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The heart with impaired glucose tolerance: A time bomb

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Background & Objectives: Heart failure and arrhythmias occur more frequently in patients with type 2 diabetes (T2DM) than in the general population. T2DM is preceded by a prediabetic condition, characterized by impaired glucose tolerance or impaired fasting glucose, marked by elevated reactive oxygen species (ROS) and subclinical cardiovascular defects. Moreover, multifunctional Ca^{2+} calmodulin-dependent protein kinase II (CaMKII) is ROS-activated and CaMKII hyperactivity promotes heart disorders. However, a link between prediabetes and CaMKII in the heart is unprecedented.

Aim: The aim of the present study was to prove the hypothesis that increased ROS and CaMKII activity contribute to the initial events in the development of heart failure and arrhythmogenic mechanisms, life-threatening in the overt T2DM.

Methods & Results: Echocardiography, electrocardiography, biochemical and intracellular Ca^{2+} (Ca^{2+}i) determinations were performed in fructose-rich diet -induced impaired glucose tolerance, a prediabetes model, in rodents. Fructose-rich diet rats showed systolic dysfunction and hypertrophy associated with increased CaMKII activity, ROS production, oxidized CaMKII and enhanced CaMKII-dependent ryanodine receptor (RyR2) phosphorylation compared to rats fed with control diet. Notably, cell shortening, in isolated cardiomyocytes, showed a significant increase in fructose-rich diet vs. control diet myocytes. Moreover, isolated cardiomyocytes from fructose-rich diet showed increased spontaneous Ca2+i release events associated with spontaneous contractions, which were prevented by KN-93, a CaMKII inhibitor, or addition of Tempol, a ROS scavenger, to the diet. Fructose-rich diet myocytes showed increased diastolic Ca^{2+} during the burst of spontaneous Ca^{2+}i release events. Mice treated with Tempol or with sarcoplasmic reticulum-targeted CaMKII-inhibition by transgenic expression of the CaMKII inhibitory peptide AIP (SR-AIP mice), were protected from fructose-rich diet-induced spontaneous Ca^{2+}i release events, spontaneous contractions and arrhythmogenesis *in vivo*, despite ROS increases. Because the discrepancy observed at the whole organ level (systolic dysfunction) and at the cellular level (increase contractility) we thought that the loss of contractile units at the whole heart, due to apoptosis, could explain this controversy. The apoptotic ratio Bax/Bcl2 was increased in fructose-rich diet vs control diet rats (273.6±39.7%) as well as TUNEL positive nuclei. Moreover, isolated mitochondria from fructose-rich diet rats showed significant more swelling (DO 0.34±0.05 control diet vs 0.53±0.03 fructose-rich diet) and enhanced membrane depolarization than control diet mitochondria evaluated by JC-1 fluorescence in intact cardiomyocytes. Fructose-rich diet SR-AIP mice showed less TUNEL positive nuclei than their matched fructose-rich diet control mice. In addition, FRD control mice co-treated with fructose and Tempol, also showed less apoptosis than the one induced by the treatment with fructose alone. On the other hand, mitochondria swelling could be also prevented in S2814A mice, which ryanodine receptor (RyR2) cannot be phosphorylated by CaMKII.

Conclusions: RyR2 phosphorylation by ROS-activated CaMKII, contributes to impaired glucose tolerance-induced arrhythmogenic and apoptotic mechanisms, suggesting that CaMKII inhibition could prevent prediabetic cardiovascular complications and/or evolution.

Biography

Julieta Palomeque is working as an assistant professor in National University of La Plata. She is a member of International Society for Heart Research (ISHR). Her PHD work focus on the study of excitation contraction coupling (ECC) through measuring intracellular ions by epifluorescence and confocal microscopy. During her postdoctoral residency at Dr. R Hajjar´s laboratory (Massachusetts General Hospital & Harvard Medical School, Boston, USA), she gained expertise in heart failure models, gene transfer, fluorescence techniques and intracellular ions measurements. Currently, she is studying the basis of diabetic cardiomyopathy in a prediabetic model.

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