

Effect of exercise training with intake of acetic acid on lipid metabolism and endurance performance

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Abstract Previously, we found that acetic acid had effects on lipid metabolism in skeletal muscles and has functions that work against obesity and obesity-linked type 2 diabetes through the activation of AMP-activated protein kinase (AMPK). During exercise, AMPK is activated in skeletal muscle according to exercise intensity and it increases fatty acid oxidation. The purpose of this study was to investigate the interactive effects of chronic intake of acetic acid and exercise training on lipid metabolism and endurance performance. Six-week-old SD rats were randomly assigned to four groups: water-injected (rest-water), acetic acid-injected (rest-ace), exercise-trained after injection of water (water-ex), and exercise-trained after injection of acetic acid (ace-ex) for 4 weeks. Body weight (BW) in rest-ace and ace-ex groups was significantly lower than rest-water group. Exercise-training groups showed an increase of exercise capacity, by the addition of intake of acetic acid, lipid oxidation was promoted during exercise tolerance test. Skeletal muscle of rats treated with acetic acid and exercise training led to higher expressions of cytochrome c (cycs), and tended to stimulate expressions of peroxisome proliferator-activated receptor coactivator 1- α (PGC1- α) and MHC1 genes than those of rest-water group. Those results indicate that treatments both of exercise training and intake of acetic acid contribute to enhancement of lipid metabolism and improvement of exercise capacity.

Keywords : AMPK, lipid metabolism, exercise, acetic acid, skeletal muscles

Introduction

Previously, we reported that oral administered acetic acid contributed to suppression of lipogenesis in the liver and to the reduction of lipid accumulation in adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which exhibit hyperglycemic obesity with hyperinsulinemia and insulin resistance. (1) In addition, OLETF rats administered with acetic acid showed a higher rate of oxygen consumption and a smaller size of lipid droplets in white adipose

tissues (2). Under fed condition, orally administered acetic acid is immediately taken up from the digestive organs and excreted into the blood stream in rats (1, 3, 4). Then, acetic acid is absorbed by tissues such as skeletal muscle or liver, and converted to acetyl-CoA with concomitant formation of AMP by the catalytic activity of acetyl-CoA synthetase (AceCS) in the cytosol(5,6). We observed that the AMP/ATP ratio increased in the liver and muscle of acetic acid administered OLETF rats, which enhanced phosphorylation and

activation of AMPK in both tissues (1, 2).

AMPK is a heterotrimeric protein kinase which has been found to play a key role in regulation of whole-body energy by phosphorylating key metabolic enzymes in both biosynthetic and oxidative pathways (7). Various cellular or metabolic stresses that either inhibit ATP synthesis (e.g., heat shock (8), hypoxia (9), or glucose starvation (10)) or that enhance ATP consumption such as physical exercise (11, 12) increase the intracellular AMP/ATP ratio, leading to AMPK activation. Well known function of AMPK is an inactivation of acetyl-CoA carboxylase (ACC) which is the rate-limiting enzyme of fatty acid synthesis. Activated AMPK phosphorylates ACC, which leads to decrease of intracellular malonyl-CoA, block of fatty acid synthesis, activation of carnitine palmitoyl-CoA transferase I, increase of fatty acid oxidation to generate energy, and enhancement of energy expenditure system (7). In addition, activated AMPK phosphorylates peroxisome-proliferator-activated receptor γ coactivator 1 α (PGC-1 α) and activates its downstream gene targets such as PGC-1 α itself, GLUT4, cytochrome *c* and UCP-3 (13). Activated AMPK also activates the NAD⁺-dependent type III deacetylase sirtuin-1 (SIRT1) by increasing intracellular NAD⁺/NADH ratio via accelerating NAD⁺ synthesis (14), leading to deacetylation and activation of PGC-1 α (15). In skeletal muscle, activation of AMPK-SIRT1-PGC-1 α axis resulting from either muscle contraction or chemical stimulator (2, 16) leads to increase of slow twitch muscle fiber via enhancement of mitochondrial biogenesis, oxidative metabolism, and type I myofibers.

During exercise, AMPK is activated in skeletal muscle according to exercise intensity and it increases fatty acid oxidation. In this study, in order to investigate the interactive effects of acetic acid and exercise training on lipid metabolism and exercise capacity, we examined endurance performance and lipid metabolism during exercise in rats administered acetic acid with exercise training in the preliminary study.

Materials and Methods

As the experimental animals, 6 weeks old SD rats were used. Rats were fed normal laboratory diet for 1 week to stabilize the metabolic condition. Rats were randomly assigned to four groups: water-injected (rest-water group), acetic acid-injected (rest-ace group), exercise-trained after injection of water (water-ex group), exercise-trained after injection of acetic acid (ace-ex group). Rest-water group was given distilled water at 5 ml/kg of body weight, and acetic acid group was given 1% (v/v) acetic acid of 5 ml/kg body weight daily 5 days a week for 4 weeks.

During resting or exercise training, oxygen consumption of rats were measured by an O₂/CO₂ metabolism measuring system (Muromachi Kikai). This system monitors VO₂ and VCO₂ at 3 min intervals and calculates the respiratory quotient (RQ) ratio (VCO₂/VO₂). Each rat was in a sealed chamber with a constant air flow (of 1.5 l/min) for 24 h at 25°C with free access to water and diet. Measurement was performed during the dark or light period. The consumed oxygen concentration (VO₂), RQ ratio, and energy consumption were calculated. To examine spontaneous physical activity, each rat was housed in sealed chamber equipped with an infrared sensor and the activity was measured using a Supermex system (Muromachi Kikai) concomitantly with measurement of VO₂ and VCO₂. The water-ex and acetic acid-ex groups were exercise-trained by air-tight treadmill (Muromachi Kikai) for 30 min at 18 m/min after injection of water or acetic acid daily 5 days a week for 4 weeks.

The substrate utilization rate and energy production rate were calculated using the formula (17), that is, the rate of glucose oxidation (mg/min) = 4.55VCO₂ (ml/min) - 3.21VO₂ (ml/min) - 2.87N (mg/min), the rate of lipid oxidation (mg/min) = 1.67(VO₂-VCO₂) - 1.92N, and the rate of energy production (kcal/min) = (1.07 × RQ + 3.98) × VO₂, in this formula N is the rate of urinary nitrogen excretion used to estimate protein oxidation. However, the contributions of protein oxidation were ignored

as it was considering that only a small portion of resting and exercise energy expenditure arisen from protein oxidation.

To examine exercise capacity, we carried out exercise tolerance test. Rats were housed in an air-tight treadmill (Muromachi Kikai) and the rats were challenged at 18 m/min. The speed increased 1 m/min every min until exhaustion, which is defined as touching on the shocker in the rear part of treadmill more than 10 times for 1 min.

Food consumption and body weight were recorded every day. After one month of experiment, the rats were anesthetized by intraperitoneal injection of Nembutal, and abdominal, gastrocnemius, and soleus muscles were immediately isolated, weighed, frozen in liquid nitrogen, and stored at -80°C for subsequent analysis of mRNA.

Quantitative RT-PCR analysis

Total RNA was prepared from isolated skeletal muscles by using Sepasol-RNA super I (Nacalai Tesque) and reverse-transcribed by using PrimeScript[®] RT reagent Kit with gDNA Eraser (Takara Bio) according to the manufacturer's instructions. To determine mRNA expression levels, quantitative real-time PCR analyses were performed by using the iQ5 (Bio-Rad) with KAPA SYBR Fast qPCR Kit (Nippon Genetics). The primer sequences used for the amplification were as follows: β -actin (*actb*), forward : 5'-GGAGATTACTGCCCTGGCTCCTA-3', reverse : 5'-GACTCATCGTACTCCTGCTTGCTG-3', cytochrome c (*cycs*), forward : 5'-AGCGGGACGTCTCCCTAAGA-3', reverse : 5'-CTTCCGCCCAACAGACCA-3', MHC1 (*myh7*), forward : 5'-AGAGGAAGACAGGAAGAACCTAC-3', reverse : 5'-GGCTTCACAGGCATCCTTAG-3', MHC2b (*myh4*), forward : 5'-GAGGACCGCAAGAACGTG-3', reverse : 5'-TGTGTGATTTCTTCTGTCACC-3', PGC-1 α (*ppargc1a*), forward : 5'-GACCCAGAGTCACCAAATGA-3', reverse : 5'-GGCCTGCAGTTCCAGAGAGT-3'. Data were normalized for *actb* mRNA and expressed relative

to that in muscles of rest-water group.

Statistical analysis

Data are expressed as mean \pm standard error (SE). Statistical differences were compared by one-way analysis of variance (ANOVA) followed by Tukey-Kramer post hoc analysis (Mulcell 2005). Differences between groups were considered statistically significant at $p < 0.05$.

Results

Body weight gain tended to be lower in rest-ace, water-ex, and ace-ex groups than that of rest-water group during experimental period (Fig. 1). Effects of treatments with acetic acid and exercise training on body weight gain, food intake, food efficiency, and abdominal fat content were shown in Fig. 2. The total body weight gain was significantly lower in rest-ace and ace-ex groups than that of rest-water group. While, total amount of food intake was not significantly changed among 4 groups. Food efficiencies of rest-ace, water-ex, and ace-ex groups were significantly lower as compared with rest-water group. Abdominal fat contents of rest-ace, water-ex, and ace-ex groups were significantly lower by about 60 %, 50 % and 50 %, respectively than that of the rest-water group.

Activation of AMPK by treatments of acetic acid and exercise training may increase lipid oxidation (2, 12). In order to determine whether acetic acid and exercise training change in the energy metabolic rate in the sedentary state, oxygen consumption was measured and RQ ratio was calculated (Fig. 3). Energy consumption rates in water-ex and ace-ex groups revealed significantly higher than that in rest-water group. Motor activity levels were significantly lower in rest-ace, water-ex, and ace-ex groups than that in rest-water group.

In order to investigate the effect of acetic acid and exercise training on exercise capacity and fuel utilization during exercise, rats were started off running on a treadmill at 18 m/min, and then the speed was increased by the rate of 1 m/min

until exhaustion. Exercise capacity was shown to be increased in water-ex and ace-ex groups as compared with rest-water group (Fig. 4A). Running duration was significantly longer in water-ex and ace-ex groups than that in rest-water group (Fig. 4B).

To investigate the fuel utilization during exercise, VO_2 and VCO_2 were monitored simultaneously until exhaustion (Fig. 5). Oxygen consumptions in all four groups were increased as speed increased until exhaustion. RQ ratios of all groups during

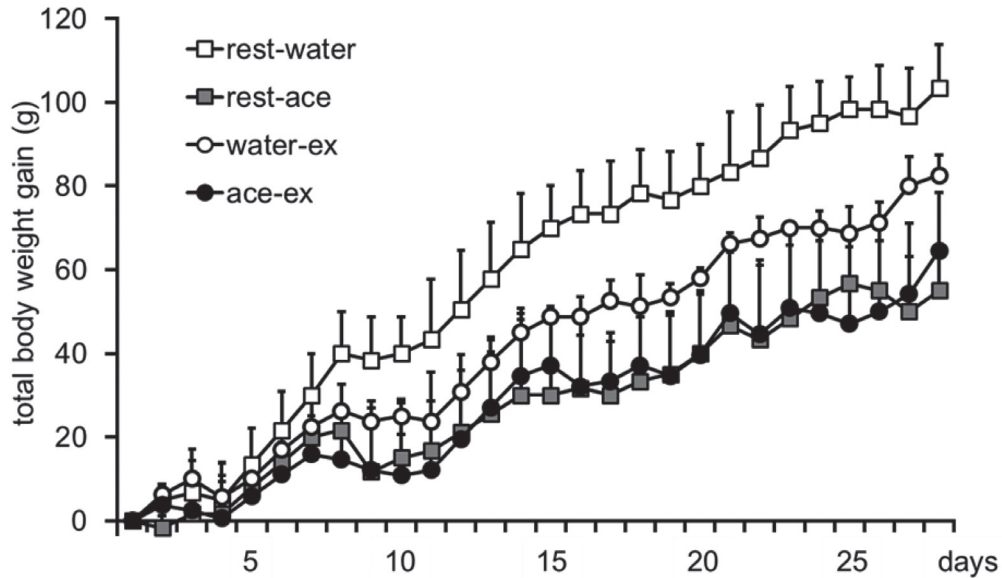


Fig. 1

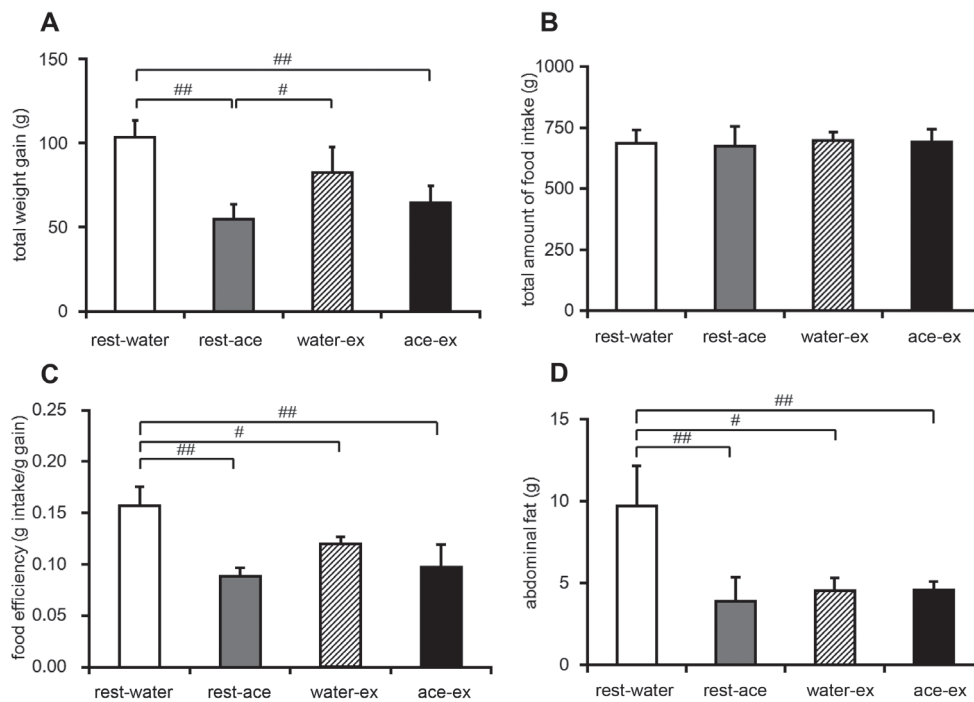


Fig. 2

exercise were increased as the speed of treadmill increased, however the ratio in rest-ace and water-ex groups tended to be lower than that of rest-water group, and the RQ ratio in ace-ex group was significantly lower in 3, 9, 12 min after beginning of the run than that of rest-water group (Fig. 5). The calculated level of glucose oxidation during exercise tended to be higher in rest-water group, while glucose oxidation in ace-ex group was relatively lower, and it was significantly lower in

3 min and 12 min after start running than that of rest-water group (Fig. 6A). While, the calculated level of lipid oxidation during exercise tended to be higher in rest-ace, water-ex and ace-ex groups as compared with rest-water group, and it was significantly higher in water-ex and ace-ex groups in 9 min after start running than that in rest-water group (Fig. 6B). To determine the effects of treatment of acetic acid and exercise training on mRNA levels related

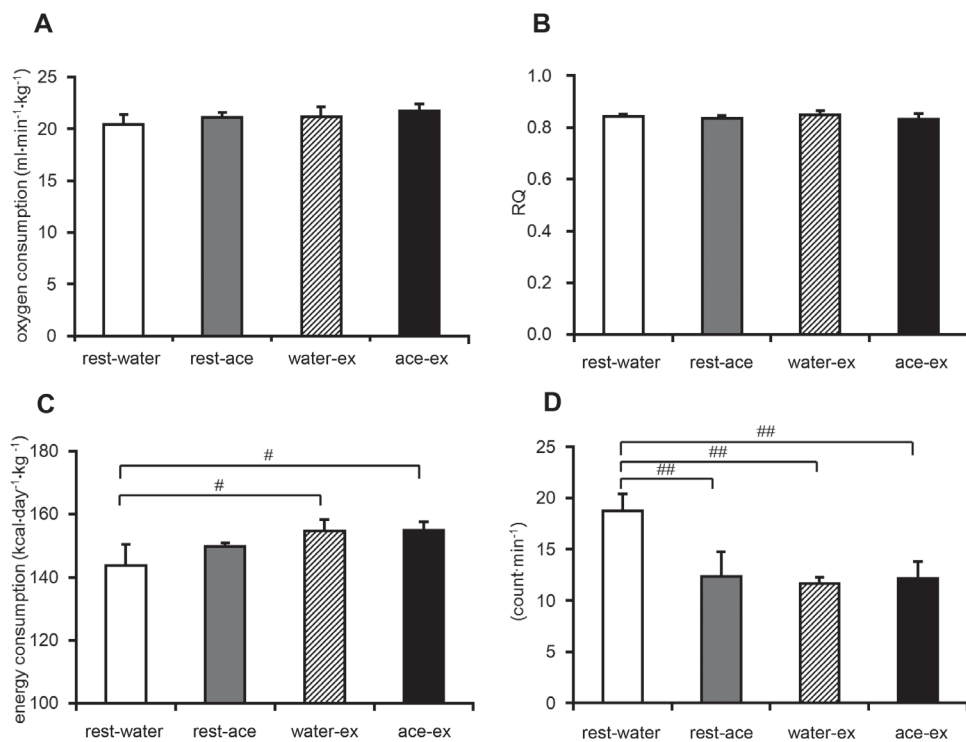


Fig. 3

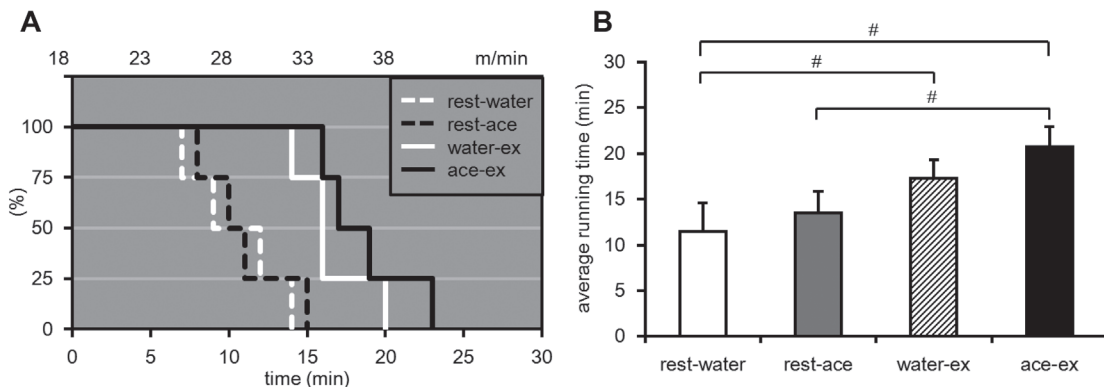


Fig. 4

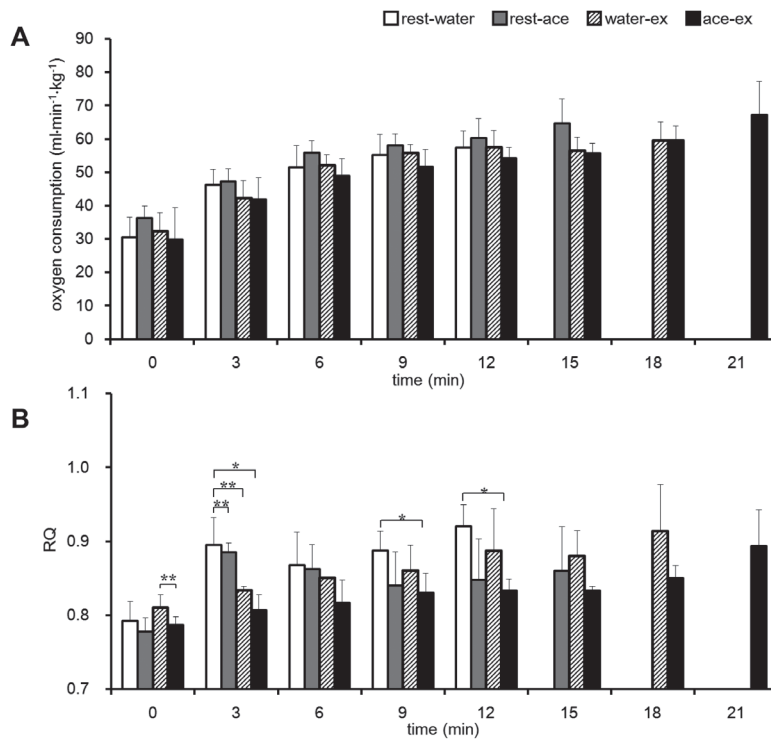


Fig. 5

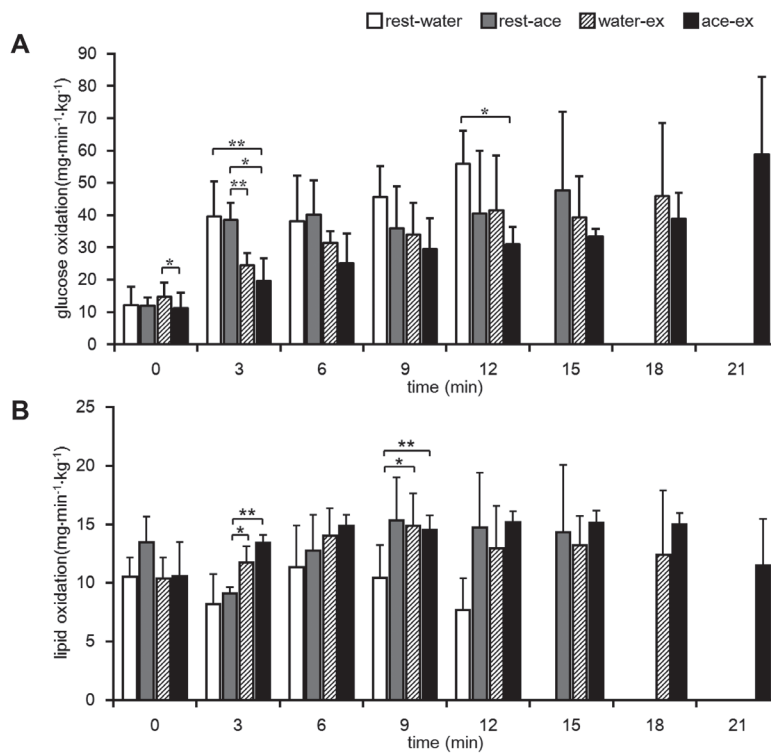


Fig. 6

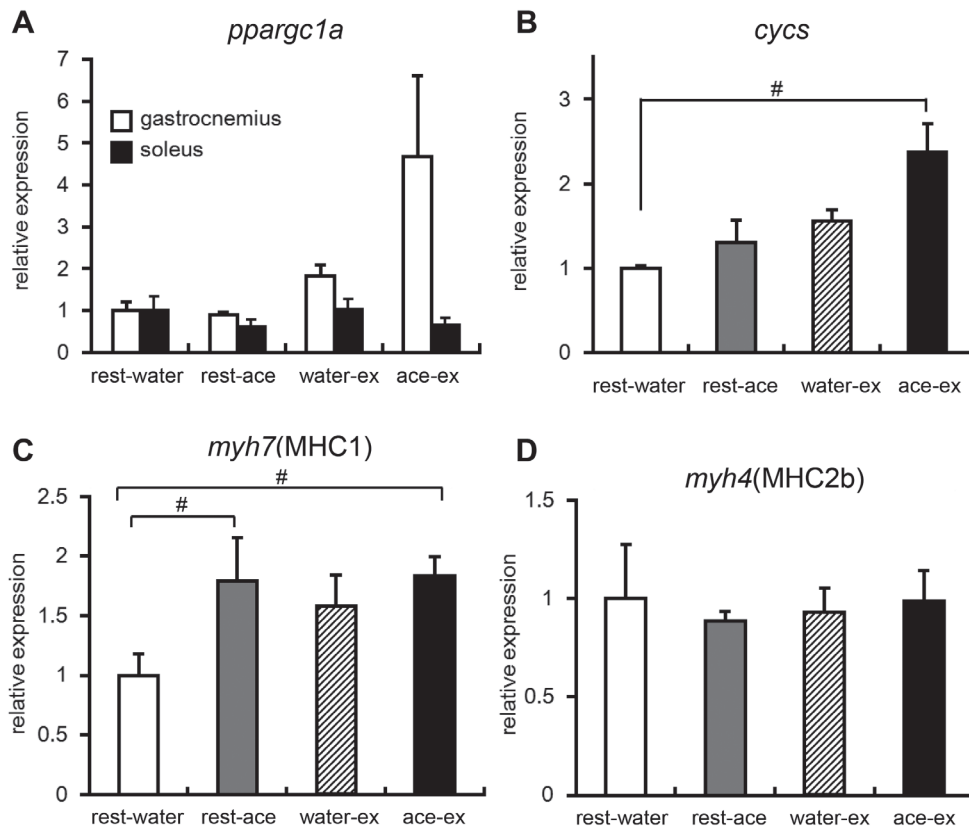


Fig. 7

to lipid metabolism in skeletal muscles, mRNA expressions of *ppargc1a*, *cycs*, *myh4*, and *myh7* which were related to metabolism and muscle fiber types were analyzed by quantitative real-time RT-PCR. Transcript of PGC-1 *a* was tended to be increased in gastrocnemius muscle of ace-ex groups, whereas it was not changed by the treatment of acetic acid or exercise in soleus muscle (Fig. 7A). Expressions of mRNA, *cycs*, *myh4*, and *myh7* genes in gastrocnemius muscle were analyzed. Expression of *cycs* was tended to be increased in rest-ace and water-ex groups, and it was significantly induced higher in ace-ex group as compared with that in rest-water group (Fig. 7B). MHC1 expression, which is expressed much in slow twitch oxidative fiber, was significantly increased in rest-ace and ace-ex groups (Fig. 7C). On the other hand, the expression of MHC2b, which is expressed in fast twitch muscle fiber, was not changed among 4 groups (Fig. 7D).

Discussion

In our previous study, we showed that chronic intake of acetic acid induced gene expressions of myoglobin and GLUT4 and also increased energy consumption in rats (2). Orally administered acetic acid was taken up from the intestine, absorbed by liver and skeletal muscles, and it increased AMP/ATP ratio in those cells (1, 2). An increase in the AMP/ATP ratio leads to the phosphorylation of AMPK. Treatment of acetic acid increased AMP/ATP ratio and promoted phosphorylation of AMPK in skeletal muscle of rats. Physical exercise is well known factor to increase AMP/ATP ratio and to activate AMPK (11, 12). In this study, we examined the effects of acetic acid and exercise training on the endurance performance and lipid metabolism of rats during exercise. Treatments of chronic intake of acetic acid and exercise training led to the reduction of abdominal fat content and result in lower weight gain. Energy consumption in rats

treated with exercise training (water-ex and ace-ex groups) were higher, while, those motor activities were lower than control group, suggesting that energy consumption that may be derived from increased basal energy metabolism was stimulated by exercise training. Endurance performance was promoted in exercise training groups. During endurance exercise, glucose utilization was lower and lipid utilization was higher in rats treated with exercise training groups than that of rest-water group. These data indicate that the treatment both of chronic intake of acetic acid and exercise training increases fat oxidation and decrease glucose oxidation during endurance exercise and it is promoted in fiber type switching to oxidative fiber in gastrocnemius muscle.

Exercise training induce muscle remodeling and mitochondrial proliferation in skeletal muscle, resulting fiber-type switch from glycolytic to oxidative fibers and enhancing lipid oxidative capacity (18-21). *Ppargc1a* expression is increased in muscle by an acute exercise or long-term exercise training (22-27). Increased *ppargc1a* expression in muscle showed an enhanced ability to exercise and improvement of peak oxygen uptake (21). Furthermore, AMPK is also activated by exercise, and activated AMPK phosphorylates PGC-1 α , then its downstream genes targets are upregulated (13). In this study we observed that skeletal muscle of rats treated with acetic acid and exercise training induced mRNA expression of cytochrome c gene and tended to increase PGC1- α gene as compared with rest-water group. Exercise-trained rats showed an increase of exercise capacity, additionally with acetic acid treatment, glucose oxidation was reduced, and lipid oxidation was promoted during exercise tolerance test. Those results indicate that treatments both of acetic acid and exercise training would contribute to enhancement of lipid metabolism and improvement of exercise capacity, which may be through the activation of AMPK and PGC1- α . These treatments have a potential to prevent life-style related diseases and increase life span.

Acknowledgement

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Figure legend

Figure 1, Total body weight gain.

Time course of body weight change of rats at 6 weeks of age administered distilled water (rest-water) or acetic acid (rest-ace) during resting period or administered distilled water (water-ex) or acetic acid (ace-ex) before exercise. Values are shown as arithmetic mean \pm SE of 3 rats of each group. n=3

Figure 2, Effect of acetic acid ingestion on total weight gain, total amount of food intake, food efficiency, and abdominal fat content.

Total body weight gain (A), total amount of food intake (B), food efficiency (C), and abdominal fat content (D) of rats administered water or acetic acid during rest period and before exercise. Values are shown as arithmetic mean \pm SE of 3 rats of each group. Statistical differences are shown as # $P < 0.05$, ## $P < 0.01$ by Tukey-Kramer's post hoc test. n=3

Figure 3, Effect of acetic acid ingestion on oxygen consumption, RQ, energy consumption, and spontaneous motor activity in the sedentary state.

Oxygen consumption and carbon dioxide production were monitored using on O₂/CO₂ metabolism measuring system for small animals in air tight chamber. The rats of energy consumption were calculated using energy consumption (kcal/day/kg)= light cycle (kcal/h/kg)*12 + dark cycle (kcal/h/kg)*12 (A), oxygen consumption, (B), RQ, (C), energy consumption, and (D), spontaneous motor activity of rats.

Values are shown as arithmetic mean \pm SE of 3 rats of each group. Statistical differences are shown as # $P < 0.05$, ## $P < 0.01$ by Tukey-Kramer's

post hoc test. n=3

Figure 4, Effect of acetic acid ingestion on exercise tolerance.

Rats were administered water or acetic acid daily (5 days a week) for 4 weeks and then they were exercised by forced running on a treadmill at 18 m/min. The speed increased by 1 m/min every 1 min until exhaustion. Exhaustion is defined as touching on the shocker more than 10 times for 1 min. Exercise tolerance is shown as a Kaplan-Meier survival curve (A). Average running duration is shown in panel B. Values are shown as arithmetic mean \pm SE of 4 rats of each group. Statistical differences are shown as # $P < 0.05$ by Tukey-Kramer's post hoc test.

Figure 5, Effect of acetic acid ingestion on the oxygen consumption and RQ during exercise tolerance test.

During exercise tolerance test, oxygen consumption and carbon dioxide production were monitored using on O_2/CO_2 metabolism measuring system for small animals in air tight chamber. (A), Oxygen consumption. (B), RQ. Values are shown as arithmetic mean \pm SE of 3-4 rats of each group. Statistical differences are shown as * $P < 0.05$ ** $P < 0.01$ vs rest-water by student t-test. rest-water n=4, rest-ace n=4, water-ex n=3, ace-ex n=3

Figure 6, Effect of acetic acid ingestion on glucose and lipid oxidation during exercise tolerance test.

Glucose (A) and lipid oxidation (B) during exercise tolerance test were calculated as described in "Materials and Methods". Values are shown as arithmetic mean \pm SE of 3-4 rats of each group. Statistical differences are shown as * $P < 0.05$ ** $P < 0.01$ vs rest-water by student t-test. rest-water n=4, rest-ace n=4, water-ex n=3, ace-ex n=3

Figure 7, Effect of chronic intake of acetic acid and exercise training on gene expressions in skeletal muscles.

Quantitative RT-PCR analysis was performed

using total RNA isolated from gastrocnemius and soleus muscle and of rats administered distilled water or acetic acid with sedentary or exercise training. (A), *ppargc1a* expression in gastrocnemius muscle and soleus muscle. (B-D), *cycs*, *myh7*, and *myh4* expressions in gastrocnemius muscle. Values are shown as arithmetic mean \pm SE of 3-5 rats of each group. Statistical differences are shown as # $P < 0.05$ by Tukey-Kramer's post hoc test.

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酢酸摂取と運動が脂肪代謝と運動耐久性に及ぼす影響

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要旨 これまで我々は、酢酸の摂取が骨格筋内のAMP活性化プロテインキナーゼ（AMPK）の活性化を介して脂質代謝と肥満、肥満に関連した2型糖尿病の予防に効果があることを示唆してきた。AMPKは運動によって骨格筋で活性化し、脂肪酸酸化を促進する。この研究は、4週間の継続的な酢酸摂取と運動トレーニングが運動中の脂肪代謝と運動耐久性に及ぼす影響について調べることを目的とした。

6週齢のSD系雄ラットを安静期に水を摂取するrest-water群、酢酸を摂取するrest-ace群、運動前に水を摂取するwater-ex群、運動前に酢酸を摂取するace-ex群に無作為に分け実験を行った。酢酸を継続的に摂取すると水摂取に比較して腹腔内脂肪量の減少と体重増加の抑制がみられた。また継続的な酢酸摂取および運動トレーニングにより、耐久性運動下でのグルコース利用の抑制および脂肪酸酸化の促進が見られた。酢酸摂取および運動トレーニング群の腓腹筋では、MHCIおよびcytochrome c等の遅筋線維マーカー遺伝子が増加していた。継続的な酢酸摂取と運動トレーニングにより、脂肪代謝と運動耐久性の向上が示唆された。

Keywords : 脂質代謝, AMPK, 運動, 酢酸, 骨格筋