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Beneficial effect of soluble guanylate cyclase stimulator BAY 41-2272 on cardiovascular remodeling in angiotensin II-induced hypertensive rats

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Background

BAY 41-2272 is a new type of soluble guanylate cyclase (sGC) stimulator developed recently. Although some beneficial effects of this compound on hemodynamics in hypertension and in heart failure have been reported, those on cardiovascular remodeling remains unknown. The purpose of this study is to investigate the effects of BAY 41-2272 on cardiocyte hypertrophy and extracellular matrix (ECM) formation in the heart of angiotensin II (Ang II)-induced hypertensive rats.

Material and Methods

Eight-week-old male Wistar rats with hypertension induced by subcutaneous infusion of Ang II (250 mg/kg/min) were simultaneouslly treated orally with 10 mg/kg BAY 41-2272 twice daily for 2 weeks. BAY 41-2272 significantly reduced systolic blood pressure during the first 10 days of the treatment group compared with Ang II -infused group (200 ± 20 vs 154 ± 27 mmHg at day10, mean ± S.E., $p < 0.05$), however blood pressure reduction became insignificant at day14. As expected, plasma level of cGMP of the treated group rose by 133% ($p < 0.05$) compared with control. Despite the incomplete suppression of blood pressure elevation, heart/body weight and cross-sectional size of cardiocytes were significantly decreased by BAY 41-2272 (4.20 ± 0.34 vs 3.68 ± 0.20 mg/g, 36.3 ± 2.7 vs 25.9 ± 3.7 μm^2, $p < 0.01$). Ang II increased the number of coronary adventitial fibroblasts expressing α-smooth muscle actin, a marker for myofibroblast activation, in the left ventricle, however, BAY 41-2272 markedly reduced it by 77% ($p < 0.05$). When assessed by picrosirius red, levels of Ang II-induced increase in collagen deposition surrounding coronary arteries and in myocardial interstitium were significantly reduced by 26% ($p < 0.01$) and 29% ($p < 0.05$), respectively, following the treatment. The real time-quantitative PCR revealed that BAY 41-2272 significantly down-regulated Ang II-induced gene expressions of type 1 collagen (-49%, $p < 0.01$), transforming growth factor-β1 (-66%, $p < 0.01$) and Ang II type 1 (AT1) receptor expression (-59%, $p < 0.05$), in the left ventricle.

Conclusion

BAY 41-2272 effectively attenuated cardiovascular remodeling in the hypertensive rat heart, suppressing expressions of AT1 receptor and its down-stream ECM-related genes. Our findings suggest that sGC stimulator BAY 41-2272 has beneficial effects on hypertensive heart disease, counteracting the remodeling-promoting action of Ang II.