BENEFICIAL REPOLARISATION-NORMALIZING EFFECT OF A POLYUNSATURATED FATTY ACID, DHA IN TRANSGENIC LONG QT TYPE 2 RABBIT MODEL

Tibor Hornyik[1,3,4], Alessandro Castiglione[3,4,5], Eike M. Wülfers[6], Lucilla Giammarino[4,5], Iask Edler[7], Jessica J. Jowais[8], Marina Rieder[3,4,5], Stefanie Perez-Feliz[3,6], Zsuzsanna Bősze[9], András Varró[1,2], Michael Brunner[3,10], Sara I. Liin[7], Hans Peter Larsson[8], Katja E. Odening[3,4,5] and István Baczkó[1]

[1]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary; [2]ELKH-SZTE Research Group for Cardiovascular Pharmacology, Eötvös Loránd Research Network, Szeged, Hungary;
[3]Department of Cardiology and Angiology I, University Heart Center Freiburg, Medical Faculty, University of Freiburg, Freiburg, Germany;
[4]Department of Translational Cardiology/Electrophysiology,Institute of Physiology, University of Bern, Bern, Switzerland;
[5]Translational Cardiology, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;
[6]Institute of Experimental Cardiovascular Medicine, University Heart Center Freiburg—Bad Krozingen, Medical Faculty, University of Freiburg, Freiburg, Germany;
[7]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden;
[8]Department of Physiology and Biophysics, University of Miami, Miami, FL, USA;
[9]Animal Biotechnology Department, NARIC Agricultural Biotechnology Institute, Gödöllő, Hungary; and
[10]Department of Cardiology and Medical Intensive Care, St. Josefskrankenhaus, Freiburg, Germany

Current therapies of congenital long QT syndrome (LQTS) fail to prevent arrhythmic events in up to 40% of the patients. Docosahexaenoic acid (DHA), a polyunsaturated fatty acid activates the repolarizing I_{Ks} current if both α- (KvLQT1) and β (KCNE1) –subunits to I_{Ks} are functionally intact.
The potential beneficial (repolarisation-normalizing) effects of DHA in transgenic LQT1 (KCNQ1-Y315S, loss of I_{Ks}), LQT2 (HERG-G628S, loss of I_{Kr}), LQT5 (KCNE1-G52R, decreased I_{Ks}) and LQT2-5 (loss of I_{Kr}/decreased I_{Ks}) rabbits were investigated.
In vivo telemetric ECG analyses in wild-type (WT), LQT1, LQT2, LQT5 and LQT2-5 rabbits were performed at baseline and after 10μM/kg DHA i.m. to assess changes in heart rate corrected QT (QTc) and short term variability of QT (STV_{QT}). *Ex vivo* monophasic action potential measurements in Langendorff-perfused hearts were carried out to investigate DHA-induced (20μM) changes in action potential duration (APD_{75}) and action potential (AP) triangulation (APD_{90}-APD_{30}).
Baseline QTc (ms±SEM) was significantly longer in LQT1, LQT2 and LQT2-5 than in WT (166±3.8, 165±3.7, and 167±12.1 vs. 144±14.3; $p<0.05$). Baseline STV_{QT} (ms±SEM) was increased only in LQT2. *In vivo*, DHA shortened QTc through activation of I_{Ks} only in WT (-12.0±1.9, $p<0.01$) and in LQT2 (-20.7±1.7, $p<0.01$). Furthermore, in LQT2, DHA normalized STV_{QT}. Similarly, *ex vivo*, DHA shortened APD_{75} (ms±SEM) only in WT and in LQT2 (-12.3±2.2 and -18.1±3.5, $p<0.01$). Moreover, AP triangulation was decreased by DHA in LQT2 (-5.8±1.8, $p<0.01$). Importantly, DHA didn't increase the spatial dispersion of repolarisation (QT and APD_{75} dispersion).
DHA exerts a beneficial repolarisation-normalizing effect through activation of I_{Ks} in LQT2 with intact α- and β-subunits to I_{Ks}. DHA could thus represent a novel therapeutic tool in LQT2 syndrome.

Keywords: long QT syndrome, impaired repolarization reserve, transgenic LQT rabbit models, polyunsaturated fatty acid, docosahexaenoic acid (DHA)