Introduction

The renin-angiotensin system (RAS) plays an important role in the pathogenesis of hypertension as well as cardiovascular diseases and chronic kidney diseases. Among the most frequently studied RAS gene polymorphisms are the angiotensin-converting enzyme insertion/deletion (I/D), angiotensinogen M235T and angiotensin II receptor type 1 A1166C polymorphisms. A significant correlation was found between the I/D polymorphism and cardiovascular morbidity and mortality rates. However, there was no significant correlation between I/D, M235T, A1166C polymorphism and arterial hypertension ***(Kujawa et al., 2010).***

Angiotensin II, acting through type 1 angiotensin (AT1) receptors, contributes to the pathophysiology of diverse disorders from progressive renal disease to cardiac hypertrophy and atherosclerosis ***(Hilgers and Mann, 2002).***

In addition, recent studies have suggested that AT1 receptors may contribute to disease pathogenesis through direct effects on cellular immune responses and inflammation ***(Crowley et al., 2009).***

In contrast, actions of AT1 receptors may have protective effects in other disorders. For instance, in a model of obstructive uropathy, the absence of AT1 receptors on

hematopoietic cells is associated with enhanced levels of renal fibrosis ***(Nishida et al., 2002).***

In humans with systemic lupus erythromatosus (SLE), the contribution of the RAS to the development of renal disease is less clear. Although lower serum angiotensin converting enzyme (ACE) levels have been associated with reduced severity of renal disease in some studies. RAS has been considered one of the probable pathophysiologic mechanisms involved in SLE progression. Genetic polymorphism of the RAS has been associated with the clinical course of renal disease ***(Prkacin et al., 2001).***

Aim of the Work

This work aimed to determine the frequency of angiotensin II type 1A (AT1) receptor gene polymorphism among a group of Egyptian children with lupus nephritis. The relationship between angiotensin II type 1A (AT1) receptor gene polymorphism and histological classes of lupus nephritis as well as the clinical and laboratory markers of lupus nephritis were demonstrated.

Renin Angiotensin System

The critical role of the circulating renin angiotensin system (RAS) in the regulation of arterial pressure and sodium homeostasis has been recognized for many years. Although every organ system in the body has elements of the RAS (Figure 1), the kidney is unique in having every component of the RAS with compartmentalization in the tubular and interstitial networks as well as intracellular accumulation. Recent attention has been focused on the existence of unique RAS in various organ systems. Various studies have demonstrated the importance of the tissue RAS in the brain, heart, adrenal glands, and vasculature as well as in the kidney ***(Mitchell and Navar, 1995) and (Navar et al., 2006).***

Over the past years, the RAS was elucidated, in response to certain stimuli. Renin, a proteolytic enzyme produced by the kidney, is released into the circulation and acts on angiotensinogen (AGT), a circulating protein (alpha2-globulin) produced by the liver. Renin cleaves AGT to produce angiotensin I (Ang I) a small fragment of only 10 amino acids ***(Wang et al., 2000).*** Ang I has no biological action in itself, but is converted to Ang II, an active octapeptide, by angiotensin-converting enzyme (ACE), an enzyme present on the cell surface of many cells and particularly on vascular endothelial cells ***(Ortiz et al., 2001).***

Ang II is the most powerful biologically active product of the RAS, although there are other bioactive Ang peptides, including Ang III and Ang IV ***(Paul et al., 2006).***

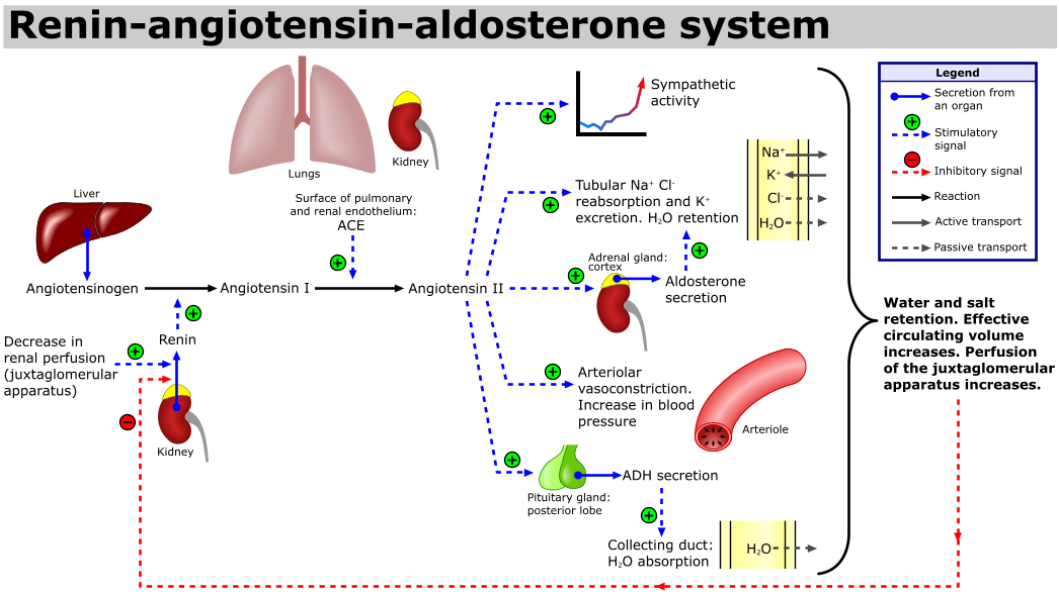
In this regard, the kidneys, as well as the adrenal glands, are unique in terms of the tissue concentrations of Ang II, which are much greater than can be explained by the concentrations delivered by the arterial blood flow ***(Ingert et al., 2002).*** There is substantial evidence that the major fraction of Ang II present in renal tissues is generated locally from AGT delivered to the kidney as well as from AGT locally produced by proximal tubular cells. Ang I delivered to the kidney can also be converted to Ang II ***(Rosivall and Navar, 1983) and (Komlosi et al., 2003).***

Under normal circumstances, renin is the rate-limiting step in the formation of Ang II. AGT is the only known precursor protein to the family of angiotensin peptides. Systemic AGT originates primarily from hepatocytes where it is constitutively secreted, and is present in the plasma in stable concentrations (half-life of 16 h, in contrast to 20 min for renin) ***(Brasier and Li, 1996).***

As all blood leaving the kidneys and liver eventually flows through the lung, the pulmonary vascular endothelium plays a major role in the rapid conversion of Ang I into Ang II. Finally, Ang II will bind to specific cell surface Ang receptors to elicit multiple actions ***(Wang et al., 2000).***

Ang I and Ang II can be generated by alternate enzymatic pathways other than renin, such as tonin and cathepsin D, which can promote the formation of Ang I by cleavage of AGT. Similarly, enzymes other than ACE, such as trypsin, cathepsin G or heart chymase, can facilitate the conversion of Ang I into Ang II. However, the contribution of these alternative pathways in Ang II production in humans is still unclear ***(Ren et al., 2002).***

On the other hand, another carboxypeptidase, ACE2, cleaves only a single amino acid from the C terminals of Ang I to form the nonapeptide Ang 1–9, whereas ACE2 does not convert Ang 1–9 to Ang II. Therefore, it is possible that ACE2 regulates ACE-dependent Ang II formation by stimulating an alternative pathway for Ang I degradation. ACE2 also directly converts Ang II to Ang 1–7 ***(Shaltout et al., 2007).***



ACE: Angiotensin converting enzyme; **ADH:** Anti-diuretic hormone

Figure (1): The renin angiotensin system ***(Quoted from Basso and Terragno, 2001).***

ACE can promote the degradation of bradykinin, substance P and other small peptides. Although the physiological role of this enzymatic conversion is unclear, pharmacological blockade of ACE with specific inhibitors leads to an accumulation of bradykinin and substance P, which may be responsible for some of the beneficial effects (antihypertensive), but also some of the adverse effects (angioedema, cough) of ACE inhibitors ***(Ortiz et al., 2001).***

Ang- (1-7) is a metabolite of Ang II. Considerable interest in Ang- (1-7) and its receptor aroused in the last few years since it became apparent that it can counterbalance most of Ang II effects. Thus Ang- (1-7) has vasodilator and hypotensive effects as well as antiarrhythmic and cardioprotective roles ***(Santos et al., 2008).***

Ang II receptors:

The Ang receptors are a class of G protein-coupled receptors with Ang II as their ligands (Figure 2) ***(De Gasparo et al., 2000).*** They are important in the RAS as they are responsible for the signal transduction of the vasoconstricting stimulus of Ang II ***(Higuchi et al., 2007).***

The Ang II receptor type 1 ***(AT1)*** is the best elucidated Ang receptor. The ***AT1*** subtype is found in the heart, blood vessels, kidney, adrenal cortex, lung and brain and mediates the vasoconstrictor effects. ***AT2*** is probably involved in vascular growth. The activated receptor in turn couples to $G_{q/11}$ and $G_{i/o}$ and

thus activates phospholipase C and increases the cytosolic Ca^{2+} concentrations, which in turn triggers cellular responses such as stimulation of protein kinase C. Activated receptor also inhibits adenylate cyclase and activates various tyrosine kinases ***(De Gasparo et al., 2000).***

AT2 receptors are more plentiful in the fetus and neonate. The ***AT2*** receptor remains controversial. Effects mediated by the ***AT2*** receptor are suggested to include inhibition of cell growth, fetal tissue development, modulation of extracellular matrix, neuronal regeneration, apoptosis, cellular differentiation, and may be vasodilation and left ventricular hypertrophy ***(D'Amore et al., 2005).***

Most of the Ang II hypertensinogenic actions are generally attributed to the ***AT1*** receptors ***(Ito et al., 1995). AT1*** receptor transcript has been localized to proximal tubules, the thick ascending limb of the loop of Henle, glomeruli, arterial vasculature, vasa recta, arcuate arteries, and juxtaglomerular cells ***(Tufro-McReddie et al., 1993).*** In rodents, there are two ***AT1*** receptor subtypes, with ***type 1a*** being the predominant subtype in all nephron segments, whereas ***type 1b*** is more abundant than ***type 1a*** only in the glomerulus ***(Bouby et al., 1997).*** In mature kidneys, ***type 1a*** receptors have been localized to the luminal and basolateral membranes of several segments of the nephron, as well as on the renal microvasculature in both cortex and medulla, smooth muscle cells of afferent and

efferent arterioles, epithelial cells of the thick ascending limb of Henle, proximal tubular apical and basolateral membranes, mesangial cells, distal tubules, collecting ducts, and macula densa cells ***(Paxton et al., 1993); (Harrison-Bernard et al., 1997)and (Miyata et al., 1999).*** This evidence is consistent with the localization of the transcript for the ***AT1*** receptor subtypes in all of the renal tubular and vascular segments ***(Miyata et al., 1999).*** Nevertheless, renal microvascular functional studies obtained from mice lacking the ***type 1a*** receptor gene have shown that the afferent arteriole has both ***type 1a*** and ***type 1b*** receptors, whereas the efferent arteriole only expresses ***type 1a*** receptors ***(Harrison-Bernard et al., 2003).*** The distinction of ***AT1*** is, however, not relevant to humans, in which a single ***AT1*** receptor type is found ***(Reckelhoff, 2001).***

The regulation of intrarenal Ang II receptors in hypertensive conditions is complex because vascular and tubular receptors respond differently during high Ang II states ***(Navar et al., 2002).*** In general, high Ang II levels decrease glomerular ***AT1*** receptor expression but increase tubular ***AT1*** receptor levels **(Cheng et al., 1995).**

A nucleotide substitution (A/C in position 1166) in the gene of AT_1 receptor was described. Some studies reported an increased prevalence of the C allele in hypertensives ***(Bonnardeaux et al., 1994)***. These results were confirmed by

some authors ***(Wang et al., 1997); (Bentos et al., 1997) and (Szombathy et al., 1998***) but not by others ***(Castellano et al., 1996); (Schmidt et al., 1997) and (Takami et al., 1998).*** The A/C 1166 polymorphism was associated with aortic stiffness ***(Benetos et al., 1997)***, left ventricular mass ***(Takami et al., 1998)*** and ***(Osterop et al., 1998)***, and coronary vasoconstriction ***(Amant et al., 1997)***. It was reported to be a risk factor for myocardial infarction in synergism with the *ACE* gene deletion polymorphism ***(Tiret et al., 1994).*** These associations could be due to an effect of the AT_1 receptor gene variant or to an effect of an as yet unidentified gene locus in linkage disequilibrium with the AT_1 polymorphism. In that regard, it is important to determine whether or not the gene variant leads to an altered expression and/or function of the gene product ***(Lifton, 1995).***

The ***AT2*** receptor is highly expressed in human and rodent kidney mesenchyme during fetal life and decreases dramatically after birth ***(Norwood et al., 2000). AT2*** receptors have been localized to the glomerular epithelial cells, proximal tubules, collecting ducts, and parts of the renal vasculature of the adult rat ***(Miyata et al., 1999).*** Although the role of ***AT2*** receptors in regulating renal function remains uncertain, it has been suggested that ***AT2*** receptor activation counteracts ***AT1*** receptor effects by stimulating formation of bradykinin and nitric oxide (NO), leading to increases in interstitial fluid concentration of cyclic guanosine monophosphate ***(Carey and Siragy, 2003a). AT2*** receptor activation seems to influence

proximal tubule sodium reabsorption either by a cell membrane receptor-mediated mechanism or by an interstitial nitric oxide-cyclic guanosine monophosphate pathway ***(Jin et al., 2001).***

Other poorly characterized subtypes include the ***AT3*** and ***AT4*** receptors. The ***AT4*** receptor is activated by the Ang II metabolite which is Ang IV, and may play a role in regulation of the central nervous system (CNS) extracellular matrix, as well as modulation of oxytocin release ***(Benoist et al., 2011).***

The Ang- (1-7) Mas receptor is the recently identified receptor of the biologically active heptapeptide Ang- (1-7). The Ang- (1-7) Mas receptor is expressed in several organs including heart, kidney, blood vessels, testis and brain. Studies with Ang- (1-7) Mas receptor knockout mice have demonstrated the key role of this receptor in cardiovascular regulation as well as in the regulation of learning and memory ***(Alenina et al., 2008).***

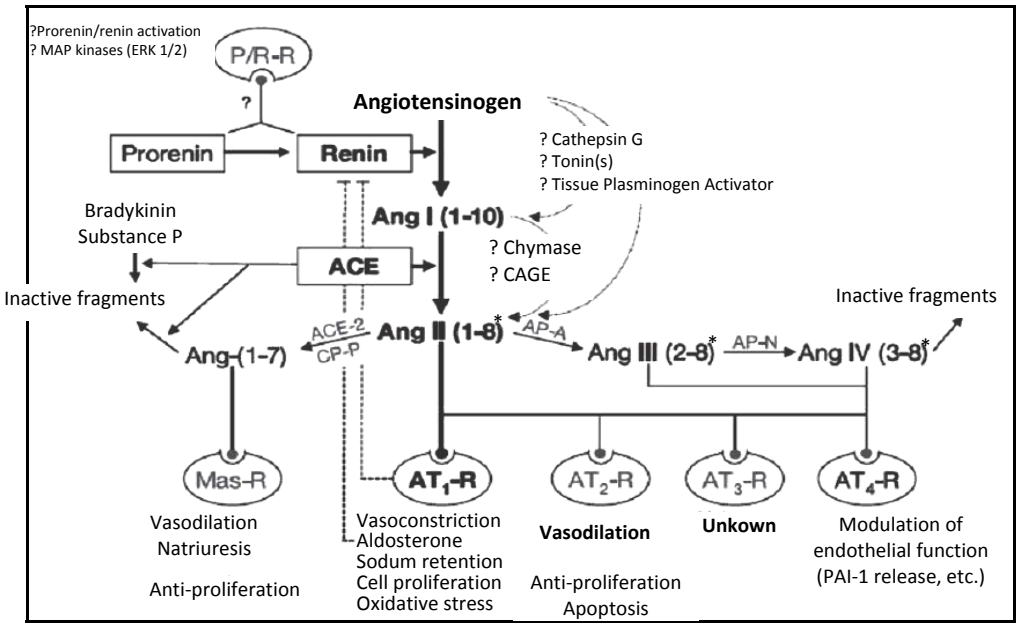


Figure (2): Pivotal role of the renin/prorenin receptor in Ang II production and cellular responses to renin ***(Nguyen et al., 2002)***

The classical RAS pathway is highlighted in boldface type. Renin, normally secreted in response to underperfusion of the kidneys (not shown), cleaves the decapeptide Ang I from angiotensinogen, and Ang I is converted to Ang II by ACE. The dashed lines indicate feedback inhibition of renin secretion, which occurs both via a direct ***AT1*** receptor mediated action of Ang II ("short loop") and via ***AT1***-mediated restoration of blood pressure and volume ("long loop"). Other pathways that are speculative or of unproven physiological significance in vivo are depicted in light text. Ang II can be converted to Ang- (1-7) by ACE 2 or other carboxypeptidases. Ang II can also be cleaved by aminopeptidases to form Ang III and Ang IV. These peptides exert their biological effects by binding to various subtypes of Ang receptors. In addition, Ang- (1-7) can be formed directly from Ang I by the action of endopeptidases (not shown), and further metabolism of peptides to inactive fragments involves several amino-, carboxy-, and endopeptidases. A number of other proteolytic enzymes are shown that potentially can contribute to Ang I or Ang II synthesis. Lastly, both renin and prorenin may exert direct cellular actions by binding to specific pronin/renin receptor. ACE = angiotensin-converting enzyme; Ang = angiotensin; AP-A/AP-N = aminopeptidase A/aminopeptidase N; AT-R = Ang receptor subtype; CAGE = chymostatin-sensitive Ang II-generating enzyme; CP-P = carboxypeptidase P; MAP = mitogen-activated protein; Mas-R = Mas receptor; P/R-R = prorenin/renin receptor; PAI-1 = plasminogen activator inhibitor-1; * = number of amino acids.

Physiolocal effects of Ang II:

Renal effects

All of the understood clinical effects of Ang II are mediated at the ***AT1*** receptor sites. Ang II binds to the zona

glomerulosa, stimulating secretion of aldosterone. Aldosterone then stimulates sodium retention and water reabsorption in the kidney ***(Timmermans et al., 1993a).***

The intrarenal RAS may explain the primary role of Ang II as a paracrine substance in the control of renal function. The direct intrarenal actions of Ang II include renal vasoconstriction, tubular sodium reabsorption, sensitivity of tubuloglomerular feedback, modulation of pressure-natriuresis, and promotion of renal tissue growth ***(Carey and Siragy, 2003a).***

Under normal conditions, Ang II constricts both the afferent and efferent arterioles and stimulates mesangial cell contraction, which results in reduced renal blood flow, glomerular filtration rate (GFR), and filtered sodium load ***(Carey and Siragy, 2003a).***

On the other hand, in conditions characterized by severe impairment of renal perfusion, such as renal artery stenosis, the afferent circulation, which is dilated as a result of autoregulation, is relatively refractory to the constrictive actions of Ang II, and the predominant constriction of efferent arterioles by Ang II plays a major role in maintaining glomerular perfusion pressure and, thus, GFR ***(Paul et al., 2006).***

Extra renal

Some of the responses to ***AT1*** stimulation by Ang II are coronary, efferent arteriole, and cerebral vasoconstriction.

Ang II also binds to ***AT1*** receptor sites in the heart, mounting positive ionotropic and chronotropic effects. In addition angiotensin II can activate the sympathetic nervous system ***(Timmermans et al., 1993a).***

Ang II may also increase vascular tone by indirect mechanisms. Ang II increases sympathetic discharge via direct action at various brain structures that lack a blood–brain barrier, and can also potentiate the release of norepinephrine from adrenergic nerve varicosities within peripheral tissues. This sympathetic effect is normally blunted or even suppressed in vivo by the vasoconstriction-induced rise in arterial pressure, which loads baroreceptors and results in a reflex decrease in sympathetic nerve activity ***(Lohmeier et al., 2000).***

Although systemic Ang II may affect CNS function at selected sites, the brain is largely isolated from the circulating RAS by the blood-brain barrier. Therefore, local Ang II synthesis by a brain RAS has been proposed to play a role in central blood pressure regulation ***(Paul et al., 2006).***

Pathological effects of Ang II:

Renal effects

Sustained elevation of intrarenal Ang II induces proteinuria accompanied by progressive injury of the glomerular filtration barrier, which is composed of the glomerular endothelium, glomerular basement membrane, and podocytes (glomerular

visceral epithelial cell) ***(Miller et al., 1991); (Hoffmann et al., 2004) and (Whaley-Connell et al., 2006).***

Extra renal effects

Locally produced Ang II induces inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation. It also regulates the gene expression of bioactive substances, and activates multiple intracellular signaling pathways, all of which might contribute to tissue injury. Clinical and preclinical studies on the effects of pharmacological investigations with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) support the notion that Ang II exerts a cardinal role in the pathogenesis of hypertension and renal injury via activation of ***AT1*** receptors when inappropriately activated ***(Timmermans et al., 1993b) and (Navar et al., 2000).***

Overactivation of the intrarenal RAS may thus contribute to the pathophysiology of sodium-retaining states, such as hypertension and congestive heart failure (CHF) ***(Carey and Siragy, 2003a).***

Importantly, because the kidney plays a crucial role in the development of hypertension, hypertension is both a cause and consequence of renal disease ***(Navar, 2005) and (Paul et al., 2006).*** Accordingly, the Seventh Report of the Joint National Committee (JNC7), the European Society of Hypertension/ European Society of Cardiology (2003 ESH-ESC), and the Japanese Society of Hypertension (JSH2004) recommended that ACEIs and ARBs be used in concert with diuretics as first-line