Abstract: P1614

Soluble guanylate cyclase as a therapeutic target in heart failure: myocardial gene expression in response to sGC stimulation in pressure overload

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Topic(s):
Basic Science - Cardiac Diseases:Heart Failure

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Background: Heart Failure (HF) is associated with endothelial dysfunction and reduced bioavailability of NO with insufficient stimulation of sGC and reduced production of cGMP. Therefore, the impairment of the NO-sGC-cGMP pathway results in vasoconstriction, platelet aggregation, inflammation, fibrosis and most importantly maladaptive cardiac hypertrophy. The restoration of the NO-sGC-cGMP pathway is an attractive pharmacological target for HF therapy.

Purpose: Riociguat is an NO independent stimulator of the sGC that sensitizes the sGC to endogenous NO and directly stimulates sGC to produce cGMP. We therefore hypothesized that Riociguat prevents pathological effects occurring during HF.

Methods: Pressure overload was induced by transverse aortic constriction (TAC) in 8 weeks old male C57Bl6/N mice. Three weeks after TAC when cardiac hypertrophy has developed either Riociguat (RIO; 3 mg/kg) or a Solvent was administered daily for 5 more weeks (n=12 per group). Animals with sham surgery and same drug regime served as controls. The heart function in all groups was evaluated weekly by small animal echocardiography. Eight weeks after surgery, the transcriptome of the left ventricles (LV) of sham and TAC mice were analysed by RNA Sequencing. Differentially expressed genes (DEG) were categorised using Ingenuity Pathway Analysis (IPA).

Results: TAC resulted in a steady decrease of left ventricular fractional shortening (FS) in the mice until week 3. When Riociguat treatment commenced, the systolic LV function of the TAC+Rio group recovered significantly whereas the solvent group showed a further decline until week 8 (FS 21.4±3.4 % vs. 9.5±2 %, p<0.001). Both sham groups (Sham+Sol and Sham+Rio) showed no changes in the heart function over time. Regarding the hypertrophic response to LV pressure overload, Riociguat treatment attenuated significantly the increase of the left ventricular mass (LVM 208.3±15.8mg vs. 148.9±11.8mg, p<0.001) after TAC. In line with the reduced LVM, histological staining showed a significantly reduced fibrosis and myocyte cross sectional area in the TAC+Rio group compared to TAC+Sol group. Regarding the myocardial transcriptome, the treatment with Riociguat resulted in less changes of gene expression pattern after TAC (TAC+Sol vs. Sham+Sol 3160 DEG; TAC+Rio vs. Sham+Rio 2237 DEG). The expression of heart failure marker genes like ANP (Nppa), BNP (Nppb), ß-Myosin Heavy Chain (Myh7) and the Collagens 1 and 3 (Col1a1, Col1a2, Col3a1) were significantly decreased in TAC+Rio, when compared to TAC+Sol. IPA analysis revealed that the activation of biological pathways in response to TAC, like actin cytoskeleton- and Integrin signalling, renin-angiotensin or cardiac hypertrophy signalling was attenuated when Riociguat was administered.

Conclusion: Riociguat attenuates pressure overload induced LV remodelling resulting in less hypertrophy, improved heart function and less alteration of gene expression pattern.
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