RENIN SECRETORY CAPACITY IN HEMODIALYSIS PATIENTS

THESIS

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CONTENTS

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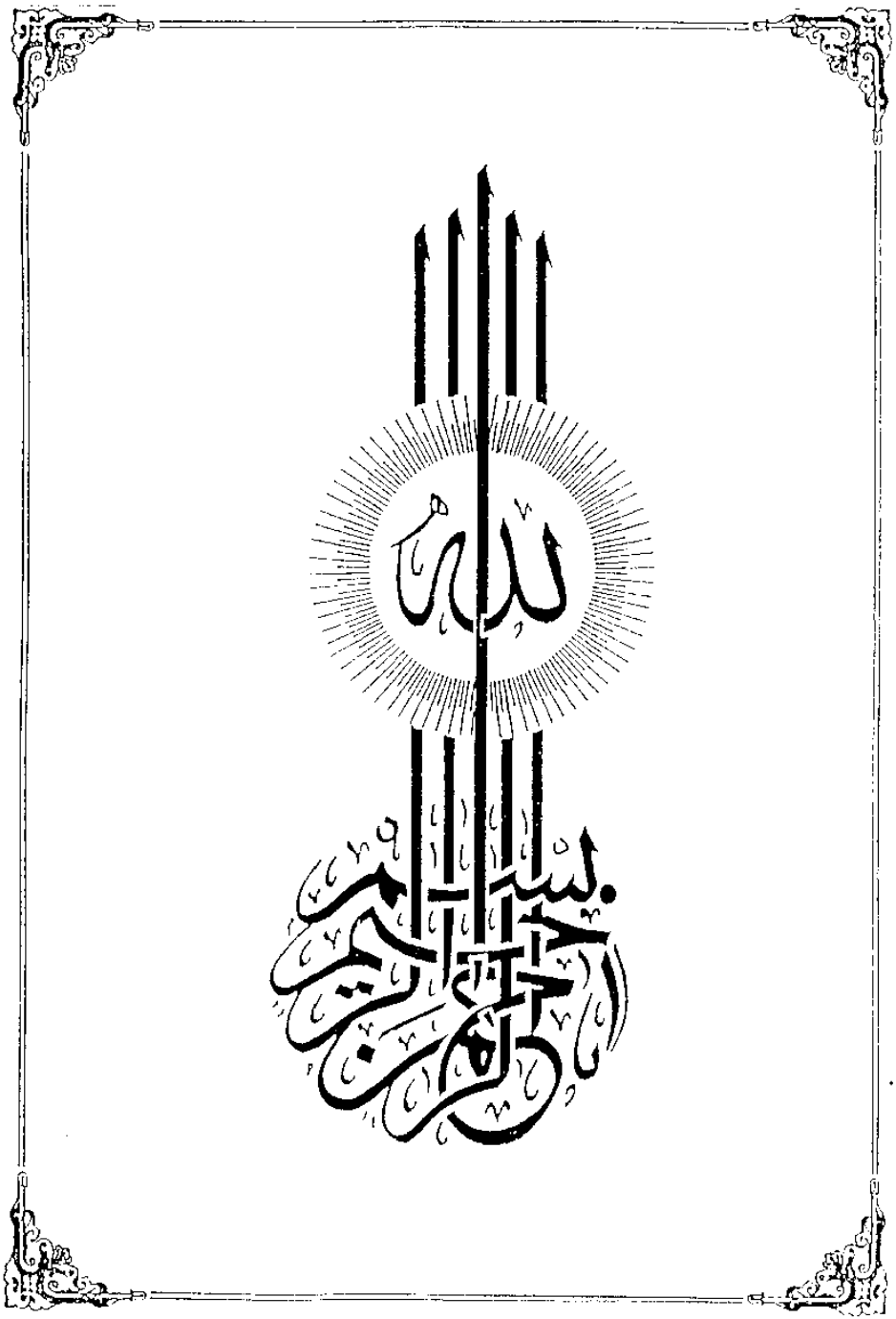

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INTRODUCTION AND AIM OF THE WORK

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It is known that plasma renin level varies among patients with end stage renal failure. Some patients with renin dependant hypertension have severe hypertension which is difficult to control by hemodialysis (Schalekamp et al. 1973). For such patients bilateral nephrectomy have been advocated by some authers (Hampers et al. 1976). Others preferred the use of of vasodilators and antirenin drugs (Brown et al. 1976).

Because of the importance of renin, the work aimed at studying the aspects of renin secretion along one session heamodialysis as regards its pre and post-dialysis levels and their correlation to blood pressure, electrolyte changes, urea & creatinine levels, duration of hemodialysis and body weight. Also, the work aimed to give a short reveiw about the physiological and pathological aspects of renin.

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REVIEW

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RENIN ANGIOTENSIN SYSTEM

HISTORICAL NOTE

The idea that the kidneys may play a part in the genesis of certain types of hypertenion originated from the observations of Richard Bright in 1827 in patinets with nephritis. Further support for this idea came when Tigerstedt and Bergman in 1898 found that crude extract of the kidndey when injected in experimental animals produced a rise in blood pressure. They called this pressor substance renin. (Skeggs et al. 1976).

In 1934 Goldblatt discovered that moderate reduction of renal blood flow by means of silver renal artery clamp produced persistant arterial hypertension "Goldblatt hypertension". Few years later investigators had detected the pressor activity of renal venous blood following renal artery constriction and had attributed this effect to renin (Douglas W.W. 1975).

In 1940 two groups, each working independently, Page and Helmer in the united states and Broun-Menedez in Aregentina, showed that renin itself is not a direct

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pressor agent, but they found that renin acts on plasma producing a vasoconstrictive substance. Page and Helmer called it angiotensin, Broun- Menedez called it hypertensin. In 1958 it was agreed to rename the pressor substance angiotensin and the plasma substrate angiotensinogen (Skeggs et al. 1976).

Peart and Skeggs in the period 1954 - 1958 isolated angiotensin from bovine plasma. Shortly after, Schwyzer and Bumpus were able to synthesize anigotensin. Gross in 1958 suggested that renin angiotensin system was involved in the electrolyte balance and aldosterome secretion by the adrenal cortex. Davis 1961, Ganong and Mulsow 1961 demonstrated that saline extract of kidney can stimulate aldosterone release (Douglas W.W. 1975).

Skeggs, was the first to detect angiotensin converting enzyme in the horse plasma (Skeggs et al. 1969).

Recently Blair-West et al. 1971, showed that a third form of angiotensin called angiotensin III may play a role though it had a weaker direct pressor effect.

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PHYSIOLOGY OF

RENIN-ANGIOTENSIN SYSTEM

Renin is a proteolytic enzyme secreted by the kidney into the bloodstream. This glycoprotein has a molecular weight of 40,000 in humans. The kidneys and blood also contain a larger, relatively inactive renin, with a molecular weight of approximately 60,000. This protein, called prorenin, prerenin, big renin or simply inactive renin, is apparently the precussor of the active form. An even larger form (big big renin) has also been identified in renal tissue (Ganong, 1981).

Renin activity in the granular epitheloid cells was identified by immunofluorescent methods and a correlation was found between the granulation index and renin content of the kidney and Cook was able to remove granules from individual epitheloid cells and found that they contained renin (Black 1979).

Inactive renin is converted to active renin by tissue kallikrein then the active from acts on a glycoprotein in the α_2 globulin fraction of the proteins in

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the cirulcating plasma, releasing a decapeptide, angiotensin I. The α_2 globulin is synthessized in the liver and is called angiotensinogen or renin substrate. Converting enzyme is a dipeptidly carboxypeptidase that splits off histidyl-leucine from the physiologically inactive angiotensin I, forming the octapeptide angiotensin II (Ganong 1981).

Because the largest concentration of converting enzym is found in the lung, it was untill recently beleived that conversion occured only there (Ng & Vane 1967).

A specific converting enzyme was recently demonstrated to be present in the juxtaglomerular apparatus of the kidney (Granger et al. 1972). Lymph draining the kidney contains considerably higher concentrations of angiotensin II than are found in either arterial or renal venous blood. It must have been generated within the kidney (Bailie et al. 1971).

Angitensin I has a half-life period of 80 minute while angiotensin II has a shorter half-life of about 1-2 minutes. The enzymes that destroy angiotensin II are

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collectively called angiotensinase which includes aminopeptidase that removes the aspergin residue from NH_2 terminus of the peptide. The heptapeptide produced is called angiotensin III, and has a physiological activity of ¼ to ½ that of angiotensin II. Further hydrolysis to remove the next aminoacid arginin inactivates angiotensin III completely. Hydrolysis in the middle region by endopeptidases and C-terminal phenylalanine by carboxypeptidase fragments the compound completely (Ganong 1981).

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

The sequence of reactions are illustrated in Fig. I.

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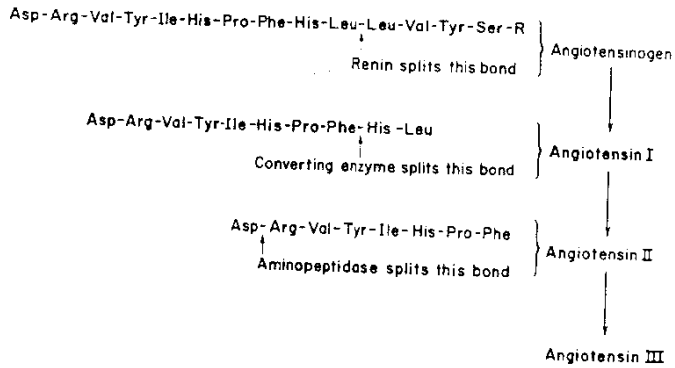

Figure 1: Structure of angiotensins I, II, and III. R, remainder of protein. The structure shown is that of angiotensin II in humans, dogs, rats, and many other mammals. Bovine and ovine angiotensin II have valine instead of isoleucine in position 5.

Ganong 1981

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Actions of angiotensins:

Angiotensin I has no known function apart from being, a precursor of angiotensin II (Ganong 1981).

Angiotensin II has the main effects of the renin angiotensin system as:

A) On the cardiovascular system:

On the heart angiotensin has a direct positive inotropic effect with weak chornotropic action but this occurs only in vitro while those effects are complicated by the indirect mechanisms controlling the heart in vivo (Dempay et al. 1971).

On the blood vessels, angiotensin II produces arteriolar vasoconstriction and a rise of systolic and diastolic blood pressure being the most potent vasoconstrictor known. It is about 40 times more potent than norepinephrine (Gnong 1981).

Intravenous administration of angiotensin II produces vasoconstriction most marked in the vessels of the skin, splanchnic region and kidney. The precapillary vessels are the most affected, the postcapillary vessels

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and veins are the least affected. The effect on the vessels of skeletal muscles, brain, heart & adrenal glands is moderate. The pulmonary vessels are not affected at all. The vascular response to angiotensin is due to two components, direct action on the smooth muscle fibres, and indirect action on the sympathetic nervous system (Beevers et al. 1975). In man intravenous infusion of angiotensin causes vasoconstriction by direct action, but in certain vascular beds like the hand and foot, the vasoconstrictor action is mediated by the sympathetic effect and can be blocked by α-adrenergic blochers (Douglas W.W. 1975).

B) On the central Nervous system:

Angiotensin has a central sympathetic stimulatory action mainly on the area postrema in the medulla. It potentiates adrenergic transminion at peripheral neuroeffector sete, and facilitates ganglionic transmission and so modulates the sympathetic functions. Angiotensin can spicifically stimulate drinking but not accompanied with eating so it increases water intake and stimulates the activity of supraoptic neuclei and secretion of ADH (Douglas W.W. 1975).

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