STUDY OF HUMAN ATRIAL NATRIURETIC FACTOR IN FUNCTIONAL RENAL FAILURE OF CIRRHOSIS

Thesis
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CLINICAL AND CHEMICAL PATHOLOGY

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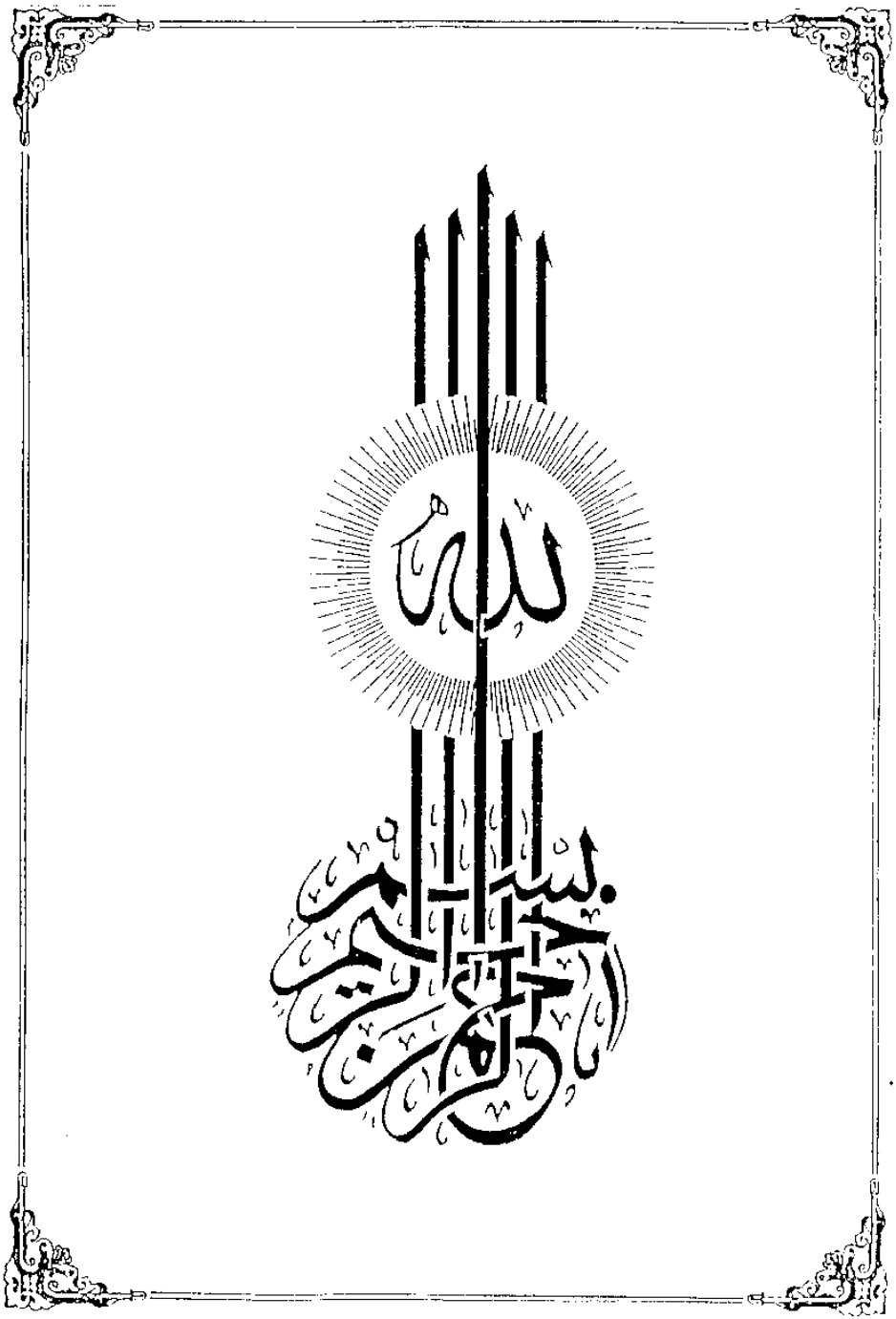

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INTRODUCTION AND AIM OF THE WORK

Introduction:

Patients with advanced liver disease develop a fatal syndrome of acute renal failure referred to as functional renal failure of cirrhosis (FRFC). Renal arterial and arteriolar vasoconstriction have been suggested to be the cause of this syndrome ***(Morgan et al., 1988)***.

Human atrial natriuretic peptides (ANP) synthesized and stored in the atrial myocardial granules are powerful relaxants for renal vasculature ***(Geller et al., 1984)*** as well as causing marked enhancement of renal salt and water excretion ***(Ballerman and Brenner, 1985)***.

A disturbance in release and/or functions of the human ANP could lead to renal arterial vasoconstriction and variation in renal sodium handling as seen in functional renal failure of cirrhosis ***(Morgan et al., 1988)***.

Aim of the work:

This work aims to study the level of circulating human atrial natriuretic peptide in patients with functional renal failure of cirrhosis (FRFC) and to compare

its level with those in patients with cirrhosis without renal impairment and in patients with acute renal failure in an attempt to clarify its role in the pathophysiology of FRFC.

The second aim is to compare the levels of ANP in plasma when assayed without extraction with those obtained after preliminary extraction.

REVIEW OF LITERATURE

Chapter I:

A. THE ATRIAL NATRIURETIC PEPTIDE

For centuries, the heart's mechanical function as a pump to maintain blood pressure for tissue perfusion has been described. Later on, the heart has also been identified as an endocrine organ in that it secretes a hormone variously referred to as atrial polypeptide, atriopeptin, auriculin, cardionatrin or atrial natriuretic peptide (ANP) ***(Cantin and Genest, 1986)***. Since then studies have been in continuous progress to elucidate this hormone's physiological importance, mechanism of action, and pathophysiologic significance in the development of certain cardiovascular and renal diseases as well as other conditions with sodium and water imbalance ***(Cosgrove, 1989)***.

1. Historical background:

In ***1956, Kish*** was the first to describe the presence of secretory granules in the cardiac atria. During the same year, the role of the atria as sites for sensing changes in blood volume was demonstrated by ***Henry and his colleagues (1956)*** when an increase in the urinary flow rate was observed in response to inflation of

the left atrium of dogs by a balloon. These membrane-bound granules were found to be similar to those found in polypeptide-hormone-producing cells ***(DeBold et al., 1979)***. In ***1979, DeBold*** discovered that sodium deprivation leads to atrial hypergranulation, whereas sodium loading causes degranulation. Furthermore, it was shown that tissue homogenates of rat atrial myocardium resulted in a brisk and a marked increase in sodium excretion when injected intravenously in a test animal ***(DeBold et al., 1981)***.

2. Site of production:

DeBdd et al. (1981) reported that myocardial cells of the cardiac atria, but not the ventricles, contained secretory granules. However,several years later, ***Yasue and his colleagues (1989)*** were able to document the release of ANP from the ventricle in patients with dilated cardiomyopathy. They reported a significant increase in plasma ANP levels between the root of the aorta and the anterior interventricular vein, which drains the blood from the left ventricle but not from the atria, and this correlated well with impairment of left ventricular function ***(Yasue et al., 1989)***.

Oberhansli and his colleagues (1990) suggested that a reinduction of the ANP gene may occur in compensated congenital heart disease with ventricular overload and some degree of ventricular hypertrophy. Thus, both atrial and ventricular cardiocytes secrete ANP, yet in different ways. Atrial cardiocytes secrete ANP by means of a regulated pathway, because they store ANP, contain abundant secretory granules and appear to respond to appropriate stimuli. Neonatal ventricular cardiocytes release ANP rapidly after synthesis ***(Pasterac et al., 1990)***.

3. Biosynthesis and molecular structure of ANP:

Three peptides have been isolated from human extracts ***(Yandle et al., 1986)***. The molecular weight of the isolated ANP varies from 2,500-13,000 dalton ***(Laragh, 1985)***. The 28-amino acid peptide (α-human atrial natriuretic peptide (α-h-ANP)) is the biologically active molecule and is thought to be cleft from the C-terminal of the pro-ANP during release. This is the principal circulating form of ANP ***(Misono et al., 1984)*** (fig. 1).

Human atrial natriuretic peptide is synthesized as a 151-amino acid pre-pro-ANP precursor and is stored as a 126-amino acid pro-ANP in atrial myocyte granules ***(Misono et al., 1984)***.