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Pharmacological activation of the soluble guanylate cyclase inhibits pressure overload-induced cardiac hypertrophy

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Background and Aim: Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of the chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.

Methods: We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated on animals served as controls. Experimental and control groups were treated with 10 mg/kg/day cinaciguat (Cin) or placebo (Co) p.o., respectively. The development of cardiac hypertrophy was investigated by echocardiography. We performed the left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess the cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.

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Results: Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMI): 3.15 ± 0.09 AB-Co vs. 2.13 ± 0.04 g/kgBW Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384 ± 0.015 AB-Co vs. 0.293 ± 0.008 g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37 ± 0.04 AB-Co vs. 14.55 ± 0.12 μ m Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414 ± 19 AB-Co vs. 341 ± 19 μ l Sham-Co) were observed while the ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure (182.27 ± 7.86 AB-Co vs. 174.63 ± 4.53 mmHg AB-Cin, $p = n.s.$), but effectively attenuated the left ventricular hypertrophy (LVMI: 2.64 ± 0.06 g/kgBW, HW/TL: 0.339 ± 0.009 g/cm, CD: 15.08 ± 0.10 μ m, $p < 0.05$ vs. AB-Co).

Conclusion: Our results demonstrate that chronic stimulation of the NO-cGMP signaling pathway by pharmacological activation of the soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.

KEYWORDS: aortic banding, pressure overload, cinaciguat, myocardial hypertrophy.

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