Role of hexose-sugar-induced post-translational modifications in contractile myofilament dysregulation

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Diabetes is associated with increased risk of heart failure, but the cellular mechanisms of cardiomyocyte vulnerability in the diabetic heart are not well understood. Glucose handling defects are evident and metabolic derangement is linked with functional disturbance. Our *in vivo* and *in vitro* investigations suggest that intracellular proteins involved in cardiomyocyte contractile function are susceptible to irreversible glycation post-translational modification. Using mass spectroscopy techniques, we have demonstrated that human and rodent cardiac troponin complex proteins and the cardiac actin filament are modified by advanced glycation end-products *in vivo*. Our *in vitro* studies provide new evidence that fructose sugar also modifies cardiac troponin-C, by Schiff-base attachment to lysine and oxidation of methionine residues. In addition to glucose-related cardiomyocyte damage, fructose sugar may also play a role in cardiomyocyte pathology in diabetes.

Plasma and cardiac fructose levels are elevated in diabetic patients and evidence suggests that some unique properties of fructose (vs glucose) have specific cardiomyocyte consequences. We have previously demonstrated that cardiomyocytes have the capacity to transport and utilize fructose, and recent studies have provided new evidence that cardiomyocytes express all of the necessary proteins for fructose metabolism. When dietary fructose intake is elevated and myocardial glucose uptake compromised by insulin resistance, increased cardiomyocyte fructose flux represents a hazard involving unregulated glycolysis and oxidative stress. We have shown that fructose has an acute influence on cardiomyocyte excitation-contraction coupling and can provide metabolic fuel to facilitate contraction in a glucose-deplete setting. In a chronic setting of excess dietary fructose, disturbances in key cardiomyocyte Ca^{2+} handling processes are evident, associated with oxidative stress and activation of cell death pathways. The high reactivity of fructose supports the contention that fructose accelerates subcellular hexose sugar-related protein modifications, such as O-GlcNAcylation and advanced glycation end-product formation. These studies aim to elucidate the contribution of fructose and glucose to cardiomyocyte functional disturbance in diabetes to identify new targets for treatment of diabetic cardiomyopathy.