Interactions of exercise training and lipoic acid on skeletal muscle glucose transport in obese Zucker rats

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Saengsirisuan, Vitoon, Tyson R. Kinnick, Melanie B. Schmit, and Erik J. Henriksen. Interactions of exercise training and lipoic acid on skeletal muscle glucose transport in obese Zucker rats. J Appl Physiol 91: 145–153, 2001.—Exercise training (ET) or the antioxidant R(+)α-lipoic acid (R-ALA) individually increases insulin action in the insulin-resistant obese Zucker rat. The purpose of the present study was to determine the interactions of ET and R-ALA on insulin action and oxidative stress in skeletal muscle of the obese Zucker rat. Animals either remained sedentary, received R-ALA (30 mg·kg·body wt ·day−1), performed ET (treadmill running), or underwent both R-ALA treatment and ET for 6 wk. During an oral glucose tolerance test, ET alone or in combination with R-ALA resulted in a significant lowering of the glucose (26–32%) and insulin (29–30%) responses compared with sedentary controls. R-ALA alone decreased (19%) the glucose-insulin index (indicative of increased insulin sensitivity), and this parameter was reduced (48–52%) to the greatest extent in the ET and combined treatment groups. ET or R-ALA individually increased insulin-mediated glucose transport activity in isolated epitrochlearis (44–48%) and soleus (37–57%) muscles. The greatest increases in insulin action in these muscles (80 and 99%, respectively) were observed in the combined treatment group. Whereas the improvement in insulin-mediated glucose transport in soleus due to R-ALA was associated with decreased protein carbonyl levels (an index of oxidative stress), improvement because of ET was associated with decreased protein carboxyls as well as enhanced GLUT-4 protein. However, there was no interactive effect of ET and R-ALA on GLUT-4 protein or protein carbonyl levels. These results indicate that ET and R-ALA interact in an additive fashion to improve insulin action in insulin-resistant skeletal muscle. Because the further improvement in muscle glucose transport in the combined group was not associated with additional upregulation of GLUT-4 protein or a further reduction in oxidative stress, the mechanism for this interaction must be due to additional, as yet unidentified, factors.

THE INSULIN RESISTANCE SYNDROME (11), or syndrome X (32), is a multifaceted condition characterized by the clustering of a number of atherogenic risk factors, including essential hypertension, glucose intolerance, insulin resistance of skeletal muscle glucose metabolism, hyperinsulinemia, dyslipidemia, and central obesity. The etiology of this condition is associated with the initial development of insulin resistance and reactive hyperinsulinemia, and individuals with this condition are at a markedly elevated risk of cardiovascular disease (32). The obese Zucker (fa/fa) rat is a well-defined animal model for studying the insulin resistance syndrome, as it exhibits severe skeletal muscle insulin resistance (6, 19, 22) attributable to defects in insulin signaling (1) and GLUT-4 glucose transporter protein translocation (6, 14, 28).

One effective intervention for ameliorating the insulin resistance of skeletal muscle glucose transport and the compensatory hyperinsulinemia in the obese Zucker rat is exercise training. Moderate- and high-intensity exercise training by the obese Zucker rat is associated with improvements in glucose tolerance (3, 9, 37), primarily due to enhanced skeletal muscle glucose transport activity (9, 13, 21, 37). Increased insulin action on the glucose transport process after exercise training by the obese Zucker rat likely develops because of the upregulation of GLUT-4 protein expression (2, 7, 13, 37) and enhanced insulin-stimulated GLUT-4 protein translocation to the sarcolemma (13).

Increasing evidence indicates that insulin resistance may be associated with increased oxidative stress and that antioxidant therapy may be beneficial (reviewed in Refs. 8 and 17). α-Lipoic acid (ALA, also known as thiotic acid) is a water-soluble biological antioxidant (30) that can modulate glucose metabolism in insulin-sensitive cells and tissues (17). ALA enhances glucose transport into L6 myocytes (12), isolated rat diaphragm (16), perfused rat heart preparations (39), and isolated rat skeletal muscle (20). Moreover, when administered in vivo, ALA reduces blood glucose in hyperglycemic streptozotocin-diabetic rats (27), improves glucose tolerance and skeletal muscle glucose transport in the obese Zucker rat (27, 31, 38), and enhances glucose tolerance and peripheral insulin-stimulated glucose disposal in Type 2 diabetic patients (23–25, 29). Importantly, Streeper et al. (38) demonstrated
that the beneficial metabolic effects of ALA in conditions of insulin resistance are stereospecific, with the \( R^+ \)-enantiomer being more effective than the \( S^- \)-enantiomer, consistent with in vitro findings (12).

Whereas it is clear that both endurance exercise training and ALA treatment individually are effective interventions for improving insulin action in insulin-resistant skeletal muscle, at present there is no information regarding how these two interventions might interact to modulate insulin action in the obese Zucker rat when used in combination. In this context, the purpose of the present study was to test the hypothesis that endurance exercise training and chronic treatment with the \( R^+ \)-enantiomer of ALA (R-ALA) in combination could improve insulin action in the obese Zucker rat to a greater extent than either intervention used individually. Specifically, obese Zucker rats underwent 6 wk of exercise training and 6 wk of parenteral administration of R-ALA individually and in combination, and glucose tolerance, insulin-stimulated glucose transport, muscle GLUT-4 protein level, and tissue protein carbonyl level [a marker of oxidative stress (10, 33)] were determined. The investigation of these interactions could be especially important in the context of designing interventions that substantially improve insulin action in insulin-resistant states.

**METHODS**

**Animals and treatments.** Female obese Zucker rats (Hsd/Ola:ZUCKER-fa, Harlan, Indianapolis, IN) were received at 5–6 wk of age, weighing 150–160 g. The animals were housed in a temperature-controlled room (20–22°C) at the Central Animal Facility of the University of Arizona. A reversed 12:12-h light-dark cycle (lights on 1900–0700) was maintained so that training occurred during the dark cycle when they are most active. Animals had free access to water and chow (Purina, St. Louis, MO). All procedures were approved by the University of Arizona Animal Use and Care Committee.

The rats were randomly assigned to one of four groups: a sedentary, vehicle-treated control group; an R-ALA-treated group; an exercise-trained group; or a combined R-ALA-treated and exercise-trained group. Animals in the R-ALA-treated groups received 30 mg/kg body wt of purified R-ALA (ASTA Medica, Frankfurt, Germany) dissolved in 0.5 ml of 0.5 N NaOH. After the muscles were dissolved in 0.5 ml of 0.5 N NaOH, they were reweighed. One piece of the epitrochlearis muscles was divided into two strips (25 mg) and incubated in the absence of insulin, and the contralateral epitrochlearis muscles were dissected and prepared for in vitro incubation. Whereas the epitrochlearis muscles were incubated intact, the soleus muscle was prepared into two strips (~25 mg) and incubated. Muscles were incubated in the mounted state. Each muscle was incubated for 1 h at 37°C in 3 ml of oxygenated (95% \( O_2 \)-5% \( CO_2 \)) Krebs-Henseleit buffer (KHB) supplemented with 8 mM glucose, 32 mM mannitol, and 0.1% BSA (radioimmunoassay grade, Sigma Chemical). One epitrochlearis muscle and one soleus strip were incubated in the absence of insulin, and the contralateral epitrochlearis muscle and second soleus strip were incubated in the presence of a maximally effective concentration of insulin (2 mU/ml; Humulin R, Eli Lilly, Indianapolis, IN).

After this initial incubation period, the muscles were rinsed for 10 min at 37°C in 3 ml of oxygenated \( (95% \ O_2-5% \ CO_2) \) Krebs-Henseleit buffer (KHB) supplemented with 8 mM glucose, 32 mM mannitol, and 0.1% BSA (radioimmunoassay grade, Sigma Chemical). One epitrochlearis muscle and one soleus strip were incubated in the absence of insulin, and the contralateral epitrochlearis muscle and second soleus strip were incubated in the presence of a maximally effective concentration of insulin (2 mU/ml; Humulin R, Eli Lilly, Indianapolis, IN).

After this initial incubation period, the muscles were rinsed for 10 min at 37°C in 3 ml of oxygenated KHB containing 40 mM mannitol, 0.1% BSA, and insulin, if previously present. Thereafter, the muscles were transferred to 2 ml of KHB containing 1 mM \( 2-[1,2,3]H \)-deoxyglucose (2-DG, 300 mCi/mmole; Sigma Chemical), 39 mM \( [U-14C] \)-mannitol (0.8 mCi/mmole; ICN Radiochemicals, Irvine, CA), 0.1% BSA, and insulin, if previously present. At the end of this final 20-min incubation period at 37°C, the muscles were removed, trimmed of excess fat and connective tissue, quickly frozen, and weighed. The epitrochlearis muscles were divided into two pieces, which were individually weighed. One piece from each epitrochlearis muscle and the entire soleus strip were dissolved in 0.5 ml of 0.5 N NaOH. After the muscles were dissolved, the radioactivity was measured by liquid scintillation counting in a Beckman LS 1800 liquid scintillation spectrometer.
These protein contents were typically in the range of 0.3–0.5 g/g, and the absorbance at 280 nm using a BSA standard curve. The protein content of the final samples was quantified by reading absorbance at 280 nm using a BSA standard curve.

Proteins were then reacted with 10 mM 2,4-dinitrophenylhydrazine, and an absorption coefficient of 22,000 M⁻¹ cm⁻¹ was used for subsequent determination of these same variables as described previously (18). The remaining two pieces of epitrochlearis were pooled, reweighed, and homogenized in 40 vol% of ice-cold 20 mM HEPES (pH 7.4) containing 1 mM EDTA and 250 mM sucrose. These homogenates were used for determination of total protein content by using the bicinchoninic acid method (Sigma Chemical), GLUT-4 protein level (18), total hexokinase activity (40), and citrate synthase activity (36). In addition, the contralateral soleus and plantaris muscles, liver, and heart were removed, trimmed of fat and connective tissue, quickly frozen in liquid nitrogen, and used for measurement of protein carbonyl levels using the method of Reznick and Packer (33). Briefly, pieces of frozen tissue (50–90 mg) were gently homogenized in 1.5 ml of a 50 mM phosphate buffer (pH 7.4) containing 0.1% digitonin, 1 mM EDTA, and protease inhibitors (40 μg/ml phenylmethylsulfonyl fluoride, 5 μg/ml leupeptin, 7 μg/ml pepstatin, and 5 μg/ml apronin). If needed, nucleic acids were removed with 1% streptomycin sulfate, and extracted soluble proteins were then reacted with 10 mM 2,4-dinitrophenylhydrazine (DNPH) in 2.5 M HCl for 1 h at room temperature. Proteins were precipitated with 10% TCA, and protein pellets were washed with ethanol-ethyl acetate (1:1, vol/vol) to remove free DNPH and lipid contaminants. Final precipitates were dissolved in 6 M guanidine HCl and incubated at 37°C for 10 min. The carbonyl contents of these samples were then measured using a spectrophotometric assay at 370 nm and an absorption coefficient of 22,000 M⁻¹ cm⁻¹ (33). The protein content of the final samples was quantified by reading the absorbance at 280 nm using a BSA standard curve. These protein contents were typically in the range of 0.3–0.5 g/g. In our hands, this assay had a coefficient of variance of 11%.

### Table 1. Effects of exercise training and R-ALA treatment on final body weights and heart and skeletal muscle wet weights in the obese Zucker rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight, g</th>
<th>Heart Wet Weight, mg</th>
<th>Heart Wet Weight-To-Body Weight Ratio, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>377 ± 9</td>
<td>752 ± 12</td>
<td>2.00 ± 0.05</td>
</tr>
<tr>
<td>Lipoic acid treated</td>
<td>368 ± 6</td>
<td>810 ± 19</td>
<td>2.20 ± 0.05*</td>
</tr>
<tr>
<td>Exercise trained</td>
<td>350 ± 5*</td>
<td>826 ± 36</td>
<td>2.37 ± 0.12*</td>
</tr>
<tr>
<td>Combined</td>
<td>348 ± 7*</td>
<td>864 ± 19</td>
<td>2.48 ± 0.01†</td>
</tr>
</tbody>
</table>

Values are means ± SE for 4–9 animals/group. R-ALA, R(+)-α-lipoic acid. *Significantly different from the sedentary control group; †significantly different from the α-lipoic acid (ALA)-treated group; \( P < 0.05 \).

### Results

**Body weights, heart weight, and \( V_{O_2 \text{peak}} \).** The exercise-trained and combined treatment groups had slightly lower (7–8%, \( P < 0.05 \)) final body weights compared with the sedentary group (Table 1). There were no substantive differences among the various groups for the wet weights of the epitrochlearis, soleus, and plantaris muscles (data not shown). Compared with the sedentary control group, R-ALA treatment alone, exercise training alone, or the two interventions in combination resulted in significant increases in absolute heart weight as well as in the heart wet weight-to-body weight ratio. The heart wet-to-body weight ratio of the combined treatment group was also significantly greater than that of the R-ALA treatment alone (Table 1).

**OGTT responses.** The glucose and insulin responses during the OGTT in the experimental groups are shown in Fig. 1. Compared with the sedentary group, R-ALA treatment resulted in a lowering of the glucose response, although only the difference at 15 min (12%) achieved statistical significance. Exercise training alone or in combination with R-ALA treatment caused significant decreases in the glucose (20–35%) and insulin responses (28–31%), whereas R-ALA treatment alone lowered only plasma FFA (29%) relative to the sedentary group.

**Plasma glucose, insulin, and FFA.** The fasting plasma levels of glucose, insulin, and FFA in the various groups are shown in Table 2. Exercise training alone was associated with a 12% lower glucose level compared with the sedentary group. Exercise training alone or in combination with R-ALA treatment significantly lowered both plasma insulin (23–24%) and FFA (28–31%), whereas R-ALA treatment alone lowered only plasma FFA (29%) relative to the sedentary group.
sulin (23–40%) responses at all time points during the test.

Figure 2 shows the total areas under the curves (AUC) for these glucose and insulin responses as well as the glucose-insulin index. This latter variable is defined as the product of the glucose AUC and insulin AUC, with a reduction in this value reflecting an increase in whole body insulin sensitivity (9). Whereas the reductions in the glucose AUC and insulin AUC in the R-ALA-treated group did not reach statistical significance, exercise training alone or in combination with R-ALA treatment resulted in a significant lowering of the glucose AUC (26–32%) and insulin AUC (29–30%) compared with the sedentary group. The glucose-insulin index was significantly reduced (19%) as a result of the chronic R-ALA. This parameter was reduced to the greatest extent in the groups that underwent exercise training alone and exercise training combined with ALA treatment compared with either the sedentary group (48–52%) or the R-ALA-treated group (36–40%).

Muscle glucose transport. To assess whether these alterations in whole body glucose disposal were associated with changes in the skeletal muscle glucose transport system, basal and insulin-stimulated 2-DG uptake in isolated epitrochlearis and soleus muscles were determined (Fig. 3). Basal 2-DG uptake in either muscle type was not different among the experimental groups. In the epitrochlearis, both the rate of insulin-stimulated 2-DG uptake (Fig. 3A) and the insulin-mediated 2-DG uptake (increase over basal; Fig. 3B) were enhanced by R-ALA treatment (27 and 45%) and exercise training alone (22 and 48%) and to the greatest extent in the group that completed exercise training combined with R-ALA treatment (40 and 80%). In the soleus muscle, R-ALA treatment caused an increase in the rate of insulin-stimulated 2-DG uptake that approached statistical significance (18%, \( P = 0.054 \); Fig. 3C), whereas this intervention resulted in a clear enhancement in insulin-mediated 2-DG uptake (32%; Fig. 3D). Exercise training alone increased both the insulin-stimulated rate of 2-DG uptake (28%) and insulin-mediated 2-DG uptake (52%). As with the epitrochlearis, the greatest enhancement of these parameters in the soleus was realized in the combined intervention group (52 and 93%), with the latter increase approaching statistical significance (\( P = 0.057 \)).

GLUT-4 protein and enzyme responses. GLUT-4 protein level (Fig. 4) and the activities of total hexokinase (Fig. 5) and citrate synthase (Fig. 6) enzymes were determined in the epitrochlearis, soleus, plantaris, and heart muscles. No increases in these parameters were observed in any of the muscle types following chronic treatment with R-ALA. In contrast, exercise training, alone or in combination with R-ALA treatment, caused significant increases in GLUT-4 protein level in the
epitrochlearis (31 and 45%, respectively), soleus (59 and 66%), and plantaris (27 and 34%).

Total hexokinase activity was enhanced by exercise training alone and in combination with R-ALA treatment in the epitrochlearis (56 and 78%, respectively), soleus (82 and 70%), and plantaris (152 and 123%), whereas only exercise training alone increased hexokinase activity in the heart (19%) relative to the sedentary control groups. Citrate synthase activity was increased by 44% in epitrochlearis muscle from the combination treatment group. This variable was increased by exercise training alone or in the combination treatment group in the soleus (44 and 55%, respectively) and plantaris (21 and 56%).

**Protein carbonyls.** The level of carbonyl formation in proteins is an indicator of oxidative damage in tissues (10) and reflects the degree of oxidative stress (33). The effect of the antioxidant and exercise training interventions on this marker of oxidative stress was assessed in soleus, plantaris, and heart muscles as well as in the liver (Fig. 7). R-ALA treatment alone or exercise training alone resulted in significant decreases (28–52%) in protein carbonyl levels in all tissues. No further decreases in protein carbonyl levels in these tissues were elicited when ALA treatment and exercise training were combined.

Because oxidative stress may play a role in the development of insulin resistance (8, 17), the correlation between protein carbonyl level and insulin-mediated 2-DG uptake in the soleus muscle from the various experimental groups was examined (Fig. 8). A highly significant inverse correlation was observed ($r = -0.626; P < 0.01$).

**DISCUSSION**

In the present investigation, we have confirmed the previous findings by our group and others that marked improvements in glucose tolerance and insulin action can be elicited by either endurance exercise training alone (2, 3, 6, 7, 9, 13, 21, 37) or chronic administration of the antioxidant ALA alone (26, 31, 38) in the obese Zucker rat. More importantly, we have made the new finding that the combination of exercise training and R-ALA treatment will bring about greater increases in insulin action on skeletal muscle glucose transport activity than either intervention individually (Fig. 3). The present results demonstrate that exercise training and antioxidant treatment function in an essentially additive fashion to improve insulin action in these insulin-resistant muscles. However, this interaction between exercise training and R-ALA on skeletal mus-
cle insulin action did not translate into a markedly greater improvement in whole body glucose disposal and insulin sensitivity, at least as determined by the glucose-insulin index (Fig. 2). Nevertheless, the use of exercise training and antioxidant treatment together appears promising as a combination therapy for the treatment of skeletal muscle insulin resistance.

It is clear from the present findings that the chronic administration of R-ALA alone did not significantly affect the expression of muscle GLUT-4 protein levels (Fig. 4), total hexokinase activity (Fig. 5), or citrate synthase activity (Fig. 6). This result, after 6 wk of antioxidant treatment, extends our previous finding that 2 wk of treatment with R-ALA does not substantially alter muscle GLUT-4 protein levels (38) and demonstrates that an increase in GLUT-4 protein expression is not the mechanism by which this antioxidant improves insulin action on skeletal muscle glucose transport. Whereas the exercise training-induced improvements in insulin action were associated with enhanced GLUT-4 protein in both epitrochlearis and soleus muscles (Fig. 4), the additional improvements in insulin action with antioxidant treatment were not associated with a further upregulation of muscle GLUT-4 protein levels. However, the possibility exists that, although R-ALA cannot enhance GLUT-4 protein expression, it may increase the ability of insulin to stimulate translocation of GLUT-4 to the sarcolemma and T tubules, where it can mediate glucose transport into the myocyte. This is an intriguing possibility as evidence exists that R-ALA can indeed cause activation of insulin signaling and GLUT-4 translocation in L6 myocytes and 3T3-L1 adipocytes (12, 41).

There is increasing evidence that elevated circulating FFA may be mechanistically linked to a reduction in insulin action on skeletal muscle glucose transport activity (5), possibly via inhibition of insulin receptor substrate-1 (IRS-1) phosphorylation and IRS-1-associated phosphatidylinositol-3-kinase activity (15). In the present study, both exercise training and R-ALA treatment caused significant decreases in plasma free fatty acid levels (Table 2) that were paralleled by increases in insulin-stimulated glucose transport activity in muscle (Fig. 3). However, the combination of these two interventions did not result in a further diminution in circulating FFA levels. These findings are consistent with the hypothesis that the reduction of FFA may contribute to the improvements in insulin action associated with the individual interventions. In contrast, our results indicate that the additive effect of these two interventions on insulin-stimulated glucose transport in skeletal muscle was not mediated by a further reduction in plasma FFA.

Our results provide important new information regarding the potential role of oxidative stress in the multifactorial etiology of insulin resistance and address the potential utility of exercise training or antioxidant treatment, individually or in combination, to reduce both oxidative stress and skeletal muscle insulin resistance. First, the levels of protein carbonyls in...
the various tissues from the obese Zucker rat (Fig. 7) are two- to threefold greater compared with the same tissues from insulin-sensitive lean Zucker rats (Henriksen and Saengsirisuwan, unpublished observations). Second, the results of the present study indicate that reductions in muscle protein carbonyl levels, after endurance training or an antioxidant intervention, are associated with the improvements in insulin action on glucose transport in the soleus muscle of the obese Zucker rat (Fig. 8). Indeed, in this muscle, the improvement in insulin-mediated glucose transport was significantly correlated with the reduction in protein carbonyl level after antioxidant treatment alone (r = −0.598; P < 0.05) or exercise training alone (r = −0.746; P < 0.05). Our findings with R-ALA treatment complement those of Rudich et al. (34), who demonstrated, using 3T3-L1 adipocytes, that prolonged exposure to low-grade oxidative stress (H₂O₂) markedly decreases insulin-stimulated glucose metabolism and that this effect of oxidative stress can be prevented by preexposure to ALA (35). However, our results also indicate that the relationship between oxidative stress and insulin resistance is not a simple one, as the further improvement in insulin-stimulated glucose transport in the soleus from the combined intervention group was not accompanied by a further reduction in oxidative stress. It is clear that additional, and as yet unidentified, factors are responsible for the further enhancement of insulin action in the combination group.

It is noteworthy that the R-ALA intervention allowed the obese Zucker rats to run for 18% longer than sedentary control animals during the VO₂peak test despite not having a greater peak aerobic capacity (Table 2). Moreover, the obese group that both underwent the endurance exercise training regimen and received antioxidants chronically displayed the longest run time during this test, running 8% longer than the obese animals that performed exercise training alone. Clearly, the animals receiving the antioxidant treatment, whether individually or in combination with exercise training, underwent an adaptive response that enabled them to run for 1–2 min longer before fatiguing. The underlying mechanism(s) for this response to the antioxidant intervention is not readily apparent from the data collected in the present study. The animals in the combined treatment group did possess the largest hearts (Table 1), which could have allowed for the largest maximal cardiac output. An additional possibility for the increased endurance may be the small, but statistically insignificant, increases in GLUT-4 protein, total hexokinase activity, and citrate synthase activities (Figs. 4–6) experienced in the predominantly type IIb epitrochlearis, which would be substantially recruited only at the highest workloads attained during the treadmill test. These small enhancements in the capacity for glucose transport (GLUT-4 protein expression), glucose phosphorylation (hexokinase), and glucose oxidation (citrate synthase), in conjunction with additional metabolic adaptations that remain to be identified, may have allowed these R-ALA-treated animals to catabolize glucose to a greater extent at these very high workloads and delay fatigue for the observed time period. Further studies are needed to elucidate the potential role of antioxidant supplementation, such as with R-ALA administration, in enhancing endurance during high-intensity endurance exercise both in normal and insulin-resistant subjects.

In conclusion, we have confirmed that endurance exercise training alone and chronic administration of the antioxidant R-ALA alone improve glucose tolerance and insulin action on skeletal muscle glucose transport in the markedly insulin-resistant, hyperinsulinemic, and dyslipidemic obese Zucker rat. Moreover, we have provided new evidence that the combination of these interventions is associated with greater improvements in skeletal muscle insulin action than either intervention individually. Although the enhancement of insulin action following exercise training was associated with upregulation of GLUT-4 protein expression and both exercise training and antioxidant treatment induced increases in insulin action that were associated with decreased tissue oxidative stress and circulating levels, it is clear that the interactive effects of the two interventions implemented in combination could not be attributed to additive effects on
GLUT-4 protein, protein carbonyl, or FFA levels. Further research is needed to identify the mechanisms underlying the beneficial interaction between exercise training and R-ALA in ameliorating the skeletal muscle insulin resistance of the obese Zucker rat.

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