MiRP2 RESCUES LONG QT SYNDROME TYPE 5

Szilvia Déri[1]*, Teodóra Hartai[1]*, László Virág[1], Norbert Jost[1], Alain J. Labro[2,3], András Varró[1], István Baczkó[1], Stanley Nattel[4], Balázs Ördög[1]

[1]Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary; [2]Department of Biomedical Sciences, University of Antwerp, Belgium; [3]Department of Basic Medical Sciences, University of Ghent, Ghent, Belgium; [4]Montreal Heart Institute, Department of Medicine, Université de Montréal, Montréal, Quebec, Canada

LQT5 is caused by loss of function mutations in the KCNE1 gene. KCNE1 encoding minK, a regulatory subunit of I_{Ks} channel. The minK-related peptides (MiRPs), encoded by members of the KCNE gene family, is also can modulate I_{Ks} channel function.
In this study, we aimed to investigate the effect of MiRP2 on the development of the LQT5 phenotype. KvLQT1, WT-minK, LQT5-minK variant (G52R-minK) and MiRP2 were co-expressed in different combinations. The currents were characterized by whole-cell patch clamp technique. The NanoBiT assay was applied to explore, whether MiRP2 and minK are represented in a distinct ion channel population or they co-assemble in the same ion channel complex.
Average current density was significantly lower in group 3 (KvLQT1+WT-minK+G52R-minK) compared to the group 1 (KvLQT1+WT-minK) and group 2 (KvLQT1+WT-minK+MiRP2). However, the mean current density in the presence of MiRP2 was significantly increased in group 4 (KvLQT1+WT-minK+G52R-minK+MiRP2) compared to the group 3. The KvLQT1 and minK were co-expressed with varying amount of MiRP2 for the NanoBiT experiments. The KvLQT1:minK:MiRP2 ratio was 1:2:0 (group 1), 1:2:1 (group 2) and 1:2:2 (group 3). Average relative luminescence (RLU) was 194 in group 1 which was not significantly different from group 2 (129.3 RLU). However, group 3 showed significantly lower RLU (96.7) compared to group 1.
We conclude that MiRP2 rescues the inhibitory effect of the LQT5-minK variant. Furthermore, MiRP2 is probably able to replace minK within the macromolecular complex of the I_{Ks} ion channel, therefore, MiRP2 possibly modulate the development of the LQT5 phenotype in patients.

Keywords: LQT5, slow component of the cardiac delayed rectifier potassium channel, minK- related peptide 2, NanoLuc® Binary Technology

Supported by the National Research, Development and Innovation Office (NKFIH-K-128851).