Suppressing lipolysis increases interleukin-6 at rest and during prolonged moderate-intensity exercise in humans

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Holmes, Anna G., Matthew J. Watt, and Mark A. Febbraio. Suppressing lipolysis increases interleukin-6 at rest and during prolonged moderate-intensity exercise in humans. J Appl Physiol 97: 689–696, 2004. First published April 9, 2004; 10.1152/japplphysiol.00195.2004.—IL-6 induces lipolysis when administered to humans. Consequently, it has been hypothesized that IL-6 is released from skeletal muscle during exercise to act in a “hormonelike” manner and increase lipolysis from adipose tissue to supply the muscle with substrate. In the present study, we hypothesized that suppressing lipolysis, and subsequent free fatty acid (FFA) availability, would result in a compensatory elevation in IL-6 at rest and during exercise. First, we had five healthy men ingest nicotinic acid (NA) at 30-min intervals for 120 min at rest [10 mg/kg body mass (initial dose), 5 mg/kg body mass (subsequent doses)]. Plasma was collected and analyzed for FFA and IL-6. After 120 min, plasma FFA concentration was attenuated (0 min: 0.26 mmol/l; 120 min: 0.09 ± 0.02 mmol/l; P < 0.01), whereas plasma IL-6 was concomitantly increased approximately eightfold (0 min: 0.75 ± 0.18 pg/ml; 120 min: 6.05 ± 0.89 pg/ml; P < 0.001). To assess the effect of lipolytic suppression on the exercise-induced IL-6 response, seven active, but not specifically trained, men performed two experimental exercise trials with (NA) or without [control (Con)] NA ingestion 60 min before (10 mg/kg body mass) and throughout (5 mg/kg body mass every 30 min) exercise. Blood samples were obtained before ingestion, 60 min after ingestion, and throughout 180 min of cycling exercise at 62 ± 5% of maximal oxygen consumption. IL-6 gene expression, in muscle and adipose tissue sampled at 0, 90, and 180 min, was determined by using semiquantitative real-time PCR. IL-6 mRNA increased in Con (rest vs. 180 min; P < 0.01) ~13-fold in muscle and ~42-fold in fat with exercise. NA increased (rest vs. 180 min; P < 0.01) IL-6 mRNA 34-fold in muscle, but the treatment effect was not statistically significant (Con vs. NA, P = 0.1), and 235-fold in fat (Con vs. NA, P < 0.01). Consistent with the study at rest, NA completely suppressed plasma FFA (180 min: Con, 1.42 ± 0.07 mmol/l; NA, 0.10 ± 0.01 mmol/l; P < 0.001) and increased plasma IL-6 (180 min: Con, 9.81 ± 0.98 pg/ml; NA, 19.23 ± 2.50 pg/ml; P < 0.05) during exercise. In conclusion, these data demonstrate that circulating IL-6 is markedly elevated at rest and during prolonged moderate-intensity exercise when lipolysis is suppressed.

IL-6 is a multifunctional, immune-modulating cytokine that is proposed to mediate important metabolic functions (9, 30). IL-6 is released from adipose tissue under noninflammatory conditions, contributing ~30% of the circulating IL-6 levels at rest (24), which is exacerbated after exercise (17). Recent work has demonstrated that IL-6 is released from skeletal muscle during exercise (for review, see Ref. 9). Specifically, the net leg release of IL-6 can account for the majority of the marked elevation of systemic IL-6 observed during exercise (37). Moreover, this release is potentiated by low-intramuscular glycogen stores (35) and is markedly attenuated when subjects are fed glucose throughout exercise (10). In circumstances in which muscle glycogen is low, the reliance on fatty acids as a fuel source is altered, and, therefore, these studies may suggest that one metabolic role of muscle-derived IL-6 is to act on adipose tissue to increase lipolysis, thereby providing an extracellular substrate. Two recent studies have demonstrated that recombinant human IL-6 infusion enhances lipolysis. Van Hall et al. (43) demonstrated that IL-6 infusion into healthy subjects increased adipose tissue lipolysis and increased fat oxidation in the absence of changes in other lipolytic hormones. In addition, Lyngsø et al. (22) showed that IL-6 infusion gave rise to an increase in net glycerol release in subcutaneous adipose tissue, leading these authors to conclude that IL-6 elicits lipolytic effects in human adipose tissue in vivo. Further research from transgenic mice studies also suggests that IL-6 is a lipolytic cytokine (45).

The exercise-induced increase of IL-6 has been hypothesized to have an energy-sensitizing role, sensing metabolically demanding situations, whereby it is released from contracting skeletal muscle to act in a hormonelike manner, mobilizing extracellular substrates, and/or augmenting substrate delivery during exercise (9, 30). To further investigate this potential role of IL-6 in relation to fat metabolism, in the present study, we tested the hypothesis that acute suppression of plasma free fatty acid (FFA) levels would augment IL-6 mRNA expression in muscle and adipose tissue and increase the plasma concentration of IL-6 in the circulation at rest and during prolonged moderate-intensity exercise.

METHODS

Resting Experiments

Subject characteristics. Five healthy, young men (28.8 ± 2.7 yr, 185.0 ± 3.7 cm, 76.3 ± 2.1 kg, means ± SE) volunteered to participate in this study, which was approved by the RMIT Human...
Research Ethics Committee. All subjects were informed of the experimental protocol, and the possible associated risks of the study were explained to subjects, both orally and in writing, before written, informed consent was obtained. No subject was taking any medication or had any confounding medical history.

**Experimental protocol.** Subjects reported to the laboratory in the morning after a 10- to 12-h overnight fast and rested quietly. An indwelling cannula was inserted into an antecubital vein for blood sampling and was kept patent by periodic saline infusion. A resting blood sample was taken for analysis of FFA, IL-6, epinephrine, and growth hormone (GH) (as described below). Subjects initially ingested a 10 mg/kg dose of nicotinic acid (NA; 250 mg tablets; Aspen Pharmacare) (time: 0 min), followed by three subsequent doses of 5 mg/kg at 30-min intervals. Additional blood samples were obtained at 60 and 120 min. Muscle and adipose tissue were not sampled in this resting component of the study. All subjects experienced the expected side effects of NA ingestion, which included flushing (a reddening of the skin due to peripheral vasodilation over most of the body), a sensation of heat, and a tingling sensation, which started ~15–20 min after the first dose. No subjects experienced stomach or gastrointestinal upset.

**Exercise Experiments**

**Subject characteristics.** Seven active men (24.3 ± 2.9 yr, 185.2 ± 2.2 cm, 80.4 ± 3.4 kg, means ± SE) volunteered to participate in this study, which was approved by the RMIT Human Research Ethics Committee, in accordance with the Declaration of Helsinki. All subjects were informed of the experimental protocol, and the possible associated risks of the study were explained to subjects both orally and in writing before written, informed consent was obtained. No subject was taking any medication or had any confounding medical history.

**Pre-experimental procedures.** Subjects visited the laboratory on four occasions. On the first, they performed a continuous and incremental workload test to exhaustion on an electrically braked cycle ergometer (LODE Instrument, Groningen, The Netherlands) to determine their peak pulmonary oxygen uptake ($\dot{V}O_2$peak), which averaged 4.3 ± 0.3 l/min. Subjects returned to the laboratory 1 wk later to complete a familiarization trial that consisted of cycling at 60% $\dot{V}O_2$peak for 120 min with NA ingestion (described subsequently). Tissue sampling did not occur during this trial, but subjects’ responses to NA were monitored. Expired pulmonary gases (Quark b3, COSMED, Rome, Italy) were collected and analyzed online at 30-min intervals. The purposes of the practice ride were to familiarize the subject with the protocol, confirm the subject’s tolerance to oral NA supplementation, and confirm the exercise power output of ~60% $\dot{V}O_2$peak. The absolute power output for the trials was 156 ± 5 W.

**Experimental protocol.** Each subject performed two experimental trials, separated by at least 7 days. For the day preceding each trial, subjects were provided with a food parcel [14 MJ, 80% carbohydrates (CHO)] and were required to abstain from exercise, caffeine, and alcohol. Subjects were also instructed to consume 5 ml/kg of tap water on waking to ensure euhydration. Subjects reported to the laboratory in the morning after a 10- to 12-h overnight fast and rested quietly. An indwelling cannula was inserted into an antecubital vein, as described above. Three incisions were made through the skin and fascia over the vastus lateralis muscle of one leg, and one incision was made in the ventrolateral abdominal wall, ~10 cm lateral of the navel under local anesthesia (2% lidocaine), for subsequent percutaneous muscle and adipose tissue biopsy sampling, respectively.

Trials were randomized, with subjects consuming either NA (described below) or nothing (Con) during the 60 min before exercise. Due to the mild side effects of NA (described above), we could not disguise the treatment, and, therefore, it was of no benefit to consume a placebo capsule during Con. Blood samples were obtained immediately before NA supplementation (~60 min), immediately before the start of exercise (0 min), and at 30, 60, 90, 120, 150, and 180 min during the exercise protocol. Immediately before exercise, resting muscle and adipose tissue biopsies were obtained while subjects rested on a bed. Samples were immediately frozen in liquid nitrogen and stored until analysis. Subjects subsequently moved to the cycle ergometer and, after a 5-min warm-up at 100 W, commenced cycling at the predetermined workload. Subjects ingested 100 ml of water every 60 min to ensure hydration. Additional muscle and adipose tissue samples were obtained at 90 and 180 min of exercise while subjects remained on the cycle ergometer. The elapsed time between cessation of exercise for biopsy sampling and resumption of exercise was ~0.3 s.Expired pulmonary gases were collected at 30-min intervals for the measurement of expired fractions of O2, CO2, and ventilation. All trials were performed at an ambient temperature of 19–21°C.

During the NA trial, subjects ingested a total of 45 mg/kg NA over eight individual doses: 10 mg/kg 60 min before exercise, 5 mg/kg 30 min before (~30) and immediately before (0 min) exercise, and at 30-min intervals throughout exercise.

Fat and CHO oxidation. Whole body CHO and fat oxidation rates were calculated from each of period of gas collection and estimated by using stoichiometric equations (31).

**Blood metabolites and hormonal analyses.** Venous blood was placed into precooled tubes containing EDTA for IL-6, GH, and cortisol analysis. IL-6 was analyzed by commercially available enzyme-linked immunosorbent assay (Quintakine high sensitivity IL-6 ELISA; R&D Systems Europe, Oxon, UK), and GH and cortisol were analyzed by radioimmunoassay (Coat-a-Count, Diagnostic Products). Five milliliters of whole blood were placed into precooled tubes containing lithium heparin for FFA, insulin, glucose, and lactate analysis. FFA was analyzed by an enzymatic colorimetric method (NEFA C, Wako Chemicals), and insulin was analyzed by radioimmunoassay (Coat-a-Count, Diagnostic Products). Glucose and lactate were immediately analyzed by an automated method (Yellow Springs Instruments 2300 STAT). Samples for epinephrine determination were treated with EGTA/GSH and later analyzed by radioimmunoassay (LDN, Nordhorn, Germany). All tubes were immediately spun at 1,300 rpm at 4°C for 3 min, and plasma was recovered and stored at ~80°C for the respective analysis.

**Muscle and adipose tissue IL-6 mRNA analyses.** Muscle and adipose tissue samples were extracted for total RNA by using the acid guanidium thiocyanate-phenol-chloroform extraction of Chomczynski and Sacchi (4), modified as previously described (7). IL-6 mRNA expression was determined on these samples by real-time PCR, as previously described (33). IL-6–probe and primers were designed from the human IL-6 gene sequences (GenBank/EBML accession nos. M54894 and M38669). An 81-base pair IL-6 fragment was amplified by using the forward primer 5′-GGTACATCCTCAGGCGCATCT-3′ and reverse primer 5′-GTGCCCTTTGGCTTTTAC-3′ (Sigma Geno-sys, Castle Hill, NSW, Australia). A TaqMan fluorescent probe, 5′-FAM (6-carboxyfluorescein)-GGTACTCTTTCTACACATGTCTC-3′ TAMRA (6-carboxy-tetramethylrhodamine) (Applied Biosystems), was included with the primers in each reaction. 18S mRNA was also amplified, and the TaqMan probes and primers for this gene were supplied in a control reagent kit (Applied Biosystems). Gene expression was quantified with a multiplex comparative critical threshold (Ct) method (Bio-Rad i Cycler QTM, Hercules, CA). The cycle number at which the cDNA amplification is first detected is reflected by the Ct value. For each sample, a change (Δ) in Ct value was obtained by subtracting 18S Ct from IL-6 Ct with the restaging value as the control. Restaging values for each subject were subtracted from the exercise samples for each subject to derive a Δ–ΔCt value. The expression of human IL-6 was then evaluated by $2^{-ΔCt}$. 


ingestion (0 min: 0.26 ± 0.5 nM; 120 min: 0.09 ± 0.02 nM; \( P < 0.002 \), whereas the plasma IL-6 concomitantly increased approximately eightfold (0 min: 0.75 ± 0.18 pg/ml; 120 min: 6.05 ± 0.89 pg/ml; \( P < 0.001 \)) (Fig. 1). Small increases were observed for plasma epinephrine (0 min: 0.22 ± 0.01 nM; 120 min: 0.33 ± 0.02 nM; \( P < 0.05 \)) and GH (0 min: 0.39 ± 0.04 
μg/ml; 60 min: 0.64 ± 0.04 μg/ml; \( P < 0.05 \)).

Exercise Experiments

**Respiratory responses during exercise.** In both trials, oxygen uptake was initially 57 ± 3% of maximal oxygen uptake and increased (\( P < 0.05 \)) to 67 ± 5% of \( \dot{V}_{O_2} \) peak during the last 60 min of exercise. The perceived rate of exertion and ventilation also increased (\( P < 0.05 \)) late in exercise (data not shown) and were not different between trials. Whole body CHO oxidation was lower (\( P < 0.05 \)) and fat oxidation higher (\( P < 0.05 \)) throughout exercise in Con compared with NA (Table 1).

**Plasma hormone metabolite and IL-6 responses.** Plasma FFA concentrations were not different when comparing trials before drug administration. However, consistent with our basal experiment, plasma FFA concentration was reduced (\( P < 0.05 \)) after 60 min of rest (0 min) in NA compared with Con. In Con, plasma FFA increased (\( P < 0.05 \)) during exercise, but this was completely suppressed (\( P < 0.05 \)) by NA ingestion, such that values throughout exercise were lower (\( P < 0.05 \)) in NA compared with Con (Fig. 2). Plasma IL-6 was not different at rest, and there was a tendency (\( P = 0.09 \)) for it to increase at rest after NA treatment. Although plasma IL-6 concentration increased (\( P < 0.001 \)) throughout exercise in both trials, the increase was augmented (\( P < 0.05 \)) throughout exercise in NA (Fig. 2).

Plasma glucose concentration was elevated (\( P < 0.05 \)) at 0 min in NA compared with Con, decreased (\( P < 0.05 \)) in both trials late in exercise, and was lower (\( P < 0.05 \)) in NA at 180 min compared with Con (Table 2). Plasma lactate was increased (\( P < 0.05 \)) from resting levels late in exercise, and there was no difference between trials (Table 2). Plasma insulin concentration decreased (\( P < 0.05 \)) during exercise in both trials, but there were no differences when comparing trials (Fig. 3). Both plasma epinephrine (Fig. 3) and GH (Fig. 3) increased (\( P < 0.05 \)) during exercise in both trials. However, these increases were exacerbated (\( P < 0.05 \)) in NA compared with Con after 180 min. Plasma cortisol was not significantly affected by exercise in either trial. However, after 180 min,
plasma cortisol was higher ($P < 0.05$) in NA compared with Con (Fig. 3).

**Intramuscular glycogen and IL-6 gene expression in muscle and adipose tissue.** Intramuscular glycogen content was not different when comparing the exercise trials at rest. Whereas intramuscular glycogen decreased ($P < 0.05$) during exercise in both trials, there were no significant differences either at 90 or 180 min when comparing NA with Con (Fig. 4).

Skeletal muscle IL-6 mRNA increased ($P < 0.01$) in both trials throughout exercise. In the NA trial, skeletal muscle IL-6 mRNA was elevated two- to threefold above Con levels at 180 min, but this did not reach statistical significance ($P = 0.10$) (Fig. 5). Adipose tissue IL-6 mRNA increased ($P < 0.001$) in both trials throughout exercise and was approximately sixfold higher ($P < 0.01$) in NA compared with Con at 180 min (Fig. 5). Biopsy samples were not obtained in the resting NA trial. However, comparison of the resting samples from Con in the exercise trial with the resting NA exercise trial samples (1 h after NA ingestion) revealed no differences in the parameters measured.

**DISCUSSION**

These results demonstrate that circulating IL-6 is elevated in response to acute suppression of FFAs, both at rest and during prolonged moderate-intensity exercise. Furthermore, a reduction in plasma FFA availability induced marked increases in adipose tissue IL-6 mRNA. We interpret these data to suggest that IL-6 may be released from metabolically active tissues in response to reduced FFA in the circulation.

Previous studies have demonstrated strong associations between IL-6 and lipolytic processes. Infusion of IL-6 into rats elicited a dose-dependent increase in serum FFA levels (26), and elevated plasma FFA were reported in cancer patients receiving pharmacological recombinant IL-6 infusion (38); however, a direct lipolytic effect of IL-6 could not be ascribed because epinephrine, a lipolytic hormone, was concomitantly elevated. Wallenius et al. (45) demonstrated that IL-6$^{−/−}$ mice have an increased energy intake and develop mature onset obesity, displaying a rapid increase in body fat compared with control mice. Importantly, fat mass was decreased in IL-6$^{−/−}$ mice treated with IL-6, without reducing food intake, an effect that was not observed in wild-type mice. Whereas these studies infer a lipolytic role for IL-6, a recent study using tracer isotope methodology clearly demonstrated increased adipose tissue lipolysis and increased fat oxidation during IL-6 infusion in the absence of changes in the lipolytic hormones insulin, epinephrine, or cortisol (43). Hence, one biological role of IL-6 may be to increase lipolysis, albeit a relatively modest effect compared with potent lipolytic hormones insulin and epinephrine.

IL-6 is secreted by adipose tissue in resting conditions (24, 28), accounting for ~30% of the circulating IL-6 (24), and IL-6 mRNA expression is increased in adipose tissue during (16) and following (18) exercise. Consistent with previous studies (16), we demonstrated a marked (~50-fold) increase in adipose tissue IL-6 mRNA expression during exercise in Con. However, this increase was markedly augmented in NA (Fig. 2). There are two possibilities to explain this observation.

![Fig. 2. Plasma FFA (A) and IL-6 (B) concentration before (~60, ~30, 0 min) and during (subsequent time points) 180-min cycling exercise at 62 ± 5% peak pulmonary oxygen uptake ($V_{O2\text{peak}}$) with (●) or without (○) nicotinic acid ingestion. Values are means ± SE ($n = 7$). *Different from control (Con), $P < 0.05$.](http://jap.physiology.org/)

Table 2. Plasma glucose and lactate concentration during 180-min cycling exercise at 62 ± 5% $V_{O2\text{peak}}$ with or without nicotinic acid ingestion

<table>
<thead>
<tr>
<th>Exercise Trial</th>
<th>−60</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose, mM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>5.4±0.1</td>
<td>5.3±0.1</td>
<td>5.1±0.1</td>
<td>5.1±0.1</td>
<td>4.7±0.1</td>
<td>4.6±0.1</td>
<td>4.5±0.1*</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>6.0±0.1†</td>
<td>5.2±0.1</td>
<td>5.1±0.1</td>
<td>5.0±0.1</td>
<td>4.6±0.2</td>
<td>4.2±0.2</td>
<td>3.8±0.1†</td>
<td></td>
</tr>
<tr>
<td><strong>Lactate, mM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>1.3±0.2</td>
<td>2.4±0.4</td>
<td>1.8±0.3</td>
<td>1.8±0.4</td>
<td>2.0±0.3</td>
<td>2.0±0.2</td>
<td>2.5±0.2*</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>1.1±0.1</td>
<td>1.8±0.3</td>
<td>2.6±0.4</td>
<td>2.1±0.5</td>
<td>2.0±0.3</td>
<td>2.3±0.3</td>
<td>2.7±0.3</td>
<td>3.0±0.3*</td>
</tr>
</tbody>
</table>

Values are means ± SE; $n = 7$. *Significant difference from 0 min ($P < 0.05$). †Significant difference from Con ($P < 0.05$).
First, IL-6 infusion has been demonstrated to increase adipose tissue IL-6 mRNA (18). It is possible, therefore, that NA may have increased IL-6 release from other tissues with the subsequent increase in circulating IL-6 acting on adipocytes in this manner. Second, the adipocytes may have increased IL-6 gene expression as a direct effect of NA and/or secondary to NA-induced reduced lipolysis. From our data, we are unable to determine which of these possibilities is likely to have occurred.

In the present study, we were unable to determine the source of the increase in circulating IL-6 with NA, because we did not measure arteriovenous differences across adipose tissue, contracting skeletal muscle, or other potential IL-6-releasing tissues. In normal circumstances, the net release of IL-6 from the contracting skeletal muscle can account for the majority of the circulating plasma IL-6 (37). IL-6 protein is produced neither by monocytes (34) nor hepatosplanchnic viscera (8), but a small amount of IL-6 is released from the peritendon (20) and brain (27). Of note, during a standard exercise bout (1-h two-legged bicycle exercise at 60% oxygen uptake), the adipose tissue does not release IL-6 (21). However, given the profound effects of NA on IL-6 mRNA in adipose tissue, we cannot rule out the possibility that the adipose tissue contributed to the approximately twofold increase in circulating IL-6 during exercise. Notwithstanding this, the fact that IL-6 mRNA tended to be higher in NA and that the contracting limb is the major source of the contraction-induced increase in plasma IL-6, our data suggest that the increase in plasma IL-6 with NA was due to an increase in net leg release of IL-6 during NA. Further investigation using arteriovenous balance methodology is required to determine the IL-6 release across the working leg and adipose tissue with NA at rest and during exercise.

Although NA had no effect on insulin, it increased epinephrine and GH during both the resting and exercise experiments, whereas cortisol was increased during exercise. One cannot categorically rule out the possibility, therefore, that the effects of NA on the hormonal milieu mediated the changes in IL-6. It has recently been suggested (15) that the lipolytic action of IL-6 during human in vivo studies (21, 43) may be mediated by increases in GH. This is entirely plausible because IL-6 often (39, 40, 42), but not always (1, 32), results in increases in GH production, and it is well known that GH per se can induce lipolysis (6, 25, 32). In recent studies, we have incubated 3T3 L1 adipocytes with IL-6 in the presence or absence of lipolytic hormones, including GH, and measured glycerol release as a marker of lipolysis. Rather than augment the IL-6-induced lipolysis, GH tended to attenuate this response (E. Wolspark-Petersen, A. L. Carey, M. Sachetti, G. R. Steinberg, S. L. Macaulay, M. A. Febbraio, and B. K. Pedersen, unpublished observations). Therefore, although we cannot rule out the possibility that IL-6 is not directly associated with lipolytic processes, these preliminary studies would argue against such a hypothesis.

Epinephrine has been suggested to be a hormone-mediating IL-6 production (14) and actively increases IL-6 production.
due to the changes observed in the hormonal milieu. Therefore, the observed changes in IL-6 are unlikely to be caused by cortisol. It has been demonstrated to downregulate plasma IL-6 in humans (19). Hence, it is unlikely that NA had a pronounced effect on the present measurements other than FFA.

Both IL-6 mRNA expression in (17, 35), and protein release from (35), skeletal muscle are augmented by reduced glycogen availability. In the present study, CHO oxidation was augmented in NA compared with Con (Table 1), consistent with previous findings whereby NA administration increases the rate of muscle glycogen utilization and whole body CHO oxidation during prolonged exercise (2, 3, 12). Despite this, no statistical differences were observed in intramuscular glycogen levels when comparing trials (Fig. 4), and, despite the tendency for a difference at 180 min, the glycogen levels at 90 min of exercise were almost identical, whereas the plasma IL-6 levels were much greater in NA at this time point, suggesting that glucose uptake and oxidation were elevated during the NA trial. We have reported that muscle glycogen depletion increases IL-6 levels (35); however, it appears that our present results were not solely mediated by glycogen availability. Our laboratory’s previous findings that an increase in glucose uptake and oxidation attenuate the increase in IL-6 release during exercise (10) may appear contradictory to the present results; however, glucose uptake and oxidation were increased due to CHO ingestion such that the energy demand of exercise was met. In the present study, however, energy demand was high, supporting the hypothesis that IL-6 increase is associated with increased metabolic demand. To ascertain whether the increase in IL-6 is due to the lowering of plasma FFA per se or can be attributed to NA ingestion, further investigation is required whereby NA is administered in the presence of a maintained plasma FFA concentration such as obtained through an intralipid infusion.

In conclusion, we have demonstrated that circulating IL-6 is markedly elevated at rest and during prolonged moderate-intensity exercise when lipolysis is suppressed. Significant elevation of IL-6 gene expression in adipose tissue during exercise and further with plasma FFA suppression suggests that IL-6 may be released from active tissue beds such as adipose tissue and/or skeletal muscle during exercise and under metabolic challenge to mobilize fat in an “endocrine-like” manner, and such a hypothesis warrants further investigation.

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GRANTS

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