Einblicke in die Forschungsarbeit

RESEARCH PROJECT

“Treating Cardiac Arrhythmia”

Elite Graduate Program “Human Biology”

Ludwig-Maximilians-Universität in Munich, November 2020

A new option to treat cardiac arrhythmia

Cardiovascular diseases are the top reason for death, and arrhythmia is the reason for the most sudden cardiac deaths, but the treatment options are limited due to the severe side effects of antiarrhythmic drugs. Güney Güvenç, a former student of the Human Biology - Principles of Health and Disease Elite Graduate Program, translated his mitochondrial biology knowledge into biomedical research to aim in extending the indication of two FDA approved drugs as a novel treatment option in arrhythmia.

Targeting mitochondria to cope with arrhythmia

The pathophysiology of many cardiac diseases, including cardiac arrhythmia, originates from the misregulation of calcium homeostasis. With every heartbeat, the cytosolic calcium concentration inside cardiomyocytes raises to induce contraction and declines to allow muscle relaxation. One prominent mechanism to shape calcium signaling in the cell is the mitochondrial calcium uptake via mitochondrial calcium uniporter complex (MCUC).

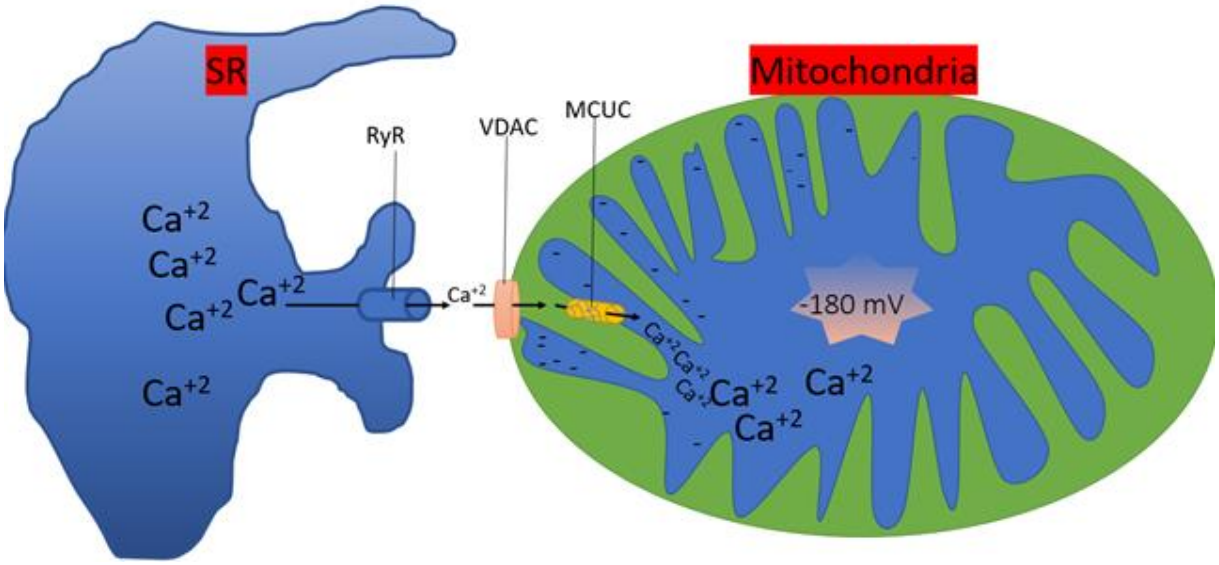
It was recently demonstrated that enhancing mitochondrial calcium uptake is a promising strategy to suppress heart muscle cells' arrhythmogenesis. However, the lack of druggable compounds that modulate the MCUC is the main challenge to further developing this strategy. In the preliminary study, more than 700 FDA and EMA approved drugs had been screened, and two drugs were found as strong candidates to be substances that enhance mitochondrial calcium uptake. These two candidates (MiCUps) are in the market to treat different diseases. Nevertheless, proving their effect on enhancing mitochondrial calcium uptake and enlightening the molecular mechanism of them in this content are required to extend their indications to treat also arrhythmia.

How MiCUps enhance mitochondrial calcium uptake

Güney investigated the molecular mechanism of these two FDA-approved drugs, which are strong candidates to be MCUC modulators (MiCUps) and, as such, could act as antiarrhythmics in addition to their current uses. To test the first hypothesis that MiCUps increase mitochondrial calcium uptake by increasing the mitochondrial membrane potential instead of directly acting on mitochondrial calcium uniporter complex (MCUC), he recorded the mitochondrial membrane potential on different cell lines. Güney has demonstrated that MiCUps could affect the mitochondrial membrane potential. However, an analysis of CRISPR/Cas9-induced MCUC subunit based knockout cell lines indicated that this increase is rather a consequence than a cause for enhanced mitochondrial calcium uptake. His data indicated that increased mitochondrial membrane potential is not the cause of the enhanced mitochondrial calcium uptake with MiCUps. After he eliminated the first hypothesis, he investigated a potential direct role of the drugs on the MCUC. He measured drug-induced changes in calcium uptake in cell lines selectively deficient for individual MCUC subunits using an aequorin bioluminescence-based assay.

Güney established a protocol that successfully reproduced the enhanced calcium uptake observed in the presence of MiCUps. In the absence of the MICU1 subunit of MCUC, these drugs could not show an effect. That might indicate that MiCUps target the MICU1 subunit of MCUC.

In summary, his study could strengthen the clinical relevance of these two MiCUps to treat cardiac arrhythmia; moreover, if required, drugs' chemical structures could be modified considering their possible interaction with the MICU1 subunit of MCUC to extend their indications.



Cardiac arrhythmia is caused by the misregulation of calcium handling. During the fast transfer of calcium from sarcoplasmic reticulum (SR) to mitochondria, MiCUps look like acting on a specific subunit of MCUC, increasing mitochondrial calcium uptake and restoring arrhythmia.

Further information:

- *www.elitenetzwerk.bayern.de*
- *http://www.mhb.uni-muenchen.de*
- *https://www.elitenetzwerk.bayern.de/en/home/funding-programs/elite-graduat-programs/overview-of-elite-gradute-program/human-biology*
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