3577
Topic Category: 4017-ASIP Signaling in cardiac disease

First Author: Camilla Schinner
LMU Munich
Institute of Anatomy Pettenkoferstraße 16 Munich
Germany
Phone:
camilla.schinner@med.uni-muenchen.de

First Author is a: Graduate Student
First Author is a member of: Not a Member of a Host EB Society
First Author Degree: MD, DO, MBBS, or equivalent

Presentation Preference: Oral

Sponsor: Jens Waschke
Sponsor Phone: +49218072610
jens.waschke@med.uni-muenchen.de
Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society
Keywords: 1. Desmosomes 2. Gap junctions

Regulation of Cardiomyocyte Cohesion and Gap Junctions via Desmosomal Adhesion

Camilla Schinner, Bernd M Erber, Jens Waschke. Institute of Anatomy, LMU Munich, Munich, Germany

Mutations in desmosomal proteins such as desmoglein-2, desmoplakin or plakoglobin can induce arrhythmogenic cardiomyopathy, a disease leading to arrhythmia and sudden cardiac death. Previous data demonstrated adrenergic signaling to be important to regulate desmosomal cohesion in cardiomyocytes. Here, we investigated how signaling pathways including adrenergic signaling, PKC and SERCA regulate desmosomal adhesion and how desmosomal adhesion controls gap junctions in cardiomyocytes. As revealed by dissociation and immunostaining experiments in cardiomyocytes, activation of PKC by PMA or adrenergic signaling increased cell cohesion and desmoglein-2 and desmoplakin localization at cell junctions whereas Trp-treatment to inhibit cadherin binding or inhibition of SERCA pump by thapsigargin reduced cardiomyocyte cohesion. Cohesion was rescued by both cAMP elevation or PMA. In parallel to increased cohesion elevated phosphorylation of the gap junctions component connexin-43 was revealed by Western blotting and immunostaining. Using a multi-electrode array, disruption of cell cohesion by Trp impaired conduction of excitation comparable to the connexin inhibitor carbenoxolone. Elevation of cAMP levels was effective to increase conduction velocity and to improve arrhythmia under baseline conditions as well as after Trp treatment. Immunoprecipitation revealed connexin-43 to interact with desmoglein-2 and β1-adrenergic receptor. Weakened cell cohesion by Trp or siRNA-mediated depletion of desmoglein-2 or plakoglobin were sufficient to block signaling via the β1-adrenergic receptor. Moreover, depletion of desmosomal proteins increased arrhythmia and reduced conduction velocity, both of which was rescued by cAMP elevation. These data demonstrate gap junction and desmosomal proteins to form a complex with the β1-adrenergic receptor. The function of this complex was regulated by cell cohesion, adrenergic and PKC signaling or inhibition of SERCA. These results support the identification of new targets to treat arrhythmogenic cardiomyopathy.