Targeting TGF-β overexpression: maximizing the antifibrotic actions of angiotensin II blockade in anti-Thy1 glomerulonephritis

H. Peters1,2, W. A. Border1 and N. A. Noble1

1Division of Nephrology, University of Utah, Salt Lake City, UT, USA and 2Department of Internal Medicine—Nephrology, Charité, Campus Charité Mitte Humboldt-University, Berlin, Germany

Introduction

Progressive accumulation of pathological extracellular matrix in the kidney is the main cause of end-stage renal disease in patients with hypertension, diabetes mellitus or glomerulonephritis. Overexpression of the profibrotic cytokine transforming growth factor (TGF-β) has been identified as key mediator of matrix accumulation in a number of human and experimental renal diseases [1]. In rats following induction of anti-Thy1 glomerulonephritis, we used reduction in TGF-β overexpression as a novel target to evaluate several strategies to maximize the antifibrotic action of angiotensin (Ang) II blockade [2]. We asked whether TGF-β expression can be reduced more effectively or even normalized by increasing the doses of Ang II-blocking drugs or by combining angiotensin-converting enzyme (ACE) and angiotensin type 1 (AT1) receptor antagonism.

Methods

Anti-Thy1 glomerulonephritis was induced in male Sprague–Dawley rats (225–280 g) fed a normal protein diet by the i.v. injection of OX-7 antibody (1.5 mg/kg). At 24 h after disease induction, rats were given the ACE inhibitor enalapril (0, 10–1000 mg/l, set 1) or the AT1 antagonist losartan (0, 50–2000 mg/l, set 2) in their drinking water. In set 3, rats were treated with enalapril (100 mg/l), losartan (500 mg/l) or a combination of both. The doses selected for enalapril and losartan had shown maximal efficacy in set 1 or 2. The animals were sacrificed 6 days after disease induction. Glomerular TGF-β1 synthesis was measured by enzyme-linked immunosorbent assay (ELISA) in the supernatant of cultured glomeruli isolated from individual rats. Matrix accumulation was estimated using periodic acid–Schiff (PAS)-stained kidney tissue by a blinded observer.

Results

Following induction of anti-Thy1 glomerulonephritis, increasing doses of both enalapril and losartan reduced glomerular TGF-β1 production in a dose-dependent manner (Figure 1A and B). A moderate decrease in pathological TGF-β overproduction was seen in rats treated with 10–20 mg of enalapril or 50–100 mg of losartan per litre of drinking water. With increasing enalapril or losartan dose, a maximal reduction in TGF-β overproduction was seen starting with 100 mg of enalapril or 500 mg of losartan in the drinking water. A further increase in enalapril or losartan dose did not decrease glomerular TGF-β production further. Side by side comparison of maximal effective doses of enalapril or losartan showed a comparable reduction in TGF-β overexpression (enalapril −46%, losartan −45%). Combined therapy with both modes of Ang II blockade did not result in additional beneficial effects (−45%). In all experiments, changes in TGF-β expression were closely correlated to the glomerular matrix accumulation (r = 0.96, P < 0.001). No therapy entirely normalized TGF-β and matrix protein overproduction.

Correspondence and offprint requests to: Harm Peters, Department of Internal Medicine—Nephrology, Charité, Campus Charité Mitte, Schumanstraße 20/21, D-10117 Berlin, Germany.

© 1999 European Renal Association–European Dialysis and Transplant Association

Fig. 1. Effect of Ang II blockade on glomerular TGF-β1 expression 6 days after induction of Anti-Thy1 glomerulonephritis (GN). The effect of increasing doses of (A) the ACE inhibitor enalapril and (B) the AT1 receptor blocker losartan in the drinking water. (C) The effect of maximal effective doses of enalapril (Ena, 100 mg/l), losartan (Los, 500 mg/l) or both (*P < 0.01 vs GN). Glomerular production of TGF-β1 served as an indicator of TGF-β1 expression (modified from [2]). Used with permission from Kidney International 1998; 54: 1570–1580
Conclusions

The present study shows that (i) TGF-β expression is a valid target in the management of fibrotic renal diseases and (ii) Ang II blockade reduces pathological TGF-β expression and matrix accumulation following tissue injury more effectively at higher doses. The data suggest that (i) ACE inhibition and AT1 receptor antagonism act through very similar pathways and (ii) Ang II blockade must be combined with other agents, which act through different pathways, in order to halt renal fibrosis more effectively.

References


Adenosine receptor antagonism in the prevention of acute cyclosporine A-nephrotoxicity in normal, diabetic and hypertensive rats

N. Heyne, S. Wolf¹, P. Petersen², S. Merten, W. Schöber, C. M. Erley¹, T. Risler¹ and H. Osswald

Centre of Clinical Pharmacology Tübingen–Stuttgart, ¹Department of Internal Medicine, Section of Nephrology and Hypertension and ²Department of Surgery, University of Tübingen, Germany

Cyclosporine A (CsA) is a principle component of immunosuppressive regimens applied in organ transplantation and autoimmune disorders. Although having considerably improved patient outcome in these diseases, acute and chronic CsA nephrotoxicity limits clinical application in certain patients. Acute CsA nephrotoxicity is characterized by renal haemodynamic and tubular alterations, resulting in a marked decline in renal function. Although generally reversible upon dose reduction or withdrawal of the drug, overt acute renal failure may result in patients where additional risk factors such as volume depletion, diabetes mellitus and arterial hypertension are present. For these patients, specific therapeutic strategies have to be developed. The present experiments were designed to elucidate the role of adenosine in acute CsA nephrotoxicity and to evaluate the nephroprotective potential of different adenosine receptor antagonists.

In standard clearance experiments, CsA (Sandimmune®, 20 mg/kg i.v.)-induced alterations in renal haemodynamics were investigated in streptozotocin diabetic (60 mg/kg i.p.), L-NAME hypertensive (Nω-nitro-L-arginine methyl ester, 50 mg/l, added to the drinking water for 8 weeks) and age-matched control rats. Glomerular filtration rate (GFR) was...