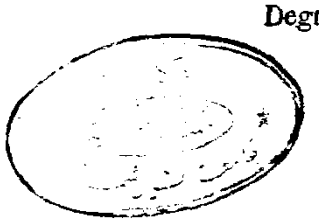
EFFECT OF ANTITHYROID DRUGS ON BLOOD CATECHOLAMINES LEVEL IN THYROTOXIC PATIENTS

THESIS

Submitted In Partial Fulfilment For Master Degree (Endocrinology and Metabolism)



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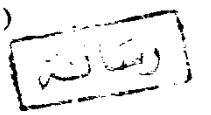

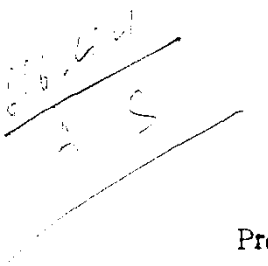

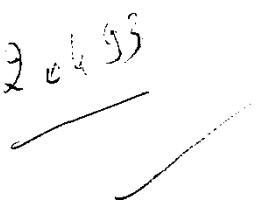

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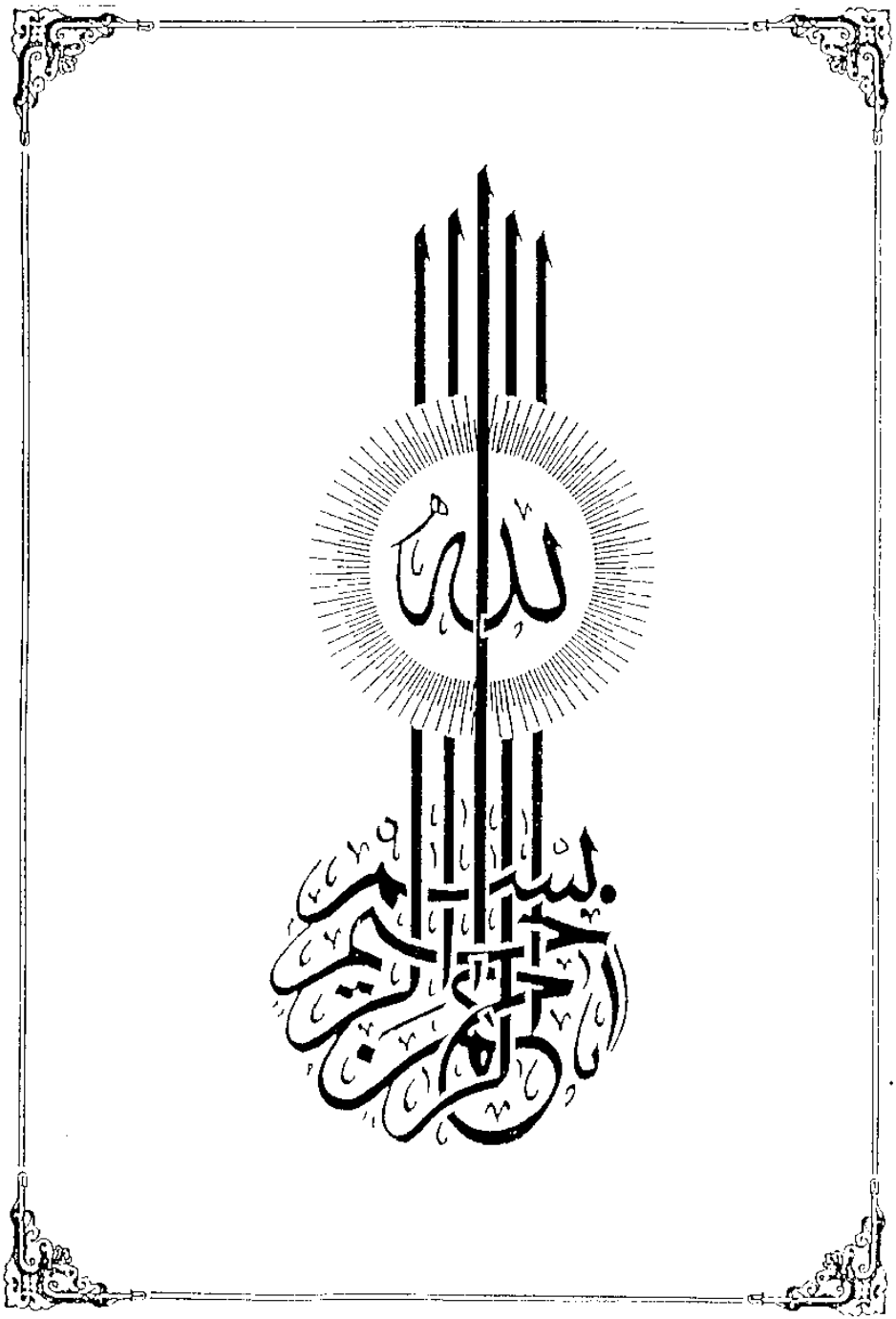

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REVIEW OF LITERATURE

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The response of many mammalian tissues to adrenergic amines is influenced by the thyroid state (Sainz and Fain, 1980) . The striking relationship between the clinical syndrome of thyrotoxicosis and the effects of catecholamines excess has been apparent for many decades. Recognition of this relationship has led several investigators to attempt control of certain clinical manifestations of thyrotoxicosis through the use of various antiadrenergic agents (Grossman et al., 1971) .

Many of the symptoms and signs of thyrotoxicosis appear to reflect altered sympathetic nervous system activity such as tachycardia and tremors . The relationship of hyperthyroidism to adrenergic sensitivity involves several mechanisms, at least one of which is receptor mediated (Davis and Lafkowitz, 1980) .

The thyroid functional state can affect the body response to catecholamines by alterations in receptor number or in phosphodiesterase activity or interaction between thyroid hormones and catecholamines may lie at sites more distal than protein kinase activation (Guarnieri et al., 1980) . Williams et al. (1977) demonstrated

increased number of B-adrenergic receptors (up regulation) in heart membranes of experimental hyperthyroidism. Kunos (1977) suggested that thyroid hormones modulate interconversion of alpha and beta adrenoceptors via allosteric transitions of a single basic structure .

Giaraldi and Marinetti (1977) showed that in tissues in which the sympathetic and parasympathetic nervous systems are antagonistic, such as heart and skeletal muscles, hyperthyroidism increases B-adrenoceptor number while reducing the number of muscarinic cholinergic receptors . In some organs such as salivary glands , however , the actions of sympathetic and parasympathetic stimuli are not antagonistic , the major effect of thyroid hormones is to increase B-adrenoceptor number without a concomitant change in cholinergic receptors (Pointon and Banerjee , 1979) .

Bray and Jacobs (1974) postulated a model for thyroid hormones-catecholamines interaction . They reported that thyroid hormones have effects on several circulating hormones whose intracellular responses are mediated by cAMP. The circulating message interacts at the cell membrane with a membrane-bound adenyl cyclase enzyme .

Receptor sites for various adrenergic receptors and inhibitor drugs are in close proximity . The interaction of these various agents at the cell membrane leads to an increase or decrease in the quantity of active adenyl cyclase which, in turn, catalizes the conversion of adenosine triphosphate (ATP) to 3', 5' adenosine monophosphate (c AMP) and pyrophosphate . c AMP, then , converts one or more inactive enzymes to an active form . These active enzymes are responsible either directly or indirectly for the various physiological or biochemical effects (Bray and Jacobs , 1974) (Figure 1) .

Alterations in thyroid function change certain responses to catecholamines without influencing others . The calorigenic effects of epinephrine are almost completely abolished by thyroidectomy and are potentiated by treatment with thyroxine (Swanson, 1956) . Similarly, the concentration of free fatty acids in plasma is reduced in hypothyroidism but increased in hyperthyroidism (Rich et al., 1959) . Moreover, treatment with thyroxine enhances the sensitivity of adipose tissues to the lipolytic effects of catecholamines (Vaughan , 1967) . Furthermore, depletion of glycogen in response to catecholamines in cardiac and skeletal muscles is augmented by thyroxine .

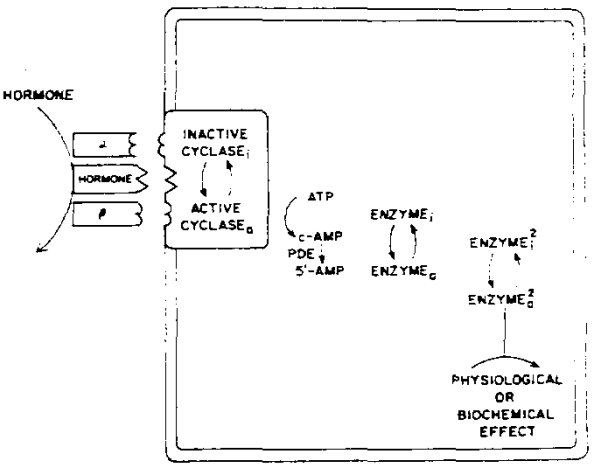

Figure (1):

Interactions between thyroid hormones and alpha and Beta adrenergic receptors (Bray and Jacobs, 1974) .

Because of their low plasma concentration, the accurate measurement of physiologic levels of norepinephrine and epinephrine in plasma has been virtually impossible until recently. Plasma catecholamines concentration vary widely in a given individual under different conditions . Two- to threefold increments occur regularly with assumption of the upright posture and larger increments occur during exercise . There is no sex difference in plasma catecholamines levels . Plasma norepinephrine (but not epinephrine) concentration increases slightly with age (Ziegler et al., 1976) .

Plasma levels of epinephrine predominently reflect adrenal medullary secretion . In contrast, plasma norepinephrine represents that proportion of neurotransmitter released by exocytosis from nerve endings and which diffuses from the synaptic cleft into the circulation and is not inactivated, although a small proportion is also secreted from the adrenal medulla (Holly and Makin,1983). Gerich et al. (1979) illustrated that under conditions of stress, when adrenomedullary epinephrine secretion is elevated severalfold , the adrenal medulla may make an appreciable contribution to the plasma norepinephrine concentration .

It is assumed in the interpretation of plasma norepinephrine measurement that the plasma concentration is an index of sympathetic neural activity . Plasma norepinephrine concentration, however, is a function of its clearance from the plasma and its entrance into the plasma and the latter is the resultant of axonal norepinephrine release, reuptake and local metabolism .

Beside the influence of thyroid hormones on adrenergic system, catecholamines affect thyroid hormones synthesis and release by controlling thyrotropin (TSH) secretion . Scanlon et al. (1978) illustrated that the system controlling TSH secretion consists of a stimulatory input represented by the hypothalamic thyrotropin-releasing hormone (TRH) and 3 inhibitory inputs represented by the feedback effect of thyroid hormones and by the inhibiting effect of hypothalamic somatostatin and dopamine, the release of the latter two being also under neurotransmitter control . Krulich (1982) reported that nor-adrenergic system has a stimulatory influence on the secretion of TSH . Krulich et al. (1982) showed that activation of adrenergic receptors can induce either stimulation or inhibition of TSH secretion depending on the type of alpha-adrenoceptor involved .

While $alpha_1$ activation conveys an inhibitory influence, $alpha_2$ activation has a stimulatory effect . Mattila and Mannisto (1980) concluded that activation of GABAergic system (which releases gamma-amino-butyric acid) is inhibitory to TSH secretion . Sharp et al. (1981) demonstrated that morphine lowers serum TSH levels .

TSH has an important influence on thyroid gland . It stimulates all phases of hormone synthesis and release and increases the vascularity, hypertrophy and hyperplasia of thyroid cells . The primary action of TSH is to activate thyroid adenyl cyclase and to increase the glandular concentration of cAMP (Gilman and Rall, 1968). Cyclic AMP can reproduce the important action of the hormone . Prostaglandin-E_1 is also capable of stimulating accumulation of cAMP in the thyroid (Zor et al., 1969). So , it has TSH-like effects on thyroid function .

Thyrotoxicosis

The first case of thyrotoxicosis was seen by Parry in 1786, but his account was not published until 1825 . This was followed in 1935 & 1840 by Graves and Basedow whose names became applied to the disorder .

Thyrotoxicosis (hyperthyroidism) is the clinical and biochemical syndrome that results when tissues are exposed to excessive thyroid hormones concentration . The clinical manifestations may be mild or severe and they may be modified by the patient's age, presence of concomitant abnormalities in various organ systems and the duration of hyperthyroidism . It may be transient or permanent (Spaulding and Utiger , 1981) .

Thyrotoxicosis is a fairly common disorder . Most cases are due to Graves disease (Toxic diffuse goiter) although nodular goiter is not uncommon . Other causes are rare . They include excessive TSH (by pituitary tumors) and excessive thyroid hormones as in increased ingestion, thyroiditis, tumors and after thyroid irradiation .

Genetic factors operate in Graves' disease and inheritance is not simple and is unlikely to be due to a single gene.

Studies of the HLA system show an association with DW 3 - DR 3 and B 8 and any genes responsible are probably linkage disequilibrium with these HLA antigens (Clark, 1982) . The female : male ratio is about 10 : 1 and, although the disease can occur in any decade , the peak is in the third and fourth decades . Graves' disease is not primarily a thyroid disease, but a multi-system syndrome consisting of one or more of the following : hyperthyroidism , diffuse thyroid enlargement, infiltrative ophthalmopathy, infiltrative dermopathy (localized or pre-tibial myxedema) and thyroid acropathy (clubbing of fingers with subcutaneous edema , fibrosis and periosteal bone formation) (Spaulding and Utiger , 1981) .

It appears virtually certain that the excessive output of thyroid hormones is due to abnormal stimulation of thyroid gland by circulating immunoglobulins . These have been demonstrated to bind at or near to the TSH-receptor on thyroid follicular cell, to induce activation of adenyl cyclase and in consequence to activate the sub-sequent steps in biosynthesis and release of thyroid hormones . Over the years, a number of names have been given to these stimulators :long-acting thyroid stimulator(LATS),

LATS protector (LATS-P), thyroid stimulating antibodies (TSAb), thyroid stimulating immunoglobulins (TSI) and the thyrotropin-receptor antibody . Some of these immunoglobulins may bind to the TSH receptor but not activate it, others may stimulate growth of thyroid but not secretion of its hormones and yet others may affect the eyes to cause exophthalmos (Clark , 1982) . Almost invariably, autoantibodies directed against other thyroid components (thyroglobulin , microsomes) can be detected in serum . TSIs are a component of the IgG fraction of serum, the corresponding antigen is the TSH receptor or a region of the thyroid plasma membrane adjacent to it . When TSI binds to the thyroid cell, the TSH receptor is activated and hence thyroid function is stimulated (Spaulding and Utiger , 1981) .

Currently, it is considered that Graves' disease is due to a genetically-determined disorder of immunological stability which allows B-lymphocytes to proliferate and secrete these antibodies, possibly because of failure either of suppressor T-lymphocyte function or of anti-idiotype antibody production (Clark , 1982) . The role of psychological factor or other stress in precipitating the disease is still debated but it is clear that the