Cardioprotective effects of a long-term combined therapy with β_1-adrenoreceptor (AR) blocker and β_2-AR agonist in an experimental model of heart failure.

L. Sodano[1], M. Donniacuo[1], G. Gritti[1], F. Rossi[1,2], B. Rinaldi[1,2], M.G. Matera[1]

[1]Centre of Excellence for Cardiovascular Diseases, Dept. of Experimental Medicine, Section of Pharmacology L. Donatelli, Second University of Naples, Italy.
[2]Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Dept. of Experimental Medicine, Section of Pharmacology L. Donatelli, Second University of Naples, Italy.

β-adrenoceptor blockers have demonstrated to exert protective effects in patients with sympathetic over-stimulation during heart failure (HF). The success of β-blockers therapy in HF is primarily attributed to protection of the heart from the increased catecholamine levels. In fact, β-blockers have shown to reduce sympathetic hyperactivity in HF, but the underlying molecular mechanisms are not understood (Gorelik et al., 2013). On the other hand, accumulating evidences suggest that β_2 receptor are cardioprotective (Zheng et al., 2005). In fact, preclinical translational studies have clearly demonstrated the therapeutic effectiveness of combined β_1-AR blockers and β_2-AR agonist therapy in animal models of CHF (Ahmet et al., 2008).
The aim of our study was to investigate the therapeutic effectiveness of the combination of β_1-AR blocker, metoprolol and a β_2-AR agonist, indacaterol, in a rat model of HF.
Myocardial infarction (MI) was performed in male Wistar rats (225-250 g; n=50) by surgical occlusion of the left anterior descended coronary artery. Four weeks after surgical procedure, echocardiography was performed to measure the level of HF. The animals were randomized in five experimental groups: sham; HF; HF+metoprolol (100mg/kg/die); HF+indacaterol (0.3mg/Kg/die); HF+metoprolol+indacaterol. Treatment was started the day after MI and continued until 10 weeks. Metoprolol and indacaterol were dissolved in the drinking water alone or in combination. Four and ten weeks postoperatively, echocardiography and blood pressure measurement were performed.
Ten weeks after MI we observed a decrease of mean arterial pressure (MAP) and ejection fraction (EF) and an increase of heart rate (HR) and LV diastolic diameter compared to sham.
Treatment with metoprolol and indacaterol alone restored partially the EF; on the other hands, the combination of the β_1-blocker and the β_2-agonist induced a significant increase of EF. The single treatments or the combination reduced MAP, HR and LV. At the end of hemodynamic evaluations, animals were sacrificed and heart and plasma were obtained to perform real-time PCR and ELISA experiments.
Our data showed that HF induced a decrease of β_1 mRNA levels but increased β_2, ANP, BNP and collagen-I mRNA levels, GRK2 expression and plasma catecholamines. The single treatments or the combination significantly decrease the cardiac evaluated markers and plasma catecholamines.
Our hemodynamic and molecular preliminary data provide a rationale of theβ_1-AR blocker and β_2-AR agonist combination for a clinical investigation in the HF treatment.

References

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