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Mitochondrial dysfunction and its impact on diabetic heart☆

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ABSTRACT

Mitochondrial dysfunction and associated oxidative stress are strongly linked to cardiovascular, neurodegenerative, and age associated disorders. More specifically cardiovascular diseases are common in patients with diabetes and significant contributor to the high mortality rates associated with diabetes. Studies have shown that the heart failure risk is increased in diabetic patients even after adjusting for coronary artery disease and hypertension. Although the actual basis of the increased heart failure risk is multifactorial, increasing evidences suggest that imbalances in mitochondrial function and associated oxidative stress play an important role in this process. This review summarizes these abnormalities in mitochondrial function and discusses potential underlying mechanisms. This article is part of a Special Issue entitled: Oxidative Stress and Mitochondrial Quality in Diabetes/Obesity and Critical Illness Spectrum of Diseases — edited by P. Hemachandra Reddy.

1. Introduction

Over the last 20 years, our understanding of the pathophysiology of chronic heart failure has advanced substantially. However, heart disease still remains the number one cause of morbidity and mortality in the industrialized world, affecting over 27 million people in the United States alone [1]. Furthermore, the prevalence of Type 2 diabetes is reaching pandemic proportions, with estimates that by the year 2025 nearly 300 million adults will be affected by diabetes mellitus [2,3]. Patients with diabetes are at increased risk of cardiovascular diseases associated mortality [4,5]. Previously, it has been shown that patients with chronic heart failure and type 2 diabetes have almost two times higher risk of all cause of mortality that of similar patients without diabetes. To put this in context, if a patient with chronic heart failure (CHF) suffers from type 2 diabetes, their risk of cardiovascular-associated death is over two times higher [4,6]. Interestingly, in many cases diabetic patients also develop heart failure even in the absence of cardiovascular risk factors such as hypertension and coronary artery disease [7,8]. Recently the term "diabetic cardiomyopathy" is used to refer the cardiovascular dysfunction in diabetic patients that is out of proportion to their underlying vascular disease [9]. Mitochondria serve as the power houses of a cell and recent reports implicate mitochondrial injury to be a major player in the pathophysiology of diabetic heart disease [10,11]. Therefore strategies to attenuate mitochondrial injury might be a potential therapeutic target for diabetic heart disease.

2. Mitochondrial dysfunction in diabetic heart

The mitochondrion serves a critical role as a platform for energy transduction, signaling, and cell death pathways related to common cardiovascular diseases such as heart failure [12]. Cardiac dysfunction in diabetic patients is caused by multiple pathologic mechanisms. Interestingly, all these mechanisms are associated with mitochondrial injury, which has been proposed to be an underlying cause, in the pathophysiology of diabetic heart disease [10,11]. Indeed, numerous animal and human studies demonstrated the frequent appearance of damaged mitochondria in the diabetic hearts [13–15]. Dysfunctional mitochondria can cause more ROS production and release pro-death factors such as cytochrome C, apoptosis inducing factor, and Smac/DIABLO [15,16]. Various ROS scavengers or antioxidants are able to reduce cardiomyocyte death and attenuate diabetic cardiac injury in experimental animal models [16,17]. However, the antioxidant-based therapies

Abbreviations: CHF, chronic heart failure; ROS, reactive oxygen species; TGA, triglycerides; FAO, fatty acid β oxidation; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; ATP, adenosine triphosphate; ADP, adenosine diphosphate; GDP, guanosine diphosphate; OXPHOS, oxidative phosphorylation; PPARα, peroxisome proliferator-activated receptor alpha; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ANT, adenine nucleotide translocator; miR, micoRNA; NAC, N-acetyl cysteine; Slc25a3, (solute carrier family-25 member 3); T2DM, (type-2 diabetes); GLP-1, glucagon-like peptide; ACC, acetyl-coenzyme A carboxylase; AMPK, 5AMP-activated protein kinase; CoA, coenzyme A; FAs, fatty acids; GLUT, glucose transporter; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; UPCs, uncoupling proteins.

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have generally not been successful in diabetic patients [18,19], suggesting that simply antagonizing existing ROS by antioxidants is not sufficient to abrogate diabetic cardiac injury. A potentially more effective treatment strategy may be to enhance the overall capacity of mitochondrial quality control to maintain a pool of healthy mitochondria that are needed for supporting cardiac contractile function in diabetic patients.

Recent evidences suggest that cardiac dysfunction in diabetic patients is linked to metabolic abnormalities and more often associated with mitochondrial dysfunction [20]. Diabetes and obesity, the major metabolic disorders, are characterized by high levels of circulating free fatty acids, which results in increased cardiac fatty acid uptake, storage and metabolism [21–23]. In heart, free fatty acids have taken up by cardiac cells such as cardiomyocytes, which are normally catabolized in mitochondrial and in some circumstances, peroxisomal fatty acid β-oxidation (FAO) pathways. Fatty acids are also incorporated into triglycerides (TAG) pools and are ultimately oxidized through β-oxidation flux [24,25]. Peroxisome proliferator-activated receptor alpha (PPARα), which is upregulated in diabetic hearts, plays significant role in modulating TAG flux [21,24,25]. In general, heart does not store significant amounts of lipid, however, it can accumulate triglycerides when fatty acid supply is high. Both in diabetic patients and animal models, the myocardial triglyceride content is notably increased compared to healthy controls [26–28].

Myocardial energy substrate preference (glucose versus fatty acid) normally varies in a dynamic manner to meet the tremendous energy needs of the mammalian heart. In healthy heart vast majority of ATP is generated by oxidation of fatty acids (FAs) and glucose in mitochondria [29] [30–32]. During normal circumstances, nonesterified or free fatty acids (FAs) are the preferred substrate in the adult myocardium, supplying 60–90% of total ATP [29,33–36]. FAs derived from circulating triglyceride-rich lipoproteins and albumin bound nonesterified FAs are oxidized in the mitochondrial matrix by FA β-oxidation (FAO) process, while pyruvate derived from glucose and lactate is oxidized by the pyruvate-dehydrogenase (PDH) complex, present within the inner mitochondrial membrane. The final product, acetyl-CoA, derived from both pathways, ultimately enters the tricarboxylic acid (TCA) cycle to generate ATP [12,37]. In heart failure with reduced ejection fraction, both animal models and human studies demonstrate alterations in the otherwise versatile capacity of the myocardium to use alternative substrates. Emerging data demonstrated a reduced cardiac fatty acid use during heart failure. Previous studies in different heart failure models showed a reduced mRNA and protein expression of FA transporters [38–41]. FA uptake has been reported to reduce both in high-salt-diet-induced heart failure and by rapid pacing [39,42]. Finally both in animal models and human subjects strongly advocate that FA oxidation is significantly reduced during cardiovascular abnormalities [38–41]. In contrast, the data on cardiac glucose use are less consistent [43–45]. In the presence of systolic dysfunction, cardiac glucose uptake was decreased in mice after aortic constriction [43], while unchanged in rats with myocardial infarction [46], and increased in Dahl salt-sensitive rats [39]. The impaired glucose oxidation that parallels systolic dysfunction might be attributable in part to mitochondrial dysfunction, reduced expression of genes involved in glycolysis and glucose oxidation, or decreased abundance of the PDH complex [39,47]. Osorio et al. showed increased glucose oxidation rates in failing dog hearts induced by rapid pacing [46], and Dávila-Román et al. demonstrated higher total rates of glucose use in patients with idiopathic dilated cardiomyopathy [48]. Thus the changes in glucose oxidation in cardiac myocytes may depend on both the stage and the pathogenesis of heart failure.

Interestingly, during uncontrolled diabetes, cardiac energy substrate preference becomes constrained because of the need for insulin for myocardial glucose uptake. Glucose utilization in the diabetic heart is diminished at least in part because of insulin resistance, impaired pyruvate dehydrogenase activity, and reduced glucose transporter (e.g. Glut4). Thus, the diabetic heart relies almost exclusively on mitochondrial FAO for ATP synthesis. This reliance on FAO has potentially detrimental consequences, which includes impaired mitochondrial respiratory function. Mitochondria are the center of both fatty acid and glucose metabolism and thus are likely to be impacted by impaired metabolism associated with diabetes. Previously studies have demonstrated the mitochondrial abnormalities in skeletal muscle of insulin resistant and diabetic humans. Furthermore, reduced expression of targets genes associated with mitochondrial oxidative phosphorylation (OXPHOS) [49–51] peroxisome-proliferator-activated receptor (PPAR) gamma, co-activator-1α (PGC-1α) was observed during heart failure in diabetes [52]. PGC-1α is a master metabolic regulator that coordinates gene expression for pathways involved in mitochondrial biogenesis and respiratory function (Fig. 1) [52]. Shulman and colleagues demonstrated a reduction in ATP synthesis and mitochondrial content in severely insulin-resistant offspring of Type 2 diabetes [53,54]. Kelley et al. found impaired mitochondrial enzyme activities and reduced mitochondrial size and number in skeletal muscle from diabetic patients [55,56]. In sum, these studies strongly implicate impaired mitochondrial function and biogenesis both in diabetic animals and human patients.

The mitochondrial function has been directly studied in multiple animal models of diabetes. In chronic Type 1 diabetes (OVE26 mice) mice model, it was demonstrated that mice had evidence of mitochondrial biogenesis that was coupled to a reduction in mitochondrial function and mitochondrial ultrastructural defects [57]. Mitochondrial state III respiration is significantly reduced in Type 2 diabetic animal models (db/db and ob/ob) [58–60]. Furthermore, there is evidence for increased cardiac mitochondrial biogenesis with ultrastructural defects in insulin resistance and diabetes animals [59,61–64]. In summary, the animal model investigations provide precise and convincing evidence that mitochondrial function is impaired in the hearts of animals with insulin resistance and diabetes. In contrast, due to limited availability of human heart samples and multiple variant, cardiac mitochondrial function has been under studied in human subjects. Nonetheless, a number of studies provide indirect evidence for altered cardiac mitochondrial function in diabetic patients. Diamant et al. studied high-energy phosphate metabolism and cardiac function in asymptomatic well-controlled diabetic men and controls using MRI and 31^{P} nuclear magnetic resonance spectroscopy (NMRS). They demonstrated a reduction in multiple indexes of diastolic function by MRI in the diabetic patients; these functional changes were associated with a reduction in the cardiac phosphocreatine/ATP ratios [65]. A reduction in cardiac phosphocreatine/ATP ratios has also been demonstrated in hearts of diabetic patients with normal cardiac function by echocardiography [66,67], suggesting that changes in mitochondrial function may precede the reduction in contractility. In another study, Anderson et al. demonstrated in the left atrial appendage tissue from Type 2 diabetic patients undergoing coronary bypass surgery that mitochondrial respiratory function was impaired and hydrogen peroxide emission was increased, suggesting an increase in oxidative stress [68,69]. Together with human data demonstrating altered lipid metabolism, these studies strongly implicate mitochondrial dysfunction in the human diabetic heart. In following sections, the potential mechanisms that contribute to mitochondrial dysfunction and leading to cardiovascular abnormalities in diabetes will be discussed.

3. Mechanism of mitochondrial dysfunction in diabetic heart

3.1. Altered energy metabolism

Heart is maximum energy consuming organ of the body and thus a subtle energy deficits can rapidly induced contractile dysfunction. The uninterrupted ATP generation is dependent on the continuous supply of oxygen and fuel substrates and on the integrity of oxidative phosphorylation (OxPhos), which produces virtually all the hearts' ATP. [70–72] While the heart can switch its substrate [fatty acids (FAs), glucose, ketones, lactate, amino acids] preference depending on