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INVITED EDITORIAL

Beyond Hepatoprotection—The Cardioprotective Effects of Bicyclol in Diabetes

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Diabetes and obesity are two major risk factors that promote cardiomyopathies such as cardiac fibrosis, atherosclerosis, hypertrophy, and heart failure [1]. Heart diseases associated with diabetes are collectively named as diabetic cardiomyopathy (DCM) [2]. DCM is a chronic and multifactorial disease characterized by metabolic disturbances, which, together with subcellular abnormalities, locally prompt inflammation, interstitial fibrosis, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis [3]. Abnormal mitochondrial function and the resulting oxidative stress due to reactive oxygen species (ROS) accumulation [3] stimulate pro-inflammatory transcription factors, which are involved in all stages of DCM, including cardiac hypertrophy, fibrosis, cardiomyocyte apoptosis, and contractile dysfunction, ultimately leading to more severe manifestations of heart failure. Cardiac hypertrophy is often associated with unfavorable changes in extracellular matrix composition and fibrosis which results from interaction of a myriad of signal transduction pathways such as calcineurin, NFAT (nuclear factor of activated T cells), interleukin (IL)-6 cytokine family, PI3K (phosphatidylinositol-3-kinase)/AKT, ERK1/2 (extracellular signal-regulated kinase 1/2), JNK (c-Jun N-terminal kinase) and p38 MAPKs (mitogen activated protein kinases), nitric oxide, TNF-α (tumor necrosis factor-α), PPAR (peroxisome proliferator-activated receptors), and phospholipase C and JAK/STAT (Janus kinases/signal transducer and activator of transcription proteins). These processes ultimately lead to the activation of the immediate early genes (c- Jun, c-Fos, c-Myc) and fetal genes (atrial natriuretic factor [ANF], β-myosin heavy chain [β-MHC], and skeletal α-actin), which are regarded as hypertrophic markers [4]. Despite significant research efforts to address the complications associated with DCM, to date the underlying pathological mechanism leading to heart failure is not fully understood. As a result, there are no effective treatment strategies available to treat DCM.

Inflammation in obese and diabetic subjects snowballs an incidence of heart disease and also exacerbates the debilitating outcome after a myocardial infarction (MI) event [4, 5]. The adverse effect of inflammation in the heart has recently gained much attention and has been a primary target for therapy for heart disease [6]. Mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling pathways are important regulatory mechanism involved in the activation of inflammation and their inhibition has proven successful in attenuating cardiac muscle damage in obesity and diabetes [7]. Inflammatory responses after ischemia reperfusion (I/R) injury plays a critical role in determining the size of MI and the extend of left ventricle remodeling and the probability for heart failure [8].

Bicyclol (4,4′-dimethoxy-5,6,5′,6′-bis(methylenedioxy)-2-hydroxymethyl-2′-methoxycarbonyl biphenyl) is a traditional Chinese medicine derivative drug synthesized from *Schisandra chinensis* with an empirical formula of C19H18O9. Bicyclol is widely used in China as an anti-hepatitis drug for chronic hepatitis B and C [9]. This drug has anti-inflammatory effects and also scavenges reactive oxygen species (ROS) and protects mitochondria [9]. The beneficial effects of bicyclol for its anti-fibrosis and anti-oxidative potentials in liver health appear to be mediated through activation of AMP protein kinase and inhibition of MAPK signaling pathway in liver. Bicyclol was approved by the Chinese Food and Drug Administration in the year 2004 for its hepatoprotective and anti-inflammatory properties [10].

Recently, Zhang et al. [11] and Chen et al. [12] demonstrated the cardioprotective effect of bicyclol in diabetes and high fat diet induced obesity in mice. Zhang et al. used

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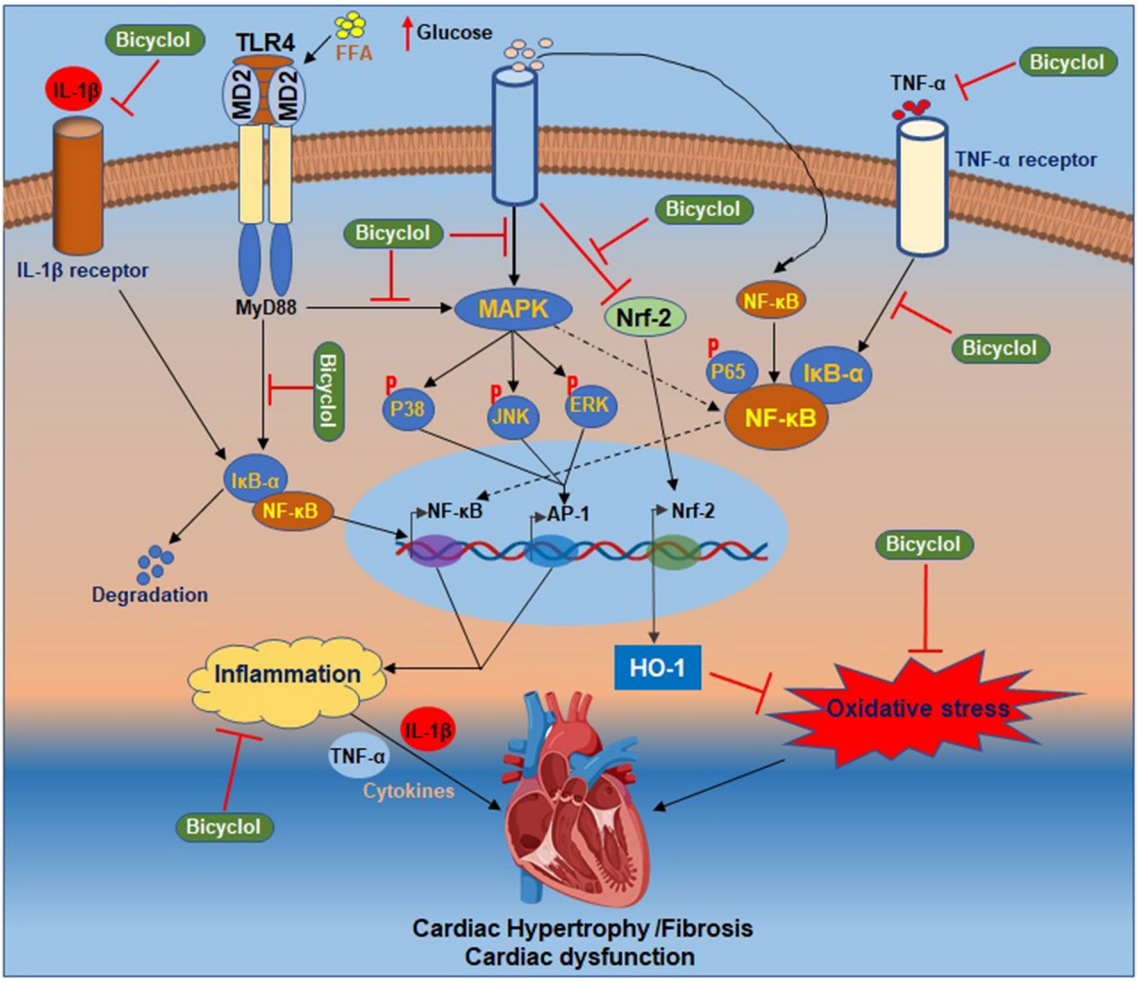

Fig. 1 Potential cardioprotective mechanisms of bicyclol in diabetic cardiomyopathy. Elevation in blood glucose or free fatty acids in diabetic heart promotes remodeling of the heart leading to hypertrophy and cardiac dysfunction. The suppression of inflammatory responses by bicyclol through inhibition of MAPK (p38, JNK, ERK) and transcription factors including NF-kB, AP-1 could lead to attenuation of hypertrophy and improvement of cardiac function in diabetic cardiomyopathy. Binding of excessive FFA to TLR4 in obese subjects activates NF-kB and promotes inflammation (see text for further details). Abbreviations: Toll-like receptor 4; Free fatty acid; Tumor necrosis factor alpha; Heme oxygenase-1

an established mouse model of Type I diabetes mellitus (T1DM) by injecting streptozotocin (STZ), while Chen et al. utilized high fat diet (HFD) induced obesity mice model in their study. Treatment with bicyclol improved cardiac function which was also associated with suppression of fibrosis, inflammation, and hypertrophy in both models (i.e., STZ-induced diabetes and HFD induced obesity). These studies suggest the potential therapeutic effects of bicyclol in cardioprotection in diabetes.

The transcription factor NF-κB is an essential mediator of inflammatory responses and induces the expression of various pro-inflammatory genes, including cytokines such as IL-6, IL-1β, and TNF-α and plays an important role in cardiovascular diseases. Metabolic abnormalities such as diabetes and obesity are characterized by pronounced activation of inflammation that can be deadly during MI. Zhang et al. [11] and Chen et al. [12] demonstrated that MAPK and NF-κB pathways were active in diabetes and obesity and treatment with bicyclol reduced the expression of inflammatory markers such as IL-6, IL-1β, and TNF-α and blunted the activation of MAPK and NF-κB signaling. Further, treatment with bicyclol inhibited the nuclear transfer of p65, reduction of phosphorylation of P38, JNK, and ERK proteins—the key players in the process of inflammation in diabetes.

The nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor that plays a key role in regulating antioxidant and detoxification responses. It is critical for cellular resistance to oxidative stress and activates several antioxidant enzymes in the heart including heme oxygenase-1 (HO-1). As shown in Fig. 1, the activation of Nrf-2/HO-1 pathway mitigates excessive ROS in DCM and also regulates key components in inflammation [13]. Downregulation of

Nrf-2/HO-1 pathway was shown to promote I/R injury and heart failure in DCM [13]. Interestingly, Zhang et al. showed that bicyclol induced Nrf2 protein and its downstream antioxidant enzyme HO-1 in T1DM mice.

Sustained elevation of blood sugar promotes structural changes and robust remodeling of the heart and results in cardiac fibrosis [14]. Bicyclol attenuated myocardial fibrosis and hypertrophy in high fat diet induced obese mice. The anti- hypertrophic benefits of bicyclol in HFD mice was associated with downregulation of β-MyHC, COL-1, TGF-β1and ANP expression both at mRNA and protein level.

In summary, the evidence presented from the two independent mouse models of diabetes and obesity [11, 12] suggests that bicyclol may quell inflammation and alleviate cardiac fibrosis and hypertrophy by targeting MAPK and NF-κB pathways. Further validation of these studies is needed to expand the clinical utility of bicyclol beyond hepatoprotection in patients with diabetes induced cardiac dysfunction.

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Declarations

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