RENIN IN CHRONIC CONGESTIVE HEART FAILURE

Essay

Submitted in Partial Fulfilment of
Master Degree (Cardiology)

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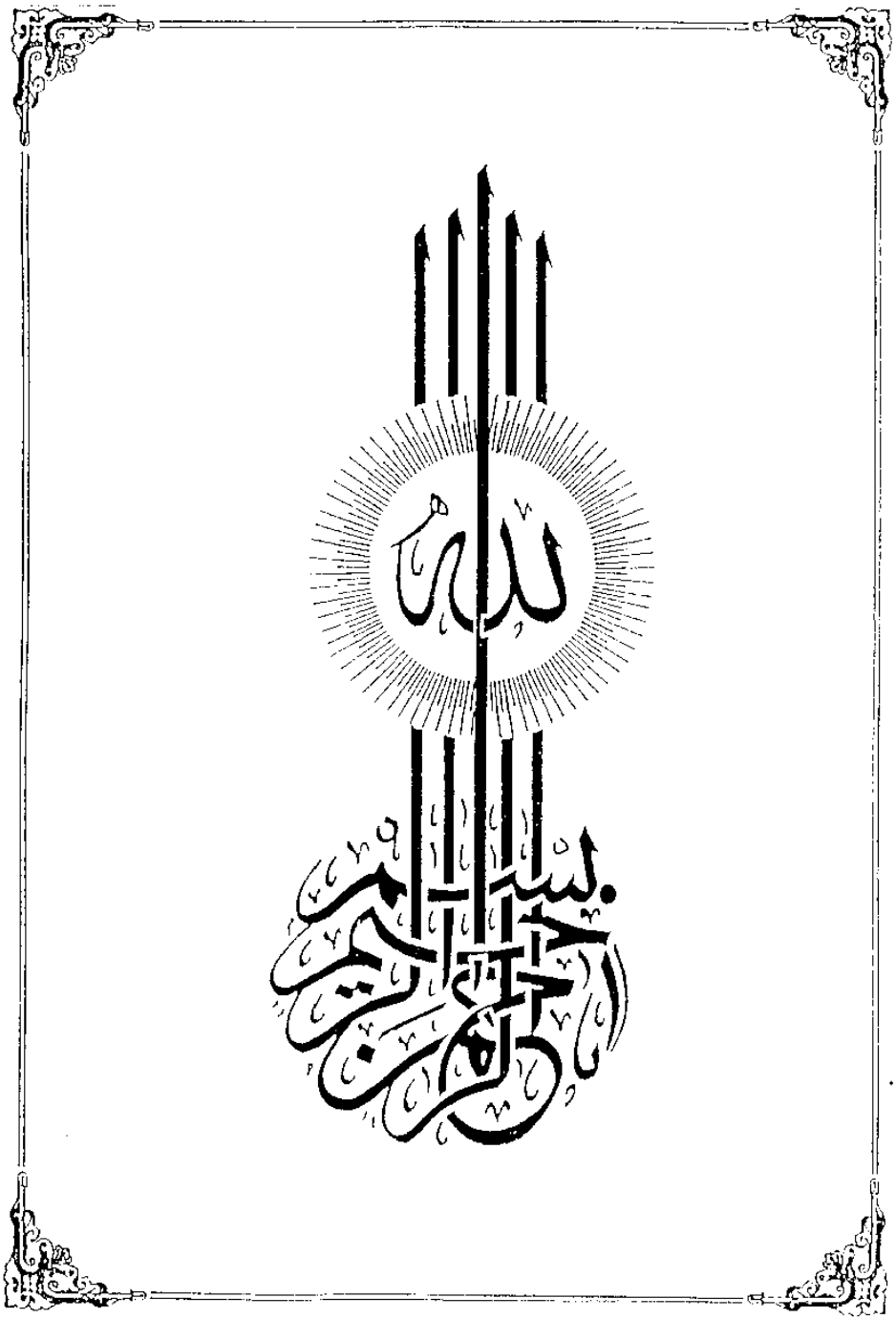
1989

To My

Parents .....



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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
ACTH	Adrenocorticotrophic Hormone
ADH	Antidiuretic Hormone
AMP	Adenosine mono-phosphate
CHF	Congestive Heart Failure
DNA	Deoxyribonucleic Acid
DOCA	Deoxycortone
EDTA	Ethylenediamine Tetra Acetic Acid
GMP	Guanosine mono-phosphate
PAC	Plasma Aldosterone Concentration
PRA	Plasma Renin Activity
RAAS	Renin Angiotensin Aldosterone System
RNA	Ribonucleic Acid
tCO_2	Total Carbon Dioxide

INTRODUCTION &
AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

Among the homeostatic mechanisms activated when the heart fails as a pump, an increase in peripheral vascular resistance and expansion of the extracellular fluid volume secondary to salt and water retention are prominent.

The contribution of the renin-angiotensin-aldosterone system (RAAS) to these two responses, and thus the pathogenesis of the clinical syndrome is well known.

Recent experimental studies in conscious animals with cardiac failure have suggested that the (RAAS) is activated early, during the acute phase after induction of low cardiac output.

During severe decompensated left ventricular failure before development of extracellular fluid volume expansion and restoration of systemic blood pressure, plasma renin activity (PRA) and aldosterone levels are markedly elevated. With stabilization of cardiac failure and extracellular fluid volume expansion PRA and aldosterone levels return to normal.

The aim of this work is to study renin in congestive heart failure.

REVIEW OF LITERATURE

The Renin-Angiotensin System

Historical Point

It is worthy to mention that renin was discovered at the close of the 19th century. The names of Tigerstedt and Bergman are associated with the first description in 1898 of renin extracted from the kidney.

Tigerstedt, was the senior worker in the partnership, he was the professor of physiology in karolinska institute, Stockholm.

Tigerstedt and Bergman established a role for the kidney in blood pressure regulation. In a classic experiment, they produced hypertension in dogs by injecting a crude extract of kidney, which they called renin.

Goldblatt 1934 called the attention of modern investigators to renal mechanisms of blood pressure control by producing hypertension in dog by clamping the renal artery. This experiment suggested the release of a presser substance from the kidney when its circulation was impaired. Since that time, a cascade of enzymes, peptide and steroid hormones and cofactors belonging to the renin angiotensin-aldosterone system have been identified and characterized.

Anatomy, Physiology and Biochemistry

Renin is a proteolytic enzyme that is synthesized, stored, and secreted mainly by the kidney.

Renin like enzymes have been extracted from a variety of organs, including the uterus, placenta, fetal membranes and amniotic fluid. (Carretero and Houle, 1970), brain (Ganten, 1971), adrenal glands (Ryan, 1967) and the submaxillary salivary gland of the white mouse (Cohen, 1972).

Although external sources have been used to explain the occasional finding of renin activity in the blood of anephric patients (Capelli, 1968) there is as yet no evidence that these external sources have any physiologic role in blood pressure regulation. Uterine renin concentration has been shown to increase during pregnancy (Carretero et al, 1972), and has been implicated as a regulator of uterine blood flow (Ferris et al, 1972).

Release of submaxillary gland renin in response to alpha stimulator and suppression in response to alpha blockers, isoproterenol or salt and DOCA have been demonstrated in vivo (Takeda, 1969) with these exceptions, little is known of the mechanisms governing the synthesis and release of the extra-renal renin-like enzymes and of their physiologic functions.

Mechanism of Renin Action

The physiologic consequences of renin release result from a sequence of enzymatic reactions that lead to the generation of an active polypeptide hormone Fig. (1).

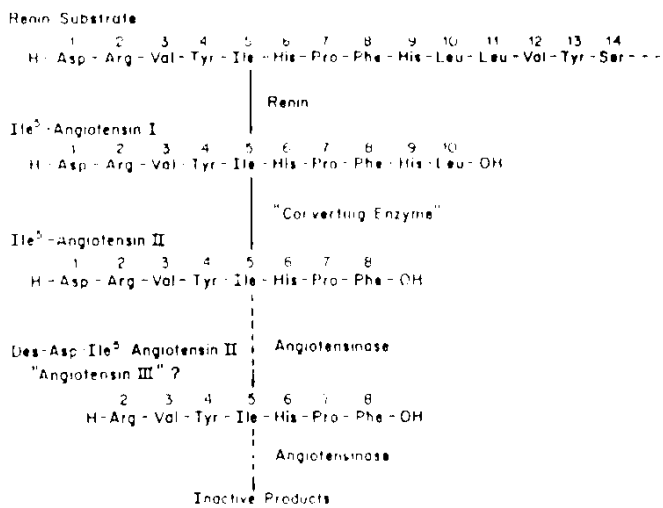

Fig. 1 : Biochemistry of the Renin-Angiotensin-Aldosterone System.

Renin is a highly specific proteolytic enzyme that has not as yet been fully purified.

The enzyme cleaves its substrate, an α_2 - globulin synthesized by the liver, to produce the decapeptide angiotensin I.

Converting enzyme, a dipeptidylcarboxypeptidase found mainly in lung but also in circulating plasma, kidney and a variety of other organ beds, removes the carboxyl terminal His-Leu from angiotensin I to produce the octapeptide angiotensin II.

Angiotensin II, a potent vasoconstrictor and stimulus of aldosterone production, is rapidly destroyed in peripheral capillary beds by a number of enzymes, the angiotensinases.

All the metabolic products of angiotensin II except the des-Asp[1] heptapeptide show little physiologic activity.

Renin release is the rate limiting step in angioltensin production; it is subject to feedback control by angiotensin II directly and indirectly through the effect of angiotensin on blood volume, blood pressure and sodium balance. (Oparil and Haber, 1974).

Renin Synthesis and Storage

Renin is synthesized and stored in membrane-bound cytoplasmic granules by cells at the vascular pole of the renal glomerulus that are generally believed to have arisen from modified smooth-muscle cells of the afferent arterioles (Edelman and Hartroft, 1961).

Both the afferent arteriole, which contains these granular cells, and the efferent arteriole which does not, are anatomically and functionally

associated with a group of specialized cells at the origin of the distal tubule that form the macula densa.

The entire structure is referred to as the juxtaglomerular apparatus (Davis, 1973) Fig. (2).

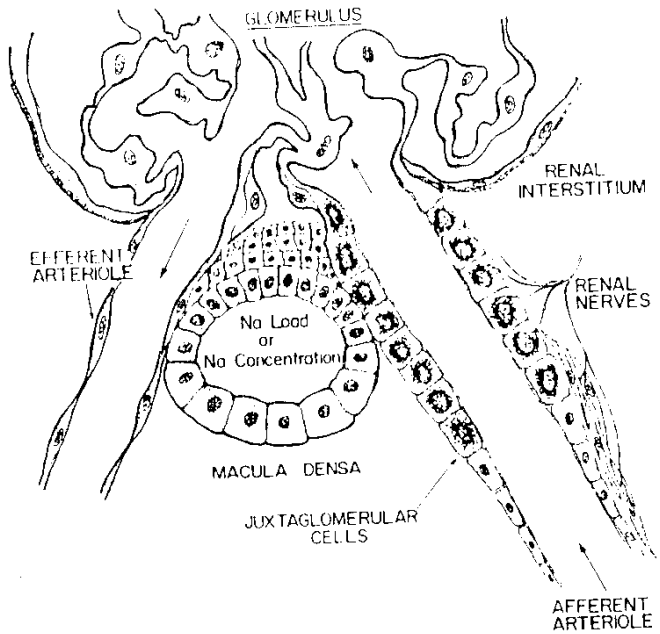

Fig. 2. The Juxtaglomerular Apparatus
After Davis, 1973.

Traditionally, intimate and fixed contact between afferent arteriole and macula densa has been described in 1960 by Oberling and Hatt.

More recently; three-dimensional analysis of serial electron micrographs has defined a different structural relation between vascular and tubular elements of the juxtaglomerular apparatus and has suggested a functional correlation (Idem, 1971).

In this model, contact between afferent arteriole and distal tubule is extensive but variable.

The vascular and tubular structures are separated by a space only 100 to 200 nm (1000 to 2000 A°) in thickness.

In addition, extraglomerular mesangial cells are in extensive and intimate contact with the macula densa.

Cytoplasmic projections of distal tubular cells penetrate into the mesangial cells, with fusion and network formation of the basement membranes (Idem, 1971).

Renin Release

Mechanisms of Renin Release :

Variability in area of contact between the elements of the juxtaglomerular apparatus provides an anatomic basis for the control of renin secretion Fig.(3).

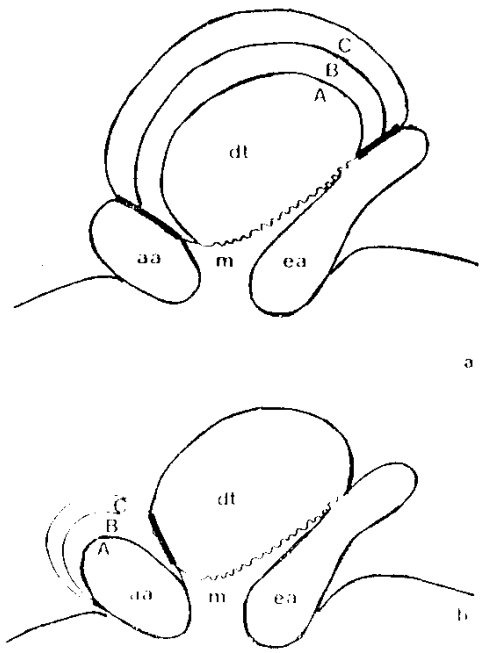

Fig. 3. Functional model of Juxtaglomerular Apparatus
After Oparil, S. et al., 1974.

If one assumes that less contact leads to an increase, and more contact to a decrease in renin secretion, the model is compatible with the two most widely held theories of the control of renin release. In keeping with the macula-densa theory, which states that renin release is regulated by changes in sodium at the distal tubule, a smaller sodium load in the distal tubule has been shown to be accompanied by a reduction in distal tubular volume and therefore decreased contact with arteriolar cells, resulting in increased renin release. Fig.(3a).

In keeping with the stretch receptor theory, which states that renin release is regulated by changes in pressure and stretch of the afferent arteriole, a smaller intra-arteriolar volume would probably be accompanied by a decrease in arteriolar contact with the macula densa cells and an increase in renin release Fig. (3b).

Although the precise cellular mechanisms governing renin release are as yet speculative, it is clear that both changes in renal perfusion pressure and either concentration or amount of sodium in the distal tubule have a regulatory effect.

The effects of blood pressure, blood volume, posture, and sodium intake on renin release are probably mediated by one of these variables. Their relative importance is a matter of active debate. (Davis, 1973).

The baroreceptor hypothesis arose from experiments in which increasing mean renal perfusion pressure led to a decrease in juxtaglomerular cell granularity. (Tobian et al, 1959).

This evidence of renin release was thought to be mediated by stretching of the afferent arteriole.