The Influence of Inhibition of the Renin-Angiotensin System on the Fibrinolytic System in the Different Types of Primary Glomerulonephritis

Rammos G, Kapnissis S, Kakaletri Constantina, Sakka Maria, Karakassis P, Ziakka Stavroula, Fragaki I. and Papagalanis N
Nephrology Department, Corgialenio Benakio Hospital, Athens

Introduction

PAI-1 is the primary physiological inhibitor of tissue-type and urokinase-type plasminogen activators (tPA and uPA, respectively), by forming an irreversible 1:1 molar complex. PAI-1 inhibits the formation of plasmin (an extracellular protease that mediates fibrinolysis) from plasminogen (1). tPA functions almost exclusively as a mediator of intravascular fibrinolysis and clot dissolution. Within normal kidneys, tPA has been identified within glomerular cells and collecting duct epithelial cells, as well. On the contrary PAI-1 is not expressed in the normal kidney (2).

PAI-1 is a multifunctional protein with actions that may be dependent on or not of its protease inhibitory effects. The protease-inhibitory actions of PAI-1 extend beyond fibrinolysis and include extracellular matrix turnover and activation of several proenzymes and latent growth factors. Not normally expressed in the kidney, PAI-1 is rapidly produced by diseased glomeruli, tubules and inflamed interstitium, in a variety of acute and chronic renal diseases. PAI-1 has been implicated in several renal pathogenetic processes, including thrombotic microangiopathies, proliferative and/or crescentic glomerulopathies and tubulointerstitial fibrosis (2).

There is an interaction between the renin-angiotensin system (RAS) and fibrinolytic system. Angiotensin II (Ang II) and its hexapeptide metabolite Ang IV stimulate plasminogen activator inhibitor-1 (PAI-1) expression in cultured endothelial cells. ACEI not only significantly lowers PAI-1 antigen and activity without lowering tPA antigen, but also prevent the degradation of bradykinin. Bradykinin is a potent stimulus for tPA secretion. Thus, ACEI would be expected to favorably alter fibrinolytic balance by decreasing PAI-1 and increasing bradykinin and tPA (3). The aim of the present study was to examine the effect of the RAS on the tPA and PAI-1 in different types of glomerulonephritis (GN).

Materials and Methods

Twenty patients (14 males) aged 45,3±15,01 years (mean ±SD) were included in the study. Kidney biopsy, was obtained in 16 patients. Six pts had focal-segmental GN, four pts membranous nephropathy, three pts membranoproliferative GN, two pts IgA nephropathy and 1 minimal change. In the remaining four pts the biopsy was considered not necessary because of a prompt remission of proteinuria after 4 weeks of corticosteroid therapy. So these patients were classified as having minimal change disease. In all patients perindopril (ACEI), valsartan (AT1RA) and combination of the two drugs were given for 8 days with wash-out period of 8 days as well, in a random fashion. At the end of each circle and at the end of the wash-out periods tPA and PAI-1 were determined in the serum.

In all patients blood was taken at 08.00 p.m. so the daily fluctuation of the levels of the PAI-1 and tPA was avoided. Salt restriction and/or diuretics were not given, so exogenic activation of RAS was excluded. The determination of PAI-1 and tPA was done with enzyme-linked immunosorbent assay (ELISA). The statistical analysis of results became with method ANOVA and t-test for independent samples.

Results

Serum and urine creatinine, BUN and electrolytes, as well as proteinuria were not different before and after this short-term administration of the two categories of the drugs or the combination.

The antihypertensive effect with either perindopril or valsartan was nearly the same. However, the combination, was more effective in lowering diastolic blood pressure than the monotherapy with valsartan alone (84,1± 8,50 mmHg vs. 91,6 ± 9,49 mmHg, p=0,013).

Compared with perindopril the valsaran increased by 20% more the tPA (27,89±21,6 ng/ml vs. 22,06±19,68 ng/ml) and decreased by 20% more the PAI-1 (46,79± 37,34 ng/ml vs. 58,39±46,53 ng/ml) in all patients. The combination of the two drugs had no additional effect in these two parameters.

In patients with membranous nephropathy, membranoproliferative GN and minimal change nephropathy, in which extensive expansion of the interstitium was not detected, there was no difference in tPA and PAI-1 levels before and after therapy with perindopril, valsartan or the combination. In IgA nephropathy in which the expansion of the interstitium was more pronounced an increase of PAI-1 levels and a decrease of tPA levels, was noted after the inhibition of RAS (PAI: p = 0,0450 tPA: p = 0,00002) .

Discussion

In recent years, PAI-1 has emerged as a critical mediator of glomerulosclerosis and renal interstitial fibrosis. PAI-1 mediates several effects that may facilitate matrix accumulation through the impairment of matrix turnover. The potential

Correspondence to: Rammos George, Semitelou 6, Athens 115 27, Greece, e-mail: rageo48@hotmail.com

importance of PAI-1 in progressive renal disease was first realised with the recognition that TGF-β is a critical mediator of renal fibrosis and that TGF-β is a powerful inducer of PAI-1 expression. It appears that PAI-1 expression may be induced at several steps along this pathway by renin, angiotensin II, angiotensin IV, aldosterone, and shear stress in addition to TGF-β-dependent induction. Several animal studies, have consolidated the link among the renin-angiotensin-aldosterone cascade, TGF-β, and PAI-1 in the pathogenesis of glomerulosclerosis (2). Indeed, PAI-1 mRNA and/or protein have been found to be increased in several renal diseases associated with fibrosis, such as obstructive nephropathy, protein-overload proteinuria, radiation nephropathy, aging, hypertensive nephropathy, antitubular basement membrane nephritis, nephrotoxicity, lipid-induced renal injury, lupus nephritis, Thy-1 nephritis, focal segmental glomerulosclerosis, diabetic nephropathy, and allograft nephropathy (2). Interestingly, an increased expression of this inhibitor of plasminogen activation has been demonstrated in IgA nephropathy (IgAN) (4).

In the present study the reduction of PAI-1 by 20% and increase of tPA by 20% after valsartan but not perindopril, suggests that as it happens in general (5), the AT1-receptor blocking is more efficient in completely blocking the RAS system. As it is known the ACEI are not totally blocks the formation of Ang II because other enzymes can produce Ang II directly from Ang I and angiotensinogene (i.e. chymase) (6). Previous studies have shown that the AT_1 antagonist losartan partially blocks Ang II–induced PAI-1 expression in rat aortic smooth muscle cells and rat microvessel endothelial cells (7).

Although these results are compatible with the study of Goodfield N et al. (8) are not in agreement with other studies (9).

Perindopril and valsartan had equivalent hypotensive effect, suggesting that the effect on fibrinolysis is independent of the antihypertensive effect of Valsartan. Indeed, the data suggest that, at equivalent hypotensive doses, an ACEI and AT1RA differ in their effects on fibrinolytic balance (9)

A wide variety of renal diseases, regardless of etiology, lead to fibrosis of the tubulointerstitial compartment (10). Ang II seems to participate in this phenomenon, by the release of several factors, including chemotactic factors, transforming growth factor-ß (TGF-ß) and PAI-1 (11). In cultured tubular cells and renal interstitial fibroblasts, Ang II causes cell proliferation and synthesis of ECM proteins, such as fibronectin, by a TGF-ß-mediated mechanism (11). Ang II, is implicated in the process of renal fibrosis by multiple mechanisms, and drugs controlling this complex vasoactive peptide are probably one of the ways of avoiding fibrosis in progressive renal diseases. (11)

In conclusion PAI-1 could be a possible therapeutic target in glomerulonephritis with pronounced interstitial expansion. Inhibition of RAS with AT1RA maybe not only delay progressive renal disease but also, perhaps even can achive disease regression if treatment is initiated before matrix accumulation has destroyed cellular structures within the kidney. It must be stressed whoever, that the same effect may have also the ACEI as suggested by a recent study in patients with IgAN (12). This effect was not observed in our study. This difference may be due to the duration of the drug administration. Contrary to the above study, in our study the drugs was administered for 8 days only.

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