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Interleukin-6 Stimulates Lipolysis and Fat Oxidation in Humans

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Although IL-6 is a key modulator of immune function, it also plays a role in regulating substrate metabolism. To determine whether IL-6 affects lipid metabolism, 18 healthy men were infused for 3 h with saline (Con; n = 6) or a high dose (High-rhIL6; n = 6) or a low dose (Low-rhIL6; n = 6) of recombinant human IL-6 (rhIL-6). The IL-6 concentration during Con, Low-rhIL6, and High-rhIL6 was at a steady state after 30 min of infusion at approximately 4, 140, and 320 pg/ml, respectively. Either dose of rhIL-6 was associated with a similar increase in fatty acid (FA) concentration and endogenous FA rate of appearance (R_a) from 90 min after the start of the infusion. The FA concentration and FA R_a continued to increase until the cessation of rhIL-6 infusion, reaching levels approximately 50% greater than Con values. The elevated levels reached at the end of rhIL-6 infusion persisted at least 3 h postinfusion. Triacylglycerol concentrations were unchanged during rhIL-6 infusion, whereas whole body fat oxidation increased after the second hour of rhIL-6 infusion. Of note, during Low-rhIL6, the induced elevation in FA concentration and FA R_a occurred in the absence of any change in adrenaline, insulin, or glucagon, and no adverse side effects were observed. In conclusion, the data identify IL-6 as a potent modulator of fat metabolism in humans, increasing fat oxidation and FA reesterification without causing hypertriacylglyceridemia. (*J Clin Endocrinol Metab* 88: 3005–3010, 2003)

INTERLEUKIN-6 IS A biologically active substance that is not only secreted by immune cells during inflammatory conditions, but is also released by adipose tissue (1) and by contracting skeletal muscle (2) in the absence of inflammation. Although little is known about the function of this release, it is possible that IL-6 is a key modulator of lipid homeostasis and metabolism, because adipose tissue and skeletal muscle are pivotal organs in the regulation of body fat and energy metabolism.

Although inconclusive, there is evidence that IL-6 may affect lipid metabolism. Stouthard *et al.* (3) studied patients with metastatic renal cell cancer during 4 h of recombinant human IL-6 (rhIL-6) infusion and observed an increase in circulating fatty acid (FA) and whole body FA rate of appearance (R_a). Importantly, however, in this study (3) all patients experienced clinical symptoms, such as fever, and consequently increased their whole body oxygen consumption. In addition, circulating hormones such as glucagon, adrenaline, and nor-adrenaline were elevated. Therefore, the researchers could not determine whether the changes in fat metabolism were a direct effect of IL-6 and whether the response was characteristic of healthy humans. Furthermore, IL-6 increases lipolysis in human breast adipocytes (4).

Infusion of IL-6 in rats increased FA and triacylglycerol (TAG) concentrations in a dose-dependent matter (5). The hypertriacylglyceridemia was caused by increased liver secretion and not decreased clearance. Recently, Wallenius *et al.* (6) demonstrated that IL-6-deficient mice developed mature-onset obesity. In addition, when the mice were treated with IL-6 for 18 d, there was a significant decrease in body weight in transgenic, but not wild-type, mice.

Taken together, these previous studies provide a rationale for testing the efficacy of IL-6 as a lipolytic factor in healthy humans, and this was the aim of the present study. To determine whether any effect of IL-6 was direct or secondary to changes in lipolytic regulatory hormones, we chose to infuse a low and a high dose of rhIL-6. The lower dose of rhIL-6 elicits a physiological plasma IL-6 concentration that can be found in healthy individuals during prolonged exercise (7). We hypothesized that rhIL-6 infusion increases lipolysis and TAG concentration in a dose-dependent matter.

Subjects and Methods

Subjects

Eighteen healthy, active, but not specifically trained, males were recruited in the study. Each was assigned to one of three groups: saline infusion (Con), low rhIL-6 infusion (Low-rhIL6), and high rhIL-6 infusion (High-rhIL6). The characteristics of the groups were similar for Con, Low-rhIL6, and High-rhIL6: age, 23 ± 1, 24 ± 1, and 26 ± 1 yr, respectively; weight, 78 ± 2, 80 ± 2, and 77 ± 2 kg; height, 183 ± 3, 184 ± 1, and 178 ± 2 cm; and body mass index, 23.4 ± 0.5, 23.5 ± 0.8, and 24.3 ± 0.7 kg/m^2. The study was approved by the ethical committee of Copenhagen and Frederiksberg communities, Denmark, and was performed according to the Declaration of Helsinki. Subjects were informed about the possible risks and discomfort involved before giving their written consent to participate.

Abbreviations: Con, Saline infusion; FA, fatty acid; GC, gas chromatography; High-rhIL6, high rhIL-6 infusion;Low-rhIL6, low rhIL-6 infusion; R_a, rate of appearance; R_d, rate of disappearance; rhIL-6, recombinant human IL-6; TAG, triacylglycerol.

Protocol

Subjects reported to the laboratory at 0700 h after an overnight fast. They voided, changed into appropriate hospital attire, and remained supine during the entire experiment. The experimental room was kept at 24 C. They were only permitted to consume *ad libitum* water during the experiment. After 10 min the femoral arteries of both legs were cannulated, one for saline or rhIL-6 infusion, the other for blood sampling. Thereafter, a catheter was placed in a forearm vein for infusion of the stable isotopes. Immediately after an arterial sample was obtained for background enrichment, a primed constant infusion of [$^2H_5$]glycerol (0.1 μmol/min·kg; prime, 1.5 μmol/kg) was started as well as a constant infusion of [U-^{13}C]palmitate (0.015 μmol/min·kg). All isotopes were purchased from Cambridge Isotope Laboratories (Andover, MA). For each subject the actual infusion rate was calculated from the infusate concentration multiplied by the infusion flow rate. Blood samples were taken as described in Fig. 1. Blood samples of 2.0 ml were taken for FA, palmitate, glycerol, and TAG measurements and palmitate and glycerol enrichment. A 5-ml blood sample was taken at each measurement for IL-6, insulin, glucagon, cortisol, and catecholamines. The total amount of blood that consumed during the study was 235 ml.

IL-6 infusates

The two concentrations of rhIL-6 (Sandoz Pharmaceuticals Corp., Basel, Switzerland) were infused in doses lower than those reported to be safe in other studies (3). The IL-6 doses were chosen on the basis of pilot experiments. We aimed to reach the plasma levels of IL-6 observed in healthy individuals during intense exercise (Low-rhIL6) or during infections (High-rhIL6). In the Low-rhIL6 trial, the rate of rhIL-6 infusion was 30 μg/h, and it was administered in saline. Due to the retention of rhIL-6 at the side of the container when dissolved in saline, we could not use this method during High-rhIL6. Hence, further pilot experiments were conducted with 2% human albumin added as dissolving and delivery medium. These pilot experiments revealed that a dose of 15 μg/h was required during this trial. Saline was infused during control infusion (Con).

Analysis

Plasma [U-^{13}C]palmitate and [$^2H_5$]glycerol enrichments were determined as described previously in detail (8). Plasma FA concentrations were determined by gas chromatography (GC; Autosystem XL, PerkinElmer Corp., Norwalk, CT) using heptadecanoic acid as internal standard, and ^{13}C enrichment of plasma palmitate was determined by GC-combustion-isotope ratio mass spectrometry (HewlettPackard 5890; Finnigan GC combustion III, Finnigan δ^{plus}, Finnigan MAT, Bremen, Germany). In preparation for GC and GC-combustion-isotope ratio mass spectrometry analysis, plasma samples were processed to make a methyl derivative of palmitate as described previously (8). The isotopic enrichment of palmitate was expressed as the Δ o/oo difference between $^{13}C/^{12}C$ of the sample and a known laboratory reference standard-related Pee Dee Belemnitella limestone. The methyl derivative of palmitate contains 17 carbons, of which 16 are palmitate; thus, the tracer-to-tracee ratio of palmitate was corrected by a factor 17/16. Glycerol enrichment was measured by GC-mass spectrometry (Automass II, Finnigan, Paris, France). In preparation for GC-mass spectrometry analysis, plasma samples were processed to make a trifluorobutyrate derivative of glycerol. The isotopic enrichment of glycerol was determined using electron impact ionization, selectively monitoring ions at a mass to charge ratio (m/z) of 252–256, representing the molecular ions of unlabeled (m/z = 252) and labeled (m/z = 256) derivatives, respectively. Plasma was analyzed enzymatically for glycerol and TAG on an automatic analyzer (Cobas Fara, Roche, Basel, Switzerland). Blood samples for IL-6 were measured by high sensitivity ELISA as previously described (9). Plasma insulin (Insulin RIA 100, Amersham Pharmacia Biotech, Uppsala, Sweden), glucagon (Linco Research, Inc., St. Charles, MO), and cortisol (Diagnostic Products, Los Angeles, CA) were determined by RIA, and plasma adrenaline and noradrenaline were determined by HPLC. These analyses were described in more detail previously (10, 11).

Physical analysis

Heart rate and blood pressure were measured every 60 min using electrocardiography and sphygmomanometry, respectively. Temperature was also measured at this time point via a tympanic probe. Expired pulmonary gases were collected and analyzed for oxygen consumption on-line using a CPX/D metabolic cart (Medgraphics, St. Paul, MN). Due to technical problems, indirect calorimetry data were not obtained in four subjects during the High-rhIL-6.

Calculations

The whole body R_a and rate of disappearance (R_d) of palmitate and glycerol were calculated using the steady state equation: Ra = Rd = F/E_a. F is the isotopic infusion rate (micromoles per minute per kilogram), and E_a is the arterial isotopic enrichment (tracer/tracee ratio). The FA $R_{a/d}$ was calculated by dividing the palmitate data by the fractional contribution of palmitate to the total FA concentration, on the average palmitate being 0.22 $\pm$ 0.01 of the total FA.

Statistics

All data are presented as the mean $\pm$ SE. To analyze changes over time and between groups, a two-way repeated measures ANOVA was used. If such an analysis revealed significant differences, a Newman-Keuls *post hoc* test was used to locate the specific differences. $P < 0.05$ was accepted as significant.

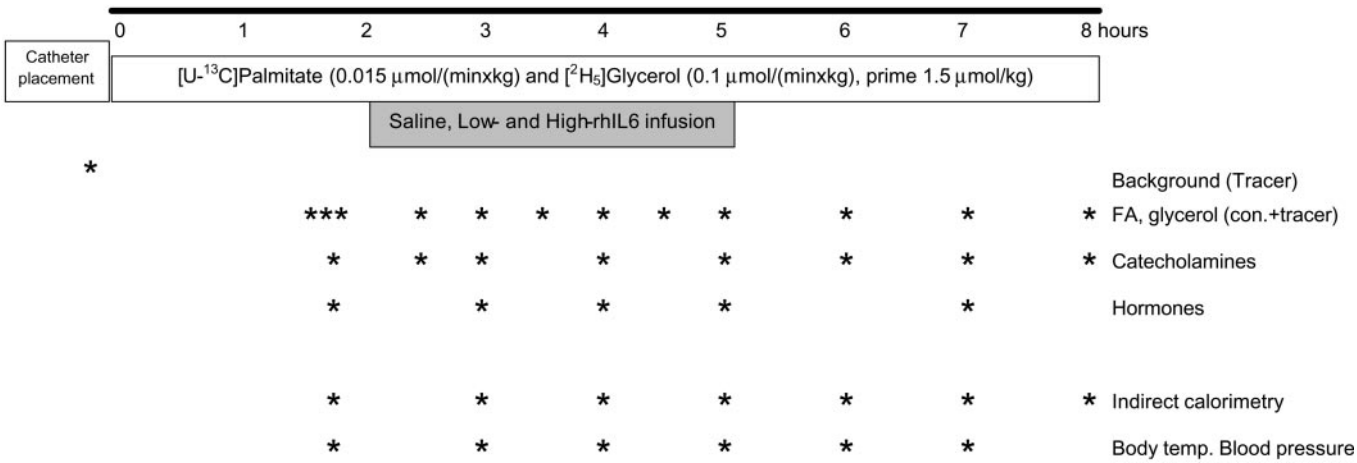

FIG. 1. Schematic of the study protocol.

Results

There were no significant differences among the trials in heart rate, body temperature, or blood pressure (Table 1). The subjects did not report any adverse effects during Con or Low-rhIL6. During High-rhIL6 all subjects experienced about 0.5 h of shivering and discomfort between 30–60 min after the rhIL-6 infusion was initiated. This effect was transient, and none of the subjects reported any severe side effects.

IL-6 and hormone concentrations (Fig. 1 and Table 2)

Arterial plasma IL-6 levels are shown in Fig. 2. During Low-rhIL6 and High-rhIL6 the mean arterial plasma IL-6 levels were 143 and 319 pg/ml, respectively. Saline infusion did not increase the concentration of IL-6. On cessation of the rhIL-6 infusion the IL-6 concentration declined rapidly, and after 1 and 2 h the concentrations were marginally elevated. The plasma hormone levels are reported in Table 2. Plasma insulin decreased over time, but there were no differences when comparing groups and no group by time interaction. Plasma glucagon levels were similar when comparing the three groups, and this hormone was not affected by either time or treatment. There were no differences in plasma cortisol concentrations when comparing the three groups at rest. Plasma cortisol concentrations did not change during Con, but increased during both Low-rhIL6 and High-rhIL6 infusion. While concentrations of plasma cortisol declined after 2 h of infusion in Low-rhIL6, they remained elevated in High-rhIL6 at 3 h of infusion. During both rhIL-6 trials, plasma cortisol levels returned to preinfusion values after 2 h of recovery. Plasma noradrenaline was not affected by time or treatment when comparing trials. In contrast, plasma adrenaline markedly increased at the onset of infusion in High-rhIL6, such that values after 60 min were greater than those in the Low-rhIL6 and Con groups. Of note, Low-rhIL6 did not affect plasma adrenaline concentrations.

Oxygen uptake and total FA oxidation (Table 3)

Oxygen uptake for both Con and Low-rhIL6 was unchanged over the entire study period, and values were not different from each other (Table 2). The respiratory exchange ratio, and thereby fat oxidation, were unchanged during Con. Low-rhIL6 did not change fat oxidation during the first hour of infusion, but thereafter fat oxidation increased and remained at the same level for the remainder of the study. After the second hour of rhIL-6 infusion energy expenditure was nearly completely covered by fat oxidation.

FA, glycerol, and TAG (Figs. 3 and 4)

The rhIL-6 infusion caused substantial changes in the FA concentration, with a similar pattern during Low-rhIL6 and High-rhIL6. A variable pattern existed during the first 90 min of rhIL-6 infusion, albeit a significant decrease was observed only after 30 and 90 min during the High-rhIL-6 compared with Con. After 2.5 h of infusion, a substantial increase in FA concentration occurred that continued until the end of the infusion for both rhIL-6 infusion rates. On cessation of rhIL-6 infusion, the FA concentration remained at virtually the level reached at the end of the rhIL-6 infusion for the next 3 h. The early changes in FA concentration were accompanied by changes in whole body FA R_a/R_d mainly during High-rhIL6. Despite a lower FA concentration after 30 and 90 min of High-rhIL6 infusion, the FA turnover rate was similar or higher (60 min) than those in the Con and Low-rhIL6 groups. After 2 h of rhIL-6 infusion a substantial similar increase in the FA turnover rate was observed for both Low- and High-IL6. The increase in FA turnover rate continued until the end of the infusion. After rhIL-6 infusion during High-rhIL6, FA turnover remained high, but FA turnover tended to decrease in the Low-rhIL6 dose. The arterial glycerol concentration was similar for all trials, except for a lower concentration after 90 min during High-rhIL6, which coincided with the low FA concentration. Substantially higher glycerol turnover rates were observed after 2 h of rhIL-6 infusion and in recovery during Low- and High-rhIL6 *vs.* Con. The patterns of changes in glycerol and FA turnover rate were similar during all trials, resulting in an FA/glycerol ratio close to 3. The arterial TAG concentration was significantly lower before treatment in Con compared with Low- and High-rhIL6 groups. The arterial TAG concentration decreased after cessation of rhIL-6 infusion for both Low- and High-rhIL6 groups, whereas the TAG concentration was unchanged in the Con group.

TABLE 1. Heart rate, blood pressure, and body temperature

	Pre	rhIL-6 infusion			5 h	6 h
		1 h	2 h	3 h		
Heart rate (beats/min)						
Con	63 ± 2	64 ± 3	63 ± 2	64 ± 3	63 ± 4	62 ± 3
Low-rhlL6	65 ± 6	68 ± 5	79 ± 5	75 ± 7	76 ± 6	74 ± 5
High-rhlL6	58 ± 2	70 ± 2	72 ± 2	72 ± 3	74 ± 4	70 ± 5
Blood pressure (mmHg)						
Con	81 ± 3	80 ± 3	82 ± 4	84 ± 5	81 ± 5	84 ± 2
Low-rhlL6	88 ± 4	86 ± 3	89 ± 4	84 ± 2	80 ± 3	87 ± 2
High-rhlL6	95 ± 3[a]	90 ± 5	88 ± 4	84 ± 4	87 ± 4	86 ± 4
Body temperature (C)						
Con	36.7 ± 0.2	36.7 ± 0.2	37.0 ± 0.2	36.9 ± 0.2	36.9 ± 0.2	36.1 ± 0.1
Low-rhlL6	36.3 ± 0.3	36.5 ± 0.3	36.6 ± 0.2	36.9 ± 0.2	37.2 ± 0.2	37.1 ± 0.2
High-rhlL6	36.7 ± 0.2	36.8 ± 0.4	37.2 ± 0.4	37.3 ± 0.2	37.1 ± 0.2	37.1 ± 0.2

Data are presented as means ± SE.
[a] Difference ($P < 0.05$) from Con.

TABLE 2. Arterial concentration of adrenaline, noradrenaline, cortisol, insulin, and glucagon

	Pre	rhIL-6 infusion				4 h	5 h	6 h
		0.5 h	1 h	2 h	3 h			
Adrenaline (nmol/liter)								
Con	0.81 ± 0.19	0.74 ± 0.20	0.76 ± 0.11	0.56 ± 0.15	0.62 ± 0.24	0.43 ± 0.08	0.30 ± 0.08	0.82 ± 0.16
Low-rhIL6	0.88 ± 0.13	0.89 ± 0.06	0.66 ± 0.08	0.68 ± 0.15	0.71 ± 0.05	0.56 ± 0.03	0.61 ± 0.05	0.92 ± 0.15
High-rhIL6	0.86 ± 0.13	1.12 ± 0.37	1.69 ± 0.32[a,b,c]	0.51 ± 0.11	0.68 ± 0.08	0.69 ± 0.24	0.49 ± 0.12	0.53 ± 0.13
Noradrenaline (nmol/liter)								
Con	1.03 ± 0.19	1.25 ± 0.21	1.11 ± 0.16	1.16 ± 0.12	0.96 ± 0.10	0.89 ± 0.08	0.67 ± 0.05	0.83 ± 0.05
Low-rhIL6	1.03 ± 0.20	1.30 ± 0.28	1.22 ± 0.30	1.10 ± 0.11	1.01 ± 0.12	0.92 ± 0.08	0.90 ± 0.09	1.13 ± 0.16
High-rhIL6	0.85 ± 0.28	1.20 ± 0.12	0.99 ± 0.11	0.86 ± 0.07	1.00 ± 0.25	1.12 ± 0.09	0.92 ± 0.27	1.16 ± 0.27
Cortisol (pg/ml)								
Con	18 ± 3		13 ± 3	10 ± 2	9 ± 2		9 ± 2[c]	
Low-rhIL6	20 ± 4		25 ± 3[a,c]	31 ± 5[a,c]	16 ± 2[a,c]		9 ± 2[c]	
High-rhIL6	19 ± 1		29 ± 3[a]	26 ± 2	31 ± 6[a,b,c]		15 ± 1	
Insulin (pmol/liter)								
Con	43 ± 9		30 ± 6[c]	30 ± 5[c]	27 ± 8[c]		28 ± 8[c]	
Low-rhIL6	35 ± 5		27 ± 3	18 ± 4[c]	22 ± 4[c]		20 ± 4[c]	
High-rhIL6	30 ± 6		38 ± 7	20 ± 5	27 ± 9		27 ± 5	
Glucagon (pg/ml)								
Con	108 ± 8		105 ± 7	114 ± 8	105 ± 5		111 ± 11	
Low-rhIL6	92 ± 7		101 ± 6	113 ± 8	114 ± 7		95 ± 3	
High-rhIL6	85 ± 17		142 ± 35	122 ± 24	135 ± 42		107 ± 31	

Data are presented as means ± SE.
[a] Difference ($P < 0.05$) from Con.
[b] Differences from Low-rhIL6.
[c] Differences from Pre.

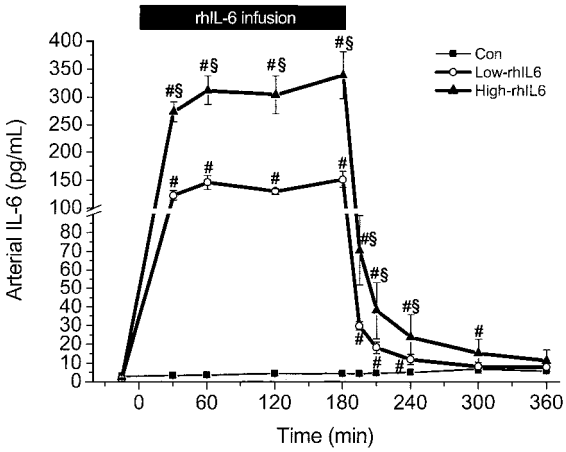

FIG. 2. Arterial plasma IL-6 before, during, and 3 h after the infusion of saline (Con) or a low or high dose of rhIL-6 (Low-rhIL6 and High-rhIL6). Data are presented as the mean ± SE. #, Difference ($P < 0.05$) from Con; §, difference from Low-rhIL6.

Discussion

The results from the present study clearly demonstrate that infusion of rhIL-6 into healthy humans increases lipolysis in the absence of hypertriacylglyceridemia or changes in catecholamines, glucagon, or insulin. These findings together with the observations that such an infusion did not result in adverse effects identify IL-6 as a novel lipolytic factor.

Unlike the High-rhIL6 treatment, Low-rhIL6 did not cause any adverse effects, and except for cortisol, no differences in hormones such as adrenaline, insulin, and glucagon were observed. Thus, the IL-6-induced lipolytic effect is not an indirect effect of adrenaline and glucagon. Despite the difference in circulating hormone concentrations and side effects when comparing the Low- and High-rhIL6, the marked enhancements in FA concentration and FA turnover were virtually the same. During both rhIL-6 infusions cortisol levels were modestly increased compared with preinfusion and Con levels. *In vivo* studies, using much higher levels than those used in the present study, suggest that glucocorticoids have no effect on (12), stimulate (13–15), or inhibit (16, 17) lipolysis, whereas in human adipocytes cortisol clearly has an antilipolytic effect (18). Furthermore, cortisol has been suggested to down-regulate β-adrenoceptor protein expression and β_3-adrenocepter-mediated adenylate cyclase activity in human adipocytes (19) and to reduce the sensitivity of adipocytes to catecholamine-stimulated lipolysis (18). Therefore, we believe that the increase in lipolysis observed in this study can be ascribed to IL-6 and not to the moderately enhanced cortisol levels.

Stouthard *et al.* (3) studied patients with metastatic renal cell cancer during 4 h of rhIL-6 infusion eliciting plasma IL-6 concentrations about 2-fold higher than those obtained using the High-rhIL6 dose of the present study. However, the increases in FA concentration and FA turnover were nearly identical to those seen in the present study. Thus, no dose-response effect on fat metabolism occurs when the IL-6 concentration is increased above 140 pg/ml. This suggests that a lower dose of rhIL-6 may exert the effect on fat metabolism, which emphasizes the potency of IL-6 as a modulator of lipolysis. Furthermore, unlike other lipolytic hormones such as adrenaline, the effect on fat metabolism persisted for hours after termination of the infusion, when the IL-6 concentration had returned to baseline values. The suggestion that IL-6 is strongly involved in fat metabolism is supported by the study by Wallenius *et al.* (6), who demonstrated that IL-6-deficient mice developed mature-onset obesity. In addition, when the mice were treated with IL-6 for 18 d, there was a significant decrease in body weight in transgenic, but not

TABLE 3. Pulmonary oxygen uptake, respiratory exchange ration, and total FA oxidation before, during, and 3 h after infusion of either saline (Con) or a low dose of rhIL-6 (Low-rhIL6)

	Pre	rhIL-6 infusion			4 h	5 h	6 h
		1 h	2 h	3 h			
Con							
Oxygen uptake (ml/min)	306 ± 18	303 ± 18	294 ± 13	295 ± 10	294 ± 9	286 ± 14	288 ± 8
RER	0.75 ± 0.02	0.73 ± 0.02	0.73 ± 0.01	0.74 ± 0.01	0.73 ± 0.01	0.74 ± 0.01	0.73 ± 0.02
Total FA oxidation (μmol · min/kg)	5.9 ± 0.5	6.5 ± 0.3	5.8 ± 0.3	5.3 ± 0.3	5.8 ± 0.2	5.8 ± 0.4	6.0 ± 0.3
Low-rhIL6							
Oxygen uptake (ml/min)	246 ± 26	262 ± 32	252 ± 29	263 ± 33	257 ± 27	262 ± 24	263 ± 29
RER	0.75 ± 0.03	0.76 ± 0.03	0.70 ± 0.02[a,b]	0.70 ± 0.04[b]	0.70 ± 0.01[a,b]	0.70 ± 0.05[b]	0.70 ± 0.04[b]
Total FA oxidation (μmol · min/kg)	5.0 ± 0.7	4.9 ± 0.4	5.6 ± 0.5[b]	5.6 ± 0.6[b]	6.1 ± 0.4[b]	6.0 ± 0.0.4[b]	6.0 ± 0.6[b]

Due to technical problems, indirect calorimetry data were not obtained during High-rhIL-6. Data are presented as mean ± SE. Total FA oxidation was determined by converting the rate of fat oxidation to its molecular equivalent, with the assumption that the average molecular weight of TAG is 860 g/mol^{-1} and multiplied by 3 to express fat oxidation in FA units, because each TAG molecule hydrolyzed three FA molecules are liberated. RER, respiratory exchange ratio.

[a] Difference ($P < 0.05$) from Con.

[b] Differences from Pre.

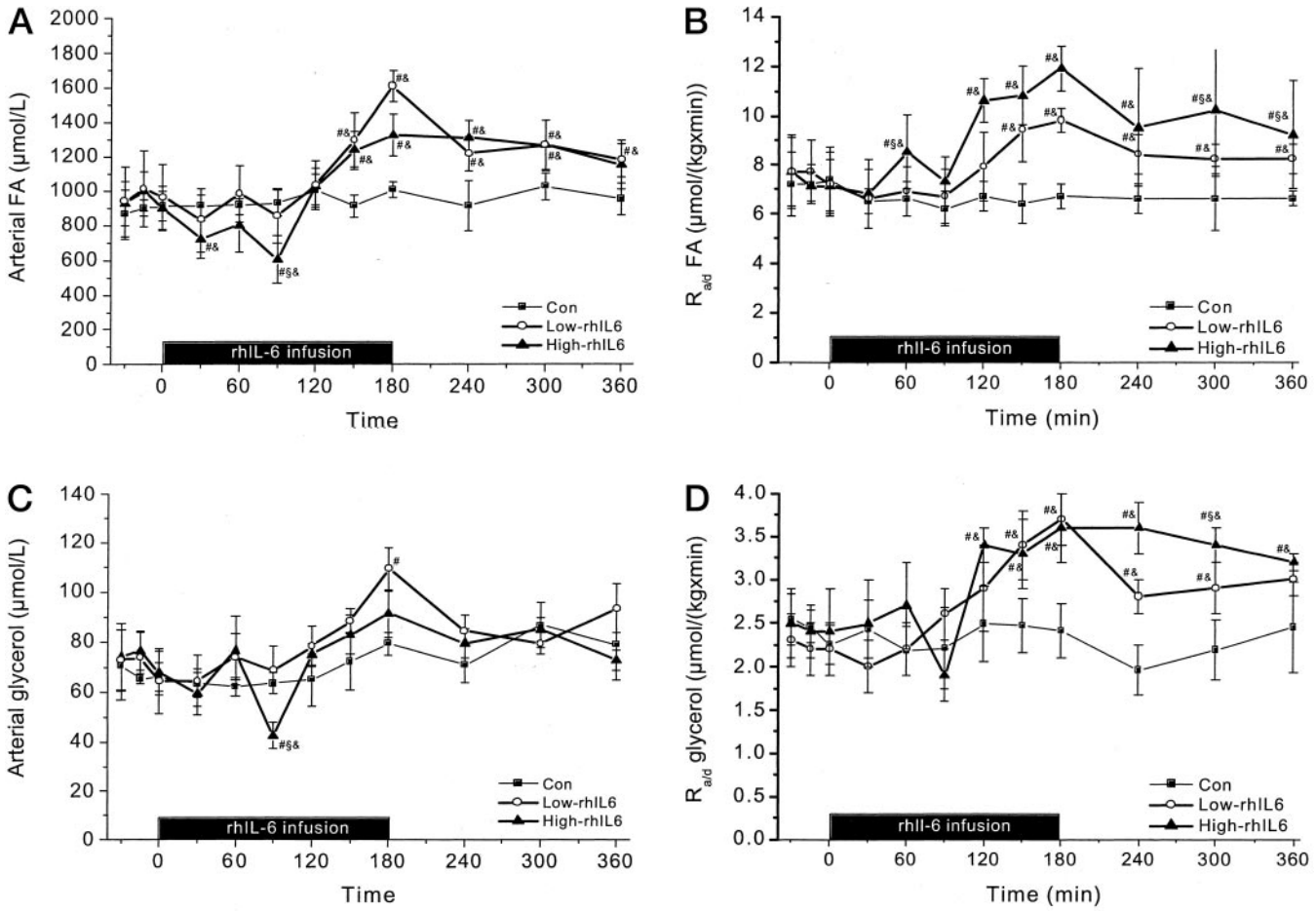

FIG. 3. Arterial FA (A) and glycerol (C) concentrations and whole body FA (B) and glycerol (D) R_a/R_d before, during, and 3 h after the infusion of saline (Con) or a low or high dose of rhIL-6 (Low-rhIL6 and High-rhIL6). Data are presented as the mean ± SE. #, Difference ($P < 0.05$) from Con; §, difference from Low-rhIL6; &, differences from preinfusion.

wild-type, mice. Studies in rats suggested that IL-6 raises TAG concentrations (5). However, in the present human study with relatively low IL-6 concentrations compared with those obtained in rats, no increase in TAG could be observed. In contrast, TAG levels were reduced after cessation of rhIL-6 infusion. Thus, the clinically negative effect of hypertriacylglyceridemia is not present with the rhIL-6 doses used in the present study.

The changes seen in FA concentration and turnover during rhIL-6 infusion suggest a complex mode of action of IL-6 on fat metabolism. During the first 90 min of rhIL-6 infusion, the FA concentration remained constant or slightly decreased,

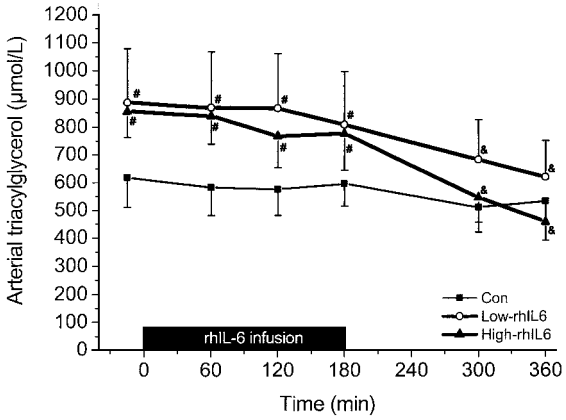

FIG. 4. Arterial TAG before, during, and 3 h after the infusion of saline (Con) or a low or high dose of rhIL-6 (Low-rhIL6 and High-rhIL6). Data are presented as the mean ± SE. #, Difference ($P < 0.05$) from Con; §, difference from Low-rhIL6.

but not in a constant fashion; the decrease seemed to be caused more by enhanced FA disappearance than by reduced FA appearance. After those first 90 min, the FA concentration and the FA R_a increased rapidly and appeared not to have reached a maximum after 3 h of infusion. In addition, the increase in FA oxidation during rhIL-6 infusion was far less than the increase in the rate of FA disappearance from the circulation, indicating a marked increase in FA reesterification. Hepatic FA reesterification to very low density lipoprotein-TAG is unlikely to play an important role in the enhanced FA reesterification, because the TAG concentration decreased with rhIL-6 infusion. On cessation of rhIL-6 infusion, the IL-6 concentration decreased rapidly, and after 3 h preinfusion levels were reached. However, the FA concentration and turnover rates were maintained at the high level seen at the end of the infusion period. Known potent lipolytic hormones, for instance, adrenaline, usually work instantaneously, and on cessation of infusion, FA metabolism normalizes fast. Thus, the changes in fat metabolism during rhIL-6 infusion are most likely not elicited directly by IL-6, but indirectly via IL-6-induced changes in other substances affecting lipid metabolism. However, when human breast adipocytes were incubated with IL-6, the glycerol release, *i.e.* lipolysis, was increased by 42%. This effect was independent of and additive to isoproterenol-induced lipolysis (4), suggesting a direct lipolytic effect of IL-6 on human adipose tissue. However, the increase in lipolysis was only observed after more then 6 h of incubation with IL-6. In conclusion, the present study identifies IL-6 as a potent modulator of fat metabolism in humans, increasing fat oxidation and FA reesterification without causing hypertriacylglyceridemia.

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