Short-term oral α-lipoic acid does not prevent lipid-induced dysregulation of glucose homeostasis in obese and overweight nondiabetic men

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Xiao C, Giacca A, Lewis GF. Short-term oral α-lipoic acid does not prevent lipid-induced dysregulation of glucose homeostasis in obese and overweight nondiabetic men. Am J Physiol Endocrinol Metab 301: E736–E741, 2011. First published July 12, 2011; doi:10.1152/ajpendo.00183.2011.—Prolonged elevation of plasma free fatty acids (FFAs) induces insulin resistance and impairs pancreatic β-cell adaptation to insulin resistance. The mechanisms whereby lipid induces these impairments are not fully defined but may involve oxidative stress, inflammation, and endoplasmic reticulum stress. α-Lipoic acid (ALA), a commonly used health supplement with antioxidant, anti-inflammatory, and AMPK-activating properties, has been shown to have therapeutic value in type 2 diabetes and its complications. Here we examined the effects of ALA on insulin sensitivity and secretion in humans under the conditions of 24-h iv lipid infusion to elevate plasma FFAs. Eight overweight and obese male subjects underwent four randomized studies each, 4–6 wk apart: 1) SAL, 2-wk oral placebo followed by 24-h iv infusion of saline; 2) IH, 2-wk placebo followed by 24-h iv infusion of intralipid plus heparin to raise plasma FFAs approximately twofold; 3) IH + ALA, 2-wk ALA (1,800 mg/day) followed by 24-h infusion of intralipid plus heparin; and 4) ALA, 2-wk ALA followed by 24-h infusion of saline. Insulin secretion rates (ISR) and insulin sensitivity were assessed with a 2-h, 20-mmol/l hyperglycemic clamp and a hyperinsulinemic euglycemic clamp, respectively. ISR was not significantly different between treatments. Lipid infusion impaired insulin sensitivity with and without ALA pretreatment. These results indicate that ALA, administered orally at this dose for 2 wk, does not protect against lipid-induced insulin resistance in overweight and obese humans.

Insulin secretion; insulin sensitivity; free fatty acids; humans

CHRONIC ELEVATION OF CIRCULATING FREE FATTY ACIDS (FFAs) contributes to the pathophysiology of insulin resistance and type 2 diabetes (13, 30). We and others have demonstrated that prolonged elevation of FFAs induces insulin resistance and β-cell dysfunction in animal models (23, 25) and humans (6–8, 18, 45–48).

Several mechanisms have been proposed for FFA-induced impairment in insulin sensitivity and β-cell function, including oxidative stress (25), inflammation (3, 4, 29), and endoplasmic reticulum (ER) stress (9). Although these mechanisms have been demonstrated in animal models and in vitro, it has been challenging to examine in humans. Recently, we have shown that the antioxidant taurine provided beneficial effects in alleviating lipotoxicity, whereas another antioxidant, N-acetylcysteine (NAC), did not (46). Although effective in rodents, the anti-inflammatory agent sodium salicylate did not elicit a protective effect against lipotoxicity at high doses in humans (47). Sodium phenylbutyrate, a drug with the known capability of alleviating ER stress, partially ameliorated lipid-induced detrimental effects on insulin action and secretion in humans (48). Therefore, multiple mechanisms are likely involved in lipid-induced impairment in insulin sensitivity and β-cell function. It is imperative to examine the outcomes of compounds that may possess multiple biological properties in these areas.

α-Lipoic acid (ALA; also known as 1,2-dithiolane-3-pentanooic acid or thioctic acid) is a naturally occurring dithiol compound that is synthesized in the mitochondrion through the enzyme lipoic acid synthase and absorbed intact from dietary sources. ALA has been shown to possess multiple biological functions, including antioxidant, anti-inflammatory, and AMPK-activated protein kinase (AMPK)-activating properties (21, 35, 37, 41, 49). It has been used in treatment of diabetes and its complications (38). In animal models, lipoic acid synthase expression is reduced under diabetic conditions (27), and ALA improves skeletal muscle glucose uptake, glucose tolerance, and insulin sensitivity (17, 40). ALA supplementation ameliorated diabetes onset in a rat model on a high-fructose diet (10). In individuals with type 2 diabetes, oral or intravenous (iv) administration of ALA also improved glucose disposal (15, 16). In addition, supplementation with ALA decreased serum levels of proinflammatory markers IL-6 and plasminogen activator-1 in patients with metabolic syndrome (39). ALA has also been shown to have the potential of improving β-cell function in vitro in some but not all studies. For instance, ALA protected β-cells from oxidative stress (24) and blocked IL-1β-mediated inhibition of glucose-stimulated insulin secretion in islet cells (34). On the other hand, it has been reported that ALA inhibits insulin secretion (42). Of particular interest, ALA alleviated oleic acid-induced oxidative stress and restored glucose-stimulated insulin secretion in isolated rat islets (36). The potential of ALA in ameliorating the detrimental effects of chronically elevated FFAs has not been investigated in humans. Therefore, the objective of this study was to examine the effects of ALA on insulin sensitivity and secretion under conditions of prolonged elevation of FFAs in humans.

RESEARCH DESIGN AND METHODS

Subjects. Five overweight and three obese, nondiabetic men (average age 46.1 ± 2.6 yr, BMI 29.4 ± 0.7 kg/m²) participated in the study. Their fasting levels of plasma parameters were as follows: glucose 5.40 ± 0.11 mmol/l, insulin 103.20 ± 13.20 pmol/l, C-peptide 1.08 ± 0.21 nmol/l, triglyceride (TG) 1.02 ± 0.21 mmol/l, and FFA 0.43 ± 0.01 mmol/l. None of the participants was taking any medication or had any known systemic illness. All subjects had normal oral glucose tolerance (in response to a 75-g OGTT) and had a negative family history of type 2 diabetes. The subjects were not hyperinsulinemic during OGTT. Informed, written consent was obtained from all participants in accordance with the guidelines of the
Research Ethics Board of the University Health Network, University of Toronto, which approved the study.

**Experimental protocol.** The experimental protocol is summarized in Fig. 1. Each participant was studied on the following four occasions, in random order, 4–6 wk apart: 1) 2-wk oral placebo followed by 24-h iv infusion of normal saline (SAL); 2) 2-wk oral placebo followed by 24-h iv infusion of intralipid (20%, 40 ml/h) plus heparin (250 U/h) to raise plasma FFAs approximately twofold (IH); 3) 2-wk oral ALA (1,800 mg/day, 300-mg tablet, 6 tablets/day, timed release tablets; Source Naturals, Bay Harbor, FL), followed by 24-h IH infusion (IH + ALA); and 4) 2-wk oral ALA at the above dose followed by 24-h saline infusion (ALA). ALA was well tolerated by all subjects (no side effects were reported), and adherence (>95%) was ascertained by pill counting. The daily dose was in the upper range of several clinical trials, showing improvement in glucose disposal (22) and diabetic polyneuropathies (32, 33, 50, 51) in type 2 diabetic patients. Although one acute study has shown that intravenous ALA is more beneficial than oral administration (15, 16), oral administration was used in our chronic study to avoid repeated iv injection. Each daily dose was divided into three equal doses to minimize the impact of rapid decline in plasma ALA levels after oral administration. ALA was administered up to and including the morning of the clamp studies. After 2-wk placebo or ALA, subjects were admitted to the Metabolic Test Centre of the Toronto General Hospital. During the stay in the hospital, the subjects were provided with an American Heart Association phase 1 diet and refrained from exercise. On each occasion, on day 1 of admission to the Metabolic Test Centre, an iv catheter was placed in a superficial vein of one forearm for infusion of saline or intralipid plus heparin and for infusion of glucose and insulin during the glycemic clamps. On day 2, after an overnight fast, a second iv catheter was placed in the opposite forearm, which was maintained in a heating blanket (65°C) to “artificialize” venous blood for blood sampling. At 0800, a 30-min baseline sampling period was started, followed by a 2-h, 20-mmol/l hyperglycemic clamp, as described previously (7). Urine glucose loss was assumed to be equal between studies for the same individual because plasma glucose levels were similar. At the end of the 2-h hyperglycemic clamp, the iv dextrose infusion was slowly tapered while avoiding hypoglycemia, allowing the blood glucose to return to basal level. Three hours later, a hyperinsulinemic euglycemic clamp was started with a primed infusion of insulin at 40 mU·m⁻²·min⁻¹ and 20% dextrose at varied rate as described previously (12).

Glucose-stimulated insulin secretion, insulin sensitivity, insulin clearance, and disposition index. Insulin secretion rates (ISR) were derived from deconvolution of plasma C-peptide concentrations during the last 30 min of the hyperglycemic clamp (44). Endogenous insulin clearance was derived as ISR divided by insulin concentrations during the last 30 min of the hyperglycemic clamp. Insulin sensitivity index (SI) was derived from the last 30 min of the hyperinsulinemic euglycemic clamp by normalization of the glucose infusion rate for glucose and insulin, which takes into account the experimental variability, in particular insulin variability, which is affected by insulin clearance. Disposition index (DI) was a product of insulin secretion rate and insulin sensitivity, i.e., DI = ISR × SI, where ISR and SI were derived from the hyperglycemic clamp and the hyperinsulinemic euglycemic clamp, respectively, as described above.

**Laboratory analysis.** Plasma glucose was assayed at the bedside using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Commercial kits were used to analyze plasma insulin (Millipore, Billerica, MA), C-peptide (Millipore), TG (Roche Diagnostics, Laval, QC, Canada), and FFA (Wako Industrial, Osaka, Japan).

**Statistics.** All statistical analyses were performed with SAS version 8.0 (SAS, Cary, NC). Plasma glucose, insulin, C-peptide, TG, and FFAs were analyzed by two-way ANOVA for repeated measurements with Tukey’s test to detect differences between treatments at each time and between times within treatment during the 24-h infusion period and differences between treatments during the last 30 min of the clamps. A P value of <0.05 was considered significant.

**RESULTS**

**Preclamp data.** Fasting levels of plasma glucose, insulin, and C-peptide concentrations were comparable in all treatment groups before and after 24-h infusion of lipid or saline (Table 1). Fasting TG and FFAs were similar before infusion of either lipid or saline. Lipid infusion for 24 h increased plasma TG approximately two- to threefold and FFA levels twofold (P < 0.05, IH and IH + ALA vs. SAL). TG and FFAs were not affected by 2-wk oral ALA treatment compared with placebo.

**Hyperglycemic clamp.** During the hyperglycemic clamp, plasma glucose levels were increased to ~20 mmol/l and maintained at this level in all treatment groups (Fig. 2A). During the last 30 min of the clamp, insulin concentrations were higher in IH (1,427.9 ± 298.3 pmol/l) compared with SAL (1,013.6 ± 198.7 pmol/l) and ALA (972.2 ± 118.4 pmol/l). Insulin concentrations in IH + ALA (1,179.7 ± 207.4 pmol/l) were not significantly different from other treatments (Fig. 2B). Plasma C-peptide concentrations were similar between treatments (Fig. 2C). ISR, derived from deconvolution of C-peptide concentrations, were similar between treatments (Table 2). Endogenous insulin clearance (89, 95, and 96% of SAL in IH, IH + ALA, and ALA, respectively, P = not significant vs. SAL) tended to decrease slightly with IH infusion.

**Hyperinsulinemic euglycemic clamp.** During the last 30 min of the hyperinsulinemic euglycemic clamp, plasma glucose levels were maintained at ~5.7 mmol/l and were well matched between treatments (Fig. 3A). To maintain plasma glucose at this euglycemic level, significantly lower glucose infusion rates were required with lipid infusion treatments (IH = 32.8 ± 4.5 μmol·kg⁻¹·min⁻¹, IH + ALA = 33.1 ± 3.2 μmol·kg⁻¹·min⁻¹, P < 0.05 vs. SAL and ALA) compared with SAL (39.4 ± 4.0 μmol·kg⁻¹·min⁻¹) and ALA (40.9 ± 3.1 μmol·kg⁻¹·min⁻¹) (Fig. 3B). Glucose infusion rates in ALA were not significantly different from SAL. Plasma insulin concentrations were higher in IH and IH + ALA compared with SAL and ALA (SAL = 515.3 ± 39.4, IH = 641.0 ± 62.3, IH + ALA = 653.8 ± 108.2, ALA = 533.3 ± 40.9 pmol/l, P < 0.05, IH and IH + ALA vs. SAL and ALA; Fig. 3C).

**SI and DI.** Parameters for insulin secretion and sensitivity are summarized in Table 2. Insulin sensitivity indexes calculated during the last 30 min of the hyperinsulinemic euglycemic clamp studies were derived from the 2-wk oral placebo or ALA (1,800 mg/day) or placebo, followed by 24-h intravenous (iv) infusion of saline or intralipid plus heparin. Insulin secretion and sensitivity were assessed with hyperglycemic and hyperinsulinemic euglycemic clamps, respectively.
mic clamp were 19 and 25% lower in IH and IH + ALA, respectively, vs. SAL (P < 0.05), indicating lipid-induced insulin resistance. Insulin sensitivity in ALA was similar to SAL. Since the calculated insulin secretion rates were not significantly different between treatments, DI followed a similar pattern as SI, with significantly lower DI in IH and IH + ALA (19 and 31%, respectively, P < 0.05, IH and IH + ALA vs. SAL and ALA), which suggests lack of compensation in insulin secretion despite the presence of insulin resistance in both lipid infusion treatments.

**DISCUSSION**

ALA is a widely used, over-the-counter health supplement that has been shown to have multiple biological functions, particularly antioxidant, anti-inflammatory, and AMPK-activat-

### Table 1. Fasting levels of plasma glucose, insulin, C-peptide, TG, and FFA before and after 24-h infusion of SAL or IH

<table>
<thead>
<tr>
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<th>SAL</th>
<th>IH</th>
<th>IH + ALA</th>
<th>ALA</th>
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<tr>
<td><strong>Glucose, mmol/l</strong></td>
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<tr>
<td>Day 1, 0800</td>
<td>5.46 ± 0.09</td>
<td>5.38 ± 0.18</td>
<td>5.40 ± 0.24</td>
<td>5.35 ± 0.13</td>
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<tr>
<td>Day 2, 0800</td>
<td>5.54 ± 0.13</td>
<td>5.71 ± 0.21</td>
<td>5.80 ± 0.16</td>
<td>5.34 ± 0.09</td>
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<td><strong>Insulin, pmol/l</strong></td>
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<tr>
<td>Day 1, 0800</td>
<td>96.15 ± 9.61</td>
<td>94.88 ± 10.39</td>
<td>121.20 ± 20.97</td>
<td>100.43 ± 11.94</td>
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<tr>
<td>Day 2, 0800</td>
<td>82.55 ± 7.59</td>
<td>110.13 ± 12.00</td>
<td>102.70 ± 9.41</td>
<td>76.28 ± 4.28</td>
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<td><strong>C-peptide, nmol/l</strong></td>
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<td>Day 1, 0800</td>
<td>0.84 ± 0.05</td>
<td>1.08 ± 0.26</td>
<td>1.22 ± 0.23</td>
<td>1.19 ± 0.28</td>
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<td>Day 2, 0800</td>
<td>0.77 ± 0.08</td>
<td>1.16 ± 0.11</td>
<td>1.05 ± 0.17</td>
<td>0.80 ± 0.07</td>
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<td><strong>TG, mmol/l</strong></td>
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<tr>
<td>Day 1, 0800</td>
<td>1.10 ± 0.11</td>
<td>1.19 ± 0.26</td>
<td>1.09 ± 0.13</td>
<td>1.14 ± 0.09</td>
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<tr>
<td>Day 2, 0800</td>
<td>1.41 ± 0.17</td>
<td>2.26 ± 0.17 + †‡</td>
<td>3.12 ± 0.37 + †‡</td>
<td>1.35 ± 0.08</td>
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<td><strong>FFA, mmol/l</strong></td>
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<tr>
<td>Day 1, 0800</td>
<td>0.40 ± 0.10</td>
<td>0.45 ± 0.05</td>
<td>0.46 ± 0.06</td>
<td>0.31 ± 0.07</td>
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<tr>
<td>Day 2, 0800</td>
<td>0.44 ± 0.04</td>
<td>0.69 ± 0.06 + †‡</td>
<td>0.85 ± 0.08 + †‡</td>
<td>0.43 ± 0.04</td>
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Data are means ± SE; n = 8. TG, triglyceride; FFA, free fatty acid; SAL, saline; IH, intralipid plus heparin; IH + ALA, 2 wk of oral α-lipoic acid (1,800 mg/day) followed by IH infusion; ALA, 2 wk of oral α-lipoic acid followed by saline infusion. Following the 2-wk oral ALA vs. placebo treatment period, infusions of SAL or IH were started on day 1 at 0800 of the inpatient investigations and continued until the end of the clamps. Hyperglycemic clamp was started on day 2, 0800. *P < 0.05 vs. SAL; †P < 0.05 vs. ALA; ‡P < 0.05 vs. day 1, 0800.

**Fig. 2. Plasma concentrations of glucose (A), insulin (B), and C-peptide (C) during the hyperglycemic clamps.** Clamps were performed on subjects in 4 randomized visits after 2 wk of oral ALA (1,800 mg/day) or placebo, followed by 24-h infusion of saline (SAL) or intralipid plus heparin (IH). Data are means ± SE. *P < 0.05 IH vs. SAL and ALA.
ing properties. It has been utilized to improve diabetic polyneuropathy and glucose disposal in diabetic patients. In this study, we examined the effects of ALA on insulin sensitivity and secretion in humans during a 24-h lipid infusion protocol. ALA did not provide protection against the detrimental effects of prolonged elevation of FFAs on insulin action and secretion, as assessed by hyperglycemic and euglycemic clamp techniques.

In the current study, ALA administered orally (1,800 mg/day) for 2 wk did not elicit beneficial effects on lipid-induced impairment in insulin sensitivity and secretion. To our knowledge, this is the first study in humans to examine the effects of oral ALA on insulin secretion and action in the context of prolonged elevation of FFAs. Benefits in improving glucose disposal and utilization in type 2 diabetic patients were shown with oral 1,200 (22) and 600–1,800 mg/day for 4 wk (16). It is noted that the effects of ALA on glucose disposal were not different between the doses of 600 and 1,800 mg/day (16), and acute parenteral administration of ALA at 1,000 mg also improved glucose disposal in type 2 diabetic patients (15). In the present study, we wished to determine whether ALA was effective in an initial dysregulation of glucose metabolism, as seen with intralipid plus heparin infusion, and whether the benefit of added AMPK activation would make treatment with this compound more effective than with antioxidants that do not activate AMPK. For these reasons, ALA was administered orally for 2 wk, and overweight and obese individuals were studied exactly as in our previous study with the antioxidants taurine and NAC (46). This current study does not exclude the possibility that longer-term or higher-dose ALA may provide protection against the detrimental effects of chronically elevated FFAs. We have shown that overweight and obese subjects are more susceptible to the detrimental effects of prolonged FFA elevation (6). The subjects in the current study had negative family history of type 2 diabetes. However, certain populations may already have been exposed to lipid-induced detrimental effects, since lowering of circulating FFAs improved insulin action and secretion in genetically predisposed individuals (1, 11, 28). We did not examine obese subjects with positive family history of diabetes or normal weight family history negative subjects. Therefore, the lack of effects of ALA should not be generalized to the population above. In addition, the lack of effects of ALA in this study should not be extrapolated to aging individ-

### Table 2. ISR, SI, and DI

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<tr>
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<th>SAL</th>
<th>IH</th>
<th>IH + ALA</th>
<th>ALA</th>
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<tr>
<td>ISR, pmol/min</td>
<td>1,295.6 ± 79.3</td>
<td>1,410.1 ± 116.0</td>
<td>1,280.4 ± 119.7</td>
<td>1,300.4 ± 101.3</td>
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<tr>
<td>S&lt;sub&gt;H&lt;/sub&gt; (×10&lt;sup&gt;−8&lt;/sup&gt;)</td>
<td>1.83 ± 0.35</td>
<td>1.48 ± 0.48&lt;sup&gt;++&lt;/sup&gt;</td>
<td>1.37 ± 0.28&lt;sup&gt;++&lt;/sup&gt;</td>
<td>1.84 ± 0.32</td>
</tr>
<tr>
<td>DI (×10&lt;sup&gt;−3&lt;/sup&gt;)</td>
<td>2.28 ± 0.35</td>
<td>1.85 ± 0.42&lt;sup&gt;++&lt;/sup&gt;</td>
<td>1.57 ± 0.20&lt;sup&gt;++&lt;/sup&gt;</td>
<td>2.27 ± 0.31</td>
</tr>
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Data are means ± SE; n = 8. ISR, insulin secretion rates; S<sub>H</sub>, insulin sensitivity index; DI, disposition index. Following the 2-wk oral ALA vs. placebo treatment period, infusions of SAL or IH were started on day 1, 0800, of the inpatient investigations and continued until the end of the clamps. Hyperglycemic clamp was started on day 2, 0800. *P < 0.05 vs. SAL; †P < 0.05 vs. ALA.

![Fig. 3](http://ajpendo.physiology.org/)

Fig. 3. Plasma concentrations of glucose (A), glucose infusion rates (B), and plasma concentrations of insulin (C) during the last 30 min of the hyperinsulinemic euglycemic clamps. Clamps were performed on subjects in 4 randomized visits after 2 wk of oral ALA (1,800 mg/day) or placebo, followed by 24-h infusion of SAL or IH. Data are means ± SE. *P < 0.05, IH and IH + ALA vs. SAL and ALA.
uals and patients with type 2 diabetes, conditions that are associated with reduced endogenous ALA synthesis (31).

It is reported that ALA decreased oxidative stress in type 2 diabetic patients with poor glycemic control (5). We have shown in rats that reactive oxygen species generation is involved in lipid-induced β-cell dysfunction (25). In humans under similar lipid infusion conditions, the antioxidant taurine, but not NAC, was effective in ameliorating lipid-induced insulin resistance and β-cell dysfunction (47). Similar to NAC, ALA has relatively low bioavailability (30%) due to first-pass metabolism (43). The tendency of ALA to restore endogenous insulin clearance is reminiscent of the significant decrease in insulin clearance observed with NAC and suggests nearly effective ALA concentrations in the liver. Therefore, the lack of effect of both ALA and NAC on improving insulin sensitivity and β-cell function in this model might be attributed to insufficient delivery to peripheral tissues. In part because of its antioxidant and AMPK-activating properties, ALA is an inhibitor of NF-κB, exhibiting anti-inflammatory properties (26). High-dose salicylate, a known IKKβ/NF-κB inhibitor, prevented lipid-induced hepatic insulin resistance in rodents (20, 29). However, sodium salicylate at maximally tolerable doses did not provide protection against insulin resistance and β-cell dysfunction in nondiabetic humans under prolonged lipid infusion (47).

This study has several limitations. First, since both clamps were performed on the same day, we cannot exclude the possibility that some of the effects of insulin secreted in the hyperglycemic clamp persisted into the hyperinsulinemic euglycemic clamp. Any potential effects are not expected to affect the conclusion of the study because the same protocol was followed for all four treatments. Second, IH infusion introduced glycerol (from lipolysis of the synthetic triglyceride emulsion and from free glycerol in the intralipid) compared with saline, which may affect glucose production. Insulin secretion was not affected by glycerol infusion in type 2 diabetic patients (2). Third, this study assessed only whole body glucose disposal (i.e., whole body insulin sensitivity). Short-term administration of ALA in rats inhibited gluconeogenesis, hence endogenous glucose production, by sequestering liver-free coenzyme A (19). Since no glucose tracer was detected by immunoreactivity of insulin (14).

In conclusion, the current study demonstrates that short-term oral administration of ALA does not provide protection against insulin resistance induced by prolonged exposure to elevated circulating FFAs in nondiabetic individuals despite its known antioxidant and anti-inflammatory properties. These findings in no way negate the potential role of oxidative stress and inflammation as potentially important mechanisms in lipid-induced insulin resistance and β-cell dysfunction, but they do demonstrate that this oral dose of ALA, administered for this duration, is not effective in preventing lipid-induced alteration of glucose metabolism. Thus, adding AMPK-activating properties to a single antioxidant compound is not likely to provide additional benefit in this model. Future studies are needed to explore the potential of a combination of multiple compounds with distinct antioxidant, anti-inflammatory, and other properties (e.g., anti-ER stress, etc.) in amelioration of lipid-induced impairment in insulin secretion and action in humans.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


14. Greene EL, Nelson BA, Robinson KA, Buse MG. alpha-Lipoic acid prevents the development of glucose-induced insulin resistance in 3T3-L1


