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Stimulation of soluble guanylate cyclase accelerates renal recovery following relief of unilateral ureteral obstruction

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Background

Unilateral ureteral obstruction (UUO) is characterized by progressive renal atrophy, tubular apoptosis and tubulointerstitial fibrosis. Pharmacological stimulation of soluble guanylate cyclase (sGC) and subsequent cGMP production have recently been found to be renoprotective. In this study, the sGC stimulator BAY 41-8543 was given to rats after relief of UUO in order to analyze the effects of enhanced NO/sGC/cGMP signaling on the subsequent renal disease recovery, concerning the renal atrophy, tubular apoptosis and tubulointerstitial fibrosis.

Methods

Male Sprague-Dawley rats underwent UUO. After 5 days, the obstruction was relieved and the rats were randomly assigned to UUO-Relief and UUO-Relief plus BAY 41-8543 (10 mg/kg body weight/day). After 7 days of treatment, effects of stimulated sGC/cGMP on plasma cGMP levels, systolic blood pressure and renal histology were determined. The symbol * indicates $p < 0.05$ UUO-Relief versus UUO-Relief plus BAY 41-8543.

Results

Untreated UUO-Relief rats showed elevation of systolic blood pressure, marked tubular atrophy, tubular apoptosis, tubulointerstitial macrophage infiltration and fibrosis. Compared to the untreated rats with UUO-Relief, BAY 41-8543 treatment increased significantly plasma cGMP levels (+104%*). This went along with significant reductions in systolic blood pressure (UUO-Relief plus BAY 41-8543 vs UUO-Relief: 112 ± 4 vs 145 ± 8 mmHg*), tubular diameter (-20%*), tubular apoptosis (-67%*) shown in TUNEL assay, tubulointerstitial macrophage infiltration (-65%*) and fibrosis (tubulointerstitial volume -38%*, expansion of matrix proteins -60%*, deposition of collagen IV -52%* and expression of alpha-smooth muscle actin -69%*).

Conclusion

Stimulation of sGC by Bay 41-8543 significantly increased cGMP production and precedes the disease resolution following relief of UUO. This involved improvements in renal atrophy, tubular apoptosis, tubulointerstitial fibrosis and macrophage infiltration. The findings suggest that pharmacological sGC stimulation is an effective approach to accelerate restoration of renal architecture and function following relief of ureteral obstruction.