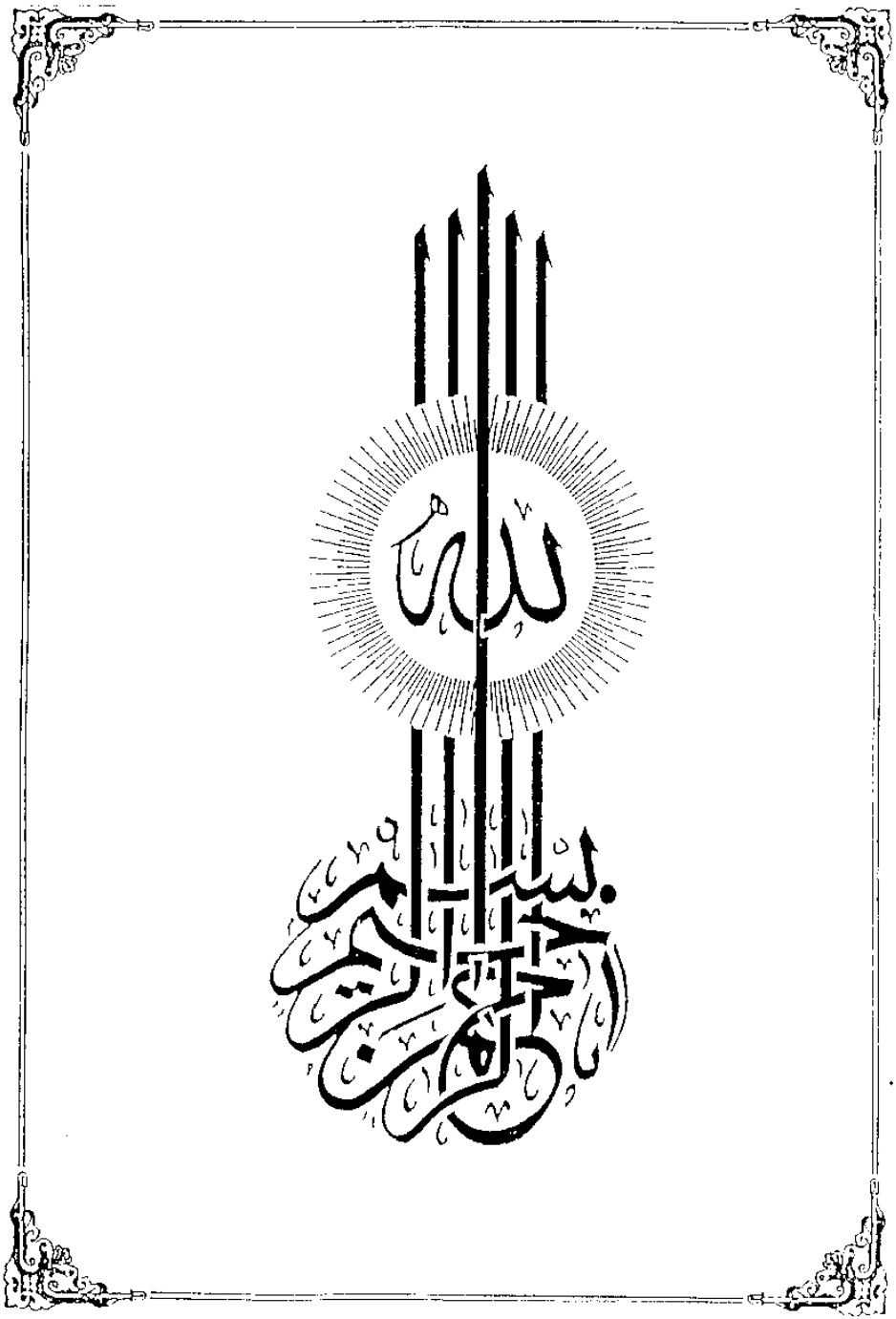


C O N T E N T S

INTRODUCTION

It is common to find in patients with diabetes mellitus disturbance in lipid metabolism evidenced by hypercholesterolaemia (Danowski et al, 1966) and (Raafat, 1973).

Since hypothyrodism is also accompanied by changes in blood lipids, the aim of this thesis is to evaluate thyroid function in diabetes and to find out to what extent this contributes to this important biochemical change which leads to most of the major complications of diabetes.

REVIEW OF LITERATURE

THYROID HORMONE SYNTHESIS AND RELEASE (Tong 1974)

Iodine and thyroid hormone

The iodine in the body is distributed as follows: 50% in muscle, 20% in the thyroid gland, 10% in skin, 6% in bone and 14% in other tissues .

Iodine is an essential constituent of the thyroid hormones tetraiodothyronine (T_4) and triiodothyronine (T_3) .

In humans the iodine secreted in hormonal form by the thyroid normally amounts to only about 50 ug/ day derived from dietafy iodine intake that normally need not exceed 200 ug/ day .

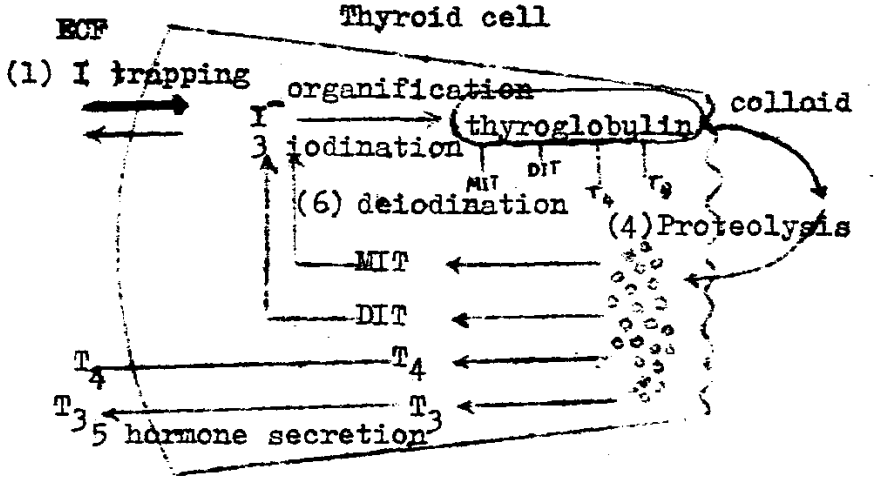
Thyroid iodine represents an iodine reserve sufficient for long as 6 monthes when exogenous supplies of iodine are compeletely cut off. Of the iodine in the thyroid more than 95% occured as stored colloid in the form of iodotyrosine and iodothyronine residues tightly bound within the polypeptide sequence of thyroglobulin .

The remaining iodine consists mainly of trapped iodine along with varied but small proportions of particulate iodeproteins, iodinated lipids and free iodothyronines and iodotyrosines.

The iodine in plasma also occur in protein bound and nonprotein bound moities. Unlike the thyroglobulin iodine of the gland, plasma protein bound iodine (BBI) Consists of the iodothyronine hormones loosely attached by nencovalent bound to the plasma proteins in a concentration of about 4 - 8 ug / 100 ml in the plasma of normal man.

The plasma inorganic iodide concentration varies with iodine intake but normally does not exceed 1 ug/ 100 ml. It is from this iodids pool where iodide is provided at a concentration of less than 10^{-7} M, that iodide is trapped by the thyroidal iodide pump and transported into the gland for the iodination of the thyroglobulin .

The pathway of iodine metabolism in the thyroid:-



1. Trapping :- Extracellular iodide is actively transperted through the basal membrane surface into the follicular cell.

2. Organification: Within the cell probably at a site very near to the surface of the apical microvilli the iodide is oxidised .

3. Binding to tyrosine and Coupling of moniodo and diiodo compound.

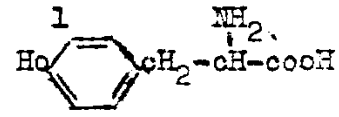
The newly iodinated thyroglobulin is promply extruded into the follicular lumen for storage.

4. Proteolysis: Stored thyroglobulin is resorbed by a pinocytosis like process and apparently through the mediation of lysosomes the thyroglobulin is hydrolyzed so free iodotyrosines and iodothyronines are released .

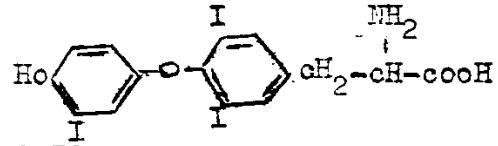
5. Hormone secretion: The iodothyronines are discharged into the E.C.F.

6. Deiodination : The iodotyrosines are deiodinated by speciefic enzymes and their iodine recycled through the iodine pool.

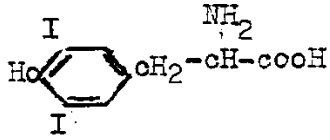
NB: All such steps are enzymatically determined .

(A) 

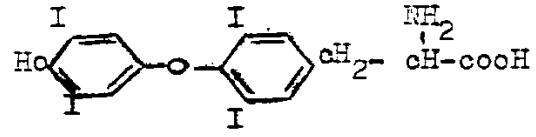
3.Monoiodotyrosine

(C) 

3.53 Triiodothyronine

(B) 

3.5 Diiodotyrosine

(D) 

Thyroxine

Active transport of the iodide:-

Concentration of the iodide by the thyroid involves an active transport process because iodide is transported into the thyroid against an electrochemical gradient. The iodide transport mechanism is deperdent on exidative phosphorylation as demonstrated by the fact that it can be inhibited by anoxia, CN^-, 2.4 Dinitrophenol and hypothermia.

Also iodide transport is competitively inhibited by such similar monovalent anions as SCN^- and ClO_4^- .

Intrathyroidal iodide is not irreversibly trapped within the gland but exists there in a diffusible form freely exchangable with external iodide. Hence previously concentrated radioiodide will exit from the gland if the transport machanism is inhibited by ClO_4^- or by respiratory inhibition via CN^-, anoxia or hypothermia .

The magnitude of the T:S ratio (which is the ratio of the iodide concentration of the thyroid to that of the serum) is most readily viewed to be the resultant of the opposing process of iodide influx and efflux. Influx component is primarily effected by an iodide pump while the efflux reflects iodide diffusion or leak .

Mode of action of TSH in the stimulation of the iodide transport mechanism:-

TSH stimulation of the iodide influx could be blocked by Actinomycin D (an antibiotic which inhibit DNA dependent RNA synthesis) and by puromycin or cycloheximide which inhibits protein synthesis.

These finding indicate that the TSH action involves the induction of enzyme which contributes to an augmentation of the capacity of the iodide pump without affecting its apparent affinity for iodide.

It might be that TSH regulates the induction of an iodide transferase .

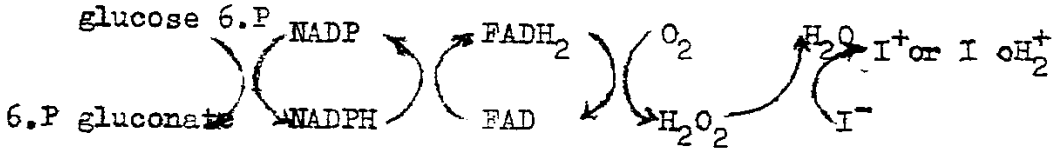
Although iodide is accumulated by isolated thyroid cells, the lumen of the intact follicle serve as a secondary reservoir for accumulated iodide and the existense of iodide concentration in the folliculer lumen indicates that an iodide pump exists both at the basal cell surface to transport iodide from the extracelluler fluid into the cell and at the apical cell surface to transport iodide from cell to lumen. Such a tandem machanism would provide for greater efficiency in the intrathyroidal iodide accumulation.

Iodide oxidation: H_2O_2 has become accepted as the agent which oxidize iodide for the iodination of thyroglobulin because of the oxidizing agent commonly present in the biological systems only O_2 and H_2O_2 with redox potentials of + 0.82 and + 1,3V respectively, are stronger oxidizing agent than iodine .

A clear demonstration of the ability of H_2O_2 to promote iodination may be by simply adding H_2O_2 to a solution of iodide and tyrosine. In the abcense of H_2O_2 no iodination will occur, upon addition of the H_2O_2 iodotyrosine formation will proceed. Than the experimentation has been directed at the characterization of the peroxidase which might catalyze the reaction between H_2O_2 and iodide .

In vitro it has been found that the peroxidase preparations stimulate H_2O_2mediated iodination reactions by as much as 100 folds, but it still remains to be ascertained that these peroxidases are in fact involved in the process of thryoglobulin iodination as it occurs in the thyroid. But against this possibility is that the rates of iodide oxidation in the thyroid are so very slow that it seem entirely reasonable to expect that H_2O_2 could be generated at adequate rates to support this process and that peroxidase action need not be involved.

At last we can correlate between iodination and glucose oxidation which might be portrayed schematically as follow:-



The well known stimulatory action of TSH on glucose oxidation and iodination can be explained either as:-

1. A primary stimulation of the glucose oxidation which would secondarily increase NADP reduction, H_2O_2 production and hence iodination .
2. Or a primary increase in iodination which would secondarily enhance reoxidation of NADPH, shift the NADP-NADPH ratio toward NADP and this increase glucose oxidation.

<u>The substitution of the iodine into the tyrosyl residues of thyroglobulin:-</u>

The name (tyrosine iodinase) has been applied to a purely hypothetical enzyme that is postulated to catalyze the substitution of iodine onto the tyrosyl residues of the