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REVIEW ARTICLE

The Protective Effect of Resveratrol on Diabetic Cardiomyopathy

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Abstract

Based on the key role of hyperglycemia-caused oxidative stress in the formation of diabetic cardiomyopathy, increased antioxidant process would best restorative approach for control of diabetic cardiomyopathy. The increased nitrative stress and peroxynitrite, activation of iNOS and TGF-B1 play a crucial role in the pathogenesis of diabetic cardiomyopathy. Reduction of the expressions of the NOS-2 and TGF-B1 appears to be one of the important mechanisms for resveratrol effect on heart.

Keywords

Type 2 diabetes, Antioxidant, Hyperglycemia, Redox status, Cardiomyopathy, Resveratrol

Introduction

Coronary artery disease leading to myocardial infarction and heart failure is a chronic complication of diabetes [1]. After a myocardial ischemic event, diabetes is associated with increased adverse outcomes in terms of both morbidity and mortality over the short and long term [2].

Diabetic cardiomyopathy, a disorder of the heart muscle in diabetic patients, is one of the major causes of heart failure. Diabetes related cardiomyopathy has been defined as diabetic-mediated ventricular dysfunction independently of any vascular disease and hypertension manifesting initially by diastolic dysfunction, later by systolic dysfunction, and finally by heart failure [3]. In older studies, several mechanisms have been discussed for onset and development of diabetic cardiomyopathy, it is thought that oxidative stress resulting from diabetes-mediated hyperglycemia, lipotoxicity and mitochondrial dysfunction plays a main role in the development of cardiomyopathy in diabetic patients [4,5].

The mechanism of diabetic cardiomyopathy are different and may related increased oxidative/nitrosative stress with induced hyperglycemia [6], and activation of its downstream effector pathways (e.g. poly(ADP-ribose) polymerase (PARP)) [7,8], changes in the composition of extracellular matrix with increased myocardial fibrosis and inflammation [9,10].

Hyperglycemia has been shown to inhibit the pro-survival effect of VEGF, leading to cell apoptosis via tyrosine nitration of PI3Kinase that results in Akt inactivation and increased p38 mitogen-activated protein kinase activation in cells [11]. NO, synthesized from L-arginine by 3 NO synthase (NOS) enzymes, is a biological mediator with multiple actions [12]. Two constitutively present enzymes are found in neuronal and endothelial cells, respectively; the third form is inducible in many cells by endotoxin and cytokines, such as interleukin-1, interferon-γ, and TNF-α [13,14].

Experimental studies have shown that induced NO synthesis has a negative inotropic effect on cardiac cells [15] and that high levels of NO produced by inducible NOS (iNOS) are cytotoxic [16,17]. Recent studies have suggested that generation of nitric oxide (NO) in the endocardium and myocardium regulates cardiac function in a paracrine and autocrine fashion [18,19]. In patients with cardiac dysfunction, can be attributed to excessive NO production resulting from cytokine-induced expression of iNOS in myocardial and vascular tissues [20,21].
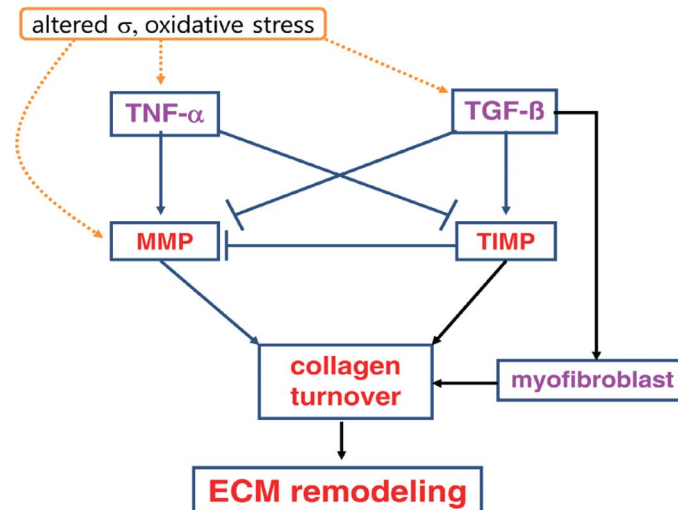
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Figure 1: Collagen turnover in the heart. Changed mechanical stress (σ) and oxidative stress may trigger TNF-α, TGF-β, and MMP. TNF-α stimulated the matrix metalloproteinases (MMP) and inhibit the tissue inhibitors of metalloproteinases (TIMP). In a result, MMP degrades collagens, but TIMP and myofibroblast inhibit collagen degradation and promote collagen synthesis, finally determine collagen ECM remodeling.

The authors showed that expression of iNOS protein with a high prevalence of TNF-alpha protein expression in cardiac myocytes related with cardiomyopathy. Some researchers have previously shown that inducible NO synthase (iNOS) expression was significantly elevated in STZ diabetic rat hearts [22] and once induced, iNOS is known to generate large amounts of NO until the enzyme is degraded [23]. Some cytokines, as example IGF-I, TGF-β1, connective tissue growth factor, platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor, have been reported to both increase cellular proliferation (intestinal smooth muscle cells or myofibroblasts) and increase synthesis of ECM or collagen [24,25].

We know that the collagen content is increased in myocardium of patients with cardiomyopathy, indicating changes in the collagenous framework of the heart [26,27]. Moreover, some authors found correlation between the myocardial collagen and fasting plasma glucose, mRNA expressions of TGF beta [28]. Also, AGEs activate several critical molecular pathways, which trigger production of profibrogenic growth factors, connective tissue growth factor (CTGF), and TGFβ1 [29,30] as well as the inflammatory response. Transforming growth factor (TGF)-β1 co-regulates MMP expression, it affects fibroblast proliferation and regulates ECM production by promoting collagen synthesis and reducing collagen degradation (Figure 1) [31,32].

Aharinejad and collageous found that TGF-β1 expression is increased in myocardium of DCM patients; and that TGF-β1 stimulation in DCM cardiac tissue significantly increased collagen type I but reduced MMP-1 [33]. Another researchers were found that resveratrol can be significant upregulation of the protein expression profiles of vascular endothelial growth factor (VEGF) [34].

For many years, new agents have been tried to get

away from oxidative attack cardiovascular disorders. Resveratrol (trans-3,5,4'-trihydroxystilbene), a polyphenolic compound and naturally occurring phytoalexin, has been designated the active agent [35] present in red wine. In a previous study, resveratrol reduced the oxidative stress and increased inducible nitric oxide synthase (iNOS) mRNA expression which leading to reduction of cardiomyocyte apoptosis and infarct size. In another study researchers showed that induced effect of resveratrol via VEGF, iNOS and eNOS increased expression. This situation provided significant cardioprotection as evidenced by the reduction of infarct area and increased capillary density [36] in the rats myocardial tissue. The definite mechanism for the beneficial effects of resveratrol may be due to nitric oxide (NO) production in endothelial cells, and in the heart [37]. Giovannini, et al. [37] and Naderali, et al. [38] demonstrated that upregulation of NO is a principal factor for the anti-ischemic function of resveratrol [39].

Hong and collageous showed that resveratrol suppress the protein expression of TGF-B1, TGFR-I (TGF-B type I receptor) and TGFR-II (TGF-B type II receptor) in renal epithelial cells [40]. In previosuly studies, resveratrol reduced the mRNA expression of the inflammatory mediators TNF-α and IL-1β, as well as the mRNA expression of collagen type I and TGF-β in the dimethylnitrosamine model of liver fibrosis in rats [41,42]. Diabetic rats supplemented with antioxidant showed decreased glucose, HbA1c and increased the plasma insulin levels. As β-cells in particular, are highly susceptible to oxidative stress, hyperglycemia and dyslipidemia [43-45] increase in oxidative stress in STZ diabetic rat which may induce apoptosis of β-cell.

In last a study has depicted that 8 weeks treatment with resveratrol (2.5 mg/kg/day; *ip*.) improves diabetic heart function through reducing ventricular inflammation and remodeling [46]. Also in the other recent study,

it has been shown that resveratrol given at 2.5 mg/kg/day orally for 4 weeks prevented from cardiac and vascular dysfunction in diabetic rats through its effect on redox balance [47].

Accumulating evidence suggests that hyperglycemia induces ROS [46] and overproduction of ROS is associated with apoptosis in the diabetic heart [48]. In response to the increased oxidative stress, the antioxidant enzymes catalase which act as a defense system, are also induced to protect the cell from oxidative stress [49]. It is observed that, in case of elevated oxidative stress, cells with increased levels of antioxidants are hypersensitive to oxidative stress rather than protected from it thus rendering the cells resistant to oxidative stress.

iNOS is induced by inflammatory cytokines and produces a much higher level of NO compared with constitutive NOS [50]. Cardiac myocytes, as well as a number of other parenchymal cells within the myocardium, including the endothelium of the coronary microvasculature, endocardium, and infiltrating inflammatory cells, are all able to expression of the NOS in response to soluble inflammatory mediators [51].

That have reported fibronectin to be elevated in the kidney, heart, and retina of diabetic rats; in human mesangial cells, hyperglycemia has also been found to induce expression of TGFβ-1, which precedes accumulation of extracellular matrix [52]. In a study, resveratrol downregulated the expression of MCP-1-related proteins, including TGF-B1, TGFR-I or II related to NAD(P)H oxidase system, demonstrating that resveratrol is effective in reducing the oxidative stress induced by oxalate in renal epithelial cells *via* the TGF-β signaling pathway [39].

The findings of some studies indicate that inhibition of oxidative and nitrosative stress with antioxidant treatment improves LV function and minimizes apoptotic cell death in STZ-induced diabetic rat. Besides NADPH oxidase and mitochondrial electron chain as a source of ROS [53,54] in the diabetic myocardium that may play an essential role in diabetic cardiac dysfunction and cardiomyopathy.

In a result, the results of these studies demonstrate that hyperglycemia induces increased expression of NOS-2 and TGF-B1 in cardiomyocytes and that the increased cardiac muscle thickness in the diabetic heart. Reduction of the expressions of the NOS-2 and TGF-B1 appears to be one of the important mechanisms for resveratrol effect on heart.

Conflict of Interests

The authors have no conflict of interest.

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