View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Kidney International, Vol. 54 (1998), pp. 646–647

EDITORIAL

Angiotensin II and endothelin in chronic glomerulonephritis

Glomerulopathies that result in substantial renal damage frequently are characterized by relentless progression to end-stage renal disease. This process typically involves glomerular sclerosis and interstitial fibrosis and occurs regardless of the nature of the initial renal insult. The mechanisms responsible for continued renal deterioration are not fully understood, but may be distinct from those responsible for the original injury. Glomerular hypertension, glomerular cell hypertrophy, and extracellular matrix accumulation all appear to be involved. Numerous studies support a role for angiotensin II (Ang II). Renal Ang II production is enhanced in chronic glomerulopathies, while the peptide can elevate intraglomerular pressure, increase glomerular cell hypertrophy, and augment extracellular matrix accumulation [1]. Ang II antagonists or synthesis inhibitors markedly slow, and can even prevent, renal deterioration in experimental models of progressive renal failure [1–3]. Studies in humans on the efficacy of angiotensin converting enzyme inhibitors (ACEI) in non-diabetic chronic renal failure have suggested, but not conclusively demonstrated, a beneficial effect on preservation of renal function [4]. This may reflect the relatively short-term nature and small sample size of these studies, but may also be an indication that factors other than Ang II play an important role in progression of renal failure.

One such factor that has been implicated in the nephrosclerotic process is endothelin (ET). ET is a potent vasoconstrictor, stimulates glomerular cell proliferation and hypertrophy, and enhances extracellular matrix accumulation [5]. Renal production of this 21-amino acid peptide is increased in virtually all forms of chronic renal disease. Since ET was only identified a decade ago, there have been no reports on the efficacy of ET antagonism in humans with renal disease; however, blockade of ET receptors ameliorates glomerular injury in a wide variety of experimental models of chronic renal failure [5]. In addition, mice transgenic for endothelin-1 develop substantial glomerulosclerosis and interstitial fibrosis, which occurs despite no detectable change in blood pressure [6]. Thus, there is ample reason to suspect that ET is involved in progressive renal failure.

The above considerations raise the question as to whether the combined blockade of ET and Ang II action would better preserve renal function in chronic glomerulopathies than is afforded by inhibition of either factor alone. This important issue has not previously been studied. Indeed, the only relevant data are from studies using a model of chronic cyclosporine nephrotoxicity in which the effect of ET receptor blockers and ACEI were compared [7]. ET receptor inhibition markedly preserved renal function, but did not affect arteriolopathy or interstitial fibrosis. In contrast, ACEI reduced structural injury, but failed to protect the glomerular filtration rate. Thus, these studies suggest that there may indeed be merit to combined inhibition of ET and Ang II action in the treatment of progressive renal failure. It is in this setting that the studies reported in this issue of *Kidney International* are so timely [8]. Benigni et al examined the effect of trandolapril (an ACEI), endothelin A (ETA) receptor blockade, or combined therapy, on renal structure and function in rats uninephrectomized one week after a single injection of rabbit anti-Fx1A antibody (accelerated passive Heyman nephritis PHN). After eight months of continuous treatment, neither agent alone significantly affected serum creatinine or proteinuria, while combination therapy markedly protected against functional deterioration and reduced the degree of proteinuria. Similarly, single drug administration did not alter tubulointerstitial damage or the number of glomeruli with sclerotic changes, while both agents together significantly ameliorated glomerular and tubulointerstitial structural injury. Thus, the combined inhibition of Ang II and ET-1 action may be better than inhibition of either agent alone in preserving renal structure and function in chronic proteinuric renal failure.

Should we now be treating chronic glomerulopathies with inhibitors of Ang II and ET action? Several considerations with regards to the Benigni et al study must be undertaken before arriving at this conclusion. First, blood pressure tended (although it was not statistically significant) to be lower in animals treated with combination therapy than with single agents alone. In addition, unlike other experimental glomerulopathy models, ACEI alone had no effect on GFR or proteinuria. The authors ascribe this lack of an ACEI effect to the relatively greater disease severity in the current study; if true, these studies could provide a rationale for combined drug therapy even in more severe stages of chronic renal failure. Lastly, an ETA receptor inhibitor was used, leaving endothelin B (ETB) receptors available for increased ET-1 binding. The significance of this is unknown, since the role of ETA and ETB receptors in mediating renal dysfunction and sclerosis in

Key words: Endothelin, angiotensin II, membranous glomerulopathy, chronic renal failure.

© 1998 by the International Society of Nephrology

humans remains speculative. Nonetheless, since ETB, but not ETA, receptor mRNA may be elevated following renal injury [9], and since ETB receptors can mediate renal vasoconstriction in the rat [5], the possibility is raised that antagonizing both ETA and ETB receptors may provide even greater benefit. Clearly, further studies are needed on the efficacy of combined therapy with ET and Ang II inhibitors in experimental glomerulopathies. If, as the studies by Benigni et al suggest, combined blockade proves beneficial, we need to rapidly examine the effects of many of the newly developed ET receptor antagonists, both alone and in combination with ACEI or Ang II receptor blockers, in chronic renal failure.

DONALD E. KOHAN
Department of Veterans Affairs Medical Center and the University of Utah, Salt Lake City, Utah, USA

Reprint requests to Donald E. Kohan, M.D., Ph.D., Medical Care Center (111), Veterans Affairs Medical Center, 500 Foothill Blvd., Salt Lake City, Utah 84148, USA.

REFERENCES

1. BRUNNER H: ACE inhibitors in renal disease. *Kidney Int* 42:463–479, 1992
2. LAFAYETTE R, MAYER G, PARK S, MEYER T: Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. *J Clin Invest* 90:766–771, 1992
3. ANDERSON S, RENNKE H, BRENNER B: Therapeutic advantage of converting enayme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77:1993–2000, 1986
4. GIATRAS J, LAU J, LEVEY AS, FOR THE ANGIOTENSIN-CONVERTING ENZYME INHIBITION AND PROGRESSIVE RENAL DISEASE STUDY GROUP: Effect of angiotensin converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 127:337–344, 1997
5. KOHAN D: Endothelins in the normal and diseased kidney. *Am J Kidney Dis* 29:2–26, 1997
6. HOCHER B, THONE-REINEKE C, ROHMEISS P, SCHMAGER F, SLOWINSKI T, BURST V, SIEGMUND F, QUETERMOUS T, BAUER C, NEUMAYER H-H, SCHLEUNING W-D, THEURING F: Endothelin-1 transgenic mice develop glomerulosclerosis, interstitial fibrosis, and renal cysts but not hypertension. *J Clin Invest* 99:1380–1389, 1997
7. KON V, HUNLEY TE, FOGO A: Combined antagonism of endothelin A/B receptors links endothelin to vasoconstriction whereas angiotensin II effects fibrosis. *Transplantation* 60:89–95, 1995
8. BENIGNI A, CORNA D, MAFFI R, BENEDETTI G, ZOJA C, REMUZZI G: Renoprotective effect of contemporary blocking of angiotensin II and endothelin-1 in rats with membranous nephropathy. *Kidney Int* 54:353–359, 1998
9. NAKAMURA T, EBIHARA I, FUKUI M, OSADA S, TOMINO Y, MASAKI T, GOTO K, FURUICHI Y, KOIDE H: Modulation of glomerular endothelin and endothelin receptor gene expression in aminonucleoside-induced nephrosis. *J Am Soc Nephrol* 5:1585–1590, 1995