NEFROLOGÍA. Vol. XX. Suplemento 1. 2000

The Endothelium in the Progression of Renal Failure: Therapeutic Implications

L. Raij
Veterans Affairs Medical Center. Minneapolis. USA.

Anatomically, the glomerulus is composed of the glomerular basement membrane (GBM); the epithelial cells, which outline the GBM in the urinary space; and the mesangium, which lies in an intracapillary position and forms the glomerular centrolobular area. The direct juxtaposition of endothelial and mesangial cells facilitates products synthesized by these cells to reach each other in high concentrations. Similar to vascular smooth muscle, mesangial cells contain actin-myosin filaments and change their contractile state in response to vasoactive substances. Thus, agents such as angiotensin II (AII), eicosanoids, endothelin-1 (ET-1), and nitric oxide (NO) synthesized and released locally can act on these cells in an autocrine and/or paracrine fashion. In the glomerulus, vasoactive agents acting upon the mesangium and/or the afferent and efferent arteriole can modulate the glomerular microcirculation under physiologic and pathologic conditions. Moreover, similar to what occurs in systemic vascular beds, the nonhemodynamic actions of vasoactive agents may also participate in the response of glomerular cells to injury and result in architectural changes of the glomerulus, such as mesangial hypertrophy and/or hyperplasia, as well as in increased mesangial cell matrix production.

Increased renal actions of Ang II or NO may be due to an actual increase in the local concentration of the individual agent and/or to a concomitant decrease in the concentration of the other. Moreover, chronic NO synthesis inhibition induces glomerular and tubulointerstitial injury as well as coronary vascular remodeling and LVH that is accompanied by increased ACE expression and activity. This would suggest that decreased vascular NO bioactivity due to endothelial dysfunction as seen in hypertension may promote vascular hypertrophy due to combined deficit of NO and local excess of Ang II. Indeed, experimentally, *in vivo* transfection of excess ACE to arterial segments results in localized vascular hypertrophy mediated by Ang II.

Ang II has been reported to activate NADH/NADPH oxidase in vascular smooth muscle cells and more recently in mesangial cells, leading to the cells' protracted synthesis of O_2^-. O_2^- has great affinity for NO, causing interaction between the two and resulting in either NO inactivation or the production of toxic peroxynitrite. Furthermore, in the glomerulus as in the vasculature in general, decreased NO bioactivity not only reduces the ability of NO to counteract Ang II actions on vascular tone but also diminishes the homeostatic role of NO in preventing vascular thrombosis, leukocyte adhesion to endothelium, and Ang II-driven mesangial cell hypertrophy/hyperplasia and production of extracellular matrix. ET-1, a powerful vasoconstrictor, is capable of reducing renal blood flow and glomerular filtration rate by acting on preglomerular resistances and inducing mesangial cell contraction. The interaction between NO and ET-1 appears to be more important under pathological than under physiological conditions. In addition, ET-1 synthesis is upregulated by Ang II and downregulated by NO. ET-1 may thus play its role late rather than early in renal pathophysiological processes in that its importance may build as the renal bioactivity of NO decreases.

From a therapeutic point of view antihypertensive agents that interfere with the local renin-angiotenisn-endothelial system are the best choices for arresting the hemodynamic and nonhemodynamic factors that promote the progression of renal failure.

Correspondence: L. Raij, M. D.
Chief, Nephrology/Hypertension
Professor of Medicine, University of Minnesota
VA Medical Center
One Veterans Drive
Minneapolis, MN 55417 USA