Department of Cell Physiology
Division of Aerospace Medicine

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General Summary

Our main research interests are gravitational physiology and aerospace medicine.

Research Activities

Gravitational physiology and aerospace medicine

1. Elucidation of the re-adaptation of attitude control after the return from long-term space flight

Astronauts returning from a long stay in space will be observed to learn more about the adaptive processes in the somatosensory system and the lower limb skeletal muscles and to acquire data that could contribute to astronaut rehabilitation after returning from space. We are collaborating with the Japan Aerospace Exploration Agency (JAXA) to perform this research. In this experiment, astronauts staying for a long time in space will be studied to measure the following items before and after their stay in orbit:

(1) Comparison of muscle activation patterns in lower limb antagonistic muscles
(2) Blood flow measurement in the lower limb skeletal muscles
(3) Body sway balance measurement

We already collected and are analyzing data from 5 astronauts. We have obtained a preliminary result that the combination of skeletal muscles that are actived while the body sway balance is maintained did not recover to a nomal combination, even months after the astronauts returned to Earth. On the other hand, the astronauts' gait motion recovered and they could walk normally immediately after they returned to Earth.

2. Biomedical analyses of human hair exposed to long-term space flight

As a sample for experimental analysis, human hair has many advantages. Hair matrix cells actively divide in a hair follicle and sensitively reflect physical conditions. The hair shaft has an advantage to record the metabolic conditions of the subject's environment. The environment of space differs from that of the Earth in many factors, such as microgravity, space radiation, and mental stresses. These factors often induce physiological changes in our body. Hair samples will give us useful physiological information to examine the effect of space flight. In space experiments, we believe that hair is a suitable biological specimen because no special hardware or handling is required. We published a paper in *PLOS ONE* reporting the results of this experiment. Regarding the results of hair shaft, we are now analyzing the data.

3. Truncated dystrophin ameliorates the dystrophic phenotype of *mdx* mice by reducing sarcolipin-mediated SERCA inhibition

Duchenne muscular dystrophy (DMD) and the less severe Becker muscular dystrophy (BMD) are due to mutations in the *DMD* gene. Previous reports show that in-frame deletion of exons 45-55 produces an internally shorted, but functional, dystrophin protein resulting in a very mild BMD phenotype. In order to elucidate the molecular mechanism leading to this phenotype, we generated exon 45-55 deleted dystrophin transgenic/*mdx* (Tg/*mdx*) mice. Muscular function of Tg/*mdx* mice was restored close to that of wild type (WT) mice but the localization of the neuronal type of nitric oxide synthase was changed from the sarcolemma to the cytosol. This led to hyper-nitrosylation of the ryanodine receptor 1 causing increased Ca^{2+} release from the sarcoplasmic reticulum. On the other hand, Ca^{2+} reuptake by the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) was restored to the level of WT mice, suggesting that the Ca^{2+} dysregulation had been compensated by SERCA activation. In line with this, expression of sarcolipin (SLN), a SERCA-inhibitory peptide, was upregulated in *mdx* mice, but strongly reduced in Tg/*mdx* mice. Furthermore, knockdown of SLN ameliorated the cytosolic Ca^{2+} homeostasis and the dystrophic phenotype in *mdx* mice. These findings suggest that SLN may be a novel target for DMD therapy.

Publications

Ohira T, Higashibata A, Seki M, Kurata Y, Kimura Y, Hirano H, Kusakari Y, Minamisawa S, Kudo T, Takahashi S, Ohira Y, Furukawa S. The effects of heat stress on morphological properties and intracellular signaling of denervated and intact soleus muscles in rats. *Physiol Rep.* 2017; **5:** pii: e13350.

Wada E, Tanihata J, Iwamura A, Takeda S, Hayasji KY, Matsuda R. Treatment with the anti-IL-6 receptor antibody attenuates muscular dystrophy via promoting skeletal muscle regeneration in dystrophin-/utrophin-deficient mice. *Skeletal Muscle.* 2017; **7:** 23.

Hyzewicz J, Tanihata J, Kuraoka M, Nitahara-Kasahara Y, Beylier T, Ruegg UT, Vater A, Takeda S. Low-Intensity Training and the C5a Complement Antagonist NOX-D21 Rescue the mdx Phenotype through Modulation of Inflammation. *Am J Pathol.* 2017; **187:** 1147-61.