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Role of the renin-angiotensin system in the progression of renal disease

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One common feature of progressive renal diseases is the proliferation of resident renal cells and accumulation of extracelullar matrix. Several studies have demonstrated that local AngII could contribute to these phenomena. AngII modulates cell growth, inducing hyperplasia/hypertrophy depending on the cell type. AngII activates mesangial cells, tubular cells and renal interstitial fibroblasts increasing the expression and synthesis of extracellular matrix proteins. Some of these effects seem to be mediated by the release of growth factors such as transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF). In experimental models of renal damage, associated to elevated renal AngII production, an upregulation in renal TGF-β expression was noted in correlation with increased extracellular matrix protein mRNA expression and deposition, that diminished in response to ACE inhibition and AT_1 receptor blockade.

A novel function of AngII is its participation in inflammatory cell recruitment. The first evidence of a potential role of AngII in immune responses was suggested by the presence of AngII receptors on human monocytes, as well as by the accumulation of mononuclear cells in the kidney of rats after 7-14 days of systemic AngII infusion. AngII may be involved in different steps in the onset and progression of inflammation. Many studies have shown that in several models of renal injury, associated or not to hypertension ACE inhibitors reduce the number of infiltrating cells at glomerular and interstitial level. We have recently demonstrated that this beneficial effect could be due to the regulation of chemokine production. Thus, in a model of immune complex nephritis, characterized by increased local AngII generation in the absence of systemic hypertension, we have observed an upregulation of renal MCP-1 (mRNA and protein), coincidentally with mononuclear cell infiltration. Both facts were markedly reduced by treatment with the ACE inhibitor quinapril. This MCP-1 upregulation was seen in glomerular and tubular epithelial cells, as well as in infiltrating mononuclear cells, suggesting that MCP-1 is produced by both intrinsic and infiltrating cells in paracrine/autocrine fashion.

The molecular signaling pathways elicited upon AngII stimulation has been extensively investigated. We have demonstrated that AngII activates the nuclear factor-κB (NF-κB) in vascular smooth muscle and mesangial cells. NF-κB plays an important role in the regulation of the expression of proinflammatory genes, cell adhesion proteins, nitric oxide synthase and angiotensinogen, and other gene products involved in inflammation, immune response, renal damage and cell proliferation. In a normotensive model of immune glomerulonephritis, we found elevated tissue NF-κB activity that was well correlated with mononuclear cell infiltration and renal MCP-1 expression that diminished by ACE inhibition.

We have recently observed that after systemic infusion of AngII increases renal NF-κB activity due to both resident renal cells and infiltrating monocytes. Moreover, in other pathological settings associated to local AngII production, as an experimental models of atherosclerosis and wounded aortic endothelium, the elevated tissue NF-κB activity was correlated with MCP-1 and leukocyte adhesion molecule VCAM-1 expression, respectively. All these data strongly suggest that NF-κB could be involved in the pathogenesis of renal and cardiovascular diseases. In addition, the anti-inflammatory effect of ACE inhibitors may be due to the decreased activation of NF-κB.

Although AngII has been considered the effector peptide of the renin angiotensin system, other angiotensin peptides also posses biological activities. AngII presents some physiological functions similar to AngII in cardiovascular and central nervous systems. In renal interstitial fibroblasts and mesangial cells AngIII induced c-fos gene expression, increased TGF-β mRNA expression and fibronectin production, suggesting that this peptide could participate in the control of cell proliferation and to the matrix accumulation observed during renal damage. In addition, we have observed that AngIII also upregulated MCP-1 gene expression, as occurs with AngII (unpublished data). These data supports the hypothesis that AngII is not the one and only effector peptide of the RAS, and afford more information to modify our classical view of this system.