Laboratories
Physical Fitness

Shigeru Takemori, *Professor and Director* Hideki Yamauchi, *Assistant Professor*

General Summary

Research activities in our division have been focused on the plasticity of skeletal muscle and on preventive medicine against sarcopenia and metabolic syndrome in terms of exercise physiology.

Research Activities

Age-related difference in autophagic adaptation and the effect of resistance exercise in rat soleus muscle atrophied with unloading

We have reported that unloading selectively affected type I fibers in aged rats disrupts myofibrils with a decrease in sarcomeric proteins, forming inclusion bodies and accumulating abnormal mitochondria. In the present study we aimed to clarify age-related differences in autophagic adaptation and the effects of intermittent resistance-exercise, which is known to ameliorate sarcopenia, in unloaded muscles of rats. Unloading-induced atrophy with a degenerative decrease in myofibrillar protein concentration was more prominently observed in aged rats (2 years old) than in young rats (4 months old). F-box (Fbx) 32, a muscle-specific ubiquitin ligase, increased, along with an increase in ubiquitinated protein, by unloading in both aged and young rats. Light chain 3 (LC3)-II, an autophagy marker protein, and mitochondrial calcium uniporter (MCU), a key protein activating mitochondrial biogenesis and of signaling pathways for muscle hypertrophy, increased with unloading in young rats but decreased in aged rats. Proliferator-activated receptor-gamma coactivator 1 (PGC1), playing roles similar to those of MCU, decreased with unloading to a specifically greater extent in aged rats than in young rats. Intermittent resistance-exercise ameliorated atrophy similarly in the rats of both ages, while the levels of LC3-II, MCU, and PGC1 were still lower than control levels in aged rats but not in young rats. In conclusion, autophagic adaptation and myogenic response were critically different with age in the rat soleus. These differences might be responsible for age-related muscle responsiveness to unloading and training.

The effects of eccentric contraction on unloaded skeletal muscle.

We have been studying the effect of eccentric contraction (ECC) on the contractile ability, protein signals, intramuscular microstructure to find optimized intensity of ECC for rehabilitation practice to induce muscle protein synthesis while suppressing deteriorative damages. Practical objective muscle of rehabilitation is generally in a catabolic process. Therefore, we studied the effects of ECC on the unloaded muscle of rats that have been tail-suspended for a short period (72 hours). Plantaris muscle received 30 sessions of ECC with stretching to the length of maximal isometric twitch tension (L_0) from 0.9 L_0

during 0.3 second tetanic contraction elicited by 50 Hz supramaximal electrical stimulation through tibial nerve under anesthetized condition. One hour after the series of ECC sessions, muscle was dissected for analysis with x-ray diffraction and electrophoresis. Significant structural changes were not observed in control and unloaded muscles. Incomplete isometric tetanus tension elicited by 40 Hz stimulation was significantly reduced in the tail-suspended muscle compared with the non-suspended muscle. Therefore, catabolic processes would make skeletal muscle more susceptible to damages induced by ECC probably through deterioration in excitation-contraction coupling. It seems safe to limit ECC intensity at a lower level in general rehabilitation practice.

Effect of 2,3-butanedione monoxime on the structure of extraocular muscle revealed by x-ray diffraction

Extraocular muscles show diverse range of contraction modality from slow sustained contraction to fast instantaneous twitches. We performed x-ray diffraction experiments of extraocular muscle to obtain structural characteristics of the muscle. Skinned fibers of extraocular muscle lacked a sampling peak on the myosin layer line at 0.05/nm suggesting a possibility that the extraocular muscle have more mobile myosin heads with a wider range of motion compared with other muscles. To elucidate whether the higher mobility is due to a larger proportion of mobile intermediate of myosin heads hydrolyzing ATP, we examined the effect of 2,3-butanedione monoxime, which is known to shift myosin heads from a mobile intermediate to a stable one. Skinned fibers were prepared from fast type muscle, slow type muscle, and extraocular muscle of male rabbits. X-ray diffraction experiments were carried out at the BL6A station of the Photon Factory in the High Energy Accelerator Research Organization. Although 2,3-butanedione monoxime failed to induce the sampling peak on the myosin layer line at 0.05/nm, it unexpectedly enhanced the intensity at 0.04/nm in the extraocular muscle. The myosin heads in the extraocular muscle fibers might be intrinsically arranged to form a simple lattice structure.

Effects of chronic exercise combined with dietary restriction on the ultrastructure and metabolism of soleus muscle in Wistar Bonn Kobori fatty rats

Wistar Bonn Kobori fatty rats lack leptin receptors and develop chronic pancreatitis and diabetes with obesity. Our recent analysis of the ultrastructure and metabolism of this rat's pancreatic tissue indicated that adequate habitual exercise combined with dietary restriction improved pancreatic exocrine and endocrine functions and prevented the development of diabetes. This prevention of diabetes is in contrast with dietary restriction without exercise, which had little effect on pancreatic functions and the development of diabetes. Exercise is believed to improve pancreatic function through metabolic adaptation in the metabolism of the involved muscles or in cardiopulmonary function. Therefore, we further investigated the effects of dietary restriction and exercise on the ultrastructure and metabolism of the involved muscle and on the improvement of diabetes. Dietary restriction and exercise improved mitochondrial lipid accumulation and swelling, oxidative metabolism, and glucose uptake ability in soleus muscle. These changes might help prevent the development of diabetes in the rat. The results partly support the impor-

tance of habitual exercise in preventing diabetes in obese persons.

Habitual exercise with dietary restriction enhances hepatic fatty acid binding protein 1 expression and ameliorates fatty liver in hyperphagic fatty rats

Weight control solely depending on dietary restriction might cause a failure in lipid metabolism and progression of fatty liver. Fatty acid binding protein 1 (FABP1) is generally postulated to work as a fatty acid delivery controller to intracellular organelles. Therefore, we studied the dynamics of FABP1 at conditions of dietary restriction and habitual exercise combined with dietary restriction in male Zucker fatty rats. With ordinary dietary conditions, the rats became obese with a fatty liver, increases in serum free fatty acid and hepatic fatty acid translocase (FAT)/CD36, and a slight decrease in FABP1. Dietary restriction without exercise exacerbated fatty liver with a decrease in hepatic FABP1 and an increase in hepatic FAT/CD36. On the other hand, dietary restriction and exercise improved fatty liver with a decrease in serum levels of free fatty acid and hepatic FAT/CD36 and an increase in hepatic FABP1. The hepatic triglyceride content levels negatively correlated with hepatic FABP1 protein expression levels. These results suggest that hepatic FABP1 plays a crucial role in the development and progress of fatty liver in hyperphagic Zucker fatty rats.