RENIN – ANGIOTENSIN – ALDOSTERONE SYSTEM IN DIABETES MELLITUS

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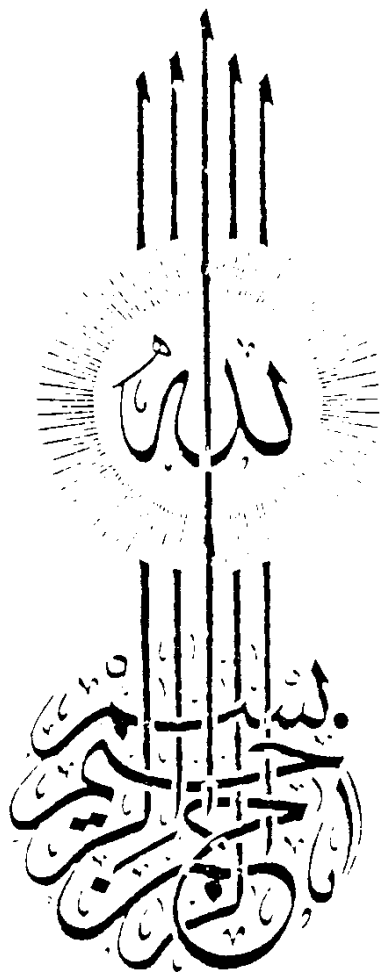

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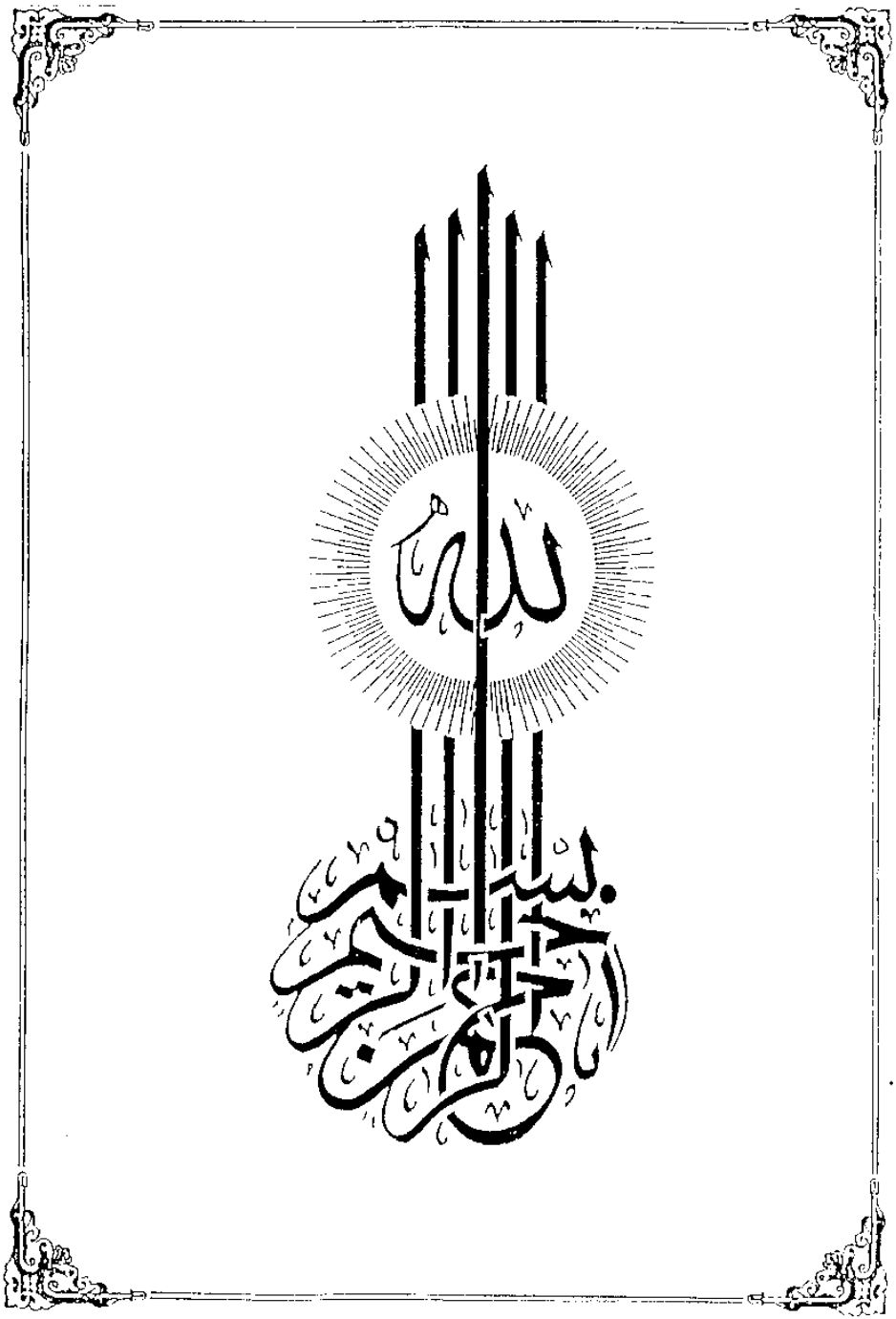

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CONTENTS

INTRODUCTION

INTRODUCTION

Numerous abnormalities in the renin-angiotensin system have been described in diabetes mellitus . Plasma renin activity has been noted to be low , normal or high in diabetic patients (Trujillo , et al., 1989) . They found that the mean plasma renin activity level was significantly low in hypertensive diabetic group , but was not significant between the control and normotensive diabetic groups .

However , Packer , et al ., (1987) , found that plasma renin is lower in the diabetics than in the non-diabetic control subjects .

Drury , et al., (1982) . reported that plasma renin activity was higher in the diabetic patients with retinopathy than in the uncomplicated diabetic patients . They raised the possibility that renin-angiotensin system might be implicated in the pathogenesis of diabetic microvascular complications .

Aim of the work

The aim of the work is to evaluate the renin-angiotensin-aldosterone system in patients with diabetes mellitus both complicated and non-complicated , and try to correlate any changes in this system with the complications occurring in diabetes mellitus.

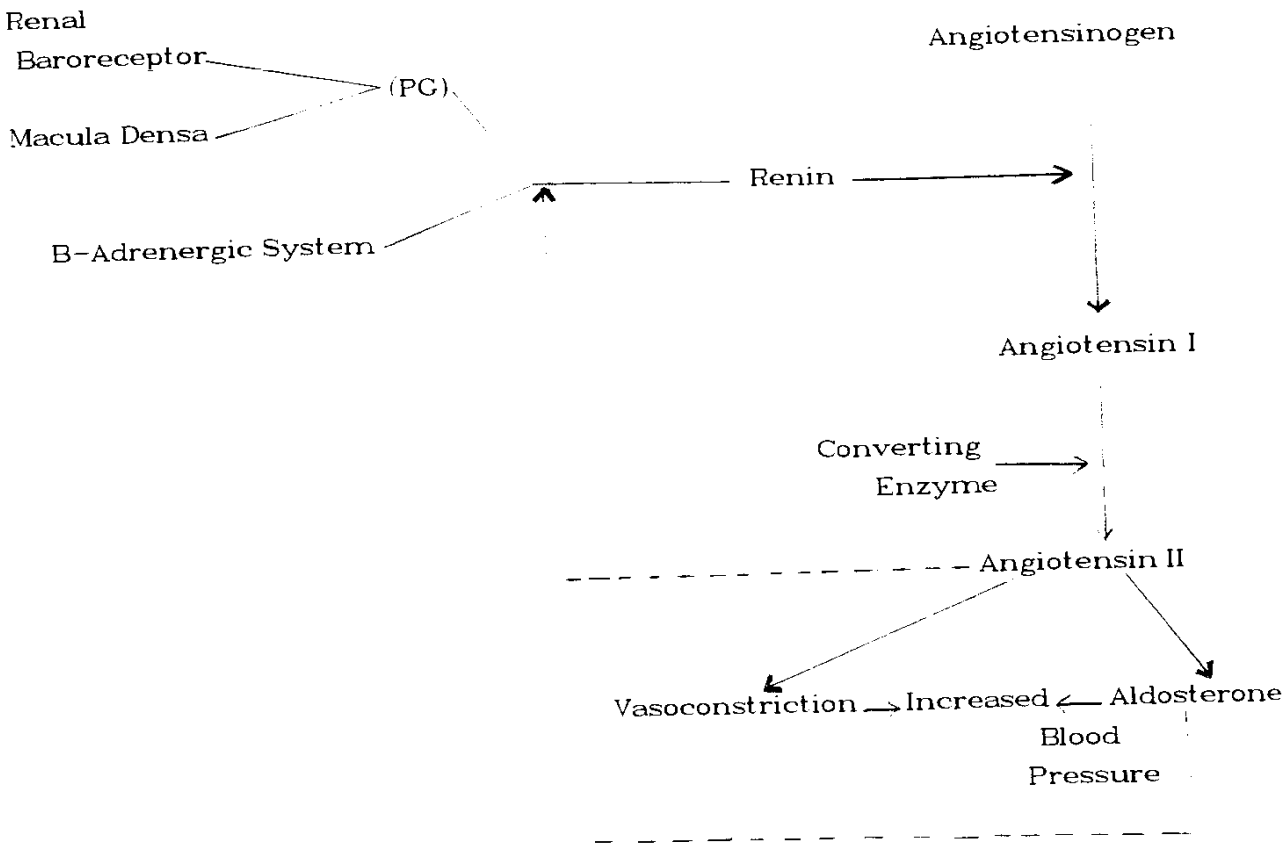
REVIEW OF LITERATURE

THE RENIN- ANGIOTENSIN -ALDOSTERONE SYSTEM

A Cascade system (fig. 1) , comprised of renin , angiotensin-II (A-II) and aldosterone , plays a key role in blood pressure homeostasis , regulation of circulating volume and maintenance of sodium - potassium balance (Hsueh and Tuck , 1990). This control system is unique in that it seem designed to protect tissue perfusion by first rapidly defending blood pressure , via angiotensin vasoconstriction . This is followed by a slower-acting limb that restores flow , via aldosterone induced renal sodium retention , an effect which in turn osmotically expands the volume of the blood and extacellular fluids (Laragh , 1981) . In normal humans it acts in concert with vasodilating and other vasoconstricting systems to maintain constant arterial pressure over a wide range of physical activity and sodium intake . Abnormalities of the renin-angiotensin-aldosterone system basically manifest as two major clinical defects one is an abnormal blood pressure response and the other an abnormal serum potassium concentration (Hsueh and Tuck , 1990) .

BIOCHEMISTRY

Renin is an aspertyl protease that catalyzes the cleavage of the decapeptide angiotensin-I (A-I) from angiotensinogen (α_2-globulin), produced by the liver. Renin , secreted by the juxtaglomerular cells of the kidney , has a molecular mass of 40,000 to 44,000 , it is a glycoprotein and is generally homologous in amino acid sequence and



(Figure 1)
The renin-angiotensin-aldosterone cascade . Solid lines represent positive influence and dashed lines represent negative influence (Hsueh , 1983) .

three dimensional structure (Oparil and Harber , 1974 & Peach , 1977). In humans , renin cleaves a leu-val bond to form angiotensin-I from the amino (NH_2) - terminus of the substrate .The substrate levels can influence the rate of renin reaction . The plasma renin substrate concentration is increased by the administration of glucocorticoids , estrogens , A-II , bilateral nephrectomy and hypoxia (Kotchen and Guthrie , 1980). Angiotensinogen concentration is decreased in the plasma of patients with liver disease or adrenal insufficiency . Different molecular weight renin substrates appear in plasma during pregnancy or administration of oral contraceptives (Hsueh , 1983) . In the absence of alteration in renin substrate concentration , changes in plasma renin activity reflect changes in renin secretion . In humans the half-life (T-1/2) of circulating renin is about 90 minutes (Derkx , et al., 1978) .

Angiotensin-I (A-I) is converted to the bioactive octapeptide angiotensin-II (A-II) by the angiotensin-converting enzyme (ACE) , a dipeptidylcarboxylpeptidase found in the vascular endothelium of the lung , kidney , and a variety of other organs (Erdos , 1975 & Oparil , 1979) . Cardiac catheterization studies indicate that the pulmonary vascular bed is responsible for 20 to 40 % of A-I to A-II conversion (Nishimura , et al., 1978). This enzyme also inactivates the vasodilator kinins . Hence , the inhibition of the converting enzyme both inhibits the formation of A-II and prolongs the effect of the kallikrein-kinin system (Huseh and Tuck , 1990) .

The T 1/2 of circulating A-II is short , about three to five seconds , because of rapid degradation by angiotensinases in blood . Removal of NH_2 -terminal aspartic acid yields a heptapeptide .

angiotensin-III (A-III) which possesses some bioactivity . Angiotensinase activity in plasma dose not correlate with activity of renin - angiotensin system and is unimportant to blood pressure homeostasis (Hsueh and Tuck , 1990) .

RENIN BIOSYNTHESIS

Renin is produced and secreted by the juxtaglomerular (JG) cells . which are differentiaed smooth muscle cells located in the media of afferent arterioles as they enter the glomeruli (Ganong . 1991). Renin is stored in granules in the JG cells which contain prominent endoplasmic reticulum and Golgi apparatus characteristic of secretory cells . Renin is also found in a granular *Lacis cells* that are located in the junction between the afferent and efferent arterioles but its significance in this location is unknown . An area of the distal tubule near its origin . the *macula densa* . lies in close contact to JG cells at the hilus of the glomerulus . The JG cells are richly innervated by sympathetic nerves . The Lacis cells . the JG cells . and the macula densa constitute the juxtaglomerular apparatus . Like other hormones . renin is synthesized as a large preprohormone . Human preprorenin contains 406 amino acid residues .The " pre "sequence or "signal peptide" is a peptide that allows the newly forming protein to penetrate the endoplasmic reticulum membrane for further processing . The presequence is rapidly cleaved to form prorenin (Pratt . et al., 1983). The prorenin contains 383 amino acid residues and after removal of the prosequence from the N-terminal of prorenin . active renin contain 340 amino acid residues is formed . Some prorenin is converted to renin in the kidneys and some is secreted . There is very little conversion to

active renin in the circulation . Prorenin is converted to renin by tissue kallikrein . but the details of the process by which renin is formed from prorenin in vivo are still unsettled (Ganong . 1991) . In humans . relatively large quantities of prorenin . compared with renin . appear to be released by the kidney into the circulation . Fifty to ninety percent of renin in normal human plasma is prorenin (Hsueh,et al., 1978) .

EXTRARENAL RENIN

Different names have been used to describe these extrarenal renin as : tissue renin . isorenin . renin like enzymes . and angiotensin-forming enzymes (Kaplan, 1982) .

A paracrine function for locally synthesized renin is suggested by the finding of A-II receptors on a number of tissues . A single gene codes for renal and non-renal renin (Soubrier . et al., 1983). indicating that all sources of renin produce the same protein . However. processing is different in renal compared with non-renal sources . which produce mainly prorenin (Re . 1984) . The extrarenal production of renin may contribute to local production of A-II and to the variety of physiologic activities of this peptide throughout the body . Components of the renin- angiotensin system are found in the walls of blood vessels . the uterus . the placenta and the fetal membranes . there is a high concentration of protein in amniotic fluid . In addition there are tissue renin-angiotensin systems in the adrenal cortex . testis . ovary . anterior and intermediate lobes of the pituitary . pineal . and brain . However . tissue renin contributes very little to the circulating renin pool since

plasma renin activity falls to near zero after the kidneys are removed (Ganong , 1991) .

CONTROL OF RENIN RELEASE

Classically , the four major mechanisms that regulate renin release in the kidney include the baroreceptors located in the renal afferent arterioles , the macula densa , the sympathetic nervous system and the negative feedback of A-II (Davis and Freeman , 1976 & Peach , 1977 & Oates , et al. , 1979 & keeton and Campbell , 1980) . Prostaglandins and calcium may mediate some of these mechanisms and may have separate effects of their own . Other agents , such as arginine vasopressin (AVP) and potassium also affect renin release (table 1) . The interplay between these mechanisms is a complex process that ultimately determines the rate of renin release .

1) Baroreceptors In The Renal Afferent Arteriole

The presence of baroreceptors was proved by the development of a non-filtering (i.e. tubular flow removed) , denervated kidney model , that responded to hemorrhage and suprarenal aortic constriction by increasing renin production (Davis and Freeman , 1976).

Changes in transmural pressure gradient appear to be the baroreceptor stimulus to renin release , thus renin secretion is inversely related to the " stretch" of the baroreceptor. Prostaglandins (PGs) are strongly implicated as the mediators of the baroreceptor signal to the JG cells . Specifically , prostacylin (PG I_2) metabolites of