IL-6 selectively stimulates fat metabolism in human skeletal muscle

Wolsk E, Mygind H, Grøndahl TS, Pedersen BK, van Hall G. IL-6 selectively stimulates fat metabolism in human skeletal muscle. Am J Physiol Endocrinol Metab 299: E832–E840, 2010. First published September 7, 2010; doi:10.1152/ajpendo.00328.2010.—Interleukin (IL)-6 is chronically elevated in type 2 diabetes but also during exercise. However, the exact metabolic role, and hence the physiological significance, has not been elucidated. The objective of this study was to investigate the in vivo effect of recombinant human (rh) IL-6 on human fat and glucose metabolism and signaling of both adipose tissue and skeletal muscle. Eight healthy postabsorptive males were infused with either rhIL-6 or saline for 4 h, eliciting IL-6 levels of ~40 and ~1 pg/ml, respectively. Systemic, skeletal muscle, and adipose tissue fat and glucose metabolism was assessed before, during, and 2 h after cessation of the infusion. Glucose metabolism was unaffected by rhIL-6. In contrast, rhIL-6 increased systemic fatty acid oxidation approximately twofold after 60 min, and it remained elevated even 2 h after the infusion. The increase in oxidation was followed by an increase in systemic lipolysis. Adipose tissue lipolysis and fatty acid kinetics were unchanged with rhIL-6 compared with saline infusion. Conversely, rhIL-6 infusion caused an increase in skeletal muscle unidirectional fatty acid and glycero release, indicative of an increase in lipolysis. The increased lipolysis in muscle could account for the systemic changes. Skeletal muscle signaling increased after 1 h of rhIL-6 infusion, indicated by a fourfold increase in the phosphorylated signal transducer and activator of transcription (STAT) 3-to-STAT3 ratio, whereas no changes in phosphorylated AMP-activated protein kinase or acetyl-CoA carboxylase levels could be observed. Our findings suggest that an acute increase in IL-6 at a normophysiologic level selectively stimulates lipolysis in skeletal muscle, whereas adipose tissue is unaffected.

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metabolic effects of rhIL-6 infusion in humans are mediated by
an increase in phosphorylation of AMPK in skeletal muscle.

MATERIALS AND METHODS

Subjects. The ethics committee of Copenhagen, Region H, ap-
proved the protocol (H-D-2007–0012), and all aspects of the Helsinki
Declaration were respected. After giving their written and oral con-
sent, subjects underwent a physical examination, parameters of health
were examined in blood, and an electrocardiogram was recorded.
Eight nonsmoking male subjects were recruited for each intervention;
age, weight, and body mass index for the saline and rhIL-6 group were
26.0 ± 3.5 vs. 24.3 ± 3.7 yr; 81.2 ± 10.3 vs. 75.6 ± 11.1 kg, and
24.7 ± 2.0 vs. 23.1 ± 3.5 kg/m², respectively.

Subjects were enrolled if they were moderately physically active,
medication free, had a balanced diet, and did not suffer from acute or
chronic illness. Body composition of fat and fat-free mass was
measured using a dual-energy X-ray absorptiometry scanner (software
version 8.8, Lunar Prodigy; GE Medical Systems LUNAR, Prodigy
Advance, Milwaukee, WI). Subjects were scanned on the examination
day by the researcher, and for calculation of leg composition a
line from symphysis pubis to the proximal part of the trochanter major
femoris was used to define the lower extremity. The whole body
fat-free mass was 66.7 ± 7.2 vs. 62.1 ± 9.4 kg, and leg fat-free mass
was 10.9 ± 1.5 vs. 10.2 ± 1.5 kg for the saline and rhIL-6 groups,
respectively.

Experimental design. A non-cross-over design was chosen because of
the invasiveness of the protocol. Having refrained from meal
ingestion after 10:00 P.M. and exercise the previous day, subjects
reported to the laboratory at 7:00 A.M. Subjects remained supine and
fasted for the entire experimental day. Water was allowed ad libitum.
The superficial epigastric vein and the femoral vein and artery were
catheterized using the methods described by Frayn et al. (11) and van
Hall et al. (35), respectively. An antecubital vein was used for the
infusion of stable isotopes. A priming bolus of Na[H¹³CO₃] (1.5
µmol/kg), a primed continuous infusion of [6,6-D₂]glucose (17.6 µmol/
kg, 0.4 1.5 µmol·kg⁻¹·min⁻¹) and [1,1,2,3,3-D₅]glycerol (1.5 µmol/
kg, 0.1 µmol·kg⁻¹·min⁻¹), and a continuous infusion of potassium
[U-¹³C₁]palmitate (0.05 µmol·kg⁻¹·min⁻¹) was provided. All stable
isotopes (Cambridge Isotope Laboratories) were prepared under ster-
ile condition on the morning of the experiment. After 2 h of tracer
infusion to establish steady state in metabolite concentration and
enrichment of the stable isotopes, a 4-h infusion of either saline or
rhIL-6 was started, and changes were followed for another 2 h upon
cessation of the infusions. rhIL-6 (Sandoz, Basel, Switzerland) was
infused at a rate of 5 µg/ml to reach a desired systemic plasma level of
40 pg/ml. The infusion rate was chosen based on prior experience
(21, 25, 26). The rhIL-6 was dissolved in 5% human albumin (CSL
Behring, Marburg, Germany) to avoid adherence of the rhIL-6 mol-
ecule to the plastic wall of the infusion bag.

Skeletal muscle biopsies from the vastus lateralis were obtained by
the percutaneous needle biopsy method at baseline, 1 h into the
infusion, and 2 h after the cessation of infusion. Blood and visible
connective tissue were quickly removed from the biopsies before
being frozen in liquid nitrogen and stored at ~80° until analyses.
Blood was drawn every 30 min the first 3 h, after which blood was
drawn every hour.

Statistical methods. Statistical design was conferred with a biosta-
istitician. All values are given as means ± SE, except subject charac-
teristics, which are presented as means ± SD. The following data
were transformed to achieve normality: palmitate, glycerol, and glu-
cose release and uptake data and glucagon, cortisol, and muscle
protein data. Transformed data are presented as geometric means
± SE. Changes between treatments and over time were tested with a
repeated-measures ANOVA.

A post hoc t-test with Tukey correction was applied to identify time
points of statistical significance. A probability level of 5% was chosen
as being significant.

Supplemental data. The methods pertaining to the metabolite
concentration, isotopic enrichments and calculations, blood flow mea-
surements, and the skeletal muscle protein analyses are described in
detail in Supplemental data (Supplemental data for this article may be
found on the American Journal of Physiology: Endocrinology and
Metabolism website.).

RESULTS

The arterial IL-6 concentration did not change during the
saline trial. During the rhIL-6 infusion, the arterial IL-6 con-
centration reached steady state after 60 min of infusion at
10.4 ± 4.3 pg/ml (see Table 1). Upon cessation of the rhIL-6
infusion, a rapid decrease in IL-6 concentration was found,
reaching baseline values within 60 min. There was a significant
difference in systemic IL-6 concentrations between the saline
group and the rhIL-6 group (P < 0.0002). The rhIL-6 infusion
did not cause any changes in blood pressure, body temperature,
or heart rate (data not shown). The subjects did not report any
malaise or other adverse reactions and were unaffected by both
infusions.

Blood flow increased during the rhIL-6 infusion (Table 1).
During the day, adipose blood flow gradually increased in the
saline group (P < 0.003). The rhIL-6 infusion increased the
adipose tissue blood flow significantly after 90 min of rhIL-6
infusion (P = 0.002). After cessation of rhIL-6 infusion, the
adipose tissue blood flow tended to decline 2 h postinfusion.
Leg blood flow was initially comparable between the two
groups and did not change during the experiment in the saline
group, whereas leg blood flow increased after 90 min of rhIL-6
infusion. The leg blood flow was significantly affected by the
rhIL-6 infusion (P < 0.04).

Table 1. Arterial hormonal concentrations and blood flow

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Baseline</th>
<th>4th h of Infusion</th>
<th>2nd h Postinfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, pg/ml</td>
<td>0.85 ± 0.23</td>
<td>0.91 ± 0.09</td>
<td>0.89 ± 0.11</td>
</tr>
<tr>
<td>Saline</td>
<td>0.49 ± 0.12</td>
<td>42.19 ± 2.70</td>
<td>1.91 ± 0.17</td>
</tr>
<tr>
<td>rhIL-6</td>
<td>0.30 ± 0.07</td>
<td>0.24 ± 0.04</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>Epinephrine, nmol/l</td>
<td>0.42 ± 0.08</td>
<td>0.32 ± 0.03</td>
<td>0.42 ± 0.05</td>
</tr>
<tr>
<td>Cortisol, ng/ml</td>
<td>5.7 ± 3.8</td>
<td>22.9 ± 2.0</td>
<td>23.4 ± 3.3</td>
</tr>
<tr>
<td>Saline</td>
<td>10.5 ± 1.7</td>
<td>9.0 ± 6.0</td>
<td>60.9 ± 10.5</td>
</tr>
<tr>
<td>rhIL-6</td>
<td>19.9 ± 2.4</td>
<td>23.3 ± 1.7</td>
<td>22.8 ± 1.9</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>25.3 ± 3.1</td>
<td>19.5 ± 1.8</td>
<td>22.7 ± 2.5</td>
</tr>
<tr>
<td>Saline</td>
<td>46.9 ± 8.3</td>
<td>45.3 ± 7.1</td>
<td>45.2 ± 6.9</td>
</tr>
<tr>
<td>rhIL-6</td>
<td>47.9 ± 8.7</td>
<td>52.8 ± 9.0</td>
<td>60.9 ± 10.5</td>
</tr>
<tr>
<td>Leg blood flow, ml/min</td>
<td>352 ± 22</td>
<td>376 ± 37</td>
<td>357 ± 32</td>
</tr>
<tr>
<td>Saline</td>
<td>400 ± 66</td>
<td>462 ± 50</td>
<td>477 ± 50</td>
</tr>
<tr>
<td>rhIL-6</td>
<td>2.70 ± 0.36</td>
<td>2.63 ± 0.31</td>
<td>3.27 ± 0.33</td>
</tr>
<tr>
<td>Adipose tissue blood flow, ml 100 g tissue⁻¹·min⁻¹</td>
<td>2.57 ± 0.44</td>
<td>4.03 ± 0.56</td>
<td>4.24 ± 0.58</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 ± 8 subjects. Hormone concentration and
blood flow averages at baseline, last hour of infusion (4th h), and in the 2nd h
after cessation of infusion. Symbols denote a significant effect of the recom-
binant human (rh) interleukin-6 (IL-6) infusion (repeated-measures ANOVA):
*P < 0.0002, **P < 0.002, ***P < 0.05, ****P < 0.03, *P < 0.04, and **P < 0.002.
Hormones were largely unaffected by rhIL-6 (Table 1). Epinephrine levels did not differ between the two groups, and there was no effect of the rhIL-6 infusion. Cortisol concentrations were similar between the two groups at baseline and during most of the infusion and postinfusion period. However, a transient increase in cortisol was observed after 2 h of rhIL-6 infusion, whereafter the concentration decreased to baseline levels. Insulin levels were similar between groups at baseline, but rhIL-6 infusion suppressed insulin 20% ($P < 0.05$) before returning to saline group levels 1 h after the infusion. Glucagon levels were also similar at baseline in the two groups. rhIL-6 infusion led to a small increase in glucagon levels throughout the remainder of the trial ($P < 0.03$).

rhIL-6 increased whole body fatty acid oxidation, which was followed by increased lipolysis. Whole body fatty acid appearance, represented by palmitate appearance (Fig. 1B),

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**Fig. 1.** Systemic palmitate kinetics and indirect calorimetry under basal conditions, during 4 h of either saline (saline) or recombinant human (rh) interleukin-6 (IL-6) infusion, and 2 h of recovery. The arterial palmitate concentration (A), palmitate rate of appearance (Ra) (B), palmitate oxidation (C), palmitate oxidation rate relative to the palmitate rate of disappearance (D), the ratio between palmitate and glycerol rate of appearance (E), and indirect calorimetry data are shown (F). FFA, free fatty acid. Statistical analysis was not performed in D, since it is concocted of data from B and C. The gray bar denotes the period of infusion. Values are depicted as means ± SE ($n = 8$ subjects). □, Saline-infused group; △, rhIL-6-infused group. *Time points of significant differences between interventions ($P < 0.05$). §Difference between the interventions (time × treatment: $P < 0.002$). #Difference between the groups (treatment: $P < 0.0001$).
increased steadily in the saline trial during the day, averaging 1.80 ± 0.17 at baseline and increasing to 2.17 ± 0.21 μmol·kg⁻¹·min⁻¹ (time: P < 0.001) 2 h postinfusion. The palmitate concentration (Fig. 1A) and rate of appearance (Fig. 1B) were significantly increased after 180 min into the rhIL-6 infusion (P < 0.05) and remained elevated during the remaining rhIL-6 infusion (time × treatment: P < 0.002). The palmitate oxidation rate was similar at baseline (P < 0.52) (Fig. 1C) but increased almost twofold after 60 min (P < 0.05) into the rhIL-6 infusion and reached a constant plateau ~1.50 μmol·kg⁻¹·min⁻¹, whereas the saline group remained stable at ~0.75 μmol·kg⁻¹·min⁻¹ (treatment: P < 0.0001). This was mirrored in a drop in the expired volume of CO₂/O₂ (Fig. 1F).

In addition, the relative rate of palmitate disappearing from the circulation due to oxidation increased, implying that less palmitate was reesterified into triacylglycerol (Fig. 1D). No changes in the whole body intracellular reesterification were seen during the experiment for either saline or rhIL-6 infusion (Fig. 1E).

Adipose tissue fatty acid release was unaffected by rhIL-6. The net release of palmitate from adipose tissue increased throughout (time: P < 0.07) the day in both groups. There was a small but measurable and similar unidirectional uptake of palmitate by adipose tissue in both groups (different from 0, P < 0.0001; Fig. 2B). The unidirectional glycerol release over time (data not shown) increased in both groups (P < 0.03) in parallel to the palmitate release (Fig. 2C), which kept the unidirectional release ratio between glycerol and fatty acids constant throughout the study, suggesting an unchanged and similar intracellular fatty acid reesterification in both groups (Fig. 2D).

Skeletal muscle fatty acid release was increased during and after the rhIL-6 infusion. Under basal conditions, there was a net leg palmitate uptake in both groups, which further increased during the experiment in the saline group (P < 0.05; Fig. 2E). In contrast, the net uptake of palmitate in the rhIL-6 group decreased toward zero (Fig. 2E), which was most likely because of an increase in unidirectional palmitate release (150–300 min, P < 0.05; Fig. 2G) since the unidirectional uptake was unchanged (Fig. 2F). Baseline rates of unidirectional palmitate release were equal between groups (P < 0.35), and there was a treatment effect of rhIL-6 (P < 0.02; Fig. 2G). The physiological significance was apparent when the cumulative release was compared between groups (area under the curve, saline: 2.873 vs. rhIL-6: 5.368 μmol·min⁻¹·min⁻¹, P < 0.001). No change in the unidirectional release of the palmitate-to-glycerol ratio in skeletal muscle was observed during the entire experiment, suggesting an unchanged and similar intracellular fatty acid reesterification in both groups (Fig. 2H).

Whole body and tissue glucose metabolism was unaffected by rhIL-6 (Fig. 3). The systemic glucose concentration dropped marginally during the day in both groups and was comparable (Fig. 3A). The endogenous glucose release was also similar between the two groups (Fig. 3B) and decreased in an exponential fashion throughout the day (saline, baseline: 13.54 ± 0.46 vs. 360 min: 9.93 ± 0.46 μmol·kg⁻¹·min⁻¹). Both leg and adipose glucose uptake was constant throughout the day and equal between interventions (Fig. 3, C and D).

rhIL-6 infusion increased phosphorylated (p) signal transducer and activator of transcription (STAT) but not p-AMPK (Fig. 4). The ratio of the p-STAT3 to STAT3 increased more than fourfold after 1 h of infusion compared with baseline (P < 0.04) and returned to baseline values within 2 h after the cessation of infusion. There were no changes during the experiment in the p-AMPK-to-AMPK ratio or in p-acetyl-CoA carboxylase (ACC) compared with baseline values in either group.

**DISCUSSION**

The major and novel findings of the present study were that an acute elevation of IL-6 in humans at normophysiological levels caused 1) an increase in the absolute rate of fatty acid oxidation that was accompanied by an increase in the rate of lipolysis, hence increased fatty acid appearance and concentration in the blood; 2) fatty acid clearance from the blood was redirected from esterification into fat toward oxidation; 3) moreover, the systemic increase in fatty acid appearance during rhIL-6 infusion could be attributed to the increased unidirectional release of fatty acids by the leg, i.e., a likely increase in muscle lipolytic rate. In contrast to our hypothesis, no changes in fatty acid metabolism of abdominal adipose tissue were apparent during elevated IL-6; and 4) rhIL6 acutely increased skeletal muscle signaling via STAT3, however, no changes in the phosphorylation of AMPK or ACC could be observed after 4 h of acutely elevated IL-6 levels. These findings suggest that IL-6 may be an important acute and direct modulator of skeletal muscle fat metabolism. However, this does not exclude that IL-6 affects adipose tissue and liver fatty acid handling during chronic exposure.

In the present study, the increase in absolute rate of fatty acid oxidation (Fig. 1C), and the relative clearance of fatty acids directed toward oxidation away from esterification into fat (Fig. 1D), was noted after 60 min of rhIL-6 infusion. These changes were followed after 2 h by an increase in the whole body rate of lipolysis, fatty acid appearance and concentration, as shown previously (26, 37). This suggests that the IL-6-induced stimulation of fatty acid oxidation is the primary event, which in turn stimulates lipolysis to supply more fatty acids for oxidation. Another option is that IL-6 acts by enhancing or reducing levels of other metabolically active hormones. Although we observed an ~20% decrease in insulin concentration upon rhIL-6 infusion, it does not seem plausible that this decrease can fully account for the metabolic changes observed. Interestingly, from this study and others, it seems that the metabolic effects of rhIL-6 are largely independent of the doses infused and systemic concentration reached within a semiphysiological range. IL-6 concentrations ranging from 40 up to 600 pg/ml (26, 32, 37) seem to elicit a similar lipolytic response. This observation is true both for young healthy subjects (37), older subjects (26), and cancer patients (32). In the IL-6 ranges listed, the systemic concentrations of cortisol, epinephrine, and growth hormone were largely different depending on the IL-6 concentrations reached (19, 26, 32, 37). These hormones are all believed to have dose-dependent effects on metabolism. This could mean that metabolic effects of IL-6 are not mediated via any of the major hormones mentioned above. Although cortisol was affected by the rhIL-6 infusion, experiments with measurement of systemic free fatty acids following an infusion of cortisol in healthy humans (8, 16) or cortisol withdrawal in cortisol-dependant patients (7) have not proven cortisol as a lipolytic hormone. More puzzling
Fig. 2. Adipose tissue (A-D) and leg skeletal muscle (E-H) palmitate kinetics under basal conditions, during 4 h of either saline or rhIL-6 infusion, and 2 h of recovery. The column on the left shows data on adipose tissue, including net adipose tissue palmitate uptake (A), unidirectional palmitate uptake (B), unidirectional palmitate release (C), and the unidirectional palmitate to glycerol release ratio (D). The column on the right shows data on leg skeletal muscle, specifically skeletal muscle palmitate uptake (E), unidirectional palmitate uptake (F), unidirectional palmitate release (G), and the unidirectional palmitate-to-glycerol release ratio (H). The gray bar denotes the period of infusion. Values are depicted as geometric means ± SE (n = 8 ± 8). ■, Saline-infused group; △, rhIL-6-infused group. *Time points of significant differences between interventions (P < 0.05). #Difference between the groups (treatment: P < 0.02).
is the observation that, following the cessation of rhIL-6 infusion, the alterations in fat metabolism seem to persist both with regard to lipolysis and fatty acid oxidation. The minor changes in cortisol in the present studies or other hormones like growth hormone and testosterone (26, 33, 34) could be implicated in the hours following the infusion, which would suit the characteristics of these hormones better. Alternatively, the chronic metabolic effects of IL-6 on energy expenditure could be mediated via the central nervous system as implicated in rodent models (18, 38).

The major aim of this study was to identify the potential target tissue(s) of IL-6 in vivo in healthy humans. We measured across the leg with a femoral venous catheter placed distally from the inguinal ligament ensuring sampling of effluent skeletal muscle blood (35, 36). Subcutaneous adipose tissue sampling was obtained from an abdominal vein draining a large adipose tissue area of the anterior abdominal wall (11). In contrast to our hypothesis, the unidirectional fatty acid release from, or uptake by, adipose tissue, and hence net fatty acid release were not different in the rhIL-6 group compared with the saline infusion (Fig. 2, A-D). In contrast, the skeletal muscle net fatty acid uptake was markedly reduced during and after rhIL-6 infusion; actually, no fatty acid uptake by the leg could be observed. The reduction in the net fatty acid uptake was caused solely by an increase in unidirectional fatty acid release, since unidirectional fatty acid uptake was similar during the entire study. With an unchanged intracellular reesterification rate, this higher fatty acid and glycerol release indicates an increased muscle triacylglycerol breakdown. To examine whether the increase in skeletal muscle triacylglycerol breakdown could account for the systemic increase in fatty acid rate of appearance, we examined the last hour of infusion as steady state was observed for virtually all measurements. By looking at the differences between the saline and the rhIL-6 group with regard to skeletal muscle unidirectional palmitate release (Fig. 2G), we examined whether the differences could account for the systemic changes in palmitate rate of appearance (Fig. 1B). The difference in systemic palmitate rate of release between interventions was 34 μmol/min (rhIL-6: 179 ± 5 μmol/min, saline: 145 ± 8 μmol/min). The total unidirectional release of palmitate from muscle was derived by dividing leg release by the leg muscle mass and multiplying with the whole body skeletal muscle mass (rhIL-6: 102 ± 11 μmol/min, saline: 46 ± 5 μmol/min). Assuming that rhIL-6 has a similar effect on all skeletal muscle, the unidirectional palmitate release elicited by rhIL-6 infusion was 56 μmol/min compared with the systemic increase in palmitate appearance of 34 μmol/min. This suggests that the increased skeletal muscle fatty acid release indeed can account for the observed increase in systemic fatty acid appearance.

To elucidate the site of the increased fatty acid oxidation, we tried to measure skeletal muscle fatty acid oxidation. This

![Fig. 3. Systemic and tissue glucose kinetics under basal conditions, during 4 h of either saline or rhIL-6 infusion, and 2 h of recovery. A: arterial glucose concentration; B: endogenous glucose appearance; C: adipose tissue net glucose uptake; D: skeletal muscle net glucose uptake. The gray bar denotes the period of infusion. Values are depicted as means ± SE (n = 8 + 8). ■, Saline-infused group; ▲, rhIL-6-infused group.](http://ajpendo.physiology.org/doi/abs/10.220.33.6)
measurement relies on many variables to be measured for its calculation, thereby introducing substantial variability, especially under resting conditions where energy expenditure and thus fatty acid oxidation rates are low. However, during the last 2 h of rhIL-6 infusion, a relative higher rate of palmitate taken up was oxidized (saline: 27 ± 7% vs. rhIL-6: 53 ± 8%, P < 0.005). This suggests that the increase in systemic palmitate clearance toward oxidation mainly occurs in skeletal muscle. Although we observe that a relatively higher rate of palmitate taken up was oxidized in the rhIL-6 group, our data on leg skeletal muscle fat oxidation is not strong. If the increase in fat oxidation was countered closely by an increase in lipolysis, it would seem most obvious that the fatty acids liberated in skeletal muscle lipolysis would be oxidized rather than released from the leg as we observe. This could speak in favor of the liver also having a role in the increased oxidation. An alternative explanation could be that subcutaneous adipose tissue from the leg was affected by rhIL-6 in contrast to the abdominal depot. The rise in palmitate release from skeletal muscle could then be the result of superficial venous “contamination” from leg subcutaneous adipose tissue.

Fig. 4. Skeletal muscle protein concentrations under basal conditions, after 1 h of either saline or rhIL-6 infusion, and 2 h of recovery. A: phosphorylated (p) signal transducer and activator of transcription (STAT) 3-to-STAT3 ratio indexed to baseline (BL) values; B: p-AMP-activated protein kinase (AMPK)-to-AMPK ratio indexed to baseline values; C: p-acetyl-CoA carboxylase (ACC) indexed to baseline values. AU, arbitrary units. Values are depicted as geometric means ± SE (n = 8 ± 8). Filled bars, saline-infused group; open bars, rhIL-6-infused group. *Significant difference between interventions 1 h into the infusion.
Our findings agree with the effects of IL-6 seen for in situ rat soleus muscle fatty acid metabolism (4). Bruce and Dyck (4) found that increased IL-6 levels had no effect on muscle fatty acid uptake but increased exogenous as well as endogenous fatty acid oxidation. Whether endogenous fatty acids were oxidized cannot be determined in the present study. However, the observed increase in lipolysis of intramuscular triacylglycerol resulting in a higher availability/intracellular concentration of these endogenous fatty acids may well have increased their oxidation.

IL-6 has been shown to enhance lipolysis and fatty acid oxidation in rat skeletal muscle (20), L6 myotubes (26), and primary human skeletal muscle cells (1) via an increase in the phosphorylation of STAT3 and AMPK. It is well known that AMPK phosphorylates ACC, a rate-limiting step in the conversion of acetyl-CoA to malonyl-CoA. The phosphorylation of ACC inhibits its activity, which results in decreased malonyl-CoA levels that in turn inhibit the carnitine-to-palmitoyl-CoA transferase-1 ratio, a rate-limiting step for the entry of long-chain fatty acyl-CoA into mitochondria for oxidation. In this study, we show that elevating IL-6 levels acutely increases in vivo muscle signaling within 1 h as observed by a fourfold increase in the p-STAT3-to-STAT3 ratio. The activation of STAT3 returned to baseline values 2 h after cessation of rhIL-6 infusion. In contrast to our initial belief, we did not see any changes in either p-AMPK/AMPK or p-ACC. Although this is in contrast to in vitro findings, the apparent discrepancy may be explained by experimental conditions. Most findings are based on rodent cell lines (6) or rodent myocytes (20) distant from a human in vivo milieu. More importantly, the IL-6 incubation concentrations are typically >1,000-fold higher than what is seen physiologically in humans (25) or in the present study. Conversely, we cannot exclude that AMPK does play a role during endogenous IL-6 release (e.g., exercise). When Rosendal et al. (27) made subjects perform low-force exercise, during endogenous IL-6 release (e.g., exercise). When Rosendal et al. (27) made subjects perform low-force exercise, during endogenous IL-6 release (e.g., exercise).

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In conclusion, the selective nature of IL-6 to mobilize energy reserves in human skeletal muscle supports the notion that IL-6 has important autocrine/paracrine effects and conveys some of the metabolic effects of exercise. Furthermore, the sustained fat oxidation in skeletal muscle noted even after the cessation of rhIL-6 infusion could render IL-6 a mediator of the beneficial effects that exercise has on metabolic disease.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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