Cardiac hypertrophy and oxidative stress are associated with insulin resistance in fructose fed mice

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Dietary fructose intake has increased considerably in recent decades, in parallel with an increase in the incidence of insulin resistance. Cardiovascular pathologies are highly prevalent in diabetic and pre-diabetic patients yet the impact of fructose on the heart is poorly understood. The aim of this study was to determine the specific cardiac effects of a 12 week 60% high fructose dietary intervention in C57Bl/6 male mice.

Blood pressure was measured by tail cuff method to establish that the effects of fructose were independent from hypertension. Systemic insulin sensitivity was estimated by glucose tolerance test and plasma insulin levels were determined by radioimmunoassay. Hearts were collected for measurement of ventricular weight index (VWI) and myocardial production of superoxide (lucigenin chemiluminescence). Phosphorylation states of signalling proteins in myocardial tissue were analysed by western blot and gene expression analysis of Thioredoxin 2 was performed using real time PCR.

VWI was increased by 22% in the fructose fed mice (p = 0.0006) which was associated with elevated superoxide production (fructose, 553 ± 28 counts/s/mg *vs* control, 489 ± 11 counts/s/mg, p = 0.049). This was not associated with an alteration in myocardial gene expression of the antioxidant, Thioredoxin 2. Fructose feeding suppressed phosphorylation of Akt and S6 indicative of a specific cardiac insulin resistance. Hyperglycaemia (fructose, 14.4 ± 0.6 mmol/L *vs* control, 12.1 ± 0.8 mmol/L) and impaired glucose tolerance were observed, but were not associated with hypertension or body weight gain. No change in plasma insulin levels was apparent. This study demonstrates that a 12 week dietary fructose intervention induces cardiac hypertrophy associated with oxidative stress. Fructose-induced insulin resistance is apparent both systemically and intrinsic to the myocardium suggesting that a specific cardiac insulin resistance may play a role in fructose induced cardiac pathologies. Importantly, these findings were observed in the absence of any volume or pressure loading effects from hypertension or obesity. This study demonstrates that excess consumption of fructose is detrimental to cardiac structure and signalling which may represent a primary pathology in insulin resistance.