ATRIAL NATRIURETIC PEPTIDE IN THYROID DISORDERS

A Thesis
Submitted For Partial Fulfilment
of M.D. Degree in Internal Medicine

By

Hanan Mohamed Ali Amer
M.B., B.Ch. - M.Sc. in Internal Medicine

Supervisors

Prof. Dr. Hussein El Sayed El Damasy
Professor of Internal Medicine and Endocrinology

Prof. Dr. Sayed Mohamed Raafat Osman
Professor of Internal Medicine and Endocrinology

Prof. Dr. Soheir Mohamed Gamal El-Din
Professor of Internal Medicine and Endocrinology

Prof. Dr. Mohamed Alaa El-Din Hamid
Professor of Internal Medicine and Endocrinology

Faculty of Medicine
Ain Shams University

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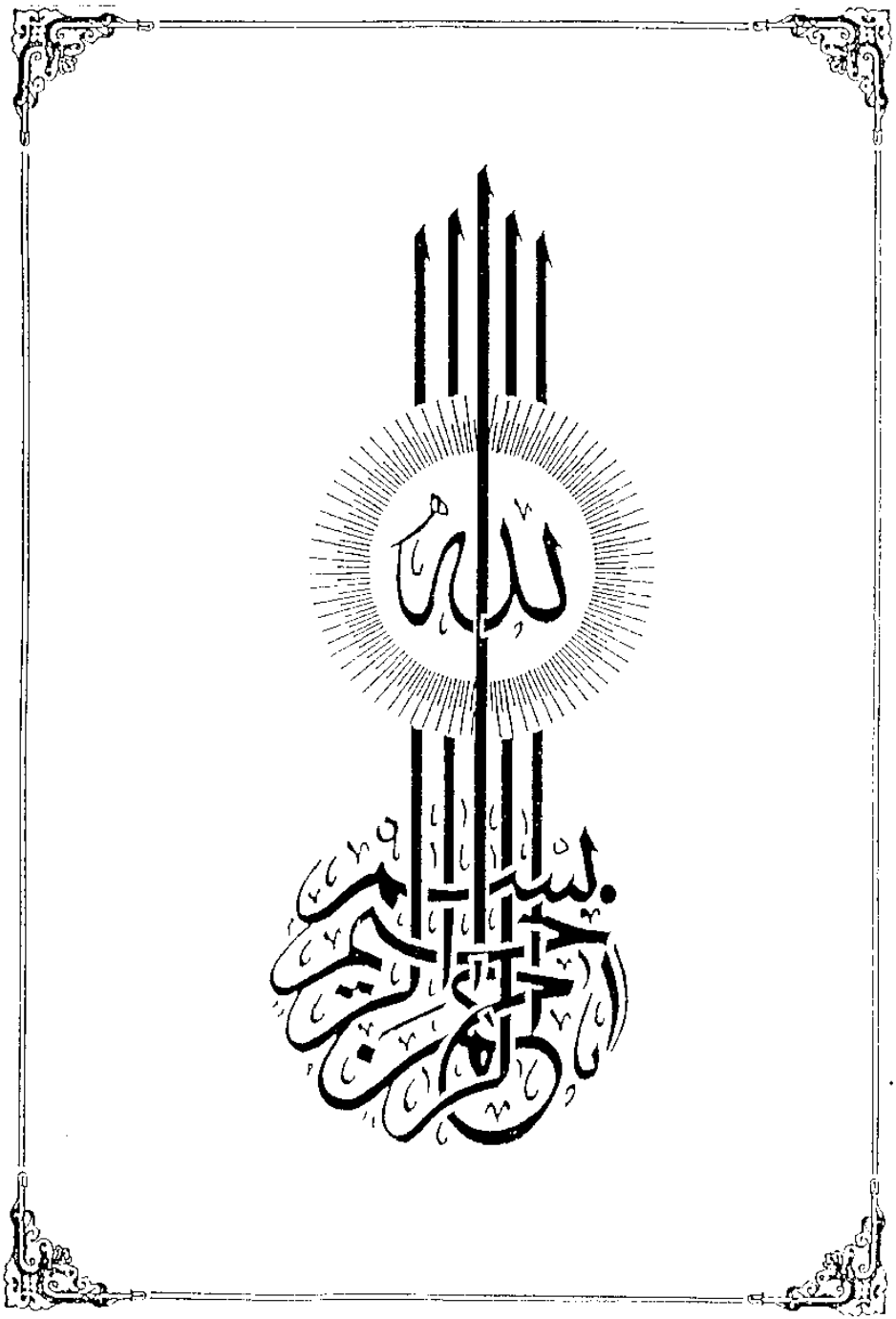

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TABLE OF CONTENTS

REVIEW OF LITERATURE

INTRODUCTION AND AIM OF WORK

Increased plasma concentration of atrial natriuretic peptide (ANP) in untreated hyperthyroid patients is reported. A significant positive correlation between the concentration of ANP and serum thyroid hormones has been found when hyperthyroid patients and healthy controls were pooled together. After restoration to euthyroid the plasma ANP concentration fell to normal (**Widescka et al., 1990b**).

The plasma ANP was decreased in severe hypothyroidism, the plasma ANP was found correlated with serum thyroxine level (**Widescka et al., 1990a**).

These results suggest that plasma ANP is frequently increased in hyperthyroidism and is decreased in severe hypothyroidism and that thyroid hormone is one of the regulatory factors for circulating ANP (**Kohno et al., 1987**).

The abnormalities in ANP dynamics in thyroid disorders may be caused by haemodynamic changes resulting from a thyroid hormone excess or deficiency (**Yamajii et al., 1988**).

Hyperthyroidism characteristically has natriuresis and vasodilatation associated with it whereas hypothyroidism is associated with impaired water excretion and vasoconstriction (**Vesely et al., 1989**).

Aim Of The Work

Is to assess changes in plasma atrial natriuretic peptide levels in patients with thyroid disorders (hyperthyroidism and hypothyroidism) and to investigate the possible role of atrial natriuretic peptide in water and electrolyte abnormalities associated with thyroid disorders.

REVIEW OF LITERATURE

ATRIAL NATRIURETIC PEPTIDE

Identity of Atrial Natriuretic Peptides:

In addition to the neuronal control of cardiovascular and renal function, several hormonal systems interact at a variety of sites to assure the maintenance of fluid and electrolyte homeostasis. Vasopressin plays a central role in this scheme where this hormone is considered the principle regulator of renal water excretion. The renin angiotensin system is another major factor regulating sodium excretion through aldosterone hormone. Recently, a third hormone system, the atrial natriuretic factors, was identified that exerts profound influences on renal, vascular and adrenal function, and thereby on the control of fluid homeostasis (**Griffin and Ojeda, 1988**).

The discovery of atrial natriuretic peptide (ANP) represents a major break through that has largely allayed the question surrounding the concept of natriuretic hormone.

Historical Background on ANP:

A. Discovery of ANP:

The control of sodium excretion by the kidney has fascinated renal physiologists and other biological scientists for many years. An

mechanical work. Morphologically this is evident from their large content of contractile elements. The rest of the cardiocytes do not share this morphological differentiation to the same degree.

In **1956, Kisch** pointed out a morphological difference between atrial and ventricular cardiocytes. He observed that atrial cardiocytes in mammals, unlike ventricular cardiocytes have morphological features of secretory cells. The most obvious difference between them is the presence of the membrane bound storage granules - the specific atrial granules - which by electron microscopy display an electron dense core and measure 250-500 nanometers. These granules are more concentrated in the central sarcoplasmic core of the atrial cardiocytes. They are adjacent to one or occasionally to both poles of the nucleus of the cardiocyte and are interpersed among the elements of a voluminous Golgi apparatus from which they arise. Numerous profiles of rough endoplasmic reticulum are also found (**Jamieson and Palade, 1964**).

These features of the mammalian atrial cardiocytes are more common in the general population of cardiocytes found in the auricles. Cardiocytes in the sino-atrial node and in specialized pathway of conduction are far less developed in this sense so that the expression of a secretory function is more often associated with cells that are also differentiated for contraction.

Bold (1979) found that experimental maneuvers leading to change in water and electrolyte balance significantly altered concentrations of these specific atrial granules in rats.

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fraction, ANP-stimulated cGMP production was dependent on ATP as a co-factor and ATP promoted a lower affinity state. This finding suggested that the kinase homology domain of NPR-A mediates the regulatory action of ATP not only for signal transduction but in the modulation of NPR-A hormone affinity.

Structure of Atrial Natriuretic Peptide:

It has been known for quite some time that atrial distension resulted in profound diuresis (increased urine flow), and the proposed mechanisms for this effect induced not only neuronal reflex activation of CNS structures (vagal afferents) but also the possible release of a volume regulatory substance from the heart.

Infusions of extracts of mammalian cardiac atrial tissue were found to stimulate significant increases in urine volume and urinary sodium excretion (natriuresis). Additionally these extracts were shown to relax precontracted vascular and gastrointestinal smooth muscle strips in vitro (a spasmolytic action) (**Griffin and Ojeda, 1988**).

Several laboratories then using a combination of biochemical and molecular techniques identified the natriuretic, diuretic and spasmolytic substances in atrial extracts as a family of peptides derived from the same precursor molecule (151 amino acids in length). The active fragments of this precursor called preatriopeptigin, identified by cDNA cloning of the human gene,

reside in the carboxy-terminus and are small peptides 24 to 28 aminoacids in length. These peptides share in common the 17-membered ring structure formed by an internal disulfide linkage and vary in the extent of their N- and C-terminal extension and are necessary for biological activities, however, the major circulating form in human is 28 aminoacids in length (ANP 99-126) from the C-terminal of a 126 residue precursor (pro-ANP) which is the principal storage form in the atrial granules (**Bold, 1985 & Matsuo and Nakazoto, 1987**).

Significant amounts of the N-terminally shortened 25 and 24 amino acids forms are present in blood. These forms possess bioactivity equal to that of the 28 aminoacid form (**Sala et al., 1987**).

The ANP isolated from atrial muscle has a molecular size of 2.500 - 13,000 daltons. Rat atrial tissues contain peptide with ANP like activities ranging from 21-126a.as. Human tissue yielded only 3 peptides containing 28, 56, 126 a.as (**Matsuo and Nakazota, 1987**).

There is a high degree of homology existing between rat pre-pro ANP which contains 152a.as and that of human which contains 151a.as (Fig I) (**Sala et al., 1987**).

Fig II shows the C-terminal 28 a.as of human pro-ANP (a.as 99-126) which has complete homology with a.as 99-125 in rat pro-ANP, except an isoleucine for methionine substitution in position 110. The core sequence is a segment of 17 a.as connected by a disulfide bridge (Figure II, B). At the N-terminal end of the molecule, the

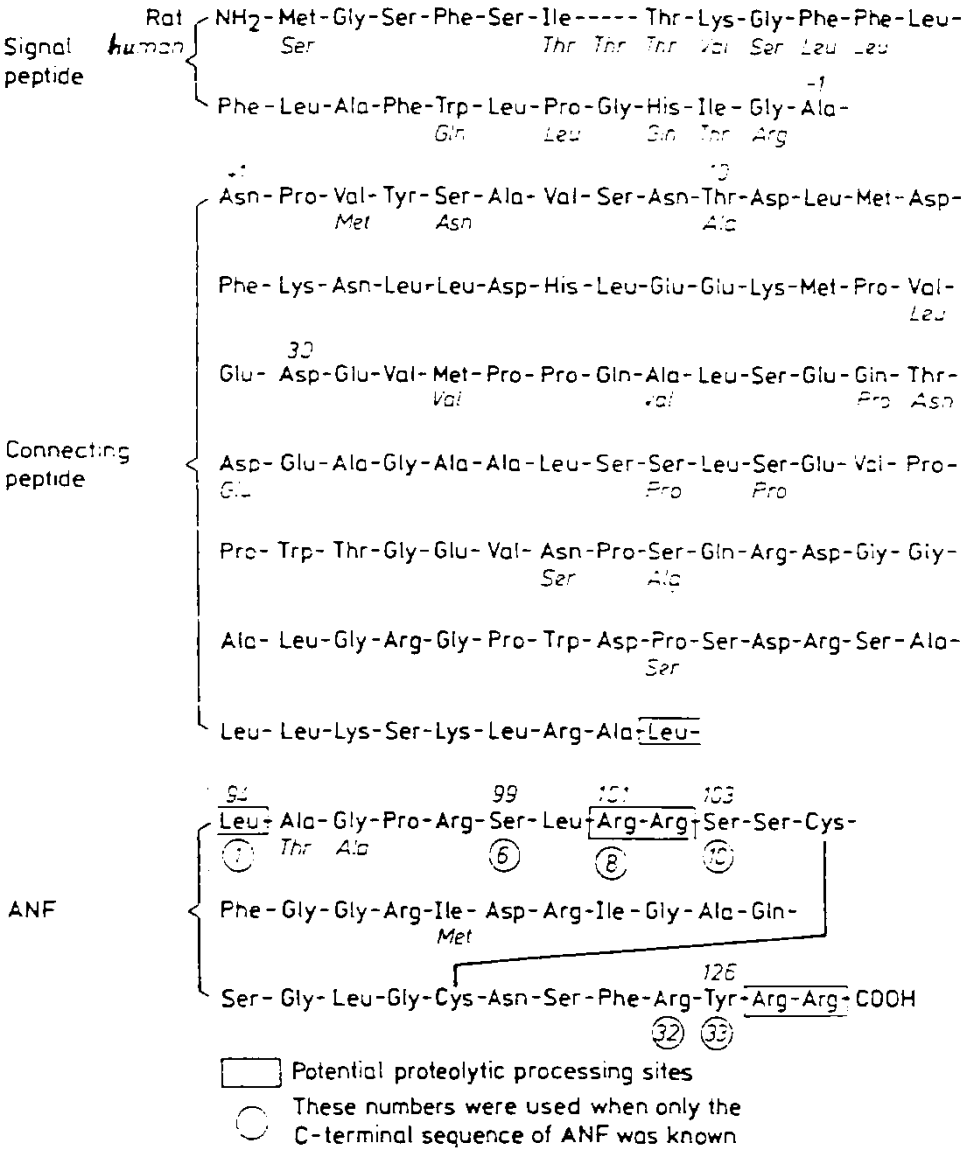

Figure (I)