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Glucolipotoxicity induced diabetic cardiomyopathy is mediated by Protein Kinase R (PKR) pathway: Evidence from in vitro and in vivo DCM Model

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Background: The role of Protein Kinase R (PKR) in inflammation and insulin resistance is well known; however, its role in diabetic cardiomyopathy (DCM) is yet to be understood. This study was aimed to investigate the role of PKR in DCM and its underlying molecular mechanism using in vitro and in vivo DCM models.

Materials and Methods: For in vivo study DCM was induced in Wistar rats with high fat diet and single injection of streptozotocin. Vital parameters were measured by non-invasive BP apparatus. Morphology, fibrosis and protein expression in heart was done by haematoxylin & eosin staining, masson's trichome/sirius red staining and western blotting, respectively. For in vitro study siRNA mediated PKR silencing was performed in H9C2 cardiomyocytes treated with high glucose and high fat to study the underlying molecular mechanism.

Results: PKR levels were found significantly higher in the DCM model along with the increased cardiac biomarkers, oxidative stress, inflammatory markers, markers of fibrosis, decreased systolic and diastolic cardiac functions, enhanced cell death and advanced glycation end-products (AGEs). Moreover, selective inhibition of PKR alleviated cardiac dysfunction, fibrosis, oxidative stress, inflammation and cell death. Additionally knockdown of PKR attenuated glucolipotoxicty-induced markers of inflammation, oxidative stress and apoptosis in cultured H9C2 cardiomyocytes.

Conclusion: Our study for the first time has demonstrated the involvement of PKR in the diabetic cardiomyopathy and that inhibition of PKR may have great therapeutic potential in the treatment of DCM by attenuating inflammation, oxidative stress, apoptosis and fibrosis.

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