Attenuation of Cardiac Hypertrophy by Tempol in GLUT4 Knockout Mice is Independent of Glutathione Reductase Expression and Concentrations of Oxidized Glutathione

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The lack of glucose uptake into the heart of Diabetic individuals may result in complications such as cardiac hypertrophy. Increased oxidative stress is a major factor regulating cardiac hypertrophy. The GLUT-4 receptor brings glucose into the cell in response to insulin signaling. This receptor has been deleted in the heart to study the effects of altered cardiac metabolism on heart structure and function. These mice have been reported to have cardiac hypertrophy. We hypothesized that increased oxidative stress due to altered glucose metabolism may be the driving force for this phenotype.

Two groups of mice, control (C0) and cardiac specific GLUT4 knockout (G4H-/-), were injected with the anti-oxidant tempol (T), or a vehicle control (V), to determine if reduction of oxidative stress could prevent cardiac hypertrophy. Heart weight to tibia length, a measurement of cardiac hypertrophy, was greater in T treated G4H-/- compared to V treated Con (8.83 ± 0.34 vs. 6.94 ± 0.32). Treatment with tempol prevented hypertrophy such that G4H-/- had similar heart:tibia length as Con (7.56 ± 0.35 vs. 6.82 ± 0.46).

Reduced glutathione (GSH) is a major antioxidant in the heart, and becomes oxidized upon use (GSSG) and must be reactivated with the enzyme Glutathione Reductase (GR). The concentrations of cardiac GSH and GSSG were measured, and a ratio of reduced to oxidized glutathione (GSH/GSSG) was calculated. GSSG levels were higher (G4H-/-, 0.0135 ± 0.0011 vs. Con, 0.0111 ± 0.0016 lmoI/g) and GSH/GSSG was lower (G4H-/-, 49.5 ± 5.9 vs. Con, 77.1 ± 6.8) in G4H-/- mice compared to Con mice. These data support the presence of oxidative stress in the G4H-/- heart. In spite of tempol treatment, GSSG was still greater (0.0129 ± 0.0020 vs. 0.0100 ± 0.0023 lmoI/g) and GSH/GSSG lower in G4H-/- vs. Con (51.5 ± 6.6 vs. 79.2 ± 14.1). Western blots were used to determine the levels of GR in the heart. Even though there were greater amounts of GSSG, and lower GSH/GSSG, there was no difference in levels of GR between G4H-/- and Con mice. Treatment with tempol did not alter GR levels in either group.

There was cardiac hypertrophy in G4H-/- mice. Our data suggests increased oxidative stress as demonstrated by lower GSH/GSSG. Even though, tempol successfully decreased cardiac hypertrophy, neither GSSG levels nor GSH/GSSG were altered. Similarly there was no change in levels of glutathione reductase as demonstrated by western blot. Therefore, it remains unclear if the anti-hypertrophic effect of tempol is accompanied by a reduction in oxidative stress. Future studies will examine expression of SOD2 and other heart-specific anti-oxidant enzymes in this model of cardiac insulin resistance.