NEFROLOGÍA. Vol. XX. Suplemento 1. 2000

How to Prevent Renal Disease Progression?

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Angiotensin II is not only a potent vasoconstrictor compound, but it can also up-regulate fibrogenic factors (such as transforming growth factor β), and other inflammatory and chemoattractant molecules including: tumor necrosis factor-α, nuclear factor κB, adhesion molecules (intercellular adhesion molecules 1 (ICAM-1), vascular adhesion molecules 1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1) and osteopontin, Angiotensin II can also induce cellular hypertrophy and cause phenotypic alterations of tubular cells. These pleiotropic effects of angiotensin II suggest that it may play a critical role in promoting renal scarring and progressive nephron loss. An inappropriate activation of angiotensin II is seen in many renal diseases.

Pharmacological manipulations that reduce angiotensin levels (ACE inhibitors) or interfere with its action (AT-1 receptor antagonists) blunt NF-κB activation, and the upregulation of many of the factors described above. The regulation of gene expression by angiotensin II occurs through specific receptors that are ultimately linked to changes in the activity of transcription factors within the nucleus of target cells. In particular, members of the NF-κB family of transcription factors are activated which, in turn, fuels at least two autocrine reinforcing loops that amplify angiotensin II and TNF-α formation. This amplification further increases NF-κB activation within the kidney. This leads to fibroblast proliferation and subsequent differentiation into myofibroblasts. Furthermore, tubular epithelial cells, in the setting of proteinuria are stimulated to produce chemoattractant and adhesion proteins to cause an inflammatory response leading to monocyte/macrophage infiltration.

The tubule cells also produce profibrotic cytokines, leading to over production of extracellular matrix.

In several clinical trials, pharmacological inhibition of the renin-angiotensin system with ACE inhibitors attenuated the decline in renal function associated with chronic renal disease. In addition ACE inhibition has been shown to decrease protein excretion in the urine. Abnormal excretion of protein in the urine is a marker of renal injury and predicts the development of overt nephropathy. Several studies have found a strong association of greater baseline proteinuria with a more rapid decline in GFR.

A variety of proteins have been shown to be toxic to tubular epithelial cells and to induce increased expression of proinflammatory cytokines and extracellular matrix proteins. It has been suggested that the antiproteinuric effect of ACE inhibitors or AT-1 receptor antagonist is a potential contributor to the renoprotective effects of these drugs.

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