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Metformin Ameliorates Diabetic Cardiomyopathy by Activating the PK2/PKR Pathway

Zhen Yang[1†], Min Wang[1†], Yuchen Zhang[1], Fei Cai[2], Botao Jiang[3], Wenliang Zha[4,5] and Wei Yu[1*]*

[1] Department of Pharmacology, School of Pharmacy, Hubei University of Science and Technology, Xianning, China, [2] Hubei Province Key Laboratory on Cardiovascular, Cerebrovascular, and Metabolic Disorders, Hubei University of Science and Technology, Xianning, China, [3] Department of Urology, Xianning Central Hospital, Xianning, China, [4] Department of Surgery, Clinic Medical College, Hubei University of Science and Technology, Xianning, China, [5] National Demonstration Center for Experimental General Medicine Education, Hubei University of Science and Technology, Xianning, China

Diabetic cardiomyopathy (DCM) is a complication of diabetes that can cause damage to myocardial structure and function. Metformin (Met) is a widely used type 2 diabetes treatment drug that exerts cardioprotective effects through multiple pathways. Prokineticin 2 (PK2) is a small-molecule secreted protein that plays pivotal parts in cardiomyocyte survival and angiogenesis. However, the role of Met in regulating the PK2 signaling pathway in DCM remains unclear. This experiment explored the effects of Met on high glucose (HG)-induced injury through the PK2/PKR pathway *in vivo* and *in vitro*. Cardiomyocytes isolated from adult or AKT-knockout mice were treated with HG (33 mmol/L) and PK2 or AKT1/2 kinase inhibitor (AKT inhibitor). Heart contraction properties based on cell shortening were evaluated; these properties included the resting cell length, peak shortening (PS), maximum speed of shortening/relengthening (±dL/dt), time to 90% relengthening (TR_{90}), and time to peak shortening (TPS). Mice with streptozotocin-induced diabetes were treated with Met to evaluate cardiac function, myocardial structure, and the PK2/PKR and AKT/GSK3β pathways. Moreover, H9c2 cardiomyocytes were exposed to HG in the absence or presence of Met with or without the PK2 antagonist PKRA7 or the AKT inhibitor, and apoptotic proteins such as Bax and Bcl-2 and the PK2/PKR and AKT/GSK3β pathways were evaluated using western blot analysis. The prolongation of TR_{90} and decreases in PS and ±dL/dt caused by HG were ameliorated by PK2 in cardiomyocytes, but the effects of PK2 were ameliorated or negated by the AKT inhibitor and in AKT-knockout mice. Diabetic mice showed metabolic abnormalities, aberrant myocardial enzyme levels, declines in myocardial systolic and diastolic function associated with myocardial fibrosis, and pronounced apoptosis, but these effects were greatly rescued by Met treatment. Moreover, PK2, PKR1, and PKR2 expression and p-AKT/AKT and p-GSK3β/GSK3β ratios were decreased in diabetic mice, and these decreases were attenuated by Met. Likewise, H9c2 cells exposed to HG showed reduced PK2/PKR expression and decreased p-AKT/AKT and p-GSK3β/GSK3β ratios, and these effects were nullified by Met. In addition, the effects of Met on cardiomyocytes exposed to HG were abolished

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****Correspondence:***
Wenliang Zha
xyzwl800@163.com
Wei Yu
yuwei0805@163.com

[†] These authors have contributed equally to this work

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