Acute elevation of plasma lipids does not affect ATP synthesis in human skeletal muscle

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Prolonged elevation of plasma triglycerides and free fatty acids (FFA) reduces insulin-stimulated glucose disposal and myocellular flux through ATP synthase (fATPase). However, the early effects of lipids per se on fATPase are as yet unclear. Thus, this study examined glucose disposal and fATPase during 3 h of FFA elevation in the presence of low plasma insulinemia. Euglycemic pancreatic clamps with low-dose insulin supplementation (6 nU·m body surface area−2·min−1) were performed in eight healthy men with (LIP) or without (CON) lipid infusion to measure whole body glucose disposal. 31P/H magnetic resonance spectroscopy of calf muscle was applied to quantify fATPase and concentrations of glucose 6-phosphate (G6P), inorganic phosphate (Pi), phosphocreatine (PCr), ADP, pH, and IMCL before and during the clamps. Lipid infusion increased plasma FFA approximately twofold and decreased glucose disposal by ∼50% (110–180 min: LIP 0.87 ± 0.45 vs. CON 1.75 ± 0.42 mg·kg−1·min−1, P = 0.002; means ± SD). Intramyocellular G6P tended to rise only under control conditions, whereas PCr, ADP, pH, and IMCL remained unchanged from fasting in LIP and CON. Although Pi concentrations increased by ∼18%, fATPase remained unchanged from fasting during the clamps (LIP 10.2 ± 2.2 vs. CON 10.5 ± 2.6 μmol·g muscle−1·min−1, P = not significant). We conclude that 3 h of lipid elevation fail to affect ATP synthesis despite marked reduction of whole body glucose uptake. This suggests that lipid-induced insulin resistance results primarily from mechanisms decreasing glucose uptake rather than from direct interference of fatty acid metabolites with mitochondrial function.

In healthy humans, plasma FFA elevation by lipid infusion mimics this mechanism of muscular insulin resistance via sequential inhibition of insulin-stimulated glucose transport/phosphorylation and glycogen synthesis (8, 17, 34, 35), in which alterations are typically observed in skeletal muscle of humans with obesity or T2DM (31, 37). Insulin-resistant individuals also frequently show reduced skeletal muscle oxidative capacity and mitochondrial flux through ATP synthase (fATPase) in parallel with increased IMCL (16, 19, 25, 28, 38, 41). This has been explained by altered mitochondrial fatty acid oxidation favoring accumulation of fatty acid metabolites and IMCL ultimately leading to insulin resistance (24). Elevated FFA might further interfere with the regulation of mitochondrial function or biogenesis, as demonstrated by reduced expression of nuclear-encoded mitochondrial genes and peroxisome proliferator-activated receptor (PPAR)γ coactivator-1 (PGC-1) during 48 h of lipid infusion in humans (33). On the other hand, high-fat diet was shown to increase fatty acid oxidation and mitochondrial biogenesis via PPARδ (14) and PGC-1α (11), whereas development of FFA-mediated insulin resistance might require incomplete fatty oxidation and generation of mitochondrial stress (20).

Aside from its intermediate and long-term action on energy metabolism, FFA elevation may cause rapid effects on mitochondrial respiration and ATP production. We have previously shown that 6 h of lipid infusion suffices to inhibit both insulin-stimulated increase of skeletal muscle fATPase and glucose disposal in healthy humans (8). Likewise, physiological concentrations of the fatty acid metabolites palmitoyl carnitine and palmitoyl-CoA were shown to inhibit ex vivo ATP production in mitochondria isolated from human and murine muscle (1). Recently, 6 h of lipid infusion resulted in decreased ex vivo mitochondrial membrane potential in young healthy humans, whereas mitochondrial content, gene expression, and ATP content remained unaffected (10). Taken together, these studies raised the issue of the sequence of events leading to FFA-induced insulin resistance and whether FFA directly through and independently of stimulation by insulin affects in vivo mitochondrial fATPase in skeletal muscle. To this end, we assessed the acute effect (within 3 h) of lipid infusion in the presence of fasting insulin levels observed in insulin-resistant states (19, 25, 29, 31, 41) on glucose disposal, transport/phosphorylation, and fATPase in calf muscle of healthy humans. Intramyocellular fATPase, glucose 6-phosphate (G6P), inorganic phosphate (Pi), adenosine 5′-diphosphate (ADP), phosphocreatine (PCr), pH, and IMCL were monitored by combined 31P and H magnetic resonance spec-

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PLASMA CONCENTRATIONS OF FREE FATTY ACIDS (FFA) relate to insulin resistance and predict type 2 diabetes mellitus (T2DM) and even cardiovascular mortality (26, 32, 34). Excessive lipid availability due to elevated FFA and ectopic lipid accumulation is considered a key factor in determining the development of skeletal muscle insulin resistance (34). Intramyocellular lipid content (IMCL) positively relates to insulin resistance in sedentary individuals (22, 26, 34), but increased intracellular fatty acid metabolites mediate the inhibition of insulin signaling and subsequent impairment of glucose transport (4, 17, 34, 42). In healthy humans, plasma FFA elevation by lipid infusion mimics this mechanism of muscular insulin resistance via sequential inhibition of insulin-stimulated glucose transport/phosphorylation and glycogen synthesis (8, 17, 34, 35), in which alterations are typically observed in skeletal muscle of humans with obesity or T2DM (31, 37). Insulin-resistant individuals also frequently show reduced skeletal muscle oxidative capacity and mitochondrial flux through ATP synthase (fATPase) in parallel with increased IMCL (16, 19, 25, 28, 38, 41). This has been explained by altered mitochondrial fatty acid oxidation favoring accumulation of fatty acid metabolites and IMCL ultimately leading to insulin resistance (24). Elevated FFA might further interfere with the regulation of mitochondrial function or biogenesis, as demonstrated by reduced expression of nuclear-encoded mitochondrial genes and peroxisome proliferator-activated receptor (PPAR)γ coactivator-1 (PGC-1) during 48 h of lipid infusion in humans (33). On the other hand, high-fat diet was shown to increase fatty acid oxidation and mitochondrial biogenesis via PPARδ (14) and PGC-1α (11), whereas development of FFA-mediated insulin resistance might require incomplete fatty oxidation and generation of mitochondrial stress (20).

Aside from its intermediate and long-term action on energy metabolism, FFA elevation may cause rapid effects on mitochondrial respiration and ATP production. We have previously shown that 6 h of lipid infusion suffices to inhibit both insulin-stimulated increase of skeletal muscle fATPase and glucose disposal in healthy humans (8). Likewise, physiological concentrations of the fatty acid metabolites palmitoyl carnitine and palmitoyl-CoA were shown to inhibit ex vivo ATP production in mitochondria isolated from human and murine muscle (1). Recently, 6 h of lipid infusion resulted in decreased ex vivo mitochondrial membrane potential in young healthy humans, whereas mitochondrial content, gene expression, and ATP content remained unaffected (10). Taken together, these studies raised the issue of the sequence of events leading to FFA-induced insulin resistance and whether FFA directly through and independently of stimulation by insulin affects in vivo mitochondrial fATPase in skeletal muscle. To this end, we assessed the acute effect (within 3 h) of lipid infusion in the presence of fasting insulin levels observed in insulin-resistant states (19, 25, 29, 31, 41) on glucose disposal, transport/phosphorylation, and fATPase in calf muscle of healthy humans. Intramyocellular fATPase, glucose 6-phosphate (G6P), inorganic phosphate (Pi), adenosine 5′-diphosphate (ADP), phosphocreatine (PCr), pH, and IMCL were monitored by combined 31P and H magnetic resonance spec-

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troscopy (MRS) during euglycemic pancreatic clamps with low-dose insulin supplementation in the presence of either lipid (LIP) or saline (CON) infusions. These experiments were part of a study that tested the effect of lipid infusion on insulin-stimulated fATPase, as reported previously (8).

MATERIALS AND METHODS

Subjects. Male glucose-tolerant volunteers (age 26 ± 2 yr, stable body weight of 73 ± 7 kg) without family history of diabetes mellitus were studied. They were neither suffering from conditions related to insulin resistance nor taking any medication. None of the study participants were on intensive physical exercise. They had medium activity indices for habitual physical activity of 1.9 ± 0.5 at work, 3.1 ± 0.5 for leisure time, and 2.8 ± 0.8 for sport as assessed by the questionnaire of Baecke et al. (3), ranging from 1.0 to 5.0.

For 3 days before the studies, participants were on an isocaloric diet (carbohydrate/protein/fat: 60%/20%/20%) and did not perform any kind of exercising. Then they fasted overnight for 12 h. The protocol was approved by the Institutional Review Board of the Medical University of Vienna, and informed consent was obtained before enrollment from all subjects and after the nature and possible consequences of the studies were explained to them. The detailed research design and methods have been reported previously (8).

Euglycemic pancreatic clamp test with low-dose insulin supplementation. After arrival at the research facility and a 1-h resting period, the participants were transported by wheelchair to the adjacent MRS Unit. Baseline MRS data were acquired at 135 to 125 min (1H-MRS) and at 125 to −5 min (31P-MRS). Then, somatostatin (0.1 μg·kg−1·min−1; UCB Pharma, Vienna, Austria) was infused starting at −5 min. A low-dose infusion of regular insulin (6 mU·m body surface area−2·min−1; Actrapid; Novo Nordisk, Bagsvaerd, Denmark) was performed from 0 to 180 min to create conditions of fasting insulinemia as observed in insulin-resistant states (19, 25, 31, 41). Euglycemia was maintained by a variable intravenous glucose infusion (20 g/dl) (8). Clamp MRS data were obtained from +60 to +170 min (1H-MRS) and between 170 and 180 min (31P-MRS). Blood samples were drawn at timed intervals for measurement of hormones and metabolites.

All participants underwent two experiments in random crossover design, once during normal saline infusion (CON) and again during intravenous lipid infusion (LIP: Intralipid 20%; Pharmacia & Upjohn, Vienna, Austria), with both administered at identical infusion rates (0–10 min: 10 ml/h; 10–360 min: 90 ml/h). Between both experiments, participants recovered for 4–8 wk at unchanged lifestyles.

MRS. All measurements were performed on a 3-T (80 cm bore) magnetic resonance spectrometer (Medspec S300-DBX; Bruker, Titingen, Germany), using a 10-cm circular double resonant 1H/31P surface coil to obtain signals from the medial head of the right gastrocnemius muscle (8, 41).

Unidirectional fATPase was measured by 31P-MRS using the saturation transfer experiment applied to the exchange between Pi and ATP (8, 9, 23, 28–30, 41). Unidirectional fATPase from Pi to ATP is the unidirectional fATPase, as reported previously (8).

Hormones and metabolites. Baseline plasma concentrations of hormones and metabolites were not different between LIP and CON days (8). Fasting plasma concentrations of glucose (5.0 ± 0.2, 4.9 ± 0.2 mmol/l), insulin (54 ± 18, 54 ± 11 pmol/l), and FFA (0.50 ± 0.21 and 0.42 ± 0.19 mmol/l) were not different under either occasion (LIP vs. CON, P = not significant). During both pancreatic clamps, plasma insulin, C-peptide, and glucagon concentrations were comparable (Table 1). Plasma glucose was maintained at fasting concentrations under both conditions (Fig. 1A). Plasma FFA nearly doubled during LIP (P < 0.001 vs. baseline) but decreased by −90% (P < 0.001 vs. baseline) during CON (LIP vs. CON, P < 0.001) (Table 1). Plasma TG exhibited a similar pattern (LIP vs. CON, P < 0.001). Lipid infusion also raised β-hydroxybutyrate (LIP vs. CON, P < 0.05), which remained unchanged during CON. Plasma lactate was ~23% lower during LIP than during CON (P = 0.0013).

Whole body glucose disposal and intramyocellular G6P. During the first 105 min of the clamps, the glucose infusion and saturation, as described previously in detail (8). Changes of G6P from baseline were determined from difference spectra (8, 35). Intracellular pH was calculated from the difference of the chemical shift between Pi and PCr (21). ADP concentrations were calculated according to the equation for the equilibrium constant for the creatine kinase reaction (8).

Table 1. Steady-state concentrations of hormones and metabolites during euglycemic pancreatic clamp tests with low-dose insulin supplementation (6 mU·m body surface area−2·min−1) on CON and LIP days in 8 healthy males

<table>
<thead>
<tr>
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<th>CON</th>
<th>LIP</th>
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<tbody>
<tr>
<td>Insulin, pmol/l</td>
<td>93 ± 13</td>
<td>90 ± 11</td>
</tr>
<tr>
<td>C-peptide, pmol/l</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>Glucagon, pmol/l</td>
<td>48 ± 14</td>
<td>49 ± 12</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.5 ± 0.1</td>
<td>5.5 ± 0.1</td>
</tr>
<tr>
<td>FFA, mmol/l</td>
<td>0.05 ± 0.03</td>
<td>1.12 ± 0.22‡</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>48 ± 14</td>
<td>643 ± 163‡</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.91 ± 0.17</td>
<td>0.64 ± 0.11†</td>
</tr>
<tr>
<td>β-Hydroxybutyrate, mmol/l</td>
<td>96 ± 0</td>
<td>460 ± 290*</td>
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Values are means ± SD. CON, control; LIP, lipid infusion. *P < 0.05, †P < 0.005, and ‡P < 0.001 for the comparison between CON and LIP.
rate (GIR) required to maintain euglycemia did not differ between LIP and CON (Fig. 1, A and B). Between 110 and 180 min, GIR was 50% lower during LIP than during CON (0.87 ± 0.45 vs. 1.75 ± 0.42 mg·kg⁻¹·min⁻¹, P = 0.002). During the pancreatic clamps, intramyocellular concentrations of G6P remained unchanged from baseline in LIP but tended to increase in CON (repeated-measures ANOVA P = 0.059), albeit without significant difference from LIP (Fig. 1C).

**Intramyocellular fATPase.** Baseline fATPse did not differ between both LIP and CON study days (11 ± 3 vs. 10 ± 4 μmol·g muscle⁻¹·min⁻¹, P = NS). During the pancreatic clamp, fATPase remained unchanged at 10.2 ± 2.2 and 10.5 ± 2.6 μmol·g muscle⁻¹·min⁻¹, without differences between LIP and CON (Fig. 2A). Correlation analysis revealed no significant relationship between metabolic parameters of lipid (FFA, TG, IMCL) or glucose metabolism (glucose, insulin, GIR, G6P) and fATPase at baseline or during the low-insulin clamp.

**Intramuscular phosphorus metabolites.** Intramyocellular Pi was similarly increased under both conditions by 8 and 12% (P = 0.05 vs. baseline for LIP and CON), without difference between LIP and CON (Table 2). Intramyocellular ADP, PCr, and pH were not affected by the clamp during LIP and CON (Table 2).

**IMCL.** IMCL in soleus muscle was unchanged at the end of the low-insulin clamp and not different between LIP and CON (Fig. 2B).

**DISCUSSION**

This study shows that modest plasma FFA concentrations for up to 3 h reduce whole body glucose disposal but do not affect myocellular fATPase in healthy humans.

Excessive plasma FFA elevation for up to 6 h leads to skeletal muscle insulin resistance associated with reduced glucose transport/phosphorylation, glycogen synthesis, and glucose oxidation (6, 10, 35). These effects are currently attributed to a rise in intramyocellular concentrations of fatty acid metabolites and subsequent interference with various steps of insulin signaling (17, 34). Alternatively, overload of the tricarboxylic acid cycle by β-oxidation of FFA could lead to incomplete fat oxidation along with impaired mitochondrial function (36). This mechanism would be particularly relevant during low-grade insulinemia, when glucose metabolism is not maximally stimulated. Of note, lipid infusion stimulates insulin secretion and decreases fasting glycemia (5) and causes marked hyperglycemia under classical basal insulin (~35 pmol/l) pancreatic clamp conditions (36). To prevent such differences in plasma insulin or glucose concentrations between the lipid and control studies, we chose a pancreatic...
Table 2. Intramyocellular concentrations of P<sub>i</sub>, ADP, PCr, and pH as determined noninvasively by 31P-MRS before (baseline) and during the euglycemic pancreact test with low-dose insulin substitution (6 mU·m body surface area<sup>-2·min<sup>-1</sup></sup>) with CON or LIP in 8 healthy males

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>90–120</th>
<th>150–170</th>
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<tbody>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt;, mmol/l muscle</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CON</td>
<td>2.63 ± 0.38</td>
<td>3.20 ± 0.40*</td>
<td>2.96 ± 0.30*</td>
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<tr>
<td>LIP</td>
<td>2.95 ± 0.62</td>
<td>3.30 ± 0.80*</td>
<td>3.15 ± 0.72</td>
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<td>ADP, µmol/l muscle</td>
<td></td>
<td></td>
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<tr>
<td>CON</td>
<td>59 ± 8</td>
<td>61 ± 10</td>
<td>59 ± 10</td>
</tr>
<tr>
<td>LIP</td>
<td>56 ± 6</td>
<td>57 ± 4</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>PCr, mmol/l muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>21 ± 2</td>
<td>21 ± 3</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>LIP</td>
<td>22 ± 2</td>
<td>22 ± 2</td>
<td>23 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON</td>
<td>7.09 ± 0.02</td>
<td>7.10 ± 0.02</td>
<td>7.09 ± 0.02</td>
</tr>
<tr>
<td>LIP</td>
<td>7.08 ± 0.01</td>
<td>7.09 ± 0.02</td>
<td>7.09 ± 0.02</td>
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Values are means ± SD. PCr, phosphocreatine; MRS, magnetic resonance spectroscopy. *P < 0.05 for the within-group comparison between low-insulin period and baseline.

This study shows that 2–3 h of lipid infusion combined with a small rise in plasma insulin within the pathophysiological range do not affect fATPase. Previous studies using in vivo and ex vivo measurements of mitochondrial oxidative phosphorylation demonstrated a regulatory effect of insulin on skeletal muscle ATP production, mitochondrial protein synthesis, and enzyme activities (2, 8, 18, 30, 40, 41). In healthy humans, postprandial-like plasma insulin concentrations stimulate ATP production and protein synthesis (2, 8, 30, 40, 41). Most recently, lipid infusion for 6 h without inhibition of endogenous insulin secretion decreased the ex vivo-measured muscle inner mitochondrial membrane potential but did not affect citrate synthase activity, ATP content, or mitochondrial content or gene expression (10). Short-term insulin deprivation, on the other hand, decreases ATP production in mitochondria isolated from skeletal muscle of type 1 diabetic patients (18). In agreement with the present study, small increases in plasma insulin did not alter ATP production by mitochondria isolated from skeletal muscle of healthy humans (2).

In the present study, myocellular P<sub>i</sub> concentration was similarly increased by ~8 and 12% during LIP and CON, respectively, which is in accordance with our previous finding that FFAs do not affect the insulin-stimulated rise in P<sub>i</sub> (35). Of note, the insulin-mediated increase in P<sub>i</sub> was found to be reduced in insulin-resistant first-degree relatives of patients with T2DM and in the presence of increased plasma FFA during concomitant hyperglycemia (21, 30). Moreover, myocellular ADP, PCr, and pH were comparable during LIP and CON conditions, rendering allosteric effects of these metabolites on mitochondrial ATP synthase flux or glucose transport/phosphorylation unlikely.

Because fasting plasma FFA concentrations were identified as the strongest predictor of basal myocellular fATPase in nondiabetic and T2DM patients (41), one might suspect a pathophysiological relationship between increased plasma FFA and oxidative phosphorylation in skeletal muscle. Nevertheless, fasting plasma FFAs were not increased in the insulin-resistant participants of this study despite impaired insulin-stimulated fATPase. Likewise, studies on the long-term effects of increased FFA availability revealed conflicting results regarding mitochondrial function and biogenesis in rodents. Mice on high-fat diets developed abnormalities of biogenesis, structure, and function of skeletal muscle mitochondria associated with diabetes (7). Interestingly, impairment of biogenesis of muscle mitochondria did not develop prior to the onset of overt diabetes but clearly after the development of insulin resistance (7). On the other hand, Zucker diabetic fatty rats serving as a model of T2DM exhibit normal mitochondrial function despite elevated plasma FFA (12). In high-fat-fed rats, both mitochondrial biogenesis and enzymes of the fatty acid oxidation pathway and citrate cycle were even upregulated by activation of the PPAR<sub>δ</sub> pathway (14, 15). Furthermore, mice overexpressing PGC-1<sub>α</sub> show increased myocellular mitochondrial density and fATPase but are more prone to fat-induced insulin resistance (11). These findings rather support the concept of incomplete β-oxidation, which proposes that fat-induced insulin resistance occurs despite increased transport of fatty acids into mitochondria (20).

In healthy humans, consumption of a high-fat diet for 3 days not only increased plasma FFA but resulted in coordinated downregulation of genes involved in oxidative phosphorylation and mitochondrial biogenesis (39). An even shorter time period of plasma FFA elevation induced by lipid infusion for 48 h decreased the expression of PGC-1 and nuclear-encoded mitochondrial genes in skeletal muscle (33). Thus, the duration...
of FFA exposure seems to be critical for the analysis of FFA effects on skeletal muscle mitochondria. In the present study, we assessed rapid effects of increased FFA occurring within 3 h on skeletal muscle mitochondrial fATPase, which rules out relevant alterations of enzyme expression. A recent ex vivo study found that low concentrations of FFA metabolites such as palmitoyl carnitine and palmitoyl-CoA stimulate, whereas higher concentrations inhibit, ATP production in mitochondria of human and murine muscle (1). The inhibitory effects were explained mainly by inhibition of the electron chain transport activity. In contrast, 6 h of plasma FFA elevation decreased only the inner mitochondrial membrane potential in skeletal muscle (10). These measurements were performed under ex vivo conditions and in the absence of inhibition of insulin secretion by somatostatin (10). Using the in vivo dynamic approach and matched plasma glucose and insulin concentrations, we found no acute (within 3 h) alterations of mitochondrial fATPase in skeletal muscle during lipid infusion. This suggests that direct effects of FFA on mitochondrial ATP production do not likely contribute to FFA-induced peripheral insulin resistance. Differences between our in vivo and the above-mentioned ex vivo studies could be due to differences in the composition of the lipid infusion containing a high percentage of unsaturated FFAs and in the effective FFA metabolite concentrations in the myocellular cytoplasm and the shorter duration of increased FFA exposure in the present study. Of note, we also detected no changes in IMCL in soleus muscle, which is in accordance with previous data also obtained at low plasma insulin levels (21).

This study has some limitations. The setting of an acute increase in plasma FFAs does not allow us to extrapolate the findings to long-term effects of increased lipid availability, particularly resulting from high-fat feeding of rodents. Furthermore, no biopsies were taken, so alterations of the insulin-signaling cascade or intramyocellular fatty acid metabolites are not available. In addition, only males were studied here, so possible sex-associated differences in the susceptibility to fatty acid-induced insulin resistance cannot be ruled out (13, 27).

In conclusion, acute lipid elevation for 2–3 h already reduces whole body glucose uptake but fails to affect fATPase within this time frame. These data complete the finding that prolonged lipid availability for 6 h reduces insulin-stimulated fATPase in parallel, but not prior to impairment of glucose transport/phosphorylation and development of insulin resistance in skeletal muscle of healthy men (8). This suggests that lipid-induced insulin resistance results primarily from mechanisms decreasing glucose uptake rather than from direct interference of FFA metabolites with mitochondrial function.

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DISCLOSURES

The authors have nothing to disclose.

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