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Medizinische Fakultät Mannheim
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Modulation of hERG channel in human-induced stem cell-derived cardiomyocytes from a patient with short QT syndrome type 1

Autor: Xin Li
Institut / Klinik: Institut für Experimentelle und Klinische Pharmakologie und Toxikologie
Doktorvater: Prof. Dr. T. Wieland

Background-Short QT syndrome (SQTS) is a rare, inheritable heart disease representing abbreviated corrected QT interval (QTc) and sudden cardiac death (SCD). The short QT syndrome type 1 (SQTS1) is linked to hERG channel mutations. An optimal therapy for SQTS is still lacking. An implantable cardioverter defibrillator (ICD) is recommended as first choice for the treatment, but it is not applicable to every patient. Therefore, drug therapy is required for some, especially young patients. So far, only a small number of drugs has been tested in SQTS-patients and only quinidine has been shown to be effective. Searching new effective drugs for SQTS is of clinical importance. In spite of rapid progress in searching for genetic factors in SQTS, a convincing proof of genotype-phenotype correlation remains lacking for most SQTS forms. Functional roles of most gene mutations or variants associated with SQTS have not clarified. Of note, only a small part of SQTS-patients has been proved to carry the disease-associated gene mutation and arrhythmias appear only under certain conditions even in patients carrying a clear pathogenic mutation, suggesting roles of environmental factors. Studies regarding roles of environmental factors in occurrence of arrhythmias of SQTS remain spars. Whether and how the SQTS-associated mutation influence effects of environmental factors in cardiac electrophysiology are unknown. It is known that N588K in hERG can change drug affinity, but it is not known if it can change the drug effects on channel gating kinetics in cardiomyocytes.
Aims-The study was designed to assess the changes of hERG channel current and gating kinetics caused by genetic mutation and some environmental factors and drugs using healthy donor and SQTS1-cardiomyocytes carrying the N588K mutation.
Methods-Human induced-stem cell-derived cardiomyocytes (hiPSC-CMs) from three healthy donors and an SQTS1-patient carrying the N588K mutation were generated and patch clamp, single cell contraction and calcium transient measurement techniques were used in these cells for the study.
Results-The hiPSC-CMs from the SQTS1-patient (SQTS1-hiPSC-CMS) showed enhanced hERG channel current (I_{Kr}), shortened action potential duration (APD) and arrhythmic events, the main features of SQTS. Both the activation and inactivation of I_{Kr} were attenuated. Time constants of activation and inactivation were increased and the curves of activation and inactivation were shifted to more positive potentials, whereas the recovery from the inactivation and the deactivation of I_{Kr} were accelerated in SQTS1-hiPSC-CMs. Hyperthermia (40^{o}C), Lipopolysaccharide (LPS) and reactive oxygen species (ROS) increased I_{Kr} with shifts of the activation and inactivation curves. The alterations in SQTS1-hiPSC-CMs were larger than that in healthy donor hiPSC-CMs. The effect LPS on I_{Kr} could be blocked by diphenyleneiodonium, N-acetylcysteine and chelerythine, suggesting that the effect of LPS treatment was mediated by an activation of NADPH oxidase/ROS/PKC involving pathway. High frequency (3Hz) electrical stimulation increased I_{Kr} in healthy donor but not in SQTS1-hiPSC-CMs, which may be one reason for the loss of frequency-adaptation in SQTS. Stimulation with isoprenaline and carbachol had no effect on I_{Kr}. Acidosis (pH6) inhibited I_{Kr} similarly in healthy donor and SQTS1-hiPSC-CMs. Ajmaline, amiodarone, ivabradine, flecainide, quinidine, mexiletine and ranolazine inhibited the hERG channel current (I_{Kr}) less effective in SQTS1-cells when compared with healthy donor cells. Quinidine and mexiletine decreased, but ajmaline, amiodarone, ivabradine and ranolazine increased the time to peak of I_{Kr} similarly in healthy donor and SQTS1-hiPSC-CMs. With respect to the shift of the activation and inactivation curves, the tested drugs showed differential effects in healthy donor and SQTS1-cells. Quinidine, ajmaline, ivabradine and mexiletine but not amiodarone, flecainide and ranolazine decreased the window current in SQTS1-cells. Quinidine, ajmaline, ivabradine and mexiletine affected the time constant of the recovery from inactivation differentially, but all of these drugs decelerated the deactivation of I_{Kr} in SQTS1-hiPSC-CMs.
Conclusion-Both the genetic and non-genetic factors can modulate hERG channel gating. The N588K mutation enhances the effect of hyperthermia, LPS, ROS and some drugs on hERG channel gating. Inflammation and fever may thus be potential triggers for the occurrence of arrhythmias in SQTS. Apparently, the window current-

reduction and the deceleration of the deactivation of hERG channels may be critical properties for antiarrhythmic drugs such as ajmaline, ivabradine, quinidine and mexiletine to suppress the occurrence of arrhythmic events in SQTS1-hiPSC-CMs.