Angiotensin-II Behaves as an Endogenous Pro-inflammatory Molecule

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Abstract

Angiotensin-II regulates vascular tone, stimulates the release of pro-inflammatory cytokines, activates NF-κB, increases oxidant stress, and suppresses nitric oxide synthesis, and thus, it functions as an inflammatory molecule. Since ACE is present in many tissues, this suggests that angiotensin-II may play a significant role in atherosclerosis, congestive cardiac failure, stroke, bipolar disorder, schizophrenia, dementia, Alzheimer’s disease, psoriasis, atopic and non-atopic dermatitis, eczema, several acute and chronic inflammatory diseases, and cancer, conditions in which inflammation is an aetiopathogenic factor. Thus, ACE inhibitors and/or angiotensin-II receptor blockers could be of benefit in these conditions. Furthermore, structural analogues of ACE inhibitors and angiotensin-II receptor blockers could be developed that possess anti-inflammatory actions without significant action on the cardiovascular system. ©

INTRODUCTION

Renin, a proteolytic enzyme, produced by the juxtaglomerular cells surrounding the afferent arterioles of glomeruli in the kidney acts on angiotensinogen (a circulating α2 globulin made in the liver) to form the decapeptide angiotensin-I (Ang-I). Ang-I is converted by angiotensin converting enzyme (ACE) to angiotensin-II (Ang-II) that, in turn, can be converted to form heptapeptide angiotensin-III (Ang-III). ACE is a dipeptidyl carboxypeptidase of 15 Kda. Ang-II controls blood pressure and modulates renin-angiotensin-aldosterone system. ACE is present in many tissues including: the uterus, placenta, vascular tissue, heart, brain, adrenal cortex and kidney, leukocytes, alveolar macrophages, peripheral monocytes, neuronal cells and epididymal cells.1

The two major classes of angiotensin receptors are AT1 and AT2. AT1 exists as two subtypes α and β. Actions of Ang-II and Ang-III are mediated by the AT1 receptor. Angiotensinases, present in several tissues, rapidly destroy Ang-II. In addition to circulating renin-angiotensin, many tissues have a local renin-angiotensin system and thus, have the ability to produce Ang-II. Factors that control renin release include: juxtaglomerular cells that sense the renal perfusion pressure; the macula densa cells, which are chemoreceptors that sense the amount of sodium load presented to the distal tubule of the kidney; the sympathetic nervous system; and dietary potassium and sodium intake. ACE is not only leads to the formation of Ang-II but also inactivates vasodilatory substances like bradykinin. Ang-II produced in situ interacts with other humoral factors to exert specific action on cells and tissues.

ANGIOTENSIN-II INITIATES AND PERPETUATES INFLAMMATION

Ang-II increases the release of reactive oxygen species (ROS).2-6 ROS activate NF-κB (nuclear factor-kappa B, known to initiate inflammatory process) that increases the transcription of pro-inflammatory cytokines, adhesion molecules, and NADPH oxidase.7, 8 Ang-II enhanced ROS production by activating NADPH oxidase and stimulated the DNA-binding activity of NF-κB in human neutrophils.9 Ang-II suppressed both PPAR-α (peroxisome proliferator-activated receptor-α) and PPAR-γ mRNA and protein and increased the transcription of monocyte chemotactic protein-1 (MCP-1), macrophage colony stimulating factor (M-CSF), endothelial-selectin (E-selectin), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and activated NF-κB in the aorta of male apolipoprotein E-deficient mice.10 These studies suggest that Ang-II augments inflammation.

Ang-II enhanced mononuclear cell recruitment by activating nuclear factor-kappa B and monocyte chemoattractant protein-1 synthesis in experimental immune complex nephritis.7 Ang-II infusion elevated...
the synthesis and concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and chemokine monocyte chemoattractant protein-1 (MCP-1), elevated tissue levels of NF-κB, and inflammatory cell infiltration. These events ultimately cause inflammation. These changes were observed mainly in the renal tissue. ACE inhibitor, quinapril, inhibited the renal over expression of TNF-α. These results explain why ACE inhibitors have renoprotective action. This so since, ACE inhibitors suppress Ang-II production and thus, prevent Ang-II induces inflammation in the renal tissue. Paradoxically, TNF-α down regulated ACE activity in human endothelial cells, whereas vascular endothelial growth factor (VEGF) that promotes angiogenesis, increased membrane bound ACE and ACE mRNA levels which, in turn, was inhibited by pretreatment of the cells with TNF-α or IL-1β. This suggests that there is a cross talk between pro-inflammatory TNF-α and ILs and ACE and ACE receptors.

TNF-α and IL-1 and IL-6 augment ROS and cause vascular dysfunction. Subjects with hypertension, pre-eclampsia, diabetes mellitus, and atherosclerosis not only show vascular dysfunction but also have high plasma levels of IL-6, TNF-α, and ROS. Aortic vascular smooth muscle cells (VSMCs) when exposed to IL-6 showed upregulation of Ang-II type 1 receptor and protein expression that resulted in an increase in Ang-II-induced free radical generation. Experimental animals treated with IL-6 showed enhanced vascular Ang-II type 1 receptor expression, Ang-II-induced vasoconstriction, increased vascular ROS production, impaired endothelium-dependent vasodilatation and reduced NO generation. Ang-II type 1-receptor knockout mice do not show vascular dysfunction when exposed to IL-6, their tissues are deficient in ACE, had reduced ROS generation and oxidative stress and atherosclerosis. These data suggest that enhanced levels of TNF-α, IL-1, IL-6, and Ang-II cause vascular dysfunction, enhance ROS generation and initiate and perpetuate atherosclerosis. This implies that ACE inhibitors and Ang-II receptor antagonists could be of benefit in atherosclerosis, diabetes mellitus, hypertension, myocardial infarction, Alzheimer’s disease, dementia, and schizophrenia, in which inflammation plays a significant role.

Factors that regulate/control Ang-II action

Irbesartan, an angiotensin II type 1 (AT1) receptor antagonist, reduced the number of macrophages, T lymphocytes, and HLA-DR+ inflammatory cells, immunoreactivity for COX-2/mPGES-1 (prostaglandin E2-dependent synthase), MMPs (metalloproteinases), gelatinase activity, and increased collagen content in human carotid plaques and stabilized atheromatous plaque. Overexpression of heme oxygenase-1 (HO-1), which produces carbon monoxide that is known to have potent vasodilator, platelet anti-aggregator, and anti-inflammatory actions, reduced Ang-II–stimulated PGE2, levels, enhanced cell survival, and attenuated Ang-II-mediated injury in the ascending limb of the loop of Henle of kidney. Ang-II infusion induced hypertension, leukocyte infiltration of the heart, perivascular and interstitial infiltration, and fibrosis. Heat shock treatment not only reduced these pro-inflammatory actions of Ang-II, but also blocked Ang-II-induced expression of IL-6 and ICAM in the heart, and induced high level of expression of HSP (heat shock protein)-27 and Hsp-70 proteins. Vascular endothelial growth factor (VEGF) mediates the pro-inflammatory actions of Ang-II especially in the vascular tissue since blockade of VEGF attenuated Ang-II-induced vascular inflammation and remodeling. These results suggest that Ang-II interacts with HO-1, HSPs and VEGF and that Ang-II is a pro-inflammatory molecule.

ACE inhibitors modulate free radical and nitric oxide generation

Both ACE inhibitors and Ang-II receptor blockers/antagonists have significant anti-inflammatory actions. ROS, especially superoxide anion, inactivate nitric oxide (NO), a potent vasodilator and platelet anti-aggregator. Thus, Ang-II decreases NO levels and this could be one mechanism by which Ang-II plays a role in several clinical conditions. Ang-II enhances the formation of endothelin, a potent vasoconstrictor that is known to have a role in hypertension, cardiac failure, and pre-eclampsia. Hence, an increase in ACE activity results in an increase in the formation of Ang-II, ROS, endothelin, and a decrease in NO and bradykinin. These events could initiate and perpetuate hypertension and atherosclerosis. Since ACE is present in many tissues, in whichever tissue ACE activity is enhanced there could occur damage to those tissues/organisms.  

ACE inhibitors and Ang-II receptor antagonists suppress inflammation

ACE inhibitors are useful not only in the treatment of hypertension but also in heart failure and left ventricular dysfunction. Although, ACE inhibitors were less effective compared with calcium antagonists and angiotensin-receptor blockers in the treatment of hypertension, no significant differences in total number of major cardiovascular events between these drugs was noted. This suggests that ACE inhibitors have other desirable actions that go beyond their ability to reduce Ang-II formation. This could be due to the putative anti-inflammatory action of these compounds.

Valsartan, an Ang-II receptor blocker, suppressed ROS generation in leukocytes, NF-κB binding activity and the expression of total cellular p65 expression (a protein component of NF-κB) in mononuclear cells, and plasma C-reactive protein concentrations in normal subjects.  

Candesartan, an angiotensin-II type 1 receptor blocker, reduced plasma levels of CRP (C-reactive protein), urine concentrations of 8-epi-prostaglandin F2α and 8-
hydroxydeoxy-guanosine, which are indicators of inflammation and oxidative stress, in patients with essential hypertension. Olmesartan, an angiotensin-II subtype 1 receptor blocker, significantly reduced serum levels of CRP, TNF-α, and monocyte chemotactic protein-1. Graninger et al. observed that losartan and enalapril decreased plasma levels of circulating intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1). These results indicate that ACE inhibitors and angiotensin-II receptor blockers/antagonists suppress inflammation and thus, are able to prevent not only renal injury and progression of renal disease in patients with hypertension and diabetes mellitus but also suppress atherosclerosis.

**Polyunsaturated fatty acids regulate ACE activity**

Previously, I showed that polyunsaturated fatty acids (PUFAs) inhibited leukocyte ACE activity. This suggests that PUFAs could function as endogenous regulators of ACE activity, and thus regulate the formation of Ang-II. PUFAs enhance nitric oxide generation. Hence, when cell/tissue concentrations of PUFAs are low, the activity of ACE will be high leading to the formation of increased amounts of Ang-II. Plasma concentrations of PUFAs are low in hypertension, diabetes mellitus, renal diseases, rheumatoid arthritis, lupus; psoriasis, eczema, atopic and non-atopic dermatitis; atherosclerosis, insulin resistance, obesity; dementia, schizophrenia, bipolar disorders, Huntington’s disease, Alzheimer’s disease; peptic ulcer disease; and cancer. A 25-nucleotide ACE deletion-deletion polymorphism increases ACE activity and such individuals showed a higher risk of developing stroke, obesity, emphysema, bipolar affective disorders, and cancers.

Thus, in various clinical conditions the twin abnormality of low PUFA content and increased ACE enzyme activity could occur that leads to high tissue levels of Ang-II. High Ang-II levels activate NADPH oxidase that in turn causes enhanced formation of ROS and decrease in nitric oxide levels. Enhanced ACE activity and Ang-II levels and decreased cell/tissue content of PUFAs cause an increase in the generation of TNF-α, IL-1, and IL-6, which initiate and perpetuate inflammation and tissue damage. Enhanced levels of Ang-II and a deficiency of PUFAs will lead to an increase in the generation of TNF-α, IL-1, and IL-6 due to the stimulatory action of Ang-II and absence of negative feedback control that is exerted by fatty acids on the generation of these cytokines respectively.

Kaergel et al. showed that transgenic rats overexpressing both human renin and angiotensinogen genes (dTGR) develop hypertension, inflammation, and renal failure and showed renal P450-dependent AA metabolism changes that led to decreased formation epoxy-eicosatrienoic acids (5,6-, 8,9-, 11,12- and 14,15-EETs) and hydroxyeicosa-tetraenoic acids (19- and 20-HETEs) that, in turn, inhibited IL-6 and TNF-α-induced activation of NF-κB and prevented vascular inflammation. These results indicate that AA and other PUFAs not only regulate ACE activity and Ang-II levels in the tissues but also possess anti-inflammatory properties.

**CONCLUSIONS**

It is evident from the preceding discussion that free radicals and ACE activity is a common pathway in the development and progression of various diseases. Although, there were no definitive reports to suggest that long-term use of ACE inhibitors and/or Ang-II receptor antagonists prevent and/or arrest the progression of diseases in which chronic inflammation plays a significant role, it is likely that these drugs were not used for sufficiently long time to observe their beneficial actions in these diseases. Furthermore, all ACE inhibitors and Ang-II receptor blockers are not similar. For instance, non-thiol ACE inhibitor quinapril is superior to other similar drugs and has been shown to suppress inflammatory arthritis. The anti-inflammatory actions of ACE inhibitors and Ang-II receptor blockers/antagonists may also depend on the local tissue concentrations of prostaglandins, their precursors essential fatty acids, HO-1, HSPs, and VEGF (Fig. 1). Another local factor that can influence the formation of Ang-II is tissue concentrations of chymase. For instance, in the cardiovascular system Ang-II formation is chymase-dependent. Hence, full blockade of renin-angiotensin system requires the use of both ACE and

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**Fig. 1**: Scheme showing relationship between Ang-II, reactive oxygen species, pro-inflammatory cytokines, HSPs, COX-2, Cytochrome P450 enzymes, HO-1, PPARs, and inflammation and tissue damage. (-) Indicates inhibition of activity, process or synthesis. (+) Indicates increase in activity, process or synthesis. ? Indicates that this action needs to be investigated/confirmed.
chymase inhibitors. In ACE-knockout mice, local formation of Ang-II remained unchanged due to a 14-fold increase in the chymase activity.\(^{41}\) Chymase is markedly up-regulated in the diabetic kidney and is associated with the development of diabetic/hypertensive nephropathy. This up-regulation of chymase correlated significantly with the increase in blood pressure and severity of collagen matrix deposition in the kidney.\(^{32}\) These results suggest that less than optimal results seen with ACE inhibitors could be due to incomplete blockade of Ang-II formation that occurs via chymase pathway. The importance of chymase is evident from the observation that over expression of rat via chymase pathway. The importance of chymase is evident from the observation that over expression of rat

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\text{Evidence for the presence of angiotensins in normal, unstimulated alveolar macrophages and monocytes.}
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27. Kumar KV, Das UN. Effect of cis-unaturated fatty acids, prostaglandins, and free radicals on angiotensin-converting


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**Book Review**

**Practical Electrocardiography**

S. N. Chugh

Practical electrocardiography is meant for undergraduate students and practitioners to apprise them about basics of ECG.

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**Published by:**

Peepee Publishers and Distributors (P) Ltd.
7/31, Ansari Road,
Darya Ganj,
New Delhi – 110002
Tel: 9811156083/55195868
Email: peepee160@yahoo.co.in/peepee160@rediffmail.com

**Indian Price:** Rs.175/-