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Targeting caveolin-3 for the treatment of diabetic cardiomyopathy

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ABSTRACT

Diabetes is a global health problem with more than 550 million people predicted to be diabetic by 2030. A major complication of diabetes is cardiovascular disease, which accounts for over two-thirds of mortality and morbidity in diabetic patients. This increased risk has led to the definition of a diabetic cardiomyopathy phenotype characterised by early left ventricular dysfunction with normal ejection fraction. Here we review the aetiology of diabetic cardiomyopathy and explore the involvement of the protein caveolin-3 (Cav3). Cav3 forms part of a complex mechanism regulating insulin signalling and glucose uptake, processes that are impaired in diabetes. Further, Cav3 is key for stabilisation and trafficking of cardiac ion channels to the plasma membrane and so contributes to the cardiac action potential shape and duration. In addition, Cav3 has direct and indirect interactions with proteins involved in excitation–contraction coupling and so has the potential to influence cardiac contractility. Significantly, both impaired contractility and rhythm disturbances are hallmarks of diabetic cardiomyopathy. We review here how changes to Cav3 expression levels and altered relationships with interacting partners may be contributory factors to several of the pathological features identified in diabetic cardiomyopathy. Finally, the review concludes by considering ways in which levels of Cav3 may be manipulated in order to develop novel therapeutic approaches for treating diabetic cardiomyopathy.

Contents

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation; AGE, advanced glycation end product; Akt/PKB, protein kinase B; Ang II, angiotensin II; AP, antennapedia; APD, action potential duration; AVV, adeno-associated viral vector; BNP, B-type natriuretic peptide; β2AR, β2-adrenergic receptor; CAD, coronary artery disease; CAMKII, calcium/calmodulin-dependent kinase 2; Cav1, caveolin-2; Cav2, caveolin-2; Cav3, caveolin-3; CBM, caveolin binding motif; CICR, calcium induced calcium release; CIRI, cardiac-ischaemia reperfusion injury; C-MAD, C-terminal membrane attachment domain; CMR, cardiac magnetic resonance imaging; CRAC, cholesterol recognition/interaction amino acid sequence and consensus; CSD, caveolin scaffolding domain; CUPID, Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease; DCM, diabetic cardiomyopathy; DPP4, dipeptidyl peptidase-4; DRM, detergent-resistant membrane; EC, excitation–contraction; ECG, electrocardiogram; ECM, extracellular matrix; EF, ejection fraction; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; FFA, free fatty acid; FRET, fluorescence resonance energy transfer; GAPDH, glyceraldehyde phosphate dehydrogenase; GLP-1, glucagon-like peptide-1; GLUT-1, glucose transporter-1; GLUT-4, glucose transporter-4; HbA1c, glycosylated haemoglobin; HF, heart failure; IDDM, insulin-dependent diabetes mellitus; IIDM, insulin-independent diabetes mellitus; iNOS, inducible nitric oxide synthase; IPC, ischaemic preconditioning; IRS1, insulin receptor substrate 1; LDL, low-density lipoprotein; LQTS, long QT syndrome; LTCC, L-type voltage-gated calcium channel; LV, left ventricular; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; miRNA, micro RNA; MRI, magnetic resonance imaging; NADPH, nicotinamide adenine dinucleotide phosphate; ncRNA, non-coding RNA; NCX, sodium-calcium exchanger; N-MAD, N-terminal membrane attachment domain; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; ox-CaMKII, oxidised calcium/calmodulin-dependent kinase 2; PARP, poly ADP ribose polymerase; PI3K, phosphoinositide-3 kinase; PKA, protein kinase A; PKC, protein kinase C; PLB, phospholamban; PPARα, peroxisome proliferator-activated receptor alpha; PTM, post-translational modification; RAAS, renin–angiotensin–aldosterone system; RISK, reperfusion injury salvage kinase; ROCK, RhoA/Rho kinase; ROS, reactive oxygen species; RyR, ryanodine receptor; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase; SIDS, sudden infant death syndrome; SOD, superoxide dismutase; SR, sarcoplasmic reticulum; SRI, strain rate imaging; STZ, streptozotocin; T1DM, type I diabetes mellitus; T2DM, type II diabetes mellitus; TDI, tissue Doppler imaging; TGF-β1, transforming growth factor-beta 1; TNFα, tumour necrosis factor alpha; TTE, transthoracic echocardiography; TZD, thiazolidinedione; UCP, uncoupling protein; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

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1. Introduction

Diabetes encompasses a group of chronic, metabolic diseases whereby metabolic dysregulation and oxidative stress trigger the development of further complications including, cardiomyopathy, retinopathy, neuropathy and nephropathy. Diabetes is approaching pandemic proportions with a worldwide prevalence of 366 million individuals in 2011. It is estimated that by 2030 more than 550 million people will be diabetic (Diabetes, 2012). Diabetes is characterised by hyperglycaemia (>7.0 mmol/L fasting glucose) as a result of insufficient insulin secretion and/or activity (American Diabetes Association, 2010). There are two main types of diabetes, type I and type II (T1DM and T2DM), both of which are characterised by abnormal glucose metabolism. T1DM or insulin-dependent diabetes mellitus (IDDM) is caused by the autoimmune destruction of pancreatic β cells leading to insulin deficiency (American Diabetes Association, 2010). T1DM usually presents at an early age with symptoms including polyuria, polydipsia, weight loss and fatigue. In comparison, T2DM or insulin-independent diabetes mellitus (IIDM) develops due to insufficient insulin secretion or insulin resistance (American Diabetes Association, 2010). T2DM accounts for approximately 90% of cases of diabetes. Unlike T1DM, the risk of developing T2DM can be reduced by changes to diet and exercise (Diabetes, 2012).

1.1. Diabetic cardiac complications

As mentioned previously, diabetes is associated with an array of systemic conditions. For example, more than two thirds of diabetic patients develop cardiovascular complications (Boudina & Abel, 2010) with cardiovascular disease being attributed to approximately 44% and 52% of fatalities in patients with T1DM and T2DM respectively (Diabetes, 2012). Moreover, diabetes is associated with an increased cardiovascular risk, with women having a greater risk than men (5-fold and 2-fold respectively) (Kannel et al., 1974). It is currently not known why diabetes poses a greater threat to the health of the female cardiovascular system compared to that of the male although a link to oestrogen-mediated nitric oxide synthase (NOS) activity has been proposed (White et al., 2010). Also, data from two clinical trials have shown that diabetics develop larger infarcts after myocardial infarction (MI) compared to non-diabetics (Alegria et al., 2007; Marso et al., 2007), with a 2-fold risk of recurrent MI (Haffner et al., 1998). A specific cardiovascular complication associated with diabetes is diabetic cardiomyopathy (DCM). Rubler and colleagues (Rubler et al., 1972) first identified DCM (the presence of congestive heart failure (HF) in the absence of coronary artery disease) in diabetic patients over forty years ago. Since then, the clinical phenotype of DCM has been defined as HF without any clear symptoms of hypertension, coronary artery disease or vascular disease (Aneja et al., 2008).

1.2. Characteristics of diabetic cardiomyopathy

Data from both animal and human studies have led to the identification of the key features of DCM; left ventricular (LV) dysfunction, myocardial hypertrophy and fibrosis, metabolic dysregulation and defects in myocardial contractile properties. From a clinical perspective, these structural and functional disturbances have been divided into three stages; early, middle and late (Fang et al., 2004). Early stage DCM is recognised by mild LV dysfunction in the presence of a normal ejection fraction (EF) (Boyer et al., 2004). Molecular level abnormalities include cardiac steatosis and increased free fatty acids (FFA) (Maisch et al., 2011), impaired Ca^{2+} homeostasis and depleted levels of glucose transporter proteins, GLUT-1 and GLUT-4 (Rodrigues et al., 1998; Belke et al., 2000). The middle stage is characterised by diastolic and systolic dysfunction with a reduced EF (<50%) alongside hypertrophy, fibrosis and dilation (Maisch et al., 2011). Insulin resistance increases, leading to the formation of advanced glycation end products (AGEs) (Cooper, 2004) and over-activation of the renin–angiotensin–aldosterone system (RAAS) (Fang et al., 2004). There are also changes to the levels of transforming growth factor (TGF)-β1 and insulin growth factor-1 as well as increased apoptosis and necrosis (Miki et al., 2013). Finally, late stage DCM patients exhibit systolic and diastolic dysfunction in association with hypertrophy and microvascular changes, leading to HF (Miki et al., 2013). Recently, DCM has been classified into 4 different stages, with stage 4 reflecting late stage DCM but with the addition of coronary artery disease (CAD) and macroangiopathy (Maisch et al., 2011), as shown in Fig. 1.

1.2.1. Are there differences between type I and type II diabetic cardiomyopathy?

There is evidence to suggest that the pathogenic mechanism of DCM may differ during the early stages of T1DM and T2DM. In T1DM, there is a reduction in glucose uptake in the heart (Avogaro et al., 1990; Doria et al., 1991; Herrero et al., 2006). This may be linked to the down-regulation of the glucose transporter, GLUT-4, (see Section 2.1) (Camps et al., 1992). As a consequence, the heart relies on FFA as an alternative energy source, increasing FFA uptake and utilisation (Avogaro et al., 1990; Doria et al., 1991; Herrero et al., 2006). This dependence on FFA utilisation may be further exacerbated by increased levels of systemic FFA, due to increased lipolysis in the absence of insulin inhibition (Heptulla et al., 2003). However, it must be noted that insulin treatment has been shown to restore short-term cardiac metabolism (Avogaro et al., 1990). On the other hand, studies have shown the development of insulin resistance in T1DM, concurrent with increased cardiac lipid content and cardiac dysfunction (Perseghin et al., 2003; Nadeau et al., 2010).

Similarly, there is a down-regulation of GLUT-4 in T2DM, reducing cardiac glucose uptake (Armoni et al., 2005). However, cardiac responsiveness to insulin remains intact in patients with T2DM (Utriainen et al., 1998). Instead, T2DM is associated with increased systemic FFA, most likely due to obesity and the inability of adipocytes to cope with the excess calories associated with the Western diet. This increased FFA promotes FFA uptake and utilisation in the heart, outcompeting glucose as a metabolic substrate (Randle et al., 1964; Coort et al., 2004; Peterson et al., 2004). The increased use of FFA in turn further inhibits glucose utilisation, promoting the metabolic switch to FFA oxidation and metabolic inflexibility (Nuutila et al., 1992). This metabolic switch has been shown to occur before the onset of hyperglycaemia and insulin resistance (Buchanan et al., 2005). The metabolic shift from glucose to FFA usage in T1DM and T2DM marks the beginning of the pathogenic journey to DCM. Therefore, although the initial stages of disease manifestation may differ between T1DM and T2DM, the development of cardiovascular complications and end-points is closely paralleled.

1.2.2. Is diabetic cardiomyopathy a distinct phenotype?

There still remains some controversy as to whether the DCM phenotype exists and whether it is a distinct entity from other types of HF (Maisch et al., 2011; Seferovic et al., 2012; Litwin, 2013). Specifically, it is uncertain as to whether DCM is associated with T1DM. For example, observational studies have shown that clinically relevant HF is rare in T1DM patients (Torffvit et al., 2005; Lind et al., 2011). Likewise, a