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Minireview

Glucose as an agent of post-translational modification in diabetes — New cardiac epigenetic insights

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ABSTRACT

Diabetes elicits cardiac metabolic stress involving impaired glucose uptake and metabolic substrate shifts. Diabetic cardiac pathology is well documented in human patients and experimental animal models to be characterized by diastolic dysfunction, but the underlying mechanisms are not well understood. Signaling disturbances involved in cardiac insulin resistance are linked to glucose handling abnormalities. Both reversible (e.g. O-GlcNAc) and irreversible (e.g. AGEs) glucose-modifications of cardiomyocyte extracellular and intracellular proteins are implicated in structural and functional alterations underlying pathology in the diabetic heart. This review highlights some aspects of the epigenetic roles played by glucose (and related hexose sugars) in mediating diabetic cardiac pathology with specific consideration for the mechanisms impinging on post-translational modifications which have key signaling and mechanical impacts.

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Introduction

Cardiac performance is particularly sensitive to glucose availability, not only due to the reliance on glycolytic energy supply, but also because glucose is integral to many signaling processes involved in myocardial structural and functional modeling. Regulation of cardiomyocyte glucose uptake and metabolism is critical to support an unremitting activity cycle and meet the substantial fuel demands of the myocardium. Cardiomyocyte metabolism and performance are especially vulnerable to changes in systemic metabolic conditions. Specifically in diabetes, where both type 1 and type 2 diabetes are characterized by marked plasma hyperglycemia associated with systemic insulin resistance, the heart is subjected to various glucose-mediated challenges. Extracellularly, hyperglycemia can have significant pathological structural impact. Intracellularly, glycemic derangement associated with tissue insulin resistance has major ramifications on myocyte metabolic status, viability, contractility and subcellular organization.

Recent studies have generated important new advances in understanding cardiomyocyte handling of this simple hexose sugar, with significant progress in elucidating the complexities of glucose dysregulation in

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the heart. This review highlights some aspects of the epigenetic roles played by glucose (and related hexose sugars) in mediating diabetic cardiac pathology. In taking the broad perspective of epigenetic processes involving both translational and transcriptional events, we focus primarily on the endpoint mechanisms of glucose post-translational signaling and mechanical impacts. A brief discussion of emerging understanding of glucose involvement in modulating transcriptional activity is also included. To provide initial context, a general overview of the diabetic cardiomyopathy phenotype is provided — both at the intact heart and the single cardiomyocyte level. Four general aspects of glucose involvement in mediating this phenotype are then discussed in more detail — with focus on two extracellular injury processes, and two modes of intracellular glucose action.

The diabetic heart phenotype — characterized by diastolic and systolic dysfunction

Diabetic cardiomyopathy is a distinct cardiac pathology (Boudina and Abel, 2010; Marwick, 2008). Subclinical left ventricular dysfunction is evident in a substantial proportion of otherwise healthy type 2 diabetics (Fang et al., 2005). In particular, diastolic abnormality is an early sign of diabetic cardiomyopathy (Boyer et al., 2004; Zabalgoitia et al., 2001), with increased chamber stiffness and abnormal filling (Galderisi, 2006; Liu et al., 2001; van Heerebeek et al., 2008). The prevalence of diastolic dysfunction in type 1 and type 2 diabetes may be as high as 40–75% without overt coronary artery disease (Brooks et al., 2008). The early occurrence of diastolic dysfunction in young type 1 diabetic patients is especially notable and is documented in adolescents (Albanna et al., 1998; Nadeau et al., 2010; Salem et al., 2009; Shah et al., 2011). As these young patients have no confounding hemodynamic and atherosclerotic complications the case for a primary myocardial defect is compelling. A progression from diastolic to systolic dysfunction in late stage diabetes is observed clinically, and overlap of both forms of failure is common (Pappachan et al., 2013). In type 2 diabetic patients, myocardial systolic dysfunction is independently associated with glycated hemoglobin level (Fang et al., 2005). Conventional treatment strategies for systolic heart failure are generally effective in attenuating signs of systolic dysfunction in patients with advanced diabetes (Kamalesh, 2009). Successful treatments for diastolic failure have been more difficult to identify. Development of intervention and prophylactic strategies for cardiac dysfunction in diabetic patients requires further elucidation of the complex structural and functional modeling during progression from diastolic to systolic failure (Fig. 1).

At the level of the isolated heart and the single cardiomyocyte, we and others have shown experimentally that altered relaxation contributes to diastolic abnormality (Davidoff et al., 2004; Domenighetti et al., 2010; Huggins et al., 2008; Kotsanas et al., 2000). In a rodent model of type 1 diabetes, the streptozotocin (STZ) treated rat, reduced sarcoplasmic reticulum Ca^{2+} ATPase-mediated Ca^{2+} uptake during myocyte relaxation was evident (Kotsanas et al., 2000). Direct comparison of type 1 (OVE26 mouse) and type 2 (db/db mouse) diabetic models showed that prolonged Ca^{2+} transient decay was less severe in type 2 diabetic cardiomyocytes despite similar contractile impairment (Kralik et al., 2005). Cardiac insulin resistance, induced by genetic knockdown of Glut4, was linked to diastolic dysfunction with significant fibrosis and chamber dilatation (Domenighetti et al., 2010). Concurrent systolic dysfunction was observed — evident at the cellular level. Interestingly, the contractile deficit was restored to control values by supplementation with the glycolytic end-product, pyruvate, demonstrating a glycolytic dependence of cardiomyocyte excitation–contraction coupling processes involving activator Ca^{2+} handling (Huggins et al., 2008). In the type 2 diabetic obese rat (Zucker Diabetic Fatty rat), cardiomyocyte relaxation impairment was observed with maintained peak shortening (Fulop et al., 2007). In a less severe model of type 2 diabetes, the fructose-fed mouse, we have observed that cardiomyocyte systolic function is preserved, albeit in the context of reduced Ca^{2+} availability (Mellor et al., 2012). Increased myofilament responsiveness to Ca^{2+} is apparent - an adaptive shift which appears to maintain cardiomyocyte contractility in this setting, but may contribute to increased diastolic tone (Mellor et al., 2012). Longevity of the compensatory myofilament adaptations with ongoing disease progression is yet to be elucidated. The findings from these experimental investigations demonstrate that significant underlying cellular excitation-contraction coupling disturbance may occur before cardiac functional impact is observable in vivo in the insulin resistant state.

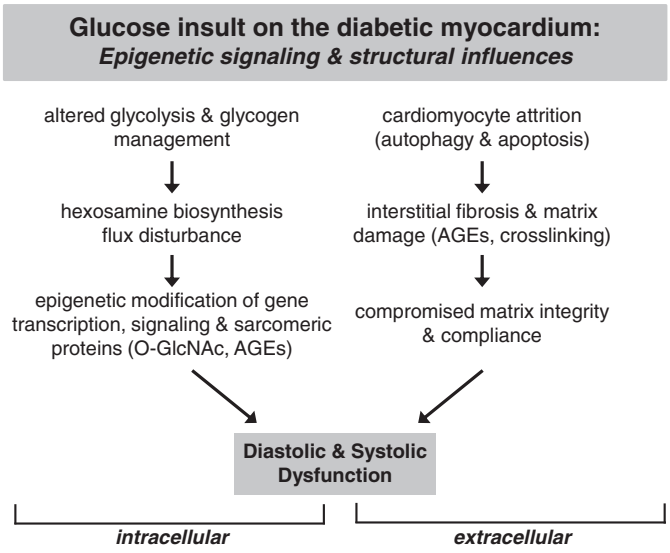

Fig. 1. *Epigenetic mechanisms of diastolic & systolic dysfunction in the diabetic heart.* In diabetes, glucose handling abnormalities are linked to both intracellular and extracellular cardiomyocyte disturbances. Altered glycolysis and glycogen management lead to disturbed flux through the hexosamine biosynthesis pathway associated with reversible (O-GlcNAc) and irreversible (AGE) modification of subcellular proteins. Increased occurrence of programmed cell death, underlies cardiomyocyte loss and promotes interstitial fibrotic response and matrix damage, exacerbated by AGE-modification. Compromised extracellular matrix integrity and compliance contribute to diastolic and systolic dysfunction in the diabetic heart.

Hyperglycemia — an extracellular matrix injury agent in the heart

Both systolic and diastolic functions are critically dependent on the complex architecture of the myocardium and maintenance of a compliant extracellular matrix structure to limit force transmission loss. The three-dimensional structural organization of cardiomyocyte sheets into myolaminae, separated by clefts of perimysial collagen, allows for sliding of adjacent muscle layers and is required for the substantial deformation of the tissue that occurs throughout the cardiac cycle (LeGrice et al., 1995). In diabetes, hyperglycemia undermines the matrix integrity through irreversible glycation of structural proteins and stimulation of collagen production (Law et al., 2012; Montagnani, 2008). Furthermore, degradation of the extracellular matrix is affected in diabetes due to reduced expression of matrix metalloproteinases and consequent lower collagen turnover (Li et al., 2012; Van Linthout et al., 2008). Distortion of the extracellular matrix complex structure through fibrosis of the endomysial collagen layer and fusing of adjacent myolaminae can lead to significant functional abnormalities.

Glycation is an irreversible non-enzymatic process where glycosylation adducts, formed in conditions of excess available glucose, are transformed through oxidation into advanced glycation end products (AGEs) (Meerwaldt et al., 2008). Formation of AGEs can be initiated by attachment of a glucose molecule to a basic amino acid residue (initially predominantly lysine) to form a Schiff base. Rearrangement of this molecular structure generates the more stable Amadori product and ultimately formation of reactive intermediates such as 3-deoxyglucosone (3-DG) and glyoxal. AGE precursors such as methylglyoxal (MGO) can