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Enhancing cGMP in anti-thy1-induced, chronic-progressive glomerulosclerosis: sGC stimulation versus PDEs inhibition

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Background

The present study analyzes the renal activity of the NO-cGMP pathway in and the effect of the specific soluble guanylate cyclase (sGC) stimulator Bay 41-2272 and phosphodiesterases (PDEs) inhibitor pentoxifylline (PTX) on a progressive model of anti-thy1-induced chronic glomerulosclerosis (cGS).

Methods

cGS was induced by injection of anti-thy1 antibody into uni-nephrectomized rats. One week after disease induction, animals were randomly assigned to: cGS, cGS+Bay 41-2272 (10 mg/kg body weight/d) or cGS+PTX (50 mg/kg body weight/d). In week 16, animals were scarified and materials analyzed.

Results

Compared to normal controls, sGC mRNA expression (alpha1 sGC +260% and beta1 sGC +310%) and NO-stimulated cGMP production (+270%) were up-regulated in the tubulointerstitium of the untreated cGS animals, while its activity was depressed in glomeruli (-50%). As compared to untreated the cGS group, Bay 41-2272 treatment significantly enhanced glomerular and tubulointerstitial NO-cGMP (+92% and +88%) signaling. This went along with markedly reduced glomerular and tubulointerstitial macrophage infiltration (-42% and -50%), number of proliferating cells (-31% and -30%), matrix protein expression (TGF-β protein -36% and -50%) and accumulation (histological matrix score -47% and -42%) as well as improved kidney function (plasma creatinine -57%). In contrast, PTX therapy only moderately, but not significantly affected the above parameters.

Conclusions

Glomerular and tubulointerstitial sGC activity were discordantly altered in anti-thy1-induced chronic glomerulosclerosis. Stimulation of sGC signaling by Bay 41-2272 limited the progressive course towards tubulointerstitial fibrosis and impaired renal function, whereas the PDEs inhibitor PTX did not significantly increase renal cGMP levels and thereby had no effects on kidney fibrosis. The results suggest that enhancing kidney cGMP levels by sGC stimulation represents a novel effective anti-fibrotic approach in progressive renal disease.