RYANODINE RECEPTOR RELATED CHANGES OF SKELETAL MUSCLE FUNCTION IN CHRONIC HEART FAILURE

University of Debrecen, Health and Science Centre, Department of Physiology

Doctoral School for Molecular Medicine, Physiology and Neurobiology Ph.D Program

Janos Almassy

supervisor: Dr. Istvan Jona

SUMMARY

In heart failure (HF) exercise intolerance characterized by skeletal muscle weakness and fatigue develops that could not be explained by the reduced muscle perfusion but rather by reduced Ca^{2+} content of the sarcoplasmic reticulum (SR) and the consequent reduction of calcium transients' amplitude, both indicating impaired calcium transport mechanisms. Our aim beside the identification of putative functional Ca^{2+}-release channel (RyR1) changes contributing to the symptoms was to elucidate the effect of a new drug K201 on channel gating. K201 has been suggested as a potential therapeutic agent in HF due to its antiarrhythmogenic action and ability to avoid muscle weakness in HF model animals. For these purpose single RyR1 channels from rats with HF were reconstituted into planar lipid bilayer and the gating behavior was studied under voltage-clamp conditions.

Significant portion of RyRs showed ~50% higher conductance compared to RyRs from control rats and the voltage dependence of the channel conductance was, showing still ohmic but rectifying, polarity dependent conductance. Altered Ca^{2+}-dependency of channel activity was also observed on RyRs from HF afflicted rats, such as reduced sensitivity to calcium dependent inactivation, which can lead to SR depletion.

K201 induced two subconductance states corresponding to approximately 24% (S1) and 13% (S2) of the maximum conductance. Dependence of event frequency and of time spent in S1 and S2 on the drug concentration was biphasic both in control and in PMI rats, with a maximum at 50 μM. At this concentration, the channel spends 26±4% and 24±4%, respectively, of the total time in these subconductive states at positive potentials, while no subconductances are observed at negative potentials. Taken together K201 action on RyR1 can be interpreted as a definite inhibition.

I also investigated the effect of a 33 amino acid toxin maurocalcine (MCa) on the gating properties of RyR from canine heart. MCa is a suitable research tool of electromechanical coupling because it mimics a DHPR segment responsible for allosteric coupling between DHPR and RyR in skeletal muscle. Our aim was to describe the potential differences of our results obtained on skeletal (RyR1) and cardiac (RyR2) type RyR in the presence of MCa. MCa induced long lived subconductive states (LLSS) of RyR2 channel, just like it did in the case of RyR1 with a slight difference: the duration of LLSSs are shorter and the frequency of LLSSs are higher compared to RyR1, indicating weaker electrostatic forces. These results highlight a different role of the MCa-binding domains in the gating process of RyR1 and RyR2.

Keywords: ryanodine receptor, skeletal muscle, heart failure, sarcoplasmatic reticulum, K201 (JTV519), maurocalcine

Kulcsszavak: rianodin receptor, vázizom, szívelégtelenség, szarkoplazmatikus retikulum, K201 (JTV519), maurocalcine