

Bradykinin and Renal Fibrosis: Have We ACE'd it?

JEAN-LOUP BASCANDS AND JOOST P. SCHANSTRA

The Renal Fibrosis Lab, Inserm U388, CHU Rangueil, Toulouse, France

In parallel with the increase in overall life expectancy, the number of patients with end-stage renal disease (ESRD) has significantly increased over the last decade (1). The best possible outcome for these patients is to undergo kidney transplantation, but in the interim they are dependent on life-long dialysis treatment (2,3). Forestalling, slowing down and, if possible, reversing the progression of renal disease to ESRD is thus the major challenge facing clinicians and researchers in nephrology daily. Any progress in this field will have major social and economic impact.

Regardless of the initial insult, most forms of renal disease progress to ESRD with irreversible loss of renal tissue and function even after the initial renal insult has subsided. A hallmark of ESRD is the appearance of tubulointerstitial fibrosis, and this has been shown to be associated with a poor long-term prognosis (4). Thus all reports that demonstrate a halting or reversal of renal tubulointerstitial fibrosis by pharmacological means are of great potential interest. One such study is reported by Okada *et al.* (5) in this issue of *JASN*.

Tubulointerstitial fibrosis is characterized by the progressive accumulation of extracellular matrix (ECM) proteins in the tubulointerstitial compartment. Two main enzyme systems are involved in ECM degradation: the plasminogen activation system and matrix metalloproteinases (MMPs). These two pathways are closely interlinked and can function in cascade (6). Urokinase-type and tissue-type (tPA) plasminogen activator convert plasminogen to plasmin, which in turn activates latent MMPs into activated MMPs, including MMP2 and MMP9. Of particular interest is the fact that this cascade is tightly regulated at the level of the plasminogen activators by the plasminogen activator inhibitor-1 (PAI-1). PAI-1 appears to play a key role in the development of renal fibrosis as described in a number of recent studies. PAI-1^{-/-} mice had attenuated renal interstitial fibrosis in a model of unilateral ureteral obstruction (UUO) compared to wild type mice (7). Furthermore it was shown that inhibition of endogenous PAI-1 by a noninhibitory PAI-1 mutant decreased ECM accumulation in a model of experimental glomerulonephritis (8). Surprisingly, the effect of PAI-1 blockade on renal fibrosis in the UUO model occurred independently of the generation of plasmin (7). Such plasmin independent effects have also been observed using the UUO

model in tPA (9) and plasminogen (10) knockout mice. However, despite these apparent contradictions concerning the role of the plasminogen activator system in ECM degradation, the induction of PAI-1 in a number of renal diseases leading to fibrosis and ESRD makes inhibition of PAI-1 expression and/or activity an interesting therapeutic target (6,11-13).

The multitude of events and factors (14-16) involved in the development of renal fibrosis is reflected by the increasing number of studies suggesting the potential anti-fibrotic effect of a number of compounds (17). However, in the majority of these studies, the protective effect of the drug in question was evaluated by administration either before, or at the time of, induction of the pathology. Such experimental therapeutic interventions do not truly mimic human pathology where treatment starts only after disease identification. This is particularly true for renal interstitial fibrosis, which is often detected at a late stage (by histological examination of renal biopsies).

Despite the impressive amount of data published over the last two decades demonstrating the ability to arrest disease progression and renal fibrosis in animal models, the only clinically used drugs with, although not initially designed to do so, anti-fibrotic properties are angiotensin converting enzyme (ACE) inhibitors (ACEi). ACEi were primarily designed as antihypertensives, but have since been shown to also slow down the progression of renal fibrosis in man (18-20). The study of Okada *et al.* (5) in this issue of *JASN* provides new insights on the mechanism by which ACEi could exert this anti-fibrotic effect.

The pharmacological effects of ACEi have long been attributed to the blockade of the conversion of angiotensin I (AI) to angiotensin II (AII). However, ACE also degrades the biologically active nonapeptide bradykinin (BK) with, interestingly, a 10x higher efficiency than for AI (21). Indeed, it has been shown in both animals and humans that BK concentrations are increased after ACEi treatment (22, 23) and there is now clear evidence that in humans BK actively participates in this protective effect (24-28).

Consistent with the anti-fibrotic effect of BK in cardiac fibrosis (29) we have recently reported that BK reduced renal fibrosis (30). Using the UUO-induced model for renal fibrosis we showed that BK B2^{-/-} mice have significantly higher tubulointerstitial fibrosis than wild type mice. Interestingly this was accompanied by decreased renal activity of plasminogen activator and MMP2. Additional *in vitro* data showed that BK via its B2 receptor stimulated plasminogen activator activity. Taken together these data strongly suggested that the anti-fibrotic effect of BK involved a B2 receptor-plasminogen activator-MMP2 cascade.

Okada *et al.* (5) show compelling data that ACEi reduces

Correspondence to Dr Jean-Loup Bascands, Inserm U388, IFR31, Hôpital Rangueil, TSA50032, 31059 Toulouse Cedex 9, France. Phone: 33-5-61-32-22-11; Fax: 33-5-62-17-25-54; E-mail: bascalou@toulouse.inserm.fr

1046-6673/1509-2504

Journal of the American Society of Nephrology

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DOI: 10.1097/01.ASN.0000143721.71748.30

renal fibrosis progression. Using a more chronic model that mimics progressive renal tubulointerstitial fibrosis occurring in patients treated with cyclosporin, the study shows that ACE inhibition significantly reversed ECM accumulation in the kidney. This study is of particular interest, since administration of the drug occurred only after induction of the pathology and after tubulointerstitial fibrosis was detected. Whilst AII type 1 receptor antagonists were without effect, the protective effect of ACEi was blocked by a BK-B2 receptor antagonist, and this was also accompanied by attenuated PAI-1 expression and an increase in plasmin activity suggesting increased ECM degradation. Inhibition of PAI-1 expression by BK treatment was confirmed in tubular epithelial cells *in vitro*.

In an arena where the role of BK in ACEi-mediated renal beneficial effects is not yet clearly established (31,32), and where there is continued controversy about the role of plasmin in ECM degradation (13,33), there is now a growing body of experimental arguments, including the Okada paper, that assign an anti-fibrotic role to BK and its B2 receptor. This effect seems to be exerted through a complex interplay with the plasminogen activation system.

Further *in vivo* studies (other models, different doses of ACEi,) are needed to confirm the role of BK in the anti-fibrotic effects of ACEi and to elucidate, quite who has the ace!

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See related editorial, "Bradykinin Decreases Plasminogen Activator Inhibitor-1 Expression and Facilitates Matrix Degradation in the Renal Tubulointerstitium under Angiotensin-Converting Enzyme Blockade," on pages 2404–2413.