Effects of Aerobic Exercise Combined with Panaxatriol Derived from Ginseng on Insulin Resistance and Skeletal Muscle Mass in Type 2 Diabetic Mice

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Summary Insulin resistance reduces insulin-induced muscle protein synthesis and accelerates muscle protein degradation. Ginseng ingestion has been reported to improve insulin resistance through the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway. We hypothesized that panaxatriol (PT) derived from ginseng in combination with aerobic exercise (EX) may further promote protein synthesis and suppress protein degradation, and subsequently maintain muscle mass through the amelioration of insulin resistance. KKAY insulin-resistant mice were divided into control, panaxatriol only (PT), exercise only (EX), and EX+PT groups. EX and EX+PT ran on the treadmill for 45 min at 15 m/min 5 d/wk for 6 wk. PT and EX+PT groups were fed a standard diet containing 0.2% PT for 6 wk. Homeostasis model assessment for insulin resistance (HOMA-R) values was significantly improved after exercise for 6 wk. Moreover, EX+PT mice showed improved HOMA-R as compared to EX mice. p70S6K phosphorylation after a 4 h fast was significantly higher in EX than in the non-exercise control, and it was higher in EX+PT mice than in EX mice. Atrogin1 mRNA expression was significantly lower in EX than in the non-exercise control, and was significantly lowered further by PT treatment. EX and EX+PT mice showed higher soleus muscle mass and cross-sectional area (CSA) of the soleus myofibers than control animals, with higher values noted for both parameters in EX+PT than in EX. These results suggest that aerobic exercise and PT ingestion may contribute to maintain skeletal muscle mass through the amelioration of insulin resistance.

Key Words skeletal muscle, aerobic exercise, insulin resistance, ginseng

Insulin is well known for its regulatory role in muscle glucose metabolism, but it is also involved in protein metabolism (1–3). Homeostasis model assessment resistance (HOMA-R), which is an index of insulin resistance, is inversely correlated with protein synthesis during hyperinsulinemic euglycemic clamp in humans (4). Thus, insulin resistance has been suggested to reduce insulin-induced protein synthesis. Moreover, insulin resistance has been shown to accelerate muscle protein degradation and muscle atrophy in db/db mice, which are insulin-resistant, and muscle protein degradation was inhibited by administration of rosiglitazone, an insulin-sensitizing agent (5). Lee et al. have reported that in insulin-resistant individuals, muscle mass loss with aging was greater than that in insulin-sensitive individuals in a longitudinal cohort study (6). These studies suggest that insulin resistance is one of the risk factors for muscle loss.

In a previous study, resistance exercise 3 d per week for 10 wk increased muscle mass in healthy subjects, whereas endurance exercise did not (7). Resistance exercise is well known to promote muscle protein synthesis and consequently, muscle hypertrophy (8, 9). In contrast, aerobic exercise has a more limited and short-lasting effect on protein synthesis (10–12). However, aerobic exercise has been shown to improve insulin resistance in animals and humans (13–15). Therefore, aerobic exercise might ameliorate insulin-induced muscle protein synthesis and inhibit muscle protein degradation, and thus prevent muscle atrophy in the insulin-resistant individual.

Insulin activates phosphoinositide 3-kinase (PI3K)/Akt signaling via the insulin receptor (IR) and insulin receptor substrate 1 (IRS-1) (3). Activation of Akt stimulates the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway and decreases the expression of the E3 ubiquitin ligases Atrogin1 and MuRF1 in skeletal muscle (16–18). mTORC1 is a key regulator of mRNA translation initiation and regulates muscle protein synthesis and subsequent muscle hypertrophy (19, 20). On the other hand, Atrogin1 and MuRF1 promote muscle protein degradation and subsequent muscle atrophy (21, 22). Thus, Akt is suggested to regulate both muscle protein synthesis and degradation, and its effects are suppressed by insulin resistance.

Ginseng has been reported to activate Akt signaling in skeletal muscle and to improve insulin sensitivity in insulin-resistant mice (23, 24). Therefore, ginseng might activate mTORC1 signaling and inhibit the ubiq-
uitin proteasome pathway via the activation of Akt signaling, thereby maintaining muscle mass in the insulin-resistant model. Saponins are one of the main active components of ginseng, and they have been shown to activate Akt signaling and improve insulin resistance (25–27). The branched-chain sugars of saponins are removed by intestinal bacterial enzymes and gastric acid, and the products upregulate biological activities (28–30). Panaxatriol (PT) results from the removal of all branched-chain sugars from saponins. Processed ginseng extract containing a high concentration of PT has been shown to improve insulin sensitivity and activate Akt signaling in insulin-resistant mice (31). Therefore, PT might be one of the components critical to ginseng-stimulated Akt signaling and improved insulin resistance in vivo.

As insulin resistance reduces insulin-induced muscle protein synthesis and accelerates muscle protein degradation, improving insulin resistance might aid in maintaining muscle mass in insulin-resistant individuals. Therefore, we hypothesized that aerobic exercise and/or PT may help maintain muscle mass by ameliorating insulin resistance. To test our hypothesis, we investigated the effects of aerobic exercise, PT supplementation, and aerobic exercise combined with PT supplementation for 6 wk on insulin resistance and muscle mass in insulin-resistant KK-Ay mice.

MATERIALS AND METHODS

Animals and diets. Five-week-old male KK-Ay/Ta Jcl (KKAy) mice were obtained from CLEA Japan, Inc. (Tokyo, Japan). The mice were housed individually in plastic cages and acclimatized in a room at 23 ± 2°C with a 12 : 12 light-dark cycle (07:00–19:00) and 40–70% humidity. Throughout the acclimation period, the mice were fed a standard diet (CE-2; CLEA Japan, Inc.). At 6 wk of age, the mice were divided into four groups matched equally for body weight and blood glucose levels. The non-exercised control and exercise (EX) groups were fed the standard diet. The panaxatriol-treated (PT) and exercise + PT (EX + PT) groups were fed a standard diet containing 0.2% PT. The mice were fed 5.5 g of food per day and tap water ad libitum. The animal care and experimental procedures were approved by the animal care committee of Lion Corporation (Odawara, Japan) (approval number: 2012-067). PT was purified from processed Panax notoginseng root containing a high concentration of dammarane-type triterpenes, as previously described (32).

Exercise protocol. The mice were trained on a rodent treadmill (Osaka Microsystems, Osaka, Japan) for 30 min/d at 5–12 m/min over a period of 5 d for accustomization to the treadmill. Then, the mice ran on the treadmill for 45 min/d, 5 d/wk for 6 wk at 15 m/min without incline. A preliminary test revealed that this exercise condition is below the lactate threshold.

Measurement of blood glucose, plasma insulin, triglyceride, and nonesterified fatty acid (NEFA), and tissue weights, and homeostasis model assessment for insulin resistance (HOMA-R). Blood glucose was measured from the tail vein with a glucose meter (Johnson & Johnson, Los Angeles, CA) at days 0, 10, 17, 31, and 38 under non-anesthesia and non-fasting. On day 42, 24 h after the last bout of exercise, the animals were euthanized by blood collection from the inferior vena cava under isoflurane anesthesia after 4 h of fasting, and the gastrocnemius, soleus, extensor digitorum longus, epididymal fat, and liver were immediately removed. After being weighed, the tissues were rapidly frozen in liquid nitrogen and stored at −80°C until analysis. Plasma insulin levels were measured using an ELISA kit (Morinaga Institute of Biochemical Science, Yokohama, Japan), according to the manufacturer’s protocol. HOMA-R was calculated using the equation: HOMA-R = fasting glucose (mg/dL) × fasting insulin (μU/mL) / 405 (33). Triglyceride and NEFA were measured using the Triglyceride E-test and NEFA C-test, respectively (Wako Pure Chemical Industries, Ltd., Osaka, Japan), according to the manufacturer’s protocols.

Histological analysis of skeletal muscle. The soleus muscle was fixed in 4% paraformaldehyde, embedded in paraffin, and subjected to standard hematoxylin and eosin (H&E) staining (34). The cross-sectional area (CSA) of the myofibers was calculated from 200 myofibers/animal using ImageJ software version 1.47 (National Institutes of Health, Bethesda, MD).

Western blotting. Western blotting was performed as previously described (35), with minor modifications. Total protein was extracted using the NucleoSpin RNA/Protein kit (Takara, Shiga, Japan) according to the manufacturer’s instructions. Proteins were separated on 4–12% sodium dodecyl sulfate-polyacrylamide gradient gels by electrophoresis and then transferred to polyvinylidene difluoride membranes (Millipore, Billerica, MA). The membranes were blocked with blocking buffer (5% skim milk in Tris-buffered saline and 0.1% Tween-20 [TBST]) for 1 h at 23°C. The membranes were then incubated overnight at 4°C with primary antibodies against phosho-Akt Ser473 (cat. no. 9271), Akt (cat. no. 9272), IR (cat. no. 3025), IRS-1 (cat. no. 3407), phospho-p70S6K (cat. no. 9205), p70S6K (cat. no. 2708), phospho-4E-BP1 (cat. no. 2215), rpS6 (cat. no. 2217) and GAPDH (cat. no. 5174) (Cell Signaling Technology, Beverly, MA). The membranes were washed with TBST and incubated for 1 h at 23°C with appropriate secondary antibodies against anti-rabbit IgG (Cell Signaling Technology). Proteins were detected using an enhanced chemiluminescence system (GE Healthcare, Harrisburg, PA, or Merck Millipore, Darmstadt, Germany) and analyzed by densitometry with a chemiluminescence system (GE Healthcare). The results of the Western blot were normalized to GAPDH, which was used as the control protein. Band intensities were quantified using ImageJ.

RNA isolation and quantitative reverse transcription PCR (qRT-PCR) analysis. Total RNA was extracted from the soleus muscle using the NucleoSpin RNA/Protein kit. The RNA concentration was measured using a NanoDrop ND-1000 spectrophotometer (Thermo Scientific, Waltham, MA). RNA (200 ng) was reverse transcribed
to cDNA with a PrimeScript RT reagent kit (Takara), according to the manufacturer’s instructions. Quantitative gene expression was studied on an ABI 7300 Real-Time PCR System (Applied Biosystems, Foster City, CA) with SYBR Green dye (Applied Biosystems) using the following cycle parameters: 95°C for 30 s and 45 cycles at 95°C for 5 s, 60°C for 30 s, and 65°C for 5 s, and 65–95°C with a heating rate of 0.5°C per second. The primer sequences were 5’-GCAGAGAGTCCGGAAGTC-3’ (forward) and 5’-CAGGTCGGTGATCGTGAG-3’ (reverse) for

Table 1. Plasma parameters.

<table>
<thead>
<tr>
<th></th>
<th>Non-exercise</th>
<th>Exercise</th>
<th>Statistical effects of treatments</th>
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<tr>
<td></td>
<td>Control PT EX EX+PT</td>
<td>PT EX Interaction</td>
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<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>282.0±12.9 270.3±10.5</td>
<td>267.1±6.8 230.0±11.8**</td>
<td>p&lt;0.05 p&lt;0.01 NS</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>64.3±18.2 61.5±12.2</td>
<td>28.4±5.3* 17.5±3.8*</td>
<td>NS p&lt;0.01 NS</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>42.9±11.1 42.1±9.5</td>
<td>18.9±3.8* 10.3±2.5*</td>
<td>NS p&lt;0.01 NS</td>
</tr>
<tr>
<td>NEFA (meq/L)</td>
<td>0.90±0.08 0.99±0.08</td>
<td>0.76±0.09 0.91±0.08</td>
<td>NS NS NS</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>221.5±27.9 215.5±21.1</td>
<td>125.2±11.6** 110.2±16.0**</td>
<td>p&lt;0.01 NS</td>
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Values are presented as means±standard errors (n=7–9). The main effects of PT supplementation and exercise, and their interactions were analyzed by two-way ANOVA. Post-hoc analyses were conducted using t-tests with the Benjamini and Hochberg false discovery rate correction for multiple comparisons. *p<0.05, **p<0.01 vs. Control; †p<0.05 vs. EX. EX, exercise; PT, panaxatriol.

Table 2. Tissue weights.

<table>
<thead>
<tr>
<th></th>
<th>Non-exercise</th>
<th>Exercise</th>
<th>Statistical effects of treatments</th>
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<tr>
<td></td>
<td>Control PT EX EX+PT</td>
<td>PT EX Interaction</td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius (mg)</td>
<td>271.4±5.8 279.7±4.5</td>
<td>289.4±5.9 295.1±6.9</td>
<td>NS p&lt;0.01 NS</td>
</tr>
<tr>
<td>Soleus (mg)</td>
<td>13.8±0.7 14.1±0.7</td>
<td>15.3±0.3* 16.3±0.4*</td>
<td>NS p&lt;0.01 NS</td>
</tr>
<tr>
<td>Extensor digitorum longus (mg)</td>
<td>16.8±0.6 17.8±0.7</td>
<td>18.5±0.4 18.7±0.4</td>
<td>NS p&lt;0.01 NS</td>
</tr>
<tr>
<td>Epidymal fat (g)</td>
<td>1.36±0.07 1.37±0.10</td>
<td>1.20±0.07 1.14±0.05</td>
<td>NS NS NS</td>
</tr>
<tr>
<td>Liver (g)</td>
<td>2.31±0.03 2.22±0.05</td>
<td>2.12±0.05** 2.11±0.05**</td>
<td>NS p&lt;0.01 NS</td>
</tr>
</tbody>
</table>

Values are presented as means±standard errors (n=7–9). The main effect of PT supplementation and exercise, and their interactions were analyzed by two-way ANOVA. Post-hoc analyses were conducted using t-tests with the Benjamini and Hochberg false discovery rate correction for multiple comparisons. *p<0.05, **p<0.01 vs. Control; †p<0.05 vs. EX. EX, exercise; PT, panaxatriol.
Atrogin1, 5′-GACTCTGCAGAGTGACCAAG-3′ (forward) and 5′-CTTCTACAATGCTCTTGATGAGC-3′ (reverse) for MuRF1, and 5′-TTGGGCGCCTGGTCACCAGGGC-3′ (forward) and 5′-GTTGTCATGGATGACCTGGGCCAGG-3′ (reverse) for GAPDH. All experiments were performed in duplicate. Gene expression was calculated using the 2^ΔΔCT method (36) and was normalized to that in the control group. The reference gene was GAPDH.

Statistical analysis. All values are expressed as means±standard errors. Repeated measures multivariate analysis of variance (MANOVA: group×time) was used to compare the differences in blood glucose level and body weight. Two-way ANOVA (exercise×PT treatment) was performed to evaluate changes in plasma parameters, tissue weight, CSA, protein and gene expression. Post-hoc analyses were conducted using t-tests with the Benjamini and Hochberg false discovery rate correction for multiple comparisons when a significant main effect and/or interaction was observed. Relationships between HOMA-R and p70S6K phosphorylation or Atrogin1 expression were determined using Spearman correlation coefficients. Statistical analyses were performed using the JMP software version 11 (SAS Institute, Cary, NC). A p-value<0.05 was considered to indicate a significant difference.

RESULTS

Blood glucose and body weight

In the EX group, blood glucose was significantly lower than in the control group from days 17 to 38 of exercise (p<0.05) (Fig. 1A). In the EX+PT group, blood glucose was significantly lower than in the control group from days 10 to 38 of exercise (p<0.001). Moreover, the blood glucose in the EX+PT group was significantly lower than that in the EX group as of day 17 (p<0.05). The blood glucose in the PT group was sig-
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Significantly lower than that in the control group as of day 10 (p<0.05). There were no significant differences in body weight among the groups during the study period (Fig. 1B).

Plasma parameters and tissue weight

Plasma parameters and HOMA-R were determined in all treatment groups after 6 wk of exercise; the results are shown in Table 1. The main effects of both PT supplementation (p<0.05) and exercise (p<0.01) were statistically significant for fasting blood glucose. A significant interaction between these two factors was not found. Fasting blood glucose in the EX+PT group was significantly lower than that in the EX group (p<0.01). There were significant effects of exercise on plasma insulin, triglyceride and HOMA-R (p<0.01). Moreover, HOMA-R was significantly lower in the EX+PT than in the EX group (p<0.05). There were no significant differences in plasma NEFA among the groups during the study period.

Tissues were weighed for all treatment groups after 6 wk of exercise; the results are shown in Table 2. The weights of the gastrocnemius muscle, soleus muscle, and extensor digitorum longus were significantly higher after exercise (p<0.01). Moreover, the soleus muscle weighed significantly more in the EX+PT group than in the EX group (p<0.05). The epididymal fat (p<0.05) and liver weights (p<0.01) were significantly lower upon exercise.

Myofiber CSA in soleus muscle

Figure 2A shows representative images of HE-stained
cross sections of the soleus muscle for each treatment group after 6 wk of exercise. The main effects of both PT supplementation ($p<0.05$) and exercise ($p<0.01$) were statistically significant for CSA (Fig. 2B). Moreover, there was a significant interaction between PT supplementation and exercise ($p<0.05$). CSA was significantly higher in the EX + PT group than in the EX group ($p<0.05$).

**Signaling pathways**

To elucidate the molecular mechanism of PT and aerobic exercise on improving insulin resistance, we evaluated the effects of PT and exercise on the expression of IR, IRS-1 and Akt phosphorylation with Western blot analysis after 6 wk of treatment. The main effects of both PT supplementation ($p<0.05$) and exercise ($p<0.01$) were statistically significant for Akt phosphorylation and IR expression (Fig. 3A and 3C). A significant interaction between these two factors was not found. Akt phosphorylation was significantly higher in the EX + PT group than in the EX group ($p<0.05$). There were no significant differences in total Akt among the groups after the treatment period (Fig. 3B). The expression of IRS-1 was significantly higher after exercise ($p<0.01$) (Fig. 3D).

$p70S6K$ and rpS6 are components of the downstream mTORC1 effector. The main effects of both PT supplementation ($p<0.05$) and exercise ($p<0.01$) were statistically significant for Akt phosphorylation and IR expression (Fig. 3A and 3C). A significant interaction between these two factors was not found. Akt phosphorylation was significantly higher in the EX + PT group than in the EX group ($p<0.05$). There were no significant differences in total Akt among the groups after the treatment period (Fig. 3B). The expression of IRS-1 was significantly higher after exercise ($p<0.01$) (Fig. 3D).
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statistically significant for p70S6K phosphorylation and total p70S6K expression (Fig. 4A and 4B). A significant interaction between these two factors was not found. p70S6K phosphorylation was significantly higher in the EX+PT group than in the EX group (p<0.05). Although the phosphorylation of rpS6 was significantly higher in the EX+PT group than in the Con group (p<0.05), the expression of total rpS6 was not significantly different (Fig. 4C and 4D).

**mRNA expression of Atrogin1 and MuRF1**

mRNA expression levels of the Akt-regulated genes Atrogin1 and MuRF1 as markers of proteolysis after 6 wk of treatment were assessed by qRT-PCR. Both PT supplementation (p<0.05) and exercise (p<0.01) had a statistically significant effect on mRNA expression of Atrogin1 and MuRF1 (Fig. 5A and 5B). A significant interaction between these two factors was not found. Atrogin1 mRNA expression was significantly lower in the EX+PT group than in the EX group (p<0.05). Correlation between HOMA-R and p70S6K phosphorylation or Atrogin1 mRNA expression

p70S6K phosphorylation had a significant inverse correlation with HOMA-R (r = -0.52, p = 0.0030) (Fig. 6A). On the other hand, the mRNA expression level of Atrogin1 was significantly positively correlated with HOMA-R (r = 0.49, p = 0.0056) (Fig. 6B).

**DISCUSSION**

In the present study, we investigated the effects of aerobic exercise, PT supplementation, and aerobic exercise combined with PT supplementation on insulin sensitivity and skeletal muscle mass in the insulin-resistant KKAy mouse model. Aerobic exercise for 6 wk improved HOMA-R, and the effect was enhanced by cotreatment with PT for 6 wk. Soleus muscle CSA and muscle mass were significantly higher than those in the non-exercised controls after 6 wk of exercise, and PT treatment had an enhancing effect. Thus, PT supplementation combined with aerobic exercise was the most effective in improving insulin sensitivity and preventing muscle atrophy associated with insulin resistance.

Insulin is well known to be involved in protein metabolism (1, 2), and HOMA-R is inversely correlated with protein synthesis during hyperinsulinemic euglycemic clamp in humans (4). Therefore, insulin resistance has been suggested to blunt insulin-induced protein synthesis. Moreover, insulin resistance facilitates muscle protein degradation, which leads to muscle atrophy in db/db mice (5). These findings suggest that insulin resistance promotes muscle atrophy by inhibiting pro-
tein synthesis and accelerating protein degradation. In the present study, we found that aerobic exercise for 6 wk improved insulin resistance and resulted in higher soleus muscle CSA and muscle mass than in the non-exercised controls in insulin-resistant KK/Ay mice. Previous studies reported that aerobic exercise does not affect muscle mass in healthy subjects or rodents (7, 37, 38). However, in insulin-resistant rats, a previous study has reported that treadmill running for 5 d per week for 6 wk significantly improved insulin resistance and muscle mass as compared with the non-exercised controls (39). The present findings are consistent with those of the previous study, and aerobic exercise is suggested to maintain muscle mass by regulating the net muscle protein balance through improvement of insulin resistance. Interestingly, aerobic exercise combined with PT supplementation further improved HOMA-R, concomitant with higher soleus muscle CSA and mass than in controls (39). The present findings are consistent with previous studies and the present study. One of the reasons for this discrepancy might be the difference in fasting time before sacrifice between previous studies and the present study. Previous studies adopted a fasting time of 12–16 h (10, 46, 47), whereas the present study adopted a time of 4 h. Activation of p70S6K by nutrition intake has been reported to be maintained for 4 h (48, 49). Therefore, activation of p70S6K in the present study may have reflected nutrition intake rather than aerobic exercise. p70S6K phosphorylation had a significant inverse correlation with HOMA-R in the present study. As p70S6K is activated by insulin (50), PT supplementation and aerobic exercise improved insulin resistance, and are suggested to increase insulin-induced p70S6K activation. p70S6K is implicated as the principal mediator of muscle protein synthesis (19). Therefore, activation of p70S6K by aerobic exercise and PT supplementation for 6 wk might be involved in marked increase of soleus muscle mass and CSA in the present study.

Aerobic exercise for 6 wk significantly increased the expression of total p70S6K in the soleus muscle of KK/Ay mice in the present study. A previous study has reported that resistance exercise performed every other day for 24 d significantly increased skeletal muscle mass concomitantly with an augmented expression of total p70S6K in skeletal muscle of rodents (45). Therefore, in the present study, the increased expression of total p70S6K might have enhanced the p70S6K activation and muscle protein anabolism in response to nutritional intake and/or exercise. Similarly, aerobic exercise and PT supplementation for 6 wk significantly increased the expression of IR and IRS-1 in the present study, which might have contributed to the insulin-induced muscle protein synthesis after nutritional intake.

Atrogin1, a ubiquitin E3 ligase, promotes the degradation of muscle proteins. Its expression is decreased by the activation of insulin signaling pathway and facilitated by the increase in the protein expression of tumor necrosis factor-α (TNF-α) in skeletal muscle (51–53). KK/Ay mice have been reported to show decreased proteins level of insulin signaling pathway and increased mRNA expression of TNF-α in skeletal muscle (54–56). Therefore, it was suggested that KK/Ay mice might upregulate the expression of Atrogin1 in skeletal muscle. In the present study, Atrogin1 expression was decreased and significantly correlated with HOMA-R after aerobic exercise and PT supplementation. As Atrogin1 expression is known to be inhibited by insulin (53), PT supplementation and aerobic exercise improved insulin resistance, and thereby decreased Atrogin1 expression. Atrogin1 facilitates the degradation of muscle proteins (21, 22). Therefore, the reduction of Atrogin1 expression by aerobic exercise and PT supplementation for 6 wk might be related to the maintenance of soleus muscle mass and CSA in the present study.

One limitation of our study is that no non-insulin-resistant control was included. The KK/Ay mouse was generated by introducing the obesity gene Ay into the KK mouse and it is considered a suitable polygenic model for insulin resistance (57, 58); however, no non-insulin-resistant control of the same strain is available. Thus, we could not evaluate the effects of aerobic exercise or PT supplementation on muscle mass or CSA in
non-insulin-resistant mice.

Long-term aerobic exercise improves insulin resistance and soleus muscle mass in insulin-resistant mice, likely by preventing the muscle atrophy associated with insulin resistance. PT ingestion augments the positive effects of aerobic training on insulin resistance and maintenance of soleus muscle mass in insulin-resistant mice. These results suggest that PT may be a novel nutritional supplement for augmenting aerobic exercise-induced insulin sensitivity and for preventing the loss of muscle mass in individuals with insulin resistance.

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REFERENCES


