Introduction:

The renin-angiotensin system (RAS) plays a fundamental role in the regulation of volume and composition of the body's extracellular fluids, and cardiovascular function. The most important site for renin synthesis, storage, and release is the juxtaglomerular apparatus, located in close contact with the afferent glomerular arteriole and macula densa of the distal convoluted tubule within the kidney ***(Lavoie and Sigmund, 2003)***.

The classical RAS pathway initiates with the proteolysis of the a2-globulin angiotensinogen by renin to form angiotensin I, which is converted by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II (All), the final effector of the system. All is then cleaved by aminopeptidases to angiotensin III and, finally angiotensin IV ***(Lumbers, 1999)***.

In addition to the circulating RAS, there are complete RASs within a variety of tissues and organs, the functions of which are quite varied. Local synthesis of all the components of the RAS has been demonstrated within the kidney, blood vessels, heart, liver, and adrenal glands. Tissue RAS activation leads to the local generation and effects of All. Thus, RAS acts as both an endocrine and paracrine system ***(Lavoie and Sigmund, 2003)***.

Since All represents the main stimulus for aldosterone synthesis and release by the glomerulosa cells, the factors regulating renin release also influence aldosterone secretion. The principal target site of aldosterone is the nephron cortical collecting duct and the adjacent convoluted tubule. Aldosterone binding to specific cytoplasmic receptors is followed by translocation of hormone-receptor complex to nuclear acceptors, RNA transcription, and synthesis of specific proteins with prolonged half-life. These enhance sodium flux from the tubular lumen to the cell cytosol, and then to the extracellular fluid and peritubular capillaries ***(Booth et al., 2002)***.

The RAS has been implicated in the pathophysiology of various diseases including hypertension, cardiac hypertrophy, and myocardial infarction as well as various progressive renal diseases. Of particular interest are newly described roles for the RAS in other situations such as retinal neovascularization and hepatic fibrosis ***(Jandeleit-Dahm and Cooper, 2006)***.

The role of angiotensin II in liver is linked to the finding that stellate cells possess ATI receptors and that its binding induces cellular contraction and proliferation. Furthermore, recent evidence suggests that the major cellular source of angiotensin II in the liver is the stellate cells. Moreover, its synthesis is upregulated after liver injury, apparently because of pronounced upregulation of angiotensin converting enzyme (ACE) ***(Moreno and Bataller,***

2008).

The Renin-Angiotensin-Aldosterone System (RAAS) was the first major vasoconstrictor system to be investigated as a possible factor responsible for renal vasoconstriction in cirrhosis. It is now well known that the activation of RAAS is particularly intense in patients with Hepatorenal syndrome (HRS) compared with patients with cirrhosis and ascites without HRS ***(Meller and Henriksen, 2004)***.

It seems that diabetes may result in an initial stage of RAAS hyperactivation, followed by a state of hypo-reninemic hypo-aldosteronism at later stages. The increased renal RAS activity in diabetics may explain their favorable response to treatment with angiotensin-converting enzyme inhibitors ***(Alrefai et al., 2002)***.

Conflicting evidence has been presented dealing with the activity of the circulating RAAS in diabetes, the older studies mainly reporting on a normal or suppressed system while more recent data indicate elevated renin and prorenin concentration in diabetic nephropathy. Increased intrarenal activity of the RAAS has also been suggested by the finding of enhanced renal plasma flow during acute angiotensin converting enzyme (ACE) inhibition and conversely reduced or abolished reduction in renal blood flow during infusion of suppressor doses of angiotensin II. Most recently reduction in renal angiotensin II receptors has been demonstrated suggesting enhanced intrarenal activity of the RAAS. Increased synthesis of angiotensin II

may play an important role in the initiation and progression of diabetic nephropathy by hemodynamic mechanisms and by promoting growth of glomerular cells ***(Parving, 2000)***.

Activity of the renin-angiotensin-aldosterone system (RAAS) is increased in patients with heart failure. Thus, alterations in blood volume, arterial pressure, and cardiac and vascular structure and function can be expected. Adaptive mechanisms may be helpful in the short term in maintaining suddenly decreased cardiac function, but in the long term chronic stimulation of the RAAS leads to adverse cardiovascular effects and progression of heart failure. The actions of angiotensin II (All) include vasoconstriction, cardiac remodeling, fibrosis, endothelin generation and sympathetic activation ***(Linger and Li, 2004)***.

The renin-angiotensin-aldosterone system (RAAS) appears to be fundamental to the left ventricular remodeling process that follows significant myocardial injury or inflammation. Key RAAS peptides, such as angiotensin II (All) and aldosterone, are associated with pathological extracellular matrix deposition, myocyte hypertrophy and pro-apoptic effects, all key drivers of the ventricular remodeling process associated with progression of this disease ***(Krum, 2008)***.

Angiotensin peptides, whether produced locally and acting in a paracrine and autocrine fashion, or derived from the circulation, may contribute in significant ways to the atherogenic process. Both ACE

expression and All content in human coronary arteries are increased in macrophages and vascular smooth muscle cells of atheromatous plaques ***(Sirawn et al., 2000)***.

A number of kidney diseases, and their progression to end-stage renal failure, are driven by the autocrine, paracrine, and endocrine effects of All. Moreover, despite the beneficial effects of ACE inhibitors, the findings that the systemic RAS is not activated in most types of chronic renal disease has led to the suggestion that it is the local intrarenal RAS that may be a particularly important determinant in the progression of renal disease ***(Nicholls and Robertson, 2000)***.