Cardioprotective Effects of a PPAR-delta Selective Agonist (GW610742X) in a Rodent Model of Congestive Heart Failure

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Introduction

Peroxisome-proliferator-activated receptor (PPAR) subfamily (-γ, -α, and -δ) are 'master' transcriptional regulators for a host of genes that regulate tissue specific nutrient metabolism and energy homeostasis (1). Whereas PPAR-α and PPAR-γ are predominantly expressed in liver and adipose tissue, respectively, PPAR-δ is ubiquitously expressed (2). Selective PPAR-δ agonists lower systemic levels of triglycerides, increase HDL cholesterol, increase tissue specific lipid oxidation, and protect against diet induced obesity in preclinical species (2). Recently, it was shown that cardiac specific knockout of PPAR-δ results in cardiac lipotoxicity, hypertrophy, and failure (3). Therefore in this study, we examined the potential therapeutic benefit of a selective PPAR-δ agonist in a rodent model of congestive heart failure. Specifically we examined the relationship between cardiac substrate metabolism, function, energetics and gene transcriptional changes in myocardial infarcted rats.

Methods

Myocardial infarction (MI) was induced in Sprague-Dawley (SD) rats via ligation of the left anterior descending coronary artery. An additional group of animals received a sham procedure, excluding coronary artery occlusion. PPAR-δ specific agonist treatment was initiated immediately post-MI in SD rats (GW610742X at 30 and 100 mg/kg/day for 4-8 wks, dietary dosing).

At 4 wks post-MI, rats were scanned. All *in vivo* MR spectroscopy/imaging experiments were performed using a double tune (^{1}H, ^{31}P) concentric surface coil setup on a 4.7T/40 cm Bruker Biospec system. Short-axis heart images were acquired using an ECG gated FLASH sequence. A cine loop was generated for each slice through the ventricles with enough delays to cover the systole (ECG was triggered by R-wave, which is end-diastole). The imaging parameters were as follows: matrix dimensions, 128x128; TE/TR, 3.7/20 ms; slice thickness, 2.0 mm; FOV, 5.0 cm; 4 averages; cine loop, 10 images. Both left ventricle (LV) and right ventricle (RV) functional parameters were analyzed. Direct ^{1}H-decoupled ^{31}P spectroscopy of the heart was performed during the same scanning session using a ^{31}P pulse power optimized to null any extraneous signal from the chest wall (TR=1s, NS=512, SW=7 kHz, 2 k data).

In a separate cohort of animals, a 1-^{13}C glucose clamp (120 min) was initiated in order to assess relative glucose vs fat oxidation in both left LV and RV. A POCE ^{1}H NMR measurement of metabolite ^{13}C enrichment in LV and RV extracts was performed at 9.4T. Gene expression analysis was performed on viable tissue from both LV and RV.

Results

Plasma free fatty acid levels were decreased and HDL was increased following 4 wks of GW610742X treatment post-MI. ECG gated cardiac MRI provided high quality images for both LV and RV functional determinations as shown in Figure 1 and Table 1. Although the MI rats had significantly reduced LV ejection fractions compared with Sham animals (~40% vs 70% respectively), PPAR-δ agonist (GW610742X) treatment had no beneficial effect on LV function in MI animals. However, treatment did result in improved RV ejection fraction (see Table 1). The improvement in RV ejection fraction as assessed by MRI was consistent with the dramatic reduction in RV hypertrophy and lung congestion measured upon necropsy (↓22-48%, P<0.01) and the 10 fold reduction in ANP gene expression in RV. Although the cardiac PCr/ATP ratio decreased by ~14% following MI (Figure 2, P<0.05), there was no significant improvement in resting cardiac energetics in rats treated with GW610742X.

The relative fat oxidation rate in both LV and RV decreased in the vehicle MI vs non-MI control rats (↓41%, P<0.01). However, GW610742X treatment was able to normalize the relative fat oxidation rate in both LV and RV groups in a dose dependent manner. These metabolic changes were consistent with a 1-3 fold increase in lipid transport/metabolism gene expression measured in both LV and RV (CD36, CPT1, PDK4, UCP3).

Conclusions

Some prevalent pathophysiological consequences of heart failure are pulmonary congestion, RV hypertrophy, and a shift toward decreased fat metabolism. In the present study, GW610742X treatment significantly reduced RV hypertrophy which was consistent with an increase in RV ejection fraction. Although GW610742X treatment resulted in normalization of both LV and RV glucose and lipid oxidation profile following MI, this metabolic alteration did not translate into a benefit in LV ejection fraction or cardiac energetics in the anesthetized rat. However, cardiac reserve was not assessed in the present study. In conclusion, for the first time a PPAR-δ specific agonist has been shown to reduce RV hypertrophy, pulmonary congestion, and normalized substrate metabolism in a rodent model of congestive heart failure.

Figure 1

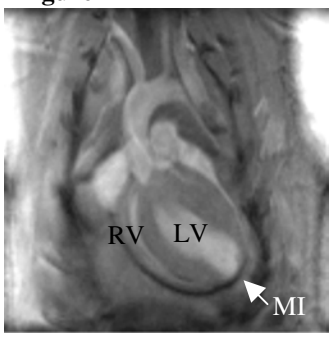

Figure 2

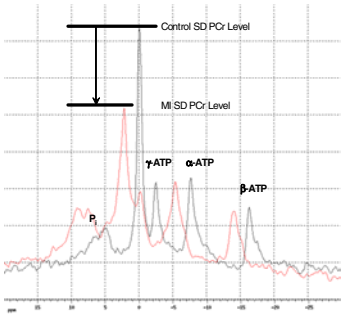

Figure 1. A long-axis cardiac MRI image of a SD rat with MI.

Figure 2. *In vivo* ^{31}P MRS of a control (black) and MI (red) heart.

Table 1 LV and RV Volume and Ejection Fraction Post-MI with and without PPAR-δ GW610742X Treatment. Vehicle, n=19; 30mg/kg, n=17; 100mg/kg, n=17.

MI, myocardial infarction; HR, heart rate; BW, body weight; EDV, end-diastolic volume; ESV, end-systolic volume; CO, cardiac output; Mass, LV mass; and EF, ejection fraction. Values are expressed as mean±SD. *P<0.05, t-test between MI+Vehicle and MI+PPAR-δ GW610742X groups.

	Vehicle (LV)	30mg/kg (LV)	100mg/kg (LV)	Vehicle (RV)	30mg/kg(RV)	100mg/kg(RV)
HR, bpm	397 ± 26	394 ± 26	386 ± 35	---	---	---
BW, g	357 ± 37	352 ± 24	342 ± 18	---	---	---
EDV, mm^3	932 ± 190	920 ± 207	940 ± 125	330 ± 103	310 ± 89.9	278 ± 41.6
ESV, mm^3	569 ± 153	553 ± 178	565 ± 108	147 ± 69.0	116 ± 58.0	107 ± 22.0
Mass, mg	1091 ± 162	1091 ± 199	1127 ± 132	---	---	---
CO, cm^3/min	144 ± 24	145 ± 28	144 ± 24	72.3 ± 17.1	76.3 ± 19.6	65.7 ± 13.2
EF, %	39.6 ± 6.3	40.8 ± 7.9	40.2 ± 6.2	56.7 ± 8.7	64.0 ± 8.7*	61.2 ± 6.3

References

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