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Review article

Potential drugs which activate nuclear factor E2-related factor 2 signaling to prevent diabetic cardiovascular complications: A focus on fumaric acid esters

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ABSTRACT

Diabetes and its cardiovascular complications have been a major public health issue. These complications are mainly attributable to a severe imbalance between free radical and reactive oxygen species production and the antioxidant defense systems. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that controls the basal and inducible expression of a battery of antioxidant enzyme genes and other cyto-protective phase II detoxifying enzymes. As a result, Nrf2 has gained great attention as a promising drug target for preventing diabetic cardiovascular complications. And while animal studies have shown that several Nrf2 activators manifest a potential to efficiently prevent the diabetic complications, their use in humans has not been approved due to the lack of substantial evidence regarding safety and efficacy of the Nrf2 activation. We provide here a brief review of a few clinically-used drugs that can up-regulate Nrf2 with the potential of extending their usage to diabetic patients for the prevention of cardiovascular complications and conclude with a closer inspection of dimethyl fumarate and its mimic members.

Contents

1. Introduction

People with diabetes are prone to severe cardiovascular complications and heart diseases remain the main cause of death in patients with diabetes [1–3]. Several mechanisms responsible for diabetic cardiovascular complications have been proposed [4–6]: (1) dysfunctional

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regulation of intracellular calcium, leading to impaired cardiac contractility; (2) mitochondrial dysfunction, leading to the over-production of reactive chemical species, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), and eventually oxidative damage and cell death; (3) overproduction of advanced glycated end-products in the heart, leading to extracellular matrix accumulation that in turn results in cardiac diastolic dysfunction and eventually functional failure; (4) abnormal cellular metabolism, leading to accumulation of toxic lipids in the heart; and (5) essential trace metal dyshomeostasis such as zinc and copper. Although these pathogeneses may be primarily caused by different mechanisms such as hyperglycemia, hyperlipidemia, inflammation, and angiotensin II, a common mechanism involved in these pathogenic causes is oxidative stress [4,6–9].

Oxidative stress reflects an imbalance between the production of free radicals and ROS and the body's ability to readily remove the reactive intermediates and repair their toxic damage. Disturbances in the normal redox state of cells will cause toxic effects through peroxides and free radicals that damage almost all components of the cell [10]. Overproduced ROS and RNS promote the development of diabetic complications, including cardiomyopathy [6,11,12]. On the other hand, antioxidants can prevent and/or treat diabetic complications [6,11,12]. Therefore, activation of endogenous anti-oxidative components has been proposed as an appealing strategy to alleviate diabetic complications [13].

Heme oxygenase-1 (HO-1) and its by-products are involved in the negative feedback regulation of inflammatory response. The loss of the anti-inflammatory HO-1 is a contributing factor of diabetic cardiovascular complications. The association of microsatellite polymorphism in the promoter region of human HO-1 gene with the risk of coronary artery disease in type 2 diabetic patients has been reported. Furthermore, type 2 diabetics with longer HO-1 gene promoter repeats (and the resulting decreased HO-1 inducibility) have increased oxidative stress and are more susceptible to coronary artery disease [14]. The deficiency of HO-1 significantly increases infarct size in normoglycemic mice and exacerbate myocardial infarction in diabetic mice [15]. In addition to the altered infarct size, mortality was two-fold higher in the diabetic HO-1 knockout mice than in the wild-type (WT) mice after ischemia/reperfusion (I/R) injury [15]. In the streptozotocin (STZ)-induced diabetes rodent models, the loss of HO-1 expression exacerbated left ventricle (LV) dysfunction and induced myofibril structure disarray, aberrant cardiac oxidative stress, inflammation, apoptosis, and impaired autophagy [16]. These data illustrate an indispensable role for HO-1 in the prevention of diabetic complications.

It was reported that the hearts of diabetic rats showed increased myocardial superoxide dismutase (SOD) activity and glutathione levels [17]. Overexpression of SOD was found to protect from cardiac morphologic changes induced by diabetes and completely reverse impaired contractility in diabetic cardiomyocytes [18]. In another study, the plasma type of glutathione peroxidases (GPx), GPx-3, was significantly up-regulated in diabetic mice compared with the control mice [19]. GPx overexpression inhibits the development of LV remodeling and diastolic dysfunction associated with diabetes [20]. These beneficial effects of GPx overexpression are thought to be associated with the attenuation of hypertrophy, apoptosis, and interstitial fibrosis of cardiomyocytes [20].

2. Nrf2 and diabetic complications

2.1. Nrf2/ARE pathway

The critical components of cellular anti-oxidative defense mechanisms include ROS scavengers, phase II detoxification enzymes, and other detoxification proteins which contain antioxidant response elements (AREs) in their promoter regions. A major regulator of the ARE is the highly conserved transcription factor, nuclear factor-erythroid (NF-E) 2-related factor 2 (Nrf2). Nrf2 is regulated by three mechanisms: (1) Keap1–Nrf2 pathway, (2) PI3K/Akt pathway, and (3) epigenetics. In the first mechanism, under normal conditions, Nrf2 is maintained in the cytoplasm by Kelch like-ECH-associated protein 1 (Keap1) and Cullin 3 [21]. Cullin 3 ubiquitinates its substrate, Nrf2, while Keap1 serves as a substrate adaptor facilitating Nrf2 ubiquitination. As a result, Nrf2 has a short half-life of only 20 min under physiological conditions [22]. During times of oxidative stress, critical cysteine residues in Keap1 are oxidized, resulting in the disruption of the Keap1–Cul3 ubiquitination system. When Nrf2 is not ubiquitinated it accumulates in the cytoplasm [23] and is translocated into the nucleus where it combines with a small protein called Maf. This heterodimer binds to the ARE in various upstream promoter regions and initiates transcription of a number of antioxidant genes, including HO-1, NAD(P)H dehydrogenase (quinone 1) (NQO1), SOD, catalase, glutathione-*S*-transferase, γ-glutamylcysteine synthase, and GPx [24,25]. In the second mechanism, the PI3K/Akt pathway (an important regulator of the cell cycle) is involved in Nrf2 activation and its nuclear translocation. Several studies have shown that a wide variety of phytochemicals from natural products, such as butin and 3′,4′-didemethylnobiletin, protect against oxidative stress-induced cell damage via the PI3K/Akt/Nrf2-dependent pathway [26,27]. The third mechanism, epigenetics, has been demonstrated in recent studies which show that several natural phytochemicals, such as curcumin and sulforaphane (SFN), can epigenetically regulate Nrf2 expression and function via demethylation of CpG islands and the inhibition of histone deacetylases (HDACs) and/or histone acetyltransferases (HATs) [28–30]. Through inducing the expression of these antioxidant enzyme genes, Nrf2 is able to amplify a wide range of cell defense processes, thereby enhancing the overall capacity of cells to detoxify potentially harmful substances. Given that the activation of Nrf2/ARE signaling influences the whole antioxidant defense system, Nrf2 can be considered a target for reducing oxidative stress and alleviating oxidative stress-associated diseases.

2.2. Nrf2 and diabetic complications

Emerging evidence has revealed that the Nrf2/ARE signaling pathway plays an important role in preventing oxidative cardiac cell injury [31,32] as well as protecting from diabetic complications [33–35]. High glucose (HG) is known not only to induce ROS and/or RNS production, but also to enhance the expression and activation of Nrf2 and its downstream genes [36,37]. However, Tan et al. observed that in tissue sections of LV obtained from autopsied heart specimens of diabetic humans, nuclear Nrf2 expression was significantly lower when compared to the control heart [38]. Furthermore, the same study also showed that Nrf2 protein expression was slightly increased in the heart of mice with two-month hyperglycemia but significantly decreased in the heart of mice with five-month hyperglycemia [38]. This suggests that Nrf2 may be adaptively overexpressed to combat diabetic damage at the early stage of diabetes, while in the late stage, the exhausted cardiac antioxidant system leads to a decrease in cardiac Nrf2 expression [39]. HG induced significantly higher levels of apoptosis even at low concentrations and in a short time in cardiomyocytes from Nrf2 knockout mice when compared to WT mice [36], indicating that Nrf2 deficiency enhances the HG toxicity. This is confirmed by observation of primary adult cardiomyocytes from diabetic mice which were shown to be dependent on Nrf2 for isoproterenol-stimulated contraction [36].

Nrf2 has a role in the prevention of diabetic renal functional impairment. Yoh et al. have reported that hyperglycemia increased both oxidative and nitrosative stress and exacerbated renal injury in Nrf2 knockout mice. This supports Nrf2 as a defense factor against diabetic nephropathy [40]. Diabetes-mediated activation and expression of Nrf2 were also observed in the kidneys of diabetic patients. In the study by Jiang et al., the glomeruli of human diabetic nephropathy patients were under oxidative stress and had elevated Nrf2 levels [41]. In