POSTER ABSTRACT PRESENTATIONS
SESSION TITLE: EPOSTERS

Abstract P356: Dual Dysfunction Of Kir2.1 Underlies Conduction And Excitation-contraction Coupling Defects Promoting Arrhythmias In A Mouse Model Of Andersen-tawil Syndrome Type 1

Alvaro Macias, Andrés González-Guerra, Ana I. Moreno-Manuel, Francisco M. Cruz, Nieves García-Quintáns, Lilian K. Gutiérrez, Marta Roche-Molina, Francisco J. Bermúdez-Jiménez, Vicente Andrés, Maria L. Vera-Pedrosa, Isabel Martínez-Carrascoso, Juan A. Bernal and José Jalife

Originally published 22 Nov 2021 | https://doi.org/10.1161/res.129.suppl_1.P356 | Circulation Research. 2021;129:AP356

Abstract

Background: Andersen-Tawil syndrome type 1 (ATS1), caused by trafficking deficient mutations in the gene *KCNJ2* coding the inward rectifier K^+ channel Kir2.1, is associated with life-threatening arrhythmias, which in some patients resemble catecholaminergic polymorphic ventricular tachycardia (CPVT), but the mechanisms are poorly understood. We tested the hypothesis that dysfunction of two different populations of mutant Kir2.1 channels, one at the sarcolemma, and the other at the sarcoplasmic reticulum (SR) membrane, directly alters conduction and intracellular calcium dynamics, respectively, to promote the ATS1 phenotype and arrhythmias that resemble CPVT.

Methods: We generated a new mouse model of ATS1 by a single i.v. injection of cardiac specific adeno-associated viral (AAV) transduction with Kir2.1$^{\Delta 314\text{-}315}$. *In-vivo* and cellular, structural and functional analyses of the model were carried out by electrocardiogram (ECG), magnetic resonance imaging (MRI), intracardiac stimulation, patch-clamping, membrane fractionation, western blot, immunolocalization and live calcium imaging.

Results: Our mouse model carrying mutant Kir2.1$^{\Delta 314\text{-}315}$ recapitulated the ATS1 phenotype without modifying ventricular function. On ECG, Kir2.1$^{\Delta 314\text{-}315}$ mice had prolonged PR, QRS and QT intervals and occasional U waves. They showed significantly slower conduction velocities than wildtype mice in response to flecaidine-induced Na^+-channel blockade, additional QT prolongation in response to isoproterenol, and increased vulnerability to cardiac fibrillation. Cardiomyocytes from Kir2.1$^{\Delta 314\text{-}315}$ mice had significantly reduced inward rectifier K^+ and Na^+ inward currents, depolarized resting membrane potential and prolonged action potential duration. Immunolocalization in wildtype cardiomyocytes and skeletal muscle cells revealed a novel SR microdomain of functional Kir2.1 channels contributing to intracellular Ca^{2+} homeostasis. Kir2.1$^{\Delta 314\text{-}315}$ cardiomyocytes showed defects in SR Kir2.1 localization and function, which contributed to abnormal spontaneous Ca^{2+} release events.

Conclusions: Cardiac-specific AAV transduction with Kir2.1$^{\Delta 314\text{-}315}$ in mice recapitulates the ATS1 phenotype by disrupting localization and function of Kir2.1 channels at the SR, and the Kir2.1-$Na_V1.5$ channelosome at the sarcolemma. These results reveal a novel dual mechanism of arrhythmogenesis in ATS1 involving defects in Kir2.1 channel trafficking and function at two different microdomains. They also provide the first demonstration at the molecular level of the mechanism underlying the overlap between ATS1 and CPVT associated with defects in intracellular calcium homeostasis.