Department of Molecular Physiology
Division of 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 preventive medicine against metabolic syndrome in terms of exercise physiology.

Research Activities

Functional and structural damages after eccentric contraction in mouse skeletal muscle
Modestly intense eccentric contraction (ECC) increases muscle mass, but strenuous ECC damages muscle. To optimize the ECC protocol for muscle growth, we examined contractility and structures of skeletal muscle after ECC. Tibialis anterior muscle in adult male mice underwent a protocol of isometric contraction, ECC, or passive stretch. Contraction was elicited by supramaximal electrical stimulation via the sciatic nerve *in situ*. Each protocol comprised 3 sets of 30 tetani or stretches or both every 10 seconds with 5-minute intervals between the sets. Contractility at optimal muscle length and electron microscopic structure was examined after the protocol. Several initial muscle lengths (1 and 0.9 optimal muscle lengths) and stretch extents (0.05, 0.1 and 0.2 optimal muscle lengths; at 2.0 optimal muscle length/second) were tested. Passive stretch caused no functional changes. Isometric contraction reduced the maximum force and contraction time of twitch more prominently at longer muscle lengths. The ECC prominently reduced maximum twitch/tetanus force and twitch contraction time and prolonged tetanus contraction. Extra force developed during ECC beyond optimal muscle length seemed crucial for the functional deteriorating effects. Microscopic observation suggested that ECC beyond optimal muscle length caused failures in excitation coupling, cross-bridge formation, and the integrity of sarcomere to induce the functional deteriorations. An ECC beyond optimal muscle length should be avoided in training protocols for muscle growth.

Mechanism underlying development of fatty liver
The pathology of fatty liver due to a high-fat diet is largely unclear. We investigated fat metabolism in rats with a fatty liver resulting from consumption of a high-fat, low-carbohydrate (HFLC) diet without an increase of total caloric intake. Four-week-old male Sprague-Dawley rats were randomly assigned to the control and HFLC groups, and rats were fed the corresponding diets *ad libitum*. Food intake per body weight was significantly lower in the HFLC group than in the control group. Thus, body weight was similar in both groups. Fat in the liver prominently accumulated in the HFLC group and was accompanied by suppression of *de novo* lipogenesis in the liver and elevation of the blood leptin level. In addition, electron microscopic observation revealed many lipid droplets accumulated within the hepatocyte and revealed a reduction in mitochondria content in

the liver derived from rats in the HFLC group. Our findings confirm that fatty liver occurred following consumption of a HFLC diet, even without increased caloric intake. Furthermore, *de novo* lipogenesis is not likely to be a crucial factor to induce fatty liver. Instead, ultrastructural abnormalities in mitochondria may decrease β-oxidation and contribute to the development of fatty liver.

Effects of chronic exercise on the exocrine and endocrine pancreas in WBN/Kob-Fatty rats

Chronic pancreatitis is an inflammatory disorder, causing a progressive and irreversible dysfunction of the exocrine and endocrine pancreas. Recently, the leptin receptor-deficient WBN/Kob-Fatty rat was developed as a model of chronic pancreatitis and diabetes with obesity. The purpose of this study was to investigate whether chronic exercise and a restricted diet increase the decreased pancreatic function of WBN/Kob-Fatty rats. Male WBN/Kob-Fatty rats (age, 6 weeks) were divided into fatty-obese (n = 10), fatty-diet restriction (n = 8), and fatty-exercise (n = 9) groups. Nonobese rats were used as a control (n = 6). The control and fatty-obese rats had free access to food, and the fatty-diet restriction rats and the fatty-exercise rats had food intake restricted to 69% and 70% of the fatty-obese level. The fatty-exercise rats voluntarily ran on a rotary wheel ergometer for 6 weeks. Mean body weight and serum levels of glucose, amylase, and triglyceride were higher in the fatty-obese rats than in other groups. Pancreatic weight and protein content in the fatty-obese rats and fatty-diet restriction rats were lower than in the control rats and fatty-exercise rats. Insulin resistance in the fatty-obese rats was the worst of all the groups. Microscope observations of pancreatic tissue revealed abnormal endocrine areas and some inflammations in the fatty-obese rats. Normal spherical islets of Langerhans were observed in the control rats and the fatty-exercise rats. The interleukin 6 level of the pancreas in the fatty-obese rats was higher than in other groups. Twelve-week-old male WBN/Kob-Fatty rats had symptoms of pancreatitis and diabetes, but nonobese rats did not. These results indicated that obesity is a major factor to aggravate pancreatitis and diabetes. Chronic exercise with a restricted diet beneficially affected the exocrine and endocrine pancreas in WBN/Kob-Fatty rats through the treatment of obesity. The decreased pancreatic function in chronic pancreatitis and diabetes might be increased by an adequate exercise habit and a restricted diet.

Publications

Kurosaka Y[1], Shiroya Y[1], Yamauchi H, Kaneko T[1], Okubo Y[2], Shibuya K[2], Minato K[1] ([1]Wayo Women's Univ, [2]Toho Univ). Effects of habitual exercise and dietary restriction on intrahepatic and periepididymal fat accumulation in Zucker fatty rats. *BMC Res Notes.* 2015; **8:** 121.