**PHARMACOLOGICAL RESCUE OF MITOCHONDRIAIN HEART FAILURE**

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Tetrahydrobiopterin (BH4) has been suggested to regulate cardiac mitochondrial function as a multifunctional cofactor and an antioxidant, an important role in the cardiovascular system. However, its mechanism on transcriptional coactivators such as peroxisome proliferator activated receptor γ coactivator-1 (PGC1) α and AMP-activated protein kinase (AMPK) signaling, major regulators of energy metabolism in heart, is unknown. Aim of this study was to assess the role of BH4 in the PGC1-α and AMPK signaling in the hearts of mammalian animal. Using a sepiapterin reductase (Spr) knockout mouse, a model of BH4 deficiency, we found that BH4 regulates transcription of PGC1-α and phosphorylation of AMPK α and β and the expression of their target proteins involved in mitochondria biogenesis (mtTFA, and ERRα), antioxidant (Prx3 and SOD2) and fatty acid utilization (CD36 and CPTI-M) in the hearts. BH4 can binds to Calcium/Calmodulin-Dependent Protein Kinase Kinase 2 (CaMKK2) then activates CaMKIV mediated CREB phosphorylation and AMPK phosphorylation in the heart of model mice. Spr KO mice have shown the development of a lethal cardiomyopathy with mitochondrial dysfunction and exogenous BH4 supplementation successfully rescued those phenotypes. These results reveal a novel molecular mechanism of BH4 in the regulation of cardiac energy metabolism and suggest that BH4 has therapeutic potential for the cardiomyopathy.