Department of Molecular Physiology
Division of Physical Fitness

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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

Chronic exercise with diet restriction prevents diabetes via inactivation of FoxO signal in skeletal muscle

WBN/Kob-Fatty (WKF) rats lack leptin receptor, and develop chronic pancreatitis and diabetes with obesity. We recently reported that diet restriction improves their hyperlipidemia, insulin resistance, and pancreatic dysfunction more effectively when combined with chronic exercise. We now investigated metabolic profiles and intracellular signals in their skeletal muscle to clarify synergistic effects of chronic exercise on diet restriction. Male WKF rats (age, 6 weeks) were divided into fatty-obese (fatty-control), fatty-diet restriction (fatty-DR), and fatty-diet restriction plus exercise (DR+Ex) groups. WBN/Kob rats were used as lean-control. Food intake of fatty-DR and fatty-(DR+Ex) groups was restricted to 69% and 70% of the fatty-obese group, respectively. The exercise of the fatty-(DR+Ex) group was voluntary wheel running. After 6 weeks of intervention, it was found that chronic exercise increased the expressions of proteins associated with glucose uptake and phospholylation, mitochondria biomarkers, and autophagy-related proteins in skeletal muscle. In addition, chronic exercise inhibited FoxO3 signal rather than FoxO1 signal, and accelerated PGC-1a protein expression. We concluded that the chronic exercise at DR condition improved metabolic functions of skeletal muscle and prevented diabetes via inactivation of the PGC-FoxO3a signaling pathway.

Repetitive low-intensity eccentric contraction has little deteriorating effect on sarcomere structure at a molecular level

Using x-ray diffraction method we have reported that eccentric contraction (ECC) of moderate intensity (elicited by 75 Hz stimulation) induces evident deterioration in sarcomere structure evidenced as marked decrease in the intensity of myosin layer-lines. In this study, we evaluated the effects of low intensity ECC. Plantar muscles under blood flow supply of 8-week F344 anesthetized male rats were electrically stimulated through nerve. Consecutive contractions of 300 msec duration were elicited 10 times at 3 s intervals at one of the following conditions; 100 Hz isometric (ISO), 50 Hz ECC, and 75 Hz ECC. To evaluate the effect of overall load, a group of muscles underwent 30 consecutive 50 Hz ECC (50 Hz ECC×30). The overall contraction load evaluated as force-time integral was 50 Hz ECC $<$ ISO $=$ 75 Hz ECC $<$ 50 Hz ECC×30. Force developing capac-

ity evaluated 1 h after the consecutive test contractions was ISO = 50 Hz ECC < 50 Hz ECC×30 < 75 Hz ECC. Although scarcely observable after 75 Hz ECC, myosin layer-lines after ISO, 50 Hz ECC, and 50 Hz ECC×30 were comparable with the control. Sarcomere deterioration represented by myosin layer-lines are sensitive to instantaneous force development, but not to overall contraction load. Therefore, in rehabilitation care, repetitive low-intensity exercise may be adoptable without inducing serious sarcomere deterioration.

Effects of polyamines on skeletal muscle

Polyamines are poly-cationic molecules which are indispensable for proliferation of the eukaryotic cells. The proposed roles of polyamines are the modulation of ion channels, nucleic acid packaging, signal transduction, cell proliferation and differentiation, as well as regulation of gene expression. In skeletal muscle, regulation of polyamine levels may be associated with muscle hypertrophy and atrophy, yet the underlying mechanisms are not established. Thus, we studied how polyamines affect the proliferation and differentiation of murine myoblast progenitor C2C12 cell line. Upon polyamine treatment of C2C12 cells during induction of myogenic differentiation, the number of myotubes significantly increased. Morphologically, polyamine-treated C2C12 cells exhibited elongated cell body with larger number of nuclei per cell. On the other hand, the polyamine did not have influence on myoblast proliferation. Furthermore, C57BL6 mice that have underwent transection of left sciatic nerve exhibited enhanced compensatory hypertrophy of the right hindlimb muscled by polyamine administration. These results demonstrate that polyamines may play an important role in myogenic differentiation rather than myoblasts proliferation.

Effect of polyamine on calcium dynamics and electrophysiological property of cardiac cells

Polyamines may be involved also in exercise induced cardiac hypertrophy as previous workers have reported. On the other hand, polyamines are reported to modulate biological functions of ionic channels so as to modify physiological excitability of cardiac cells. Therefore, increased polyamine concentration within cardiac cells may cause arrhythmia in hypertrophic hearts of athletes. To address this issue, intracellular calcium dynamics and electrophysiological activity of cardiac cells were monitored. In vitro calcium dynamics and electrophysiological activity of isolated cardiac cells were monitored by fluorescent dyes. Excitability of cardiac cells in vivo was evaluated by electrocardiograph of anesthetized 4 rats. Polyamines increased the duration of a spontaneous discharge of cardiac cells both in vitro and in vivo. Polyamine increased intracellular basal calcium concentration in isolated ordinary cardiac cells without corresponding membrane potential change. Amplitude of T-wave of electrocardiograph was increased by the addition of polyamine. Increased intracellular polyamine concentration in cardiac cells may affect hypertrophic hearts of athletes to modify electrophysiological activities.