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Nitric oxide synthases and diabetic cardiomyopathy

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ABSTRACT

Cardiovascular complications associated with diabetes significantly contribute to high mortality and morbidity worldwide. The pathophysiology of diabetic cardiomyopathy (DCM), although extensively researched upon, is partially understood. Impairment in various signaling pathways including nitric oxide (NO) signaling has been implicated in the pathogenesis of diabetes induced myocardial damage. Nitric oxide synthases (NOS), the enzymes responsible for NO generation, play an important role in various physiological processes. Altered expression and activity of NOS have been implicated in cardiovascular diseases, however, the role of NOS and their regulation in the pathogenesis of DCM remain poorly understood. In the present review, we focus on the role of myocardial NOS in the development of DCM. Since epigenetic modifications play an important role in regulation of gene expression, this review also describes the epigenetic regulation of NOS.

Contents

1. Introduction

Cardiovascular disease is a significant contributor to the high mortality and morbidity associated with diabetes. Nearly 80% of the deaths associated with diabetes are attributed to cardiac complications [1]. It has been observed that diabetic patients tend to develop heart failure in the absence of risk factors such as hypertension or coronary artery disease. The cardiovascular complications in diabetic patients in the absence or out of proportion to their underlying vascular disease have been termed as "diabetic cardiomyopathy" (DCM) [2]. It has been suggested that DCM is a frequently unrecognized pathological process in asymptomatic diabetic patients [3].

The pathophysiology of diabetic cardiomyopathy is partially understood, but both hyperglycemia and changes in cardiac metabolism contribute to the disease process. Dysregulation of multiple biochemical pathways such as enhanced reactive oxygen production, nonenzymatic glycation, polyol pathway and advanced glycation end products pathway, activation of the diacylglycerol–protein kinase C (PKC) pathway and NO signaling pathway has been proposed to link the adverse effects of persistent hyperglycemia with DCM (Fig. 1). Geraldes and King [4] have proposed that hyperglycemia may lead to alterations in cellular signaling pathways resulting in cellular dysfunction and heart failure in diabetic patients. Impaired NO signaling has been implicated in the genesis of diabetes induced myocardial damage, however, molecular mechanisms of NO signaling leading to pathogenesis of DCM remain poorly understood. In the present review, we focus on the role of myocardial NOS in the development of DCM. Since epigenetic modifications play an important role in regulation of gene expression, this review also describes the epigenetic regulation of NOS.

2. NOS in heart

NO is constitutively or inductively synthesized during a reaction catalyzed by NOS which exists in three isoforms. All the three

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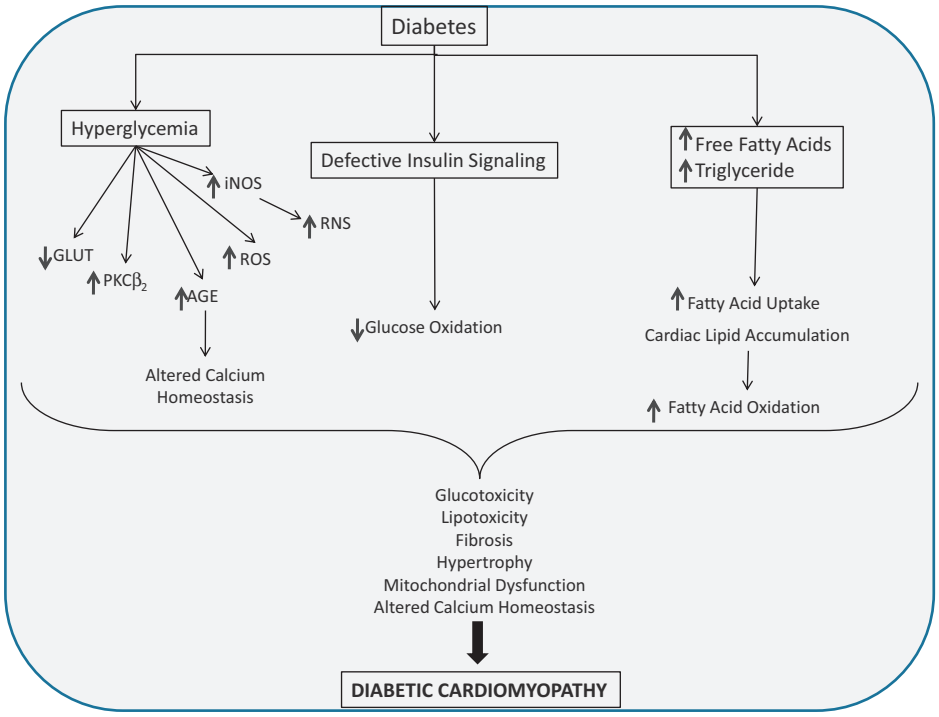

Fig. 1. Pathophysiology of diabetic cardiomyopathy: Both hyperglycemia and changes in cardiac metabolism contribute to alterations in multiple biochemical pathways such as enhanced reactive oxygen species (ROS) production, reactive nitrogen species (RNS) production, advanced glycation end products (AGE) pathway, activation of the diacylglycerol–protein kinase C (PKC) pathway and NO signaling pathway resulting in diabetic cardiomyopathy. Impaired NO signaling has been implicated in the genesis of diabetes induced myocardial damage.

NOS isoforms, namely endothelial (eNOS), neuronal (nNOS), and inducible (iNOS), are expressed in the heart although at spatially confined sub-cellular locations [5] (Fig. 2). In cardiomyocytes, eNOS localizes at the caveolae where it associates with caveolin-3 and modulates several signal transduction pathways [5]. nNOS, however, is confined to the sarcoplasmic reticulum of cardiac myocyte [6] where it regulates the activity of ryanodine receptor, sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) or the L-type Ca^{2+} channel [7].

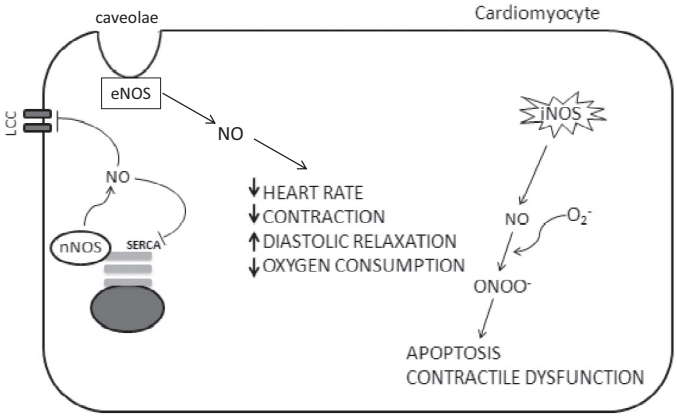

Fig. 2. Subcellular localization of NOS isoforms in cardiomyocytes: In cardiomyocytes, eNOS localizes at the caveolae where it controls heart rate, contraction, diastolic relaxation and oxygen consumption; nNOS is confined to the sarcoplasmic reticulum of cardiac myocyte where it regulates the activity of sarcoplasmic reticulum Ca2+–ATPase (SERCA) or the L-type Ca^{2+} channel (LCC); whereas, iNOS is expressed during pathological states and is localized throughout the cytoplasm. iNOS, on being induced, continuously produces NO until the enzyme is degraded, leading to the formation of peroxynitrile ($ONOO^-$) which contributes to contractile dysfunction and even apoptosis.

Whereas, iNOS is expressed during pathological states and is localized throughout the cytoplasm [8]. The functions of NOS in heart under normal physiological conditions have been reviewed by Balligand and Cannon [9].

NO is a free radical which reacts with various molecules to cause multiple biological effects. Under normal circumstances, the controlled production of NO (by eNOS) conveys antiapoptotic signal, inhibits platelet aggregation and adhesion to the vascular wall, besides playing an important role in cardiac contractile function. The vasodilatory function of NO is mediated via the activation of guanylate cyclase. NO also has cardio-protective effects [10].

Depending upon its source and level of output, NO can either play a cardio-protective or a detrimental role [9]. iNOS is absent in the healthy heart but, as the name indicates, it is induced in cells under stress conditions, including hyperglycemia, oxidative stress and hyperinsulinemia. An increased myocardial NO production can cause nitration of actin and other cytoskeletal proteins in the myocardium. This alters their structure and may have damaging effects on the contractile function of myofilaments. NO also interacts with oxygen radicals and leads to the formation of peroxynitrite, a potent oxidant, which in high concentration causes tissue damage [9].

3. NOS in cardiovascular diseases

Dysregulated expression and activity of NOS isoforms have been implicated in pathophysiology of several cardiovascular diseases including atherosclerosis, hypertension and diabetes. In general, eNOS has been found to play a protective role and nNOS has been shown to play iNOS a deterimental role in heart failure [11]. For example, Barouch et al. [5] reported that nNOS and eNOS-deficient mice developed age-related increase in LV wall thickness and mass and n/eNOS double knockout mice developed phenotype which was similar to that seen in hypertensive hypertrophic cardiomyopathy