CAPTOPRIL IN HYPERTENSIVE DIALYSIS PATIENTS

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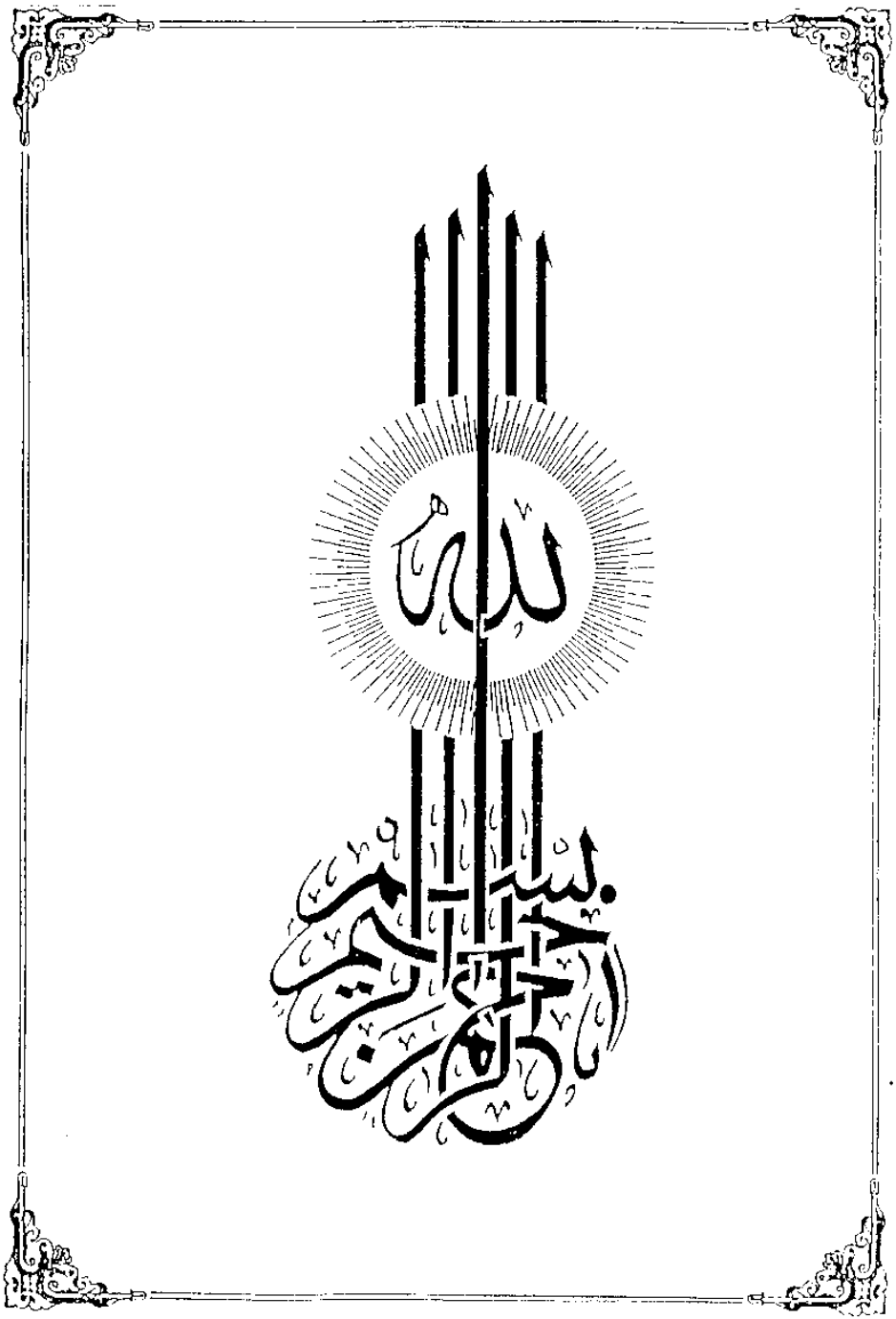

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INTRODUCTION AND AIM OF THE WORK

Hypertension in end stage chronic renal failure and - especially in uraemics on regular dialysis treatment is often observed .

For patients treated with maintenance dialysis, blood pressure monitoring and modification acquire paramount position as hypertension is a significant predisposing factor to accelerated atherosclerosis and to high incidence of cardiovascular and cerebral vascular diseases in dialysis patients (pyrpasopoulos et al 1983).

In the majority of cases, hypertension is due to increased body water, while in several cases it is due to increased peripheral resistance because of the hyperactivity of the renin - angiotensin system, therefore in many cases, hypertension is well managed by dialysis especially by ultrafiltration while this is not sufficient in other cases with high renin activity. (Robert, P. et al 1983).

Captopril, an angiotensin converting enzyme inhibitor was shown to be promising in the treatment of severe dialysis resistant hypertension of uraemics on regular dialysis therapy (Vaughan et al 1979) .

The aim of the work is to study the efficacy of captopril therapy on dialysis resistant hypertension and to report its various side effects. Also this work aimed at giving a

short review about the physiology of renin angiotensin system, pathogenesis of hypertension in chronic renal failure and the pharmacological actions of the drug .

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REVIEW

Renin - Angiotensin System

Renin is a proteolytic enzyme secreted by the kidneys. It is a glycoprotein with a molecular weight of 400,000 in humans. Anotner relatively inactive form of renin with a higher molecular weight (approximately 600000) is present in the kidneys and blood. It is apparently the precursor of the active form .

Renin activity in the granular epitheloid cells was identified by immunoflourescent methods and a correlation was found between the granulation index and renin content of the kidneys . (Black 1979).

Inactive renin is converted to active renin by tissue kallikrein then the active form acts on a glycoprotien (synthesized by the liver called angiotensinogen) releasing a decapeptide (angiotensin I). A converting enzyme (Dipeptidyl carboxy hydrolase) splits off histidyl - Leucine - from the physiologically inactive angiotensin I to form the octapeptide active form (angiotensin II). (Ganong 1981).

The largest concentration of the converting enzyme is found in the lungs, but a specific converting enzyme was demonstrated to be present in the Juxta-glomerular apparatus of the kidneys (Granger et al 1972).

Angiotensin I has a half-life about 80 minutes while angiotensin II has a shorter half-life of about 1-2 minutes. Angiotensin II is catabolised by group of enzymes called angiotensinase which includes aminopeptidase that removes the asparagine residue from NH_2 terminus of the peptide, the Heptapeptide produced is called angiotensin III which has a physiological activity of ¼ - ½ of the angiotensin II, furthermore hydrolysis to remove the next amino acid arginin inactivates angiotensin III completely , hydrolysis in middle region by endopeptidase and C terminal phenyl alanine by carboxypeptidase fragments the compound completely (Ganong 1981).

Other organs produce other angiotensin generating enzymes with renin-like activity these include, uterus, placenta, amniotic fluid and walls of blood vessels , these are called isorenin whose role is uncertain since plasma renin activity drops almost to zero when the kidneys are removed (Ganong 1981).

Asp-Arg-Val-Tyr-Lie-His-Pro-Phe-His-Leu-Val-Tyr-Ser-R] Angioten-sinogen.

renin splits this bond

Asp-Arg-Val-Tyr-Lie-His-Pro-Phe-His-Leu] Angioten-sin I.

converting enzyme splits this bond

Asp-Arg-Val-Tyr-Lie-His-Pro-Phe] Angioten-sin II.

aminopeptidase splits this bond

Angioten-sin III.

(Fig.1) Structure of Angiotensin I,II&III.

Actions of Angiotensin II (And III):-

1- Potent arteriolar vasoconstrictor .

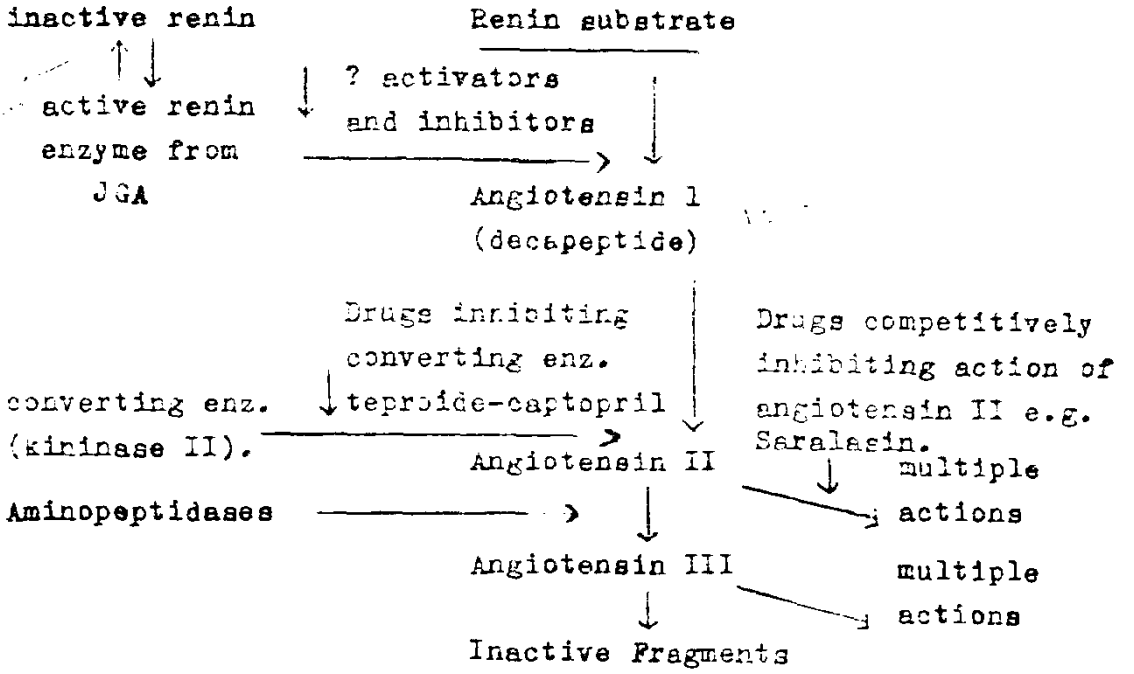
2- Direct inotropic action on the Heart .

3- It facilitates sympathetic neurotransmission at ganglia and nerve terminals.

4- Central action on vasomotor centre inhibiting vagal cardiotonic and increasing efferent sympathetic activity.

5- Central action on hypothalamic nuclei promoting thirst and antidiuretic hormone release .

6- It stimulates release of catecholamines from adrenal medulla and secretion of aldosterone from adrenal cortex (John M. Ledingham 1982).



(Fig. 2) Renin-Angiotensin System (Ledingham,M.1982).

In recent years, evidence has accumulated to involve the kallikrein - kinin - prostaglandin system in regulation of blood pressure.Kallikrein is an enzyme that reacts with inactive kininogen precursors to produce kinins with effects opposite to those of angiotensin II namely diuresis,naturesis and hypotension by vasodilation. Bradykinin the major kinin in the blood is inactivated primarily by kininase II which is the angiotensin converting enzyme (peptidyldipeptide carboxy hydrolase) that forms angiotensin II from angiotensin I. Thus inhibition of angiotensin converting enzyme (kininase II) is desirable in the treatment of hypertension since it prevents the formation of the potent vasopressor, Na and water retaining angiotensin II and prevents the degradation of the vasodilating naturetic and diuretic bradykinin (Bernard Rubin et al 1980).

Control of Renin Secretion :-

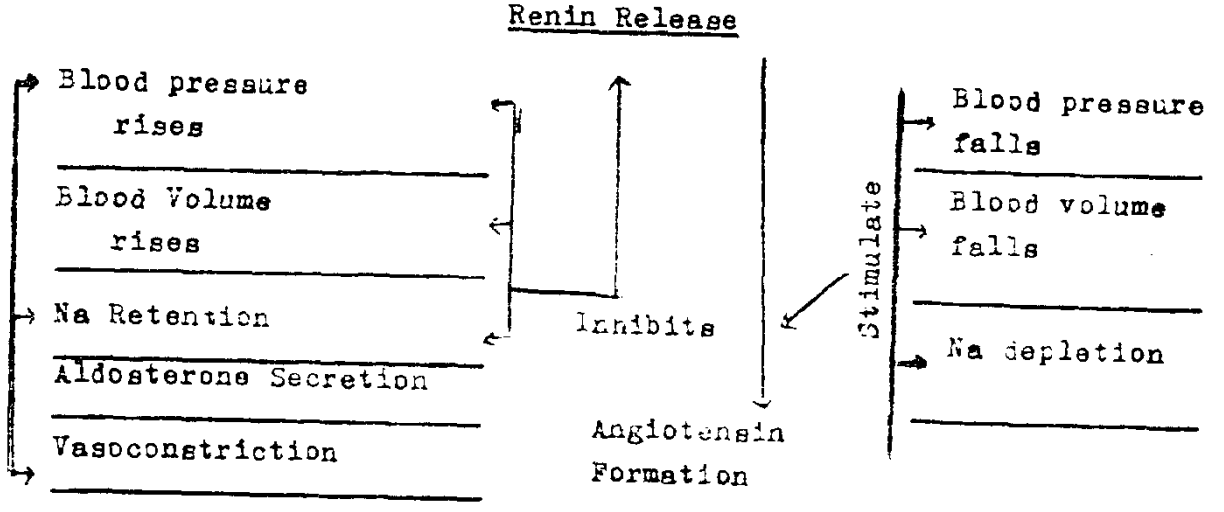
Renin is synthesized and stored in specialised Juxtaglomerular cells which form the wall of the afferent arterioles as it approaches the glomerulus. The arterioles are in an intimate contact with a specialised area in the distal tubules of the kidney known as macula densa. The afferent arterioles contains vascular receptors which are activated by reduction in the wall tension .

The macula densa controls renin secretion in response

to changes in electrolyte content of the tubular fluid. It is activated by reduction in the load of Na^+ or Cl^- in the distal tubular fluid (Ganong 1981) .

The Jurta glomerular cells are innervated by sympathetic fibers which exert an important influence on renin secretion (B. adrenergic effect). Adrenergic stimulation leads to renin release in response to assumption of upright posture or Haemorrhage (Ganong 1981).

The renal sympathetic nerves can also influence renin secretion indirectly by their effect on the arteriolar tone (∝ adrenergic effect) (Davis and Freeman 1976).



(Fig.3) Control of Renin Release. (Douglas W.W. 1975)