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Cardiac oxidative stress in diabetes: Mechanisms and therapeutic potential

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ABSTRACT

Macrovascular complications of diabetes, including diabetic cardiovascular disease (CVD), occur through a number of hyperglycaemia-induced mechanisms that include generation of oxidative stress, accumulation of advanced glycation end-products (AGE) and activation of protein kinase C (PKC). Cardiac oxidative stress is associated with increased cardiac fibrosis and hypertrophy, and reduced cardiac performance and contractility, leading to severe cardiac dysfunction and potentially fatal cardiac events. It occurs under conditions of excessive synthesis of reactive oxygen species (ROS). The ensuing activation of transcription factors such as nuclear factor-κB produces inflammation, fibrosis, hypertrophy and further oxidative stress, which itself causes DNA and membrane damage. This review summarises the mechanisms that generate ROS in the diabetic heart: mitochondrial electron leakage, activity of ROS-generating enzymes such as NADPH oxidase, xanthine oxidase and 12/15 lipoxygenase, uncoupling of nitric oxide synthase, accumulation of AGEs and activation of PKC. There is interaction between many of these ROS-generating pathways, with data from a range of published studies indicating that a common upstream pathway is the interaction of AGEs with their receptor (RAGE), which further promotes ROS synthesis. Therefore, agents targeted at decreasing ROS production have been investigated for prevention or treatment of diabetic CVD through reducing oxidative stress, and this review considers some of the studies carried out with anti-oxidant therapies and the feasibility of this approach for protecting against diabetic cardiomyopathy.

Contents

1. Introduction

1.1. Chronic hyperglycaemia and cardiovascular disease

Diabetes mellitus is a metabolic disorder where reduced insulin sensitivity and defective insulin secretion lead to hyperglycaemia through inadequate glucose storage and inappropriate glycogenolysis and gluconeogenesis. The global burden of diabetes and the threat posed by diabetes to human health has become very severe in recent years, mainly as a consequence of increased urbanisation, population ageing and changes in lifestyle that lead to increased body mass index (BMI) (Chen, Magliano, & Zimmet, 2012; Zimmet, Alberti, & Shaw, 2001). Global projections of diabetes in 2010 proposed that 439 million adults worldwide would have diabetes by 2030 (Shaw, Sicree, & Zimmet, 2010), but already 415 million adults have diabetes and this is predicted to increase to 642 million by 2040 (IDF Diabetes Atlas).

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It is the long term microvascular and macrovascular complications of chronic hyperglycaemia that lead to mortality and morbidity in diabetes. The microvascular complications affect small blood vessels and include nephropathy, neuropathy and retinopathy, while the macrovascular complications comprise cardiovascular, cerebrovascular and peripheral artery diseases (Fox et al., 2007). The current treatments for diabetes aim to control hyperglycaemia and prevent hyperglycaemia-induced tissue damage through lifestyle changes and pharmacological interventions (Fowler, 2008).

The increased risk of cardiovascular disease (CVD) in diabetic patients was made evident by the Framingham (Kannel & McGee, 1979) and the MERIT (Stamler, Vaccaro, Neaton, & Wentworth, 1993) clinical trials, which indicated that diabetic patients have a 2 to 4-fold increased risk of CVD. Furthermore, diabetic patients have a 3-fold higher mortality rate than the non-diabetic population, highlighting that this condition is potentially fatal. Diabetic CVD encompasses a range of cardiovascular conditions, including diabetic cardiomyopathy (Boudina & Abel, 2010), coronary heart disease and congestive heart failure (Kannel & McGee, 1979). Oxidative stress is believed to be involved in the pathogenesis of all of these conditions (Kayama et al., 2015) and this review will focus primarily on the role of enhanced ROS production in the development of diabetic cardiomyopathy.

1.2. Diabetic cardiomyopathy

Diabetic cardiomyopathy was first described in 1972 in four diabetic patients who presented with heart failure (Rubler et al., 1972). It is a term used to distinguish between diabetes-associated cardiomyopathy, and cardiomyopathy that is associated with other co-morbidities such as hypertension or coronary artery disease (Boudina & Abel, 2010), and these co-morbidities can significantly affect a patient's prognosis with diabetic cardiomyopathy (Ashrafi & Davis, 2011). In a study in which endomyocardial biopsies were taken from 16 diabetic patients it was determined that those subjects with symptomatic cardiac failure had the most significant myocardial changes and therefore the greatest structural and functional alterations (Das, Das, & Chandrasekar, 1987). The clinical features of diabetic cardiomyopathy include alterations in ventricular morphology such as concentric remodelling of the left ventricle leading to left ventricular hypertrophy, interstitial and perivascular fibrosis leading to reduced ventricular compliance, and diastolic dysfunction (Fig. 1) (Miki, Yuda, Kouzu, & Miura, 2013). These clinical features manifest with symptoms that include shortness of breath, fatigue, weakness and ankle oedema. In addition, asymptomatic diabetic patients and individuals with pre-diabetes can also demonstrate mild changes in cardiac function, such as diastolic dysfunction (Ashrafi & Davis, 2011; Koncsos et al., 2016).

1.3. Reactive oxygen species and oxidative stress

The term ROS encompasses free radical species, such as hydroxyl ($OH•$) and superoxide ($O_2•$), and non-radical species such as hydrogen peroxide (H_2O_2). Historically, ROS generation was thought to be a form of pathological cellular stress, but the current consensus is that synthesis and degradation of ROS are physiological, homeostatic functions of many cells (Kayama et al., 2015; Valko et al., 2007). However, if ROS levels are not balanced through appropriate regulation of production and removal, oxidative stress may occur and the modifications of proteins, DNA and lipids by excess ROS is associated with diabetic complications (Kayama et al., 2015; Valko et al., 2007). It has recently been reported that induction of diabetes in guinea pigs through streptozotocin (STZ) treatment led to abnormal cardiac contraction and relaxation, and isolated cardiomyocytes exhibited increased oxidative stress (Tocchetti et al., 2015). Furthermore, even a pre-diabetic state in rats, through administration of a single low dose of STZ, was associated with diastolic dysfunction that was accompanied by increased left ventricular mass and wall thickness (Koncsos et al., 2016). Sub-sarcolemmal mitochondrial H_2O_2 production in these pre-diabetic animals was elevated, again supporting a role for hyperglycaemia-induced cardiac dysfunction being mediated through oxidative stress.

This review summarises the pathways in diabetes that generate ROS and cause oxidative stress in the heart, illustrates the damaging effects of oxidative stress and discusses the potential role of anti-oxidant therapy as treatment for diabetic CVD, with a particular focus on diabetic cardiomyopathy.

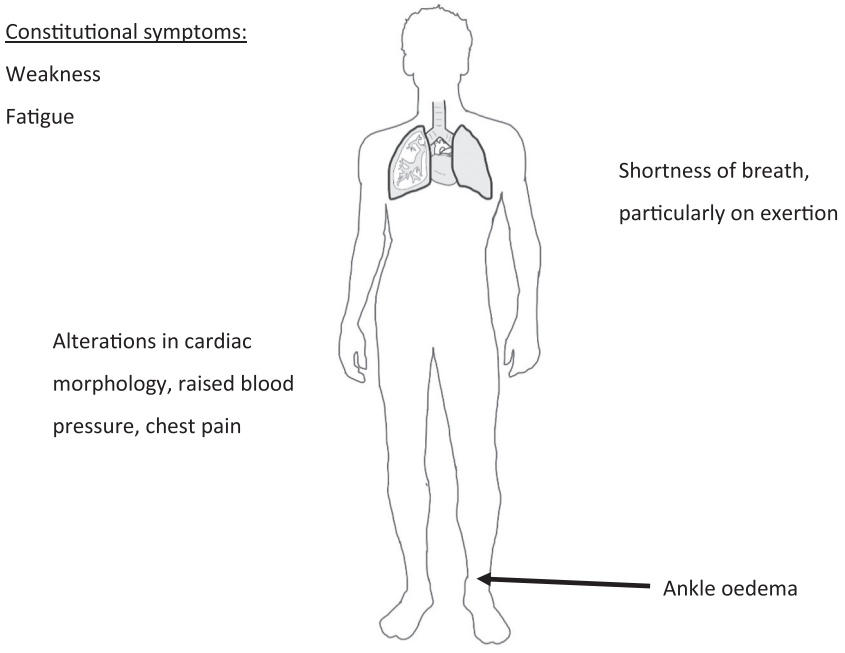

Fig. 1. Clinical features and symptoms of diabetic cardiomyopathy. The clinical features of diabetic cardiomyopathy include structural changes to the left ventricle including ventricular hypertrophy, fibrosis, reduced ventricular compliance and diastolic dysfunction. The symptoms include chest pain, elevated blood pressure, shortness of breath on exertion and ankle oedema.

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