The Antioxidant α-Lipoic Acid Enhances Insulin-Stimulated Glucose Metabolism in Insulin-Resistant Rat Skeletal Muscle

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Insulin resistance of muscle glucose metabolism is a hallmark of NIDDM. The obese Zucker (*fa/fa*) rat—an animal model of muscle insulin resistance—was used to test whether acute (100 mg/kg body wt for 1 h) and chronic (5–100 mg/kg for 10 days) parenteral treatments with a racemic mixture of the antioxidant α-lipoic acid (ALA) could improve glucose metabolism in insulin-resistant skeletal muscle. Glucose transport activity (assessed by net 2-deoxyglucose [2-DG] uptake), net glycogen synthesis, and glucose oxidation were determined in the isolated epitrochlearis muscles in the absence or presence of insulin (13.3 nmol/l). Severe insulin resistance of 2-DG uptake, glycogen synthesis, and glucose oxidation was observed in muscle from the vehicle-treated obese rats compared with muscle from vehicle-treated lean (*Fa/−*) rats. Acute and chronic treatments (30 mg · $kg^{-1} \cdot day^{-1}$, a maximally effective dose) with ALA significantly ($P < 0.05$) improved insulin-mediated 2-DG uptake in epitrochlearis muscles from the obese rats by 62 and 64%, respectively. Chronic ALA treatment increased both insulin-stimulated glucose oxidation (33%) and glycogen synthesis (38%) and was associated with a significantly greater (21%) in vivo muscle glycogen concentration. These adaptive responses after chronic ALA administration were also associated with significantly lower (15–17%) plasma levels of insulin and free fatty acids. No significant effects on glucose transporter (GLUT4) protein level or on the activities of hexokinase and citrate synthase were observed. Collectively, these findings indicate that parenteral administration of the antioxidant ALA significantly enhances the capacity of the insulin-stimulatable glucose transport system and of both oxidative and nonoxidative pathways of glucose metabolism in insulin-resistant rat skeletal muscle. *Diabetes* 45:1024–1029, 1996

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ALA, α-lipoic acid; BSA, bovine serum albumin; 2-DG, 2-deoxyglucose; KHB, Krebs-Henseleit buffer.

Insulin resistance of skeletal muscle glucose transport is a key feature in the pathogenesis of NIDDM (1–3). On initial diagnosis, most NIDDM patients are hyperinsulinemic and insulin therapy is not necessary (4). Therefore, the goal of interventions at this stage of the disease is to improve insulin action on glucose transport activity in skeletal muscle because this tissue is the primary site of whole-body glucose disposal after a meal or after exercise (5).

Nonpharmacological approaches, which improve insulin sensitivity of peripheral glucose disposal and reduce hyperinsulinemia, include weight loss (6,7), diet (7,8), and exercise (9–13). In the event that these nonpharmacological measures are ineffective, pharmacological interventions may be necessary. α-lipoic acid (ALA; also known as thioctic acid), a potent antioxidant (14,15), is a naturally occurring substance that has been previously shown to enhance glucose utilization in the isolated rat diaphragm (16) and glucose uptake by the rat heart (17). More recently, Klip et al. (18) demonstrated that ALA increased glucose transport in L_6 myotubes. However, the effect of parenteral ALA treatment on glucose metabolism in insulin-resistant skeletal muscle is currently not known.

In this context, the purpose of the present study was to assess the effect of in vivo ALA treatment on in vitro glucose metabolism in skeletal muscle from an animal model of obesity and muscle insulin resistance—the obese Zucker (*fa/fa*) rat. Specifically, we tested the effect of a single treatment with a racemic mixture of ALA on insulin-stimulated glucose transport activity and also the effect of chronic treatment with this agent on insulin-stimulated glucose transport and nonoxidative (glucose incorporation into glycogen) and oxidative (glucose oxidation) metabolism in the isolated epitrochlearis muscle and on the in vivo muscle level of glucose transporter (GLUT4) protein, glycogen, hexokinase, and citrate synthase. Finally, the effect of chronic ALA treatment on plasma glucose, insulin, and free fatty acid levels was assessed.

RESEARCH DESIGN AND METHODS

Animals. Female obese Zucker (*fa/fa*) rats and lean littermates (*Fa/−*) were purchased at 7–8 weeks of age from Harlan (Indianapolis, IN). Animals were housed two per cage and maintained on chow (Purina, St. Louis, MO) and water ad libitum. All procedures described below were approved by the University of Arizona Animal Use and Care Committee.

Acute ALA treatment. At 9–10 weeks of age, lean and obese animals were randomly assigned either to a vehicle-treated control group or a group receiving a single intraperitoneal administration of a racemic mixture of ALA (ASTA Medica, Frankfurt, Germany). Lean animals were restricted to 4 g of chow after 5:00 P.M. the evening before the experiment, while obese animals received 6 g of chow at this time. At 9:00 A.M. on the day of the experiment, lean and obese acute vehicle groups received vehicle (8.3 ml/kg body weight of 120 mmol/l Tris buffer, pH 7.4) by intraperitoneal injection, while the lean and obese acute ALA groups received 100 mg/kg body weight. Exactly 1 h later, the animals were deeply anesthetized with pentobarbital sodium (50 mg/kg body wt i.p.), and both epitrochlearis muscles were surgically removed and prepared for in vitro incubation, as described below.

Chronic ALA treatment. At 8–9 weeks of age, obese animals received either vehicle or 30 mg/kg body weight ALA by intraperitoneal injection for 10 consecutive days. In additional experiments, obese rats received ALA at various doses (5–100 mg/kg) for 10 days. All animals were food-restricted the evening before the experiment as described above for the acute treatments. Between 10:00 and 11:00 A.M., ~20 h after the final treatment, animals were weighed and 1.5 ml of blood from a cut at the tip of the tail was collected into a microcentrifuge tube containing 27 mg of EDTA and vortexed. This blood was quickly centrifuged at 13,000*g* for 2 min to separate the plasma, which was kept at −70°C until assayed spectrophotometrically for glucose (Sigma, St. Louis, MO) and free fatty acids (Wako, Richmond, VA) and by radioimmunoassay for insulin (Linco, St. Charles, MO). The animals were then deeply anesthetized with pentobarbital sodium, and both epitrochlearis muscles were surgically removed and prepared for in vitro incubation.

Measurement of in vitro glucose transport activity. Muscles from acutely or chronically treated animals were initially incubated for 60 min at 37°C in 3 ml of oxygenated Krebs-Henseleit buffer (KHB) containing 8 mmol/l glucose, 32 mmol/l mannitol, and 0.1% bovine serum albumin (BSA). The right muscle from each animal was incubated in medium containing no insulin, while the contralateral muscle was incubated in medium containing a maximally effective concentration of insulin (13.3 nmol/l). Thereafter, muscles were rinsed for 10 min at 37°C in 3 ml of oxygenated KHB containing 40 mmol/l mannitol, 0.1% BSA, and, if present previously, insulin. The muscles were then transferred to flasks containing 2 ml of oxygenated KHB, 0.1% BSA, 1 mmol/l 2-deoxy [1,2-^{3}H]glucose (2-DG) (300 mCi/mol) (Sigma, St. Louis, MO) and 39 mmol/l [U-^{14}C]mannitol (0.8 mCi/mol) (ICN Radiochemicals, Irvine, CA), and insulin, if present previously. After this final 20-min incubation at 37°C, muscles were trimmed of fat, extraneous muscle tissue, and connective tissue, frozen in liquid N_2, weighed, and dissolved in 0.5 ml of 0.5 N NaOH. Glucose transport activity was then calculated as described by Henriksen and Ritter (19). This method for assessing glucose transport activity in epitrochlearis muscles of this size has been thoroughly studied and validated (20).

Electrical stimulation of muscle contractions. For electrical stimulation of muscle contractions, the distal end of the epitrochlearis muscle was attached to a vertical Lucite rod containing two platinum electrodes. The proximal end was clipped to a jeweler's chain and attached to a Grass model FTO3 isometric force transducer. The mounted muscle was immersed in 25 ml KHB containing 8 mmol/l glucose and 32 mmol/l mannitol and continuously oxygenated with 95% O_2, 5% CO_2 at 37°C. The muscle was stimulated with supramaximal square wave pulses of 0.2 ms duration using a Grass S11 stimulator. Ten tetanic contractions were produced by stimulating at 50 Hz for 10 s at a rate of one contraction per min. Glucose transport activity was then assessed, as described above.

Measurement of in vitro glucose metabolism. Muscles were initially incubated at 37°C for 30 min in 3 ml of oxygenated KHB containing 5 mmol/l glucose, 5 mmol/l HEPES, and 0.1% BSA, with a gas phase of 95% O_2, 5% CO_2. Thereafter, muscles were incubated for an additional 2 h at 37°C in fresh medium supplemented with 5 mmol/l [U-^{14}C]glucose (10 μCi/mmol; ICN) and containing either no insulin or 13.3 nmol/l insulin. Glucose incorporation into glycogen, an index of net glycogen synthesis, and glucose oxidation were assessed, as described previously (21).

Biochemical assays. In epitrochlearis muscles of separate groups of chronically treated obese Zucker rats, assays were performed for glycogen (22), GLUT4 protein (23), total hexokinase activity (24), and citrate synthase activity (25).

Statistical analysis. All data are presented as means ± SE. The significance of differences between groups was assessed by analysis of variance with a post hoc Scheffé's *F* test (Statview II, Abacus Concepts, Berkeley, CA). *P* values of <0.05 were considered significant.

TABLE 1
Body weights and epitrochlearis muscle wet weights in the acute treatment groups

Group	Body weight (g)	Epitrochlearis weight (mg)	*n*
Lean vehicle treated	156 ± 2	30.7 ± 1.4	6
Lean acute ALA treated (100 mg/kg)	155 ± 3	31.7 ± 2.2	6
Obese vehicle treated	284 ± 16*	30.4 ± 1.2	6
Obese acute ALA treated (100 mg/kg)	279 ± 6*	28.8 ± 1.6	6

Values are means ± SE for number (*n*) of muscles indicated. *$P < 0.05$ vs. lean vehicle-treated group.

RESULTS

Effect of acute parenteral ALA treatment. The obese rats weighed significantly more ($P < 0.05$) than age-matched lean controls (Table 1). However, there were no differences between the various groups for epitrochlearis muscle wet weights. Therefore, differences in in vitro glucose transport activity likely cannot be attributed to differences in diffusion distance in these groups (26).

There were no significant differences in the rates of muscle 2-DG uptake in the absence of insulin among the four groups studied (Fig. 1). In the presence of a maximally effective concentration of insulin, the rate of 2-DG uptake was 41% less ($P < 0.05$) in muscle from the obese vehicle-treated animals compared with that of the vehicle-treated lean controls. The increase in 2-DG uptake above basal in muscles from the obese vehicle-treated animals was 58% less than the insulin-mediated increase observed in muscles from the lean animals (102 ± 12 vs. 241 ± 16 pmol · mg^{-1} · 20 min^{-1}, $P < 0.05$). A single treatment of lean animals with 100 mg/kg ALA did not significantly increase either the rate of insulin-stimulated glucose transport activity or the increase above basal due to insulin (241 ± 16 vs. 267 ± 29, $P > 0.05$). However, the acute treatment of obese animals with ALA resulted in a 34% increase ($P < 0.05$) in the insulin-stimulated rate of 2-DG uptake and a 62% greater (170 ± 25 vs. 102 ± 12, $P < 0.05$) insulin-mediated 2-DG uptake above basal compared with the obese vehicle-treated group. Insulin-stimulated 2-DG uptake in muscle from the ALA-treated obese

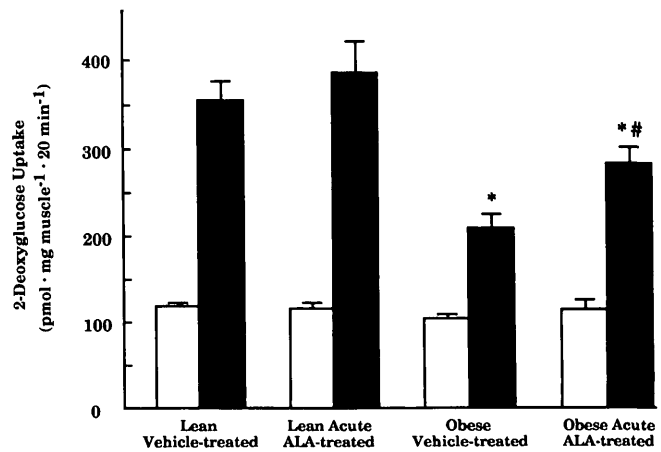

FIG. 1. Effect of acute ALA treatment on in vitro glucose transport activity in the absence (■) or presence (□) of insulin (13.3 nmol/l). Data are means ± SE for six animals per group. *$P < 0.05$ vs. lean vehicle-treated group. #$P < 0.05$ vs. obese vehicle-treated group.

TABLE 2
Body weights, epitrochlearis muscle wet weights, and plasma glucose, insulin, and free fatty acid concentrations in the chronic treatment groups

Group	Body weight (g)	Epitrochlearis weight (mg)	Plasma glucose (mmol/l)	Plasma insulin (pmol/l)	Plasma free fatty acids (mmol/l)
Lean vehicle treated	160 ± 4	30.4 ± 1.4	6.9 ± 0.6	182 ± 21	0.72 ± 0.04
Obese vehicle treated	283 ± 6*	31.4 ± 1.2	7.9 ± 0.3	1,448 ± 92*	1.82 ± 0.06*
Obese ALA treated (30 mg/kg)	282 ± 5*	29.7 ± 1.0	6.8 ± 0.5	1,206 ± 39*†	1.54 ± 0.08*†

Data are means ± SE for 6–13 animals per group. *$P < 0.05$ vs. lean vehicle-treated group. †$P < 0.05$ vs. obese vehicle-treated.

animals was still significantly less than that in muscle from the lean animals.

Effect of chronic parenteral ALA treatment. The effect of chronic treatment on muscle glucose metabolism of obese animals with 30 mg/kg ALA (a maximally effective dose, see below) was assessed. The final body weights of the obese chronically treated animals were significantly greater ($P < 0.05$) than those of the age-matched lean vehicle-treated controls, but there was no significant difference in final body weights between obese groups (Table 2). Additionally, epitrochlearis muscle wet weights were similar in the various chronically treated groups. While plasma glucose was slightly (14%) less in the chronically treated obese group compared with the control obese group, this difference did not achieve statistical significance. Plasma insulin and free fatty acids were 8- and 2.5-fold greater ($P < 0.05$), respectively, in the obese control group compared with the lean control group. Both plasma variables were 15–17% lower ($P < 0.05$) after chronic ALA treatment of the obese animals.

Basal rates of 2-DG uptake were not different in muscles from the groups studied (Figs. 2 and 3). Marked insulin resistance of glucose transport activity was observed in muscle from the obese vehicle-treated animals compared with the lean controls. Moreover, chronic treatment with 30 mg · kg^{-1} · day^{-1} ALA resulted in a 29% increase ($P < 0.05$) in the insulin-stimulated rate of 2-DG uptake and a 64% greater (175 ± 16 vs. 107 ± 14, $P < 0.05$) insulin-mediated increase in 2-DG uptake above basal compared with the obese vehicle-treated group. Results of a dose-response study (Fig. 3) indicated that chronic administration of 30 mg · kg^{-1} · day^{-1} elicited a maximal enhancement of insulin-mediated 2-DG uptake above basal in epitrochlearis from the obese Zucker rat because no further enhancement was observed following chronic treatments with 50 or 100 mg · kg^{-1} · day^{-1}. Body weights and epitrochlearis muscle weights did not differ among the various obese treatment groups (data not shown). The apparent ED_{50} of the chronic ALA effect on insulin-stimulated glucose transport activity in the epitrochlearis muscle was ~15 mg/kg. The effect of ALA treatment on the insulin-independent pathway for stimulation of glucose transport activity was investigated using muscle contractions. Interestingly, the capacity for activation of glucose transport activity above basal by electrically stimulated muscle contractions was not increased by chronic 30 mg · kg^{-1} · day^{-1} ALA treatment (148 ± 17 pmol · mg $muscle^{-1}$ · 20 min^{-1} in obese vehicle-treated group vs. 141 ± 24 in obese ALA-treated group, $n = 6$ for both), indicating that the effect of ALA is restricted to the insulin-dependent pathway.

The rate of in vitro net glycogen synthesis in the absence of insulin was not different among the groups (Fig. 4). Insulin-stimulated glycogen synthesis was 35% less ($P < 0.05$) in muscle from obese controls compared with lean controls, but was enhanced by 38% ($P < 0.05$) as a result of the chronic ALA treatment. Accordingly, the in vivo glycogen concentration was 21% greater ($P < 0.05$) in epitrochlearis muscle from chronically ALA-treated obese animals compared with obese control muscle (38.2 ± 2.2 vs. 31.6 ± 0.5 nmol/mg muscle).

Glucose oxidation was markedly impaired in muscle from the obese animals relative to the lean animals (Fig. 5). The

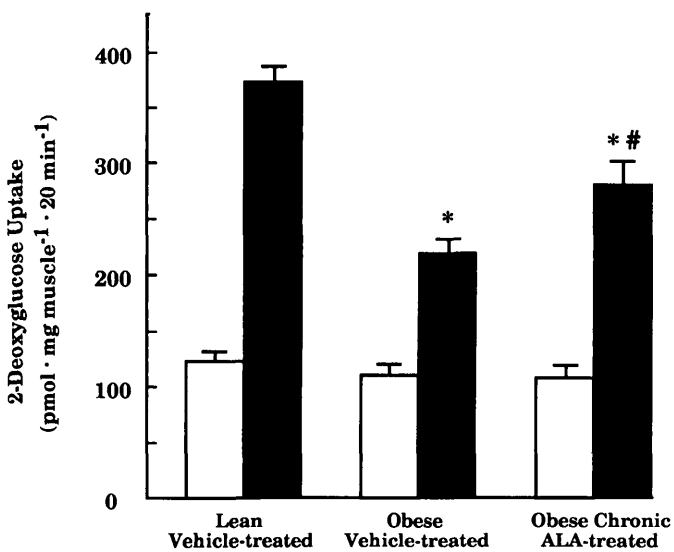

FIG. 2. Effect of chronic ALA treatment on in vitro skeletal muscle 2-DG uptake in the absence (□) or presence (■) of insulin (13.3 nmol/l). Data are means ± SE for 6–13 animals per group. *$P < 0.05$ vs. lean vehicle-treated group. #$P < 0.05$ vs. obese vehicle-treated group.

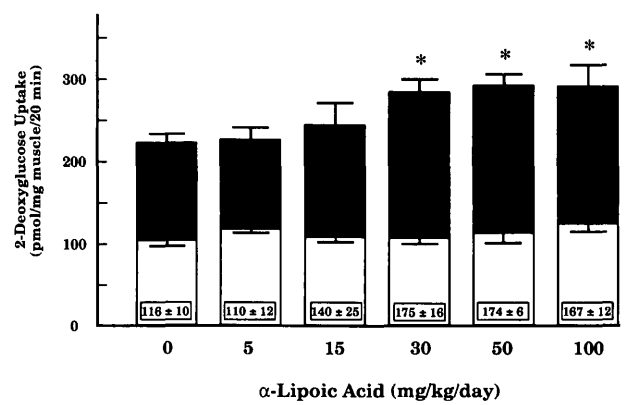

FIG. 3. Dose response of the effect of chronic ALA treatment of obese Zucker rats on in vitro skeletal muscle 2-DG uptake in the absence (□) or presence (■) of insulin (13.3 nmol/l). The number in the box at the bottom of each bar represents the absolute increase above basal due to insulin. Data are means ± SE for 5–13 animals per group. *$P < 0.05$ vs. obese vehicle-treated group for both the rate of insulin-stimulated 2-DG uptake and the increase above basal due to insulin.

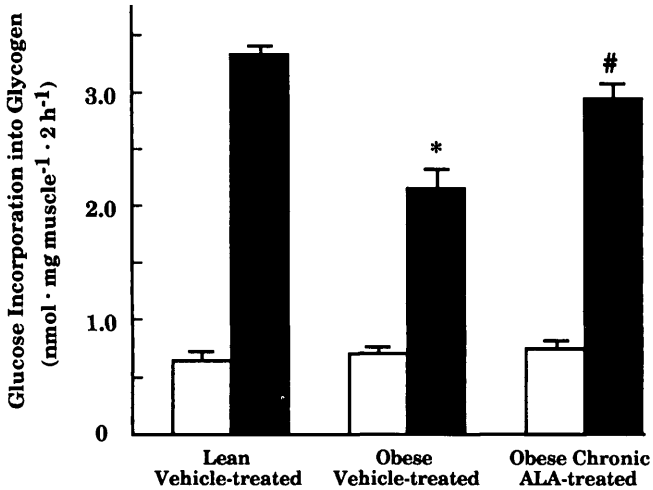

FIG. 4. Effect of chronic ALA treatment on in vitro skeletal muscle glycogen synthesis in the absence (□) or presence (■) of insulin (13.3 nmol/l). Data are means ± SE for 6–10 animals per group. *P < 0.05 vs. lean vehicle-treated group. #P < 0.05 vs. obese vehicle-treated group.

basal rate of glucose oxidation was significantly less (−44%, $P < 0.05$) in muscle from obese control rats compared with that of lean controls, and this relationship was not altered by chronic ALA treatment of the obese animals. Glucose oxidation was almost completely insulin resistant in the epitrochlearis muscle of the vehicle-treated obese Zucker rats. However, after chronic ALA treatment, the rate of insulin-stimulated glucose oxidation was 33% ($P < 0.05$) greater than the rate in the obese control group.

These improvements in glucose transport activity and in intracellular glucose disposal in the epitrochlearis muscle due to chronic ALA administration to the obese animals were not the result of significant increases in the whole muscle level of GLUT4 protein, total hexokinase activity, or muscle oxidative capacity (citrate synthase activity) (data not shown). These parameters also did not change in the soleus, plantaris, or left ventricle of the heart of the ALA-treated obese animals (E.J.H., D.L.F., S.J., unpublished observations).

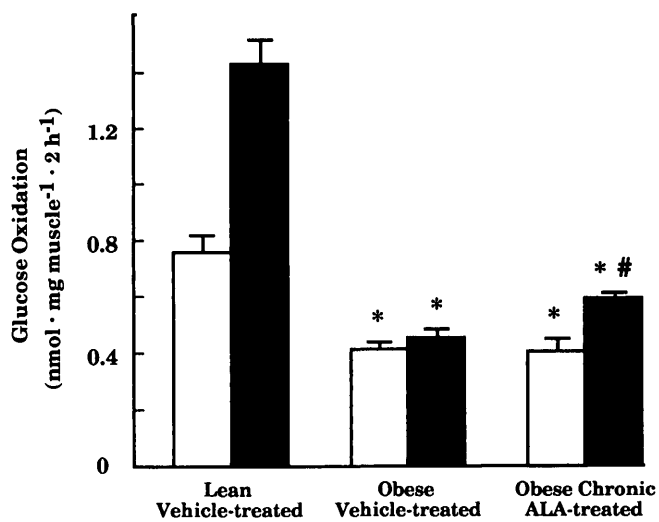

FIG. 5. Effect of chronic ALA treatment on in vitro skeletal muscle glucose oxidation in the absence (□) or presence (■) of insulin (13.3 nmol/l). Data are means ± SE for 6–10 animals per group. *P < 0.05 vs. lean vehicle-treated group. #P < 0.05 vs. obese vehicle-treated group.

DISCUSSION

The present study provides new information regarding the beneficial effects of the antioxidant ALA in ameliorating insulin resistance of muscle glucose metabolism in an animal model of obesity, hyperinsulinemia, and dyslipidemia. The most important finding is that the racemic mixture of ALA improved insulin-stimulated glucose transport activity in insulin-resistant skeletal muscle after either acute (1 h) or chronic (10 day) parenteral administration. This therefore confirms our recent findings that acute and chronic intravenous treatment of NIDDM patients with the racemic mixture of ALA improved insulin sensitivity of whole-body glucose disposal by 30–50%, as measured using the isoglycemic hyperinsulinemic clamp technique (27,28). Moreover, in the present study, we have used an isolated muscle preparation, which eliminates the influence of blood flow and substrate delivery in metabolic regulation, to assess glucose transport activity and intracellular glucose metabolism. Our results are consistent with the interpretation that the muscle glucose transport system is involved in the beneficial action of ALA. Finally, this chronic intervention provided the additional beneficial systemic effect of small (15–17%) but significant reductions in plasma insulin and free fatty acids in this animal model of hyperinsulinemia and dyslipidemia.

Intracellular glucose disposal is markedly impaired in NIDDM, as shown by decreased insulin-stimulated glycogen deposition and glucose oxidation (29). Similar defects in nonoxidative and oxidative glucose metabolism were detected in the epitrochlearis muscle of the vehicle-treated obese Zucker rats (Figs. 4 and 5). More importantly, we have made the novel finding that both nonoxidative and oxidative pathways for the insulin-mediated intracellular disposal of glucose were positively affected in insulin-resistant skeletal muscle after chronic administration of ALA. Insulin-stimulated glucose incorporation into glycogen, an index of net glycogen synthesis, was enhanced by 38% after chronic administration of ALA, and this increased capacity for insulin-stimulated glycogen synthesis may be related to the significantly elevated in vivo glycogen concentration observed in the epitrochlearis muscle from the chronically ALA-treated obese Zucker rats. The nearly complete insulin resistance of glucose oxidation in muscle from the vehicle-treated obese rats was also significantly improved (33%) by chronic ALA treatment, although this parameter still remained significantly lower than that determined in muscle from the lean animals. Because the activity of citrate synthase, a typical marker enzyme of mitochondrial oxidative capacity, was not altered by ALA treatment, it is unlikely that mitochondrial adaptations underlie this effect. It remains to be studied whether the chronic ALA treatment altered the activity of the pyruvate dehydrogenase complex, in which ALA plays a critical role as a cofactor.

The compound administered to the animals in this study consisted of equal parts of the R- and S-enantiomers of ALA, and theoretically, either enantiomer could have been responsible for the metabolic effects observed. We have conducted similar experiments using the individual enantiomers of ALA and have found that while the S-enantiomer induces small improvements in insulin action on glucose transport activity and glucose disposal in insulin-resistant skeletal muscle, the R-enantiomer induces by far the greatest metabolic improvements both systematically and locally at the level of the skeletal muscle (30; R.S.S., E.J.H., S.J., J.Y.H., D.L.F., unpub-

lished observations). This is in agreement with previous findings of much greater effects of the R-enantiomer of ALA relative to the S-enantiomer on stimulation of glucose transport activity and GLUT4 translocation in cultured L6 myotubes (16) and in the perfused rat heart (K. Rett, personal communication).

The precise cellular mechanism(s) whereby ALA interacts with the insulin-dependent glucose transport system in skeletal muscle remains to be investigated. There are, however, some interesting possibilities. The treatments with ALA may have influenced insulin receptor tyrosine kinase activity or glucose transporter (GLUT4) protein translocation, both of which are known to be defective in skeletal muscle of the obese Zucker rat (31,32). Endogenous ALA is diminished in tissues of diabetic animals, such as the liver (33). Therefore, the administration of ALA might supplement the level of this compound, thus improving biochemical processes requiring ALA. As mentioned above, ALA is a coenzyme of the pyruvate dehydrogenase complex and also the α-ketoglutarate dehydrogenase complex, and the activity of these enzymes is known to be reduced in the diabetic state (33–35). The supplementation of ALA resulted not only in improved glucose transport but also in improved glucose oxidation. In fact, several groups have reported enhanced glucose oxidation following ALA treatment in diabetic rats (33,35) and in insulin-sensitive tissues such as diaphragm muscle (16). Our observation of improved insulin-stimulated glucose oxidation in a well-established model of skeletal muscle insulin resistance extends these findings. Improvements in glucose tolerance after acute ALA administration to diabetic animals have been reported (33). Interestingly, ALA is also known to inhibit gluconeogenesis in hepatocytes (36). Collectively, these results point toward ALA being potentially effective in eliciting positive metabolic adaptations in conditions of insulin resistance and diabetes.

Several groups have reported an improvement of muscle glucose metabolism after direct administration of ALA to muscle tissues in vitro. Haugaard and Haugaard (16) described an enhanced glucose utilization in rat diaphragm incubated with ALA, while Singh and Bowman (17) noted augmented glucose transport and glycolysis in perfused hearts of normal and diabetic animals. This latter group also demonstrated that ALA administration markedly increased phosphofructokinase activity, a key glycolytic enzyme (17). Additionally, Klip et al. (18) have recently shown an ALA-mediated improvement of glucose transport in L_6 myotubes, both in the absence and in the presence of insulin. We have made similar findings in insulin-resistant skeletal muscle, in which the direct effects of ALA and insulin on glucose transport activity were essentially additive (E.J.H., R.S.S., D.L.F., J.Y.H., S.J., unpublished observations).

Sulfhydryl groups are thought to play an important role in the regulation of insulin-stimulated glucose transport activity in skeletal muscle (37,38). Because ALA contains reactive thiol groups, the interaction of these groups with cellular sulfhydryls could be one mode of action of this compound. In addition, ALA acts as a strong biological antioxidant (14,15) and reduces glucose-induced protein modification (39). This is of significance in light of the reports of Baynes (40) and Low and Nickander (41) demonstrating the important roles of oxidative stress and nonenzymatic glycation in the development of diabetic complications. Furthermore, Nagamatsu et al. (15) have shown in a rodent model of diabetes that ALA treatment similar in dosage to that used in the present study reduced oxidative stress and normalized nerve blood flow and conduction velocity. Interestingly, Johnson et al. (42) recently showed that another antioxidant, MDL 29311, lowered glucose and lipid levels in diabetic animals, indicating that free radicals may interfere with glucose metabolism. The potential interaction of ALA as an antioxidant and sulfhydryl-containing compound with the skeletal muscle glucose transport system would appear to be an important area of future research.

In summary, we have demonstrated that both acute and chronic in vivo administration of the racemic mixture of ALA significantly enhanced the insulin responsiveness of glucose transport activity in insulin-resistant skeletal muscle of the obese Zucker rat. These results indicate that the muscle glucose transport system is one site of the action of ALA. In addition, both nonoxidative and oxidative pathways for insulin-stimulated intracellular glucose disposal are significantly enhanced by chronic ALA administration. These beneficial effects of ALA on insulin action were associated with reductions in both plasma insulin and free fatty acids. The exact mode of action of ALA in improving insulin action in insulin-resistant skeletal muscle remains to be elucidated.

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