Hexose sugars and cardiomyocyte pathophysiology

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Excess sugar consumption has been linked to the development of diabetes and cardiovascular disease. Population studies have reported that the link between consumption of sugar-sweetened beverages and elevated diabetes risk is independent of body mass index, suggesting that calorie intake and fat deposition are not the underlying aetiology. Plasma fructose levels are elevated in diabetic patients and the unique properties of fructose sugar may have specific cardiomyocyte consequences. Experimentally, the systemic effects of dietary fructose have been well described and a distinct cardiac pathology is evident. But the extent to which myocardial cellular alterations reflect direct or indirect actions of elevated fructose intake has not been elucidated.

Our *in vitro* investigations have revealed that cardiomyocytes have the capacity to transport and utilise fructose (Mellor *et al.*, 2011a). Cardiac expression of the necessary proteins for fructose metabolism has been reported, including the fructose specific transporter, GLUT5, and the fructokinase enzyme. It is postulated that fructose sugar is a bad molecular alternative to glucose and in excess, can modulate subcellular protein structure and function. Where dietary fructose intake is elevated and myocardial glucose uptake compromised by insulin resistance, increased cardiomyocyte fructose utilization may contribute to 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 (Mellor *et al.*, 2011a). 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 (Mellor *et al.*, 2011b; Mellor *et al.*, 2012). New understanding of the high reactivity of fructose supports the contention that fructose may accelerate subcellular hexose-related protein modification and underlie impaired contractility in the diabetic heart (Mellor *et al.*, 2014). Understanding the contribution of fructose to cardiac pathology in diabetes is an important priority.

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