Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Glucose counteracts Isoprenaline Effects on Ion Channel Functions in Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes

Autor: Lin Qiao
Institut / Klinik: I. Medizinischen Klinik
Doktorvater: Prof. Dr. I. Akin

Background: Takotsubo syndrome (TTS) is a cardiomyopathy characterized by transient left ventricle systolic dysfunction with clinical manifestations similar to an acute myocardial infarction but without significant obstructive coronary artery disease. TTS is also associated with long QT syndrome (LQTs) and life-threatening arrhythmias. Catecholamine excess and β adrenoceptor signaling is referred to be involved in the pathogenesis of TTS, but the mechanisms are still unclear. Recent studies indicated that the disorder of glucose and fatty acid metabolism in myocardial tissue is involved in the development of TTS. However, currently available data do not provide sufficient evidence for a causal connection between diabetes mellitus (DM) and the occurrence or course of TTS. Therefore, we investigated the effects of high level of glucose on the pathogenesis of TTS, focusing on the mechanisms of LQTs and arrhythmias.
Objectives: We aimed to investigated the influence of high level of glucose on the pathogenesis of TTS, focusing on the ion channel dysfunction and prolongation of action potential duration in cardiomyocytes challenged by high level of glucose and isoprenaline.
Methods: Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), which were generated from human skin fibroblasts of two healthy donors, were treated with toxic concentration of isoprenaline (Iso, 1 mM for 1h) in presence of normal or high level of glucose (5,5 mM vs 22 mM for 14 days) to mimic the setting of TTS and DM. Patch clamp, qPCR and immunostaining were used in this study.
Results: When hiPSC-CMs were treated with high concentration of Iso, late sodium channel current (I_{Na-L}) was enhanced and transient outward potassium current (I_{to}) was suppressed. The action potential duration (APD) was therefore prolonged. Treatment with high level of glucose also prolonged APD and reduced I_{to}. However, high level glucose plus Iso treatment prevented the APD prolongation and changes of I_{Na-L} and I_{to}. High-level glucose reduced the expression levels of PI3K/Akt, β1-adrenoceptors, Gs-protein and PKA, suggesting their involvement in the protective effects of high-level glucose against toxic effects of catecholamine. Both Iso and high glucose increased the production of reactive oxygen species (ROS), but high glucose level did not influence Iso-induced ROS-generation, suggesting that the protective effects of high-level glucose against Iso did not result from changes of ROS-generation.
Conclusions: The study demonstrated that high-level glucose may protect cardiomyocytes from toxic effects of catecholamine excess through suppressing β1-adrenoceptor-Gs-PKA signaling. DM may reduce the risk for occurrence of arrhythmias due to QT-prolongation in TTS-patients.