## O-linked β-N-acetylglucosamine (O-Glc-NAc) signalling and the hexosamine pathway in diabetic cardiomyopathy

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The Framingham Heart study established the epidemiological links between diabetes and increased risk of heart failure 4 decades ago. Diabetes not only escalates risk of heart failure, but also increases its incidence > 2.5-fold, independent of age or concomitant hypertension, obesity, dyslipidaemia or coronary heart disease. Diabetic patients account for up to one third of patients in clinical heart failure trials, with diabetes an independent predictor of poor prognosis. There is however no specific therapy for the diabetic heart. Multiple mechanisms likely contribute to the cardiac complications of diabetes. The hexosamine biosynthesis pathway (HBP), an alternative fate of glucose has now emerged as a contributing factor. Minor amounts of glucose (~2-5%) normally shuttle through HBP rather than glycolysis, providing the sugar moiety O-GlcNAc for post-translational modifications to a range of proteins, whereby O-GlcNAc is attached *via* several enzymatic steps to serine/threonine residues. Transient HBP activation is a cytoprotective mechanism in many cells and tissues, particularly in the scenario of an acute stress. In contrast, diabetes-induced persistent, unchecked upregulation of HBP is now considered to play a causal role in systemic progression of diabetes complications. Regulation of myocardial function by the HBP in this context remains poorly understood.

In chronically diabetic myocardium (adult Sprague-Dawley male rats 8 weeks after the induction of streptozotocin diabetes, 55mg/kg i.v.), acute myocardial inotropic responsiveness to the α1-adrenoceptor agonist phenylephrine *ex vivo* is markedly diminished compared to analogous studies in rat hearts 8 weeks after citrate vehicle. We have recently demonstrated that acute targeting of HBP circumvents this impaired inotropic responsiveness in chronically diabetic myocardium. Acute inhibition of glutamine:fructose-6-phosphate amidotransferase (GFAT), the rate-limiting enzyme in the HBP cascade 30 min prior to phenylephrine restores myocardial inotropic responsiveness across all parameters studied (left ventricular systolic pressure, left ventricular developed pressure, LV+dP/dt and rate-pressure product). Similar benefits on myocardial inotropic responsiveness were evident following acute inhibition of O-linked β-N-acetylglucosamine transferase (which usually adds the O-GlcNAc sugar moiety to serine/threonine residues) or with acute enhancement of physiological growth signalling.

These results thus suggest that acute targeting of HBP/O-GlcNAc signalling circumvents impaired myocardial inotropic responsiveness in the diabetic heart. We have also recently obtained evidence that sustained HBP/O-GlcNAc activation is closely linked to diastolic dysfunction in the intact diabetic heart *in vivo*. A number of proteins key to cardiac function are O-GlcNAc-modified in the diabetic heart; inhibition of GFAT also improves cardiomyocyte diastolic function. Lastly, preliminary findings suggest that chronic enhancement of physiological growth signalling *in vivo* may provide a novel link between counter-regulation of excessive, unchecked cardiac HBP/O-GlcNAc signalling and prevention of diabetic cardiomyopathy. Ultimately, cardiac-directed targeting of HBP/O-GlcNAc signalling may offer new options for limiting progression to heart failure and death in chronic diabetes *in vivo*.