Diabetes Mellitus, Hypertension, and PPAR-Gamma Agonist-Rosiglitazone Alter Calcium Handling and Enhance Arrhythmogenesis

Ting-I Lee1,2, Yao-Chang Chen3, Yu-Hsun Kao1, Yung-Kuo Lin1,2, Yi-Jen Chen1,2

1Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taiwan, 2Wan Fang Hospital, Taipei Medical University, 3Department of Biomedical Engineering, National Defense Medical Center

Background: Diabetes and hypertension have significant effects on cardiac calcium (Ca2+) regulation which plays essential role in cardiac function. The effect of peroxisome proliferator-activated receptor (PPAR)-gamma agonists on Ca2+ regulation in cardiomyocytes is unclear. Objective The purpose is to investigate the effects of hypertension, diabetes, and PPAR-γ agonist-rosiglitazone on regulation of Ca2+ and electrophysiological characteristics of isolated ventricular myocytes. Methods: Indo-1 fluorometric ratio technique, whole-cell patch clamp were used to investigate intracellular Ca2+(Ca2+i), action potentials, ionic currents in ventricular myocytes from Wistar-Kyoto rats (WKY), diabetic WKY, diabetic WKY treated with rosiglitazone, spontaneously hypertensive rats (SHR), diabetic SHR, diabetic SHR treated with rosiglitazone. Western blot was used to evaluate protein expressions of sarcoplasmic reticulum ATPase (SERCA2a), Na+-Ca2+ exchanger (NCX), and ryanodine receptor (RyR). Results: Diabetic WKY and diabetic SHR had smaller sarcoplasmic reticulum Ca2+ contents, Ca2+i transients with prolonged decay portion, down-regulated SERCA2a, NCX, RyR protein expressions and smaller L-type Ca2+ currents than non-diabetic WKY and SHR, respectively. Ca2+ dysregulations in diabetes were attenuated in rosiglitazone-treated rats. Diabetes and hypertension both prolonged action potential duration, which were enhanced by rosiglitazone, and induced the genesis of triggered activity. Conclusions: Diabetes and hypertension modulate Ca2+ handling. Rosiglitazone significantly changed Ca2+ regulation and electrophysiological characteristics, and may contain arrhythmogenic potential in diabetes

Keywords: calcium handling, diabetes mellitus, hypertension