BMC Pharmacology

BioMed Central

Poster presentation

Open Access

Increased mesangial cGMP levels prevent mesangial cell proliferation and matrix expansion in experimental glomerulonephritis

Bernd Hohenstein*[1], Christoph Daniel[1], Sandra Wittmann[1], Andrea Braun[1], Johannes-Peter Stasch[2] and Christian Hugo[1]

Address: [1]Department of Nephrology and Hypertension, University Erlangen-Nuremberg, Erlangen, Germany and [2]Institute of Cardiovascular Research, Bayer HealthCare, Wuppertal, Germany

Email: Bernd Hohenstein* - bernd.hohenstein@rzmail.uni-erlangen.de

* Corresponding author

from 3rd International Conference on cGMP Generators, Effectors and Therapeutic Implications
Dresden, Germany. 15–17 June 2007

Published: 25 July 2007

BMC Pharmacology 2007, **7**(Suppl 1):P29 doi:10.1186/1471-2210-7-S1-P29

This abstract is available from: http://www.biomedcentral.com/1471-2210/7/S1/P29

Introduction

Mesangial cell proliferation is a prominent finding of various human diseases like membranoproliferative glomerulonephritis, lupus nephritis, IgA- and diabetic nephropathy. Despite increasing knowledge on disease mechanisms therapeutical options are very limited. The NO-cGMP pathway has been linked with cell proliferation and matrix expansion. In our studies, we investigated the effects of direct sGC stimulation using BAY 41–2272 and PDE 5 inhibition using vardenafil on the early phase of experimental mesangial proliferative glomerulonephritis (anti-Thy1 nephritis) in the rat.

Methods

Two separate studies were performed. First, experimental glomerulonephritis was induced in 16 rats, 8 rats received BAY 41–2272 (10 mg/kg bw) by daily oral gavage, 8 rats received placebo. Additional experiments were performed to exclude relevant effects on healthy kidneys and due to changes of blood pressure.

In a second study, 8 rats received vardenafil (10 mg/kg bw) twice daily by oral gavage and 8 rats served as placebo controls. During each experiment survival biopsies were performed on day 2, sacrificial biopsies on day 6. Blood, urine and renal tissues were collected. For measurement of glomerular cGMP levels additional, identical experiments were performed in both studies using 10 rats (5 treatment, 5 controls). Glomeruli were isolated by sequential sieving and samples were immediately shock frozen and stored until analysis.

Results

Immunohistochemical staining of frozen tissue sections localized sGC as well as PDE 5 to the mesangium. Increased cGMP levels could be detected after sGC stimulation (4005 +- 2752 fmol/l) and PDE 5 inhibition (1567 +- 417 fmol/ml) in glomerular extracts. In the presence of equal disease induction (by equal mesangiolysis score on day 2), sGC stimulation and PDE 5 inhibition significantly reduced glomerular ($P < 0.05$) and mesangial cell proliferation ($P < 0.05$) on day 6. In parallel, glomerular matrix expansion was significantly prevented in rats exposed to sGC stimulation and PDE 5 inhibition compared to placebo controls on day 6 ($P < 0.01$). In contrast, no differences could be detected regarding apoptosis (TUNEL assay), formation of microaneurysms (JG-12), platelet accumulation (PL-1), and ED-1 positive monocytes/macrophages. Proteinuria was decreased due to sGC stimulation but not to treatment with the PDE 5 inhibitor.

Conclusion

Our studies demonstrate that direct sGC stimulation as well as specific inhibition of PDE 5 lead to increased

glomerular/mesangial cGMP levels. Both substances thereby prevent mesangial cell proliferation and matrix expansion during experimental mesangial proliferative glomerulonephritis. Both treatment options could therefore be considered as a therapeutical strategy for mesangial proliferative glomerulonephritis in man.