Albiglutide, a long lasting glucagon-like peptide-1 receptor agonist, protects the rat heart against ischemia/reperfusion injury: Evidence for improving cardiac metabolic efficiency

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Introduction: The cardioprotective effects of glucagon-like peptide-1 (GLP-1) have been previously examined. However the effect of albiglutide, a long-acting GLP-1 receptor agonist, on myocardial energetics in the setting of acute myocardial ischemia/reperfusion (I/R) injury is currently unknown. Therefore, we tested the hypothesis that albiglutide may protect the heart against myocardial I/R injury by increasing carbohydrate utilization and improving cardiac energetic efficiency using a combination of MRI and MRS techniques.

Method: To examine the effect of albiglutide on the cardiac energetic profile (e.g. ATP, PCr, pH) following cardiac I/R injury, Sprague-Dawley rats were treated with albiglutide (1, 3, or 10 mg/kg/day for 3 days, SC) or vehicle and then subjected to 30 min left anterior descending artery occlusion followed by 24 hrs reperfusion. Cardiac MRI/MRS was performed at 24 hrs post-reperfusion using a double tune (^{1}H, ^{31}P) concentric surface coil on a 9.4T/30 cm Bruker system. A cine loop was generated for each imaging slice through the ventricles with a sufficient number of delays to cover the cardiac cycle. The imaging parameters were as follows: matrix dimensions, 128×128; TR/TE, 7/1.5 ms; slice thickness, 2.0 mm; FOV, 5.0 cm; number of repetition 250; cine loop, 10 images. ^{31}P MRS was performed immediately following imaging using a 3-D Image Selected *In Vivo* Spectroscopy (ISIS) sequence with outer volume suppression (TR = 4 s, NS = 512, SW = 10 kHz, 1 k data). The spectroscopic voxel of interest size was 15.8×11×17 mm and positioned to cover the LV in an oblique plane in all three orthogonal directions (Figure 1). Absolute concentrations of ATP and PCr were extrapolated using an external concentration standard. In separate animals, a euinsulinemic-hyperglycemic clamp (continuous [1-^{13}C] glucose (8 mg/kg/min)/somatostatin (1.5 μg/min) infusion via jugular vein) was performed under awake conditions for 120 min. The POCE (Proton Observe Carbon Enhanced) ^{1}H MRS measurements of metabolite ^{13}C enrichments in tissue extracts were performed using a 9.4T spectrometer. Relative cardiac carbohydrate (including glucose, glycogen, pyruvate, and lactate) and free fatty acid (FFA)/ketone oxidation in terms of relative substrate contribution to acetyl-CoA oxidation was assessed from the metabolite pool enrichments.

Figure 1

Results: Albiglutide significantly reduced left ventricle (LV) infarct size in a dose-dependent manner (↓26%, p<0.01) and increased both *in vivo* and *ex vivo* cardiac glucose uptake (↑59-67%, p<0.05) while reducing lactate efflux (↓55%, p<0.05). Additionally, albiglutide normalized cardiac energetic parameters (PCr, ATP, pH) following I/R injury while preserving cardiac function (Ejection Fraction, EF) (Figure 2). Analysis of metabolic substrate utilization directly in the heart showed that albiglutide increased the relative carbohydrate versus fat oxidation (↑112%, p<0.05) which in part was due to an increase in both glucose and lactate oxidation (Figure 2).

Conclusion: These findings suggest that albiglutide may have direct therapeutic potential for improving cardiac metabolic efficiency and energetics resulting in enhanced cardiac function in the setting of myocardial ischemic injury.
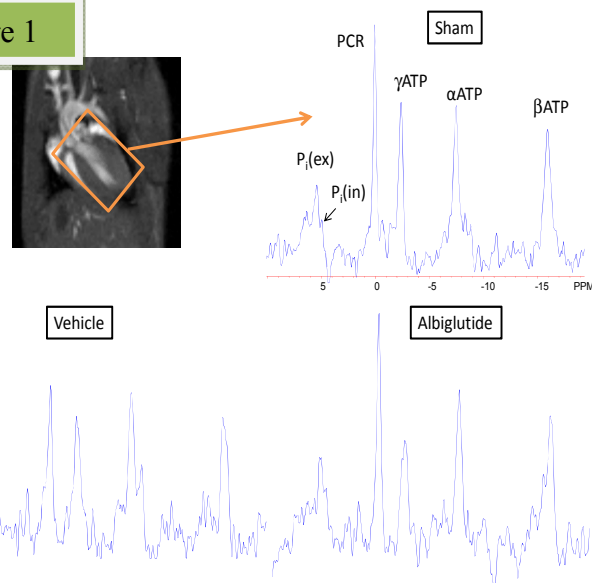

Figure 2