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Mini Review

Recent advances in understanding the biochemical and molecular mechanism of diabetic cardiomyopathy

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ABSTRACT

Cardiovascular complications account for significant morbidity and mortality in the diabetic population. Diabetic cardiomyopathy (DCM), a prominent cardiovascular complication, has been recognized as a microvascular disease that may lead to heart failure. During the past few decades, research progress has been made in investigating the pathophysiology of the disease; however, the exact molecular mechanism has not been elucidated, making therapeutic a difficult task. In this review article, we have discussed a number of diabetes-induced metabolites such as glucose, advanced glycation end products, protein kinase C, free fatty acid and oxidative stress and other related factors that are implicated in the pathophysiology of the DCM. An understanding of the biochemical and molecular changes especially early in the DCM may lead to new and effective therapies toward prevention and amelioration of DCM, which is important for the millions of individuals who already have or are likely to develop the disease before a cure becomes available.

1. Introduction

Cardiovascular complications are a chief cause of mortality and morbidity in diabetic patients. Diabetic individuals are at significantly greater risk of developing heart failure independent from other risk factors such as coronary artery disease and hypertension [1,2]. Diabetic cardiomyopathy (DCM) is defined as ventricular dysfunction in the absence of hypertension, coronary artery and valvular heart disease, which increases the risk of heart failure [3]. DCM is a multifactorial progressive disease of the myocardium where the pathogenesis of the disease is extremely complex involving many different cells, molecules, and factors. Diabetes induces dysregulated levels of metabolites such as glucose, lipids, amino acids, hormones, and nutrients, and several factors have been found to activate those myocardial cells before the damage. In this review, a major emphasis is given on diabetic-induced metabolic changes in the cardiomyopathy which induce a range of molecules and pathways involved early in the pathophysiology of DCM.

2. Hyperglycemia

Hyperglycemia has generally been considered as the key initiator of cardiomyopathy damage associated with DCM by activation and dysregulation of several metabolic pathways [4]. Hyperglycemia leads to an increase in oxidative stress by exacerbating glucose oxidation and mitochondrial generation of reactive oxygen species (ROS) which cause DNA damage and contributes to accelerated apoptosis [5]. Also increased ROS activate poly (ADP ribose) polymerase (PARP) as a reparative enzyme [6]. PARP inhibits glyceraldehyde phosphate dehydrogenase (GADPH), diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are considered to be the mediators of hyperglycemia-mediated cellular injury. PARP also promotes cardiac damage by activating nuclear factor-κβ and inducing overexpression of vasoconstrictor endothelin 1 and its receptors [7]. In addition, hyperglycemia activates local renin–angiotensin–aldosterone system (RAAS), contributing to myocyte necrosis and fibrosis [8–10]. To maintain glucose homeostasis, insulin levels increase compensatory and due to the similarities in the extracellular domains between the insulin receptor and the insulin-like growth factor (IGF-1) receptor, increased levels of insulin can promote cellular hypertrophy by binding to the IGF-1 receptor so that insulin acts as growth factor on myocytes [11,12]. Hyperglycemia and hyperinsulinemia stimulate overexpression of transforming growth factor-1 by cardiac fibroblasts, resulting in fibrous tissue deposition and extracellular matrix synthesis [8,13].

3. Advanced glycation end products (AGEs)

AGEs which are thought to contribute to arterial and myocardial stiffness, endothelial dysfunction, and atherosclerosis plaque for-

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mation, increases in diabetic patients [12,14]. Extracellular proteins, such as collagen and elastin, are particularly vulnerable to accumulation of AGE crosslink [15]. AGEs can easily make covalent cross-linkage with proteins and in this way they change the structure and function of these proteins [3]. Crosslinks in collagen and elastin cause increased myocardial stiffness and impaired cardiac relaxation [6]. Also AGEs aggravate intracellular oxidative stress which can contribute to cell damage [16]. AGEs increases vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1, and intercellular adhesion molecule-1 expression in microvascular endothelial cells through intracellular ROS generation [17]. AGEs disturb microvascular homeostasis through interaction with the receptor of AGEs (RAGE) [18,19]. AGE formation and the modulatory role of RAGE signaling bring forward possibilities of therapeutic intervention [18]. However, further research is needed to understand the cellular and molecular processes that initiate the AGEs-induced progression of DCM so that specific target of AGE-RAGE axis can be diagnosed.

4. Protein kinase C (PKC)

PKC activity was significantly increased in the membrane fraction of diabetic hearts compared with controls, and the increased activity was accompanied by a decrease in cytosolic PKC activity in these diabetic hearts [20]. The increase in membrane-bound PKC activity thus appears to be due to translocation of the enzyme from the cytosolic to membrane fraction. These results indicate that the development of DCM is accompanied with a high membrane-bound PKC level [20]. This is probably caused by the de novo synthesis of DAG in response to overflow of the glycolysis pathway in hyperglycemic conditions [21]. Accumulation of metabolites in the glycolysis pathway, such as glyceraldehyde 3-phosphate, will drive the synthesis of DAG, which in turn recruits primed PKC into the plasma membrane to render a competent kinase, a key event in its activation [21]. The level of DAG content in the diabetic heart is positively correlated with the blood glucose levels [22]. PKC has received increasing attention in the pathogenesis of cardiomyopathy as it has shown to function as an important intracellular signaling pathway for modulating cardiac myocyte development, inotropic function and cellular growth [23].

5. Free fatty acid (FFA)

Elevated FFA levels are believed to be one of the major contributing factors in the pathogenesis of diabetes [24,25]. Elevation of circulating FFAs is caused by enhanced adipose tissue lipolysis, and high tissue FFAs are caused by the hydrolysis of augmented myocardial triglyceride stores. Moreover, high circulating and cellular levels of FFAs may result in abnormally high oxygen requirements during FFA metabolism and the intracellular accumulation of potentially toxic intermediates of FFA, all of which lead to impaired myocardial performance and severe myocardial changes [24,25]. Furthermore, the availability of carnitine, an essential substrate for myocardial FFA metabolism, is usually reduced in diabetes [26]. FFA in vitro, especially saturated FFA such as palmitate which are increased in DCM, cause cardiac myocyte apoptosis [27,28]. Increased FFA oxidation promotes mitochondrial uncoupling that may result in reduced myocardial high energy reserves and contractile dysfunction [29,30]. FFA's inhibit pyruvate dehydrogenase and leads to accumulation of glycolytic intermediates and ceramides, which enhance apoptosis [31,32]. In addition, FFA metabolism for adenosine triphosphate production requires large amounts of oxygen that results in more toxic intermediates (lipotoxicity) which impair myocyte calcium handling, worsening myocardial mechanics [33,34].

6. Polyol pathway

Polyol pathway is a metabolic pathway where a part of excess glucose gets metabolized to sorbitol which is then converted to fructose. High blood glucose levels increase activity in the polyol pathway. In the polyol pathway, glucose is reduced to sorbitol by aldose reductase (AR), leading to depletion in cellular stores of NAD(P)H [35]. Reduced NAD(P)H is required for the functioning of many endothelial enzymes, including NOS and cytochrome P450, as well as for the antioxidant activity of glutathione reductase. Sorbitol is then oxidized to fructose by sorbitol dehydrogenase. Alternatively, a high polyol pathway flux consumes large amounts of ATP and may thus provide the energy supply required for endothelial-derived relaxing factor production [36]. AR is the key and rate-limiting enzyme in polyol pathway, and galactose and glucose are substrates to this enzyme which are reduced to galactitol and sorbitol, respectively. Thus, activation of the polyol pathway initiates and multiplies several mechanisms of cellular damage by activation and interaction of AR and other pathogenetic factors such as formation of AGE, activation of oxidative–nitrosative stress, PKC pathway, and PARP that may lead to initiation of inflammation and growth factor imbalances [37].

7. Oxidative stress

The production of reactive oxygen species (ROS) has been shown to be increased in patients with diabetes [38,39], and increased ROS production may be involved in the onset or development of diabetic vascular complications. It has been postulated that hyperglycemia, a key clinical manifestation of diabetes, may produce ROS through the formation of AGEs [39] and altered polyol pathway activity [38], and through the activation of NADPH oxidase via PKC [40]. Hyperglycemia-induced oxidative stress is a major risk factor for the development of micro-vascular pathogenesis in the diabetic myocardium, which results in myocardial cell death, hypertrophy, fibrosis, abnormalities of calcium homeostasis, and endothelial dysfunction [41,42]. Although these pathogenic factors cause diabetic cardiomyopathy, probably via a different mechanism, their major contribution to DCM is oxidative stress, which is derived directly from these pathogenic factors or indirectly from metabolic intermediates caused by these factors, such as the formation of AGEs and production of cytokines or peptides, such as angiotensin II [43].

8. Poly(ADP-ribose) polymerase (PARP) activation

Increased oxidative stress from chronic hyperglycemia may lead to DNA breakage which renders the DNA unstable thereby activating nuclear enzyme PARP in an attempt to repair such damage [44]. PARP activation depletes its substrate, NAD^+, slowing the rate of glycolysis and mitochondrial function and eventually leading to cell death. PARP also inhibits glyceraldehydes 3-phosphate dehydrogenase activity, which in turn increases the influx through hyperglycemia-induced activation of PKC, hexosamine pathway [45]. When PARP is overactivated, which is the case in diabetes, intracellular NAD^+ is depleted creating a redox imbalance further exacerbating the oxidative state in the cell. The beneficial effects of PARP inhibition has been illustrated by PARP-1 knockout mice. These animals are protected against streptozotocin-induced diabetes and myocardial ischemia/reperfusion injury [46,47] among other diseases. Hyperglycemia-induced activation of PKC isoforms, hexosamine flux, and AGE formation were shown to be prevented by blocking PARP activity [48].

As summarized in this review, those pathways and molecules involved in DCM have been discovered, but still, the exact molecu-

lar mechanism involved in the progression of the disease is uncertain, which makes therapeutic interventions a difficult task. Therefore, it is essential to develop animal models for DCM to reveal its mechanisms and to develop new therapeutic interventions. These insights would be helpful in deciphering the detailed diabetic related biochemical and molecular mechanism for the development of new therapeutic targets for prevention and amelioration of DCM.

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