A leaky voltage sensor domain of cardiac sodium channels causes arrhythmias associated with dilated cardiomyopathy

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4596931
Author(s) Moreau, Adrien; Gosselin-Badaroudine, Pascal; Mercier, Aurélie; Burger, Bettina; Keller, Dagmar I.; Chahine, Mohamed
Author(s) at UniBasel Burger, Bettina ;
Year 2018
Title A leaky voltage sensor domain of cardiac sodium channels causes arrhythmias associated with dilated cardiomyopathy
Journal Scientific reports
Volume 8
Number 1
Pages / **Article-Number** 13804
Mesh terms Arrhythmias, Cardiac, etiology, metabolism; Cardiomyopathy, Dilated, genetics, metabolism, physiopathology; Humans; Induced Pluripotent Stem Cells; Mutation; Myocytes, Cardiac, physiology; NAV1.5 Voltage-Gated Sodium Channel, genetics, physiology; Pedigree; Voltage-Gated Sodium Channels, genetics, physiology
Dilated cardiomyopathy (DCM) is a structural heart disease that causes dilatation of cardiac chambers and impairs cardiac contractility. The SCN5A gene encodes Na; v; 1.5, the predominant cardiac sodium channel alpha subunit. SCN5A mutations have been identified in patients with arrhythmic disorders associated with DCM. The characterization of Na; v; 1.5 mutations located in the voltage sensor domain (VSD) and associated with DCM revealed divergent biophysical defects that do not fully explain the pathologies observed in these patients. The purpose of this study was to characterize the pathological consequences of a gating pore in the heart arising from the Na; v; 1.5/R219H mutation in a patient with complex cardiac arrhythmias and DCM. We report its properties using cardiomyocytes derived from patient-specific human induced pluripotent stem cells. We showed that this mutation generates a proton leak (called gating pore current). We also described disrupted ionic homeostasis, altered cellular morphology, electrical properties, and contractile function, most probably linked to the proton leak. We thus propose a novel link between SCN5A mutation and the complex pathogenesis of cardiac arrhythmias and DCM. Furthermore, we suggest that leaky channels would constitute a common pathological mechanism underlying several neuronal, neuromuscular, and cardiac pathologies.
Publisher Springer Nature
ISSN/ISBN 2045-2322
URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6138662/
edoc-URL https://edoc.unibas.ch/78592/
Full Text on edoc No;
Digital Object Identifier DOI 10.1038/s41598-018-31772-0
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/30218094
ISI-Number WOS:000444571200012
Document type (ISI) Article