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Effect of Hypertriglyceridemia on Endotoxin Responsiveness in Humans

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Triglyceride-rich lipoproteins can inhibit endotoxin activity in vitro and in rodents. We sought to determine whether Intralipid, a triglyceride-rich fat emulsion which in contact with plasma functions similarly to endogenous lipoproteins, can alter the human response to endotoxin. Intralipid inhibited endotoxin-induced cytokine production in human whole blood in vitro in a dose-dependent manner, with maximal inhibition (up to 70%) being achieved at a concentration of 10 g/liter. In healthy men, a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg of body weight) was given midway through a 4-h infusion (125 ml/h) of either 5% glucose ($n = 5$) or 20% Intralipid ($n = 5$). The infusion of Intralipid led to an increase in triglyceride levels in serum from 95 ± 16 to 818 ± 135 mg/dl prior to endotoxin administration, i.e., levels that importantly reduced cytokine production in endotoxin-stimulated whole blood. However, in vivo hypertriglyceridemia did not influence inflammatory responses to endotoxin (fever, release of tumor necrosis factor and soluble tumor necrosis factor receptors, and leukocytosis) or even potentiated endotoxin responses (release of interleukins 6 and 8 and neutrophil degranulation). Hypertriglyceridemia does not inhibit the in vivo responses to endotoxin in humans.

Endotoxin is a lipopolysaccharide (LPS) molecule in the outer membrane of gram-negative bacteria that is considered to play a key role in the pathogenesis of gram-negative sepsis (12). Administration of endotoxin to experimental animals reproduces the major features of septic shock, and healthy humans injected with a low dose of endotoxin show clinical and laboratory responses that qualitatively mimic those found in patients with sepsis (22, 27). In recent years, it has become clear that endotoxin can be bound and subsequently inactivated by various classes of lipoproteins. Incubation of endotoxin with high-density lipoproteins, low-density lipoproteins, or chylomicrons reduces its activity in vitro, as reflected by a diminished recovery of endotoxin in the *Limulus* amebocyte lysate assay and by a reduced capacity of endotoxin to induce cytokine production by mononuclear cells (2, 5, 6, 9, 10). Moreover, lipoproteins have the ability to attenuate inflammatory responses to endotoxin in animals in vivo. High-density lipoprotein has been shown to abrogate the pyrogenic response, thrombocytopenia, and anticomplementary activity elicited by endotoxin in rabbits (31). Preincubation of endotoxin with high-density lipoproteins, low-density lipoproteins, very-low-density lipoproteins, or chylomicrons protected against endotoxin-induced death in rodents (19, 20), and infusion of chylomicrons before or up to 30 min after the administration of endotoxin improved survival in rats (20, 29). It has been hypothesized that enhanced hepatic production of triglyceride-rich lipoproteins during a gram-negative infection reflects an endogenous mechanism to limit the activity of endotoxin (14, 26). However, at present, the effect of a rise in triglyceride-rich lipoproteins on endotoxin responses in humans in vivo is unknown, at least in part because natural lipoproteins are not available for administration to humans.

Intralipid is a fat emulsion of soybean triglycerides and egg yolk lecithin, and it resembles chylomicrons with respect to particle size, plasma clearance kinetics, and interaction with lipoprotein lipase (1, 16–18, 33). Although Intralipid, in contrast to natural lipoproteins, does not contain apolipoproteins, it rapidly acquires apolipoproteins once it is in the bloodstream (7, 30). Furthermore, in vitro studies have shown that Intralipid can substitute for very-low-density lipoproteins in neutral lipid exchange processes (13). Importantly, Intralipid shares the endotoxin-neutralizing properties of triglyceride-rich lipoproteins, i.e., it inhibited LPS-induced neutrophil activation in vitro (23), infusion of Intralipid reduced LPS-induced mortality in rats (29), and Soyacal, a fat emulsion highly similar to Intralipid, was as effective as chylomicrons in reducing LPS mortality in mice when it was preincubated in the presence of plasma (19). Since Intralipid, once in contact with plasma, resembles endogenous triglyceride-rich lipoproteins in many aspects, it may be used to study the effect of elevated levels of triglyceride-rich lipoproteins on endotoxin activity in humans in vivo. Therefore, in the present study, we sought to determine whether administration of such a lipid emulsion would alter the biological responses to endotoxin in humans.

MATERIALS AND METHODS

Whole blood stimulation. LPS (from *Escherichia coli* serotype O127:B8) was purchased from Sigma Chemical Co. (St. Louis, Mo.). Intralipid (20%) was obtained from KabiVitrum (Alameda, Calif.). This fat emulsion consists of 200 g of soybean oil per liter, 12 g of phospholipids per liter, and 22.5 g of glycerin per liter. Dilutions of LPS and Intralipid were made in sterile isotonic saline (Abbott Laboratories, North Chicago, Ill.). Venous blood samples were obtained

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from six healthy subjects between the ages of 20 and 40 years. Blood was collected aseptically with a sterile collecting system consisting of a butterfly needle connected to a syringe (Becton Dickinson & Co., Rutherford, N.J.). Anticoagulation was obtained with sterile heparin (Elkins-Sinn Inc., Cherry Hill, N.J.) (final concentration, 10 U/ml of blood). Aliquots of 0.75 ml of human whole blood were added to sterile polypropylene tubes (Becton Dickinson) preloaded with 0.75 ml of Intralipid (final concentrations, 0.1, 1, and 10 g/liter) or 0.75 ml of normal saline. After the addition of LPS (100 μl; final concentration, 10 ng/ml) or an equivalent volume of normal saline, the tubes were incubated for 4 h at 37°C, after which plasma was prepared and stored at −70°C until assays were performed.

Endotoxin administration to normal humans. Thirteen male subjects, aged 29 ± 2 (mean ± standard error) years, were admitted to the Adult Clinical Research Center of the New York Hospital-Cornell University Medical Center after documentation of good health by history, physical examination, and hematologic and biochemical screening. The study was approved by the Institutional Review Board, and written informed consent was obtained from all subjects before enrollment in the study. The volunteers were admitted for 3 days, from the day before endotoxin administration until the day thereafter. Two hours before the administration of endotoxin, a radial arterial catheter was placed to continuously monitor heart rate and blood pressure (Datascope model 2000A; Datascope Corp., Paramus, N.J.) and to take blood samples. A rectal probe was inserted to allow continuous measurement of core temperature. At 7:00 a.m., a 4-h intravenous infusion of either 20% Intralipid ($n = 5$) or 5% glucose ($n = 5$) at a rate of 125 ml/h (total volume, 500 ml) was started. Midway through the infusion, at 9:00 a.m., these 10 volunteers received a bolus intravenous injection of endotoxin (National Reference Endotoxin, *E. coli* O113 [lot EC-5], generously provided by H. D. Hochstein, Bureau of Biologics, Food and Drug Administration, Bethesda, Md.) at a dose of 20 U/kg of body weight. An additional three subjects received only a 4-h infusion of 20% Intralipid (125 ml/h; total volume, 500 ml), i.e., without any injection of endotoxin. All volunteers fasted from 10:00 p.m. on the day before the endotoxin injection until 24 h after endotoxin was administered. Blood was obtained 2 h before endotoxin or placebo administration (i.e., directly before the start of the infusion with 20% Intralipid or 5% glucose; $t = -2$ h), directly before the injection of endotoxin or placebo ($t = 0$ h), and 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 24 h thereafter. All blood samples (except samples for leukocyte counts) were centrifuged at 4°C for 20 min at 1,600 × *g* and stored at −70°C until assayed.

Assays. Concentrations of triglycerides and cholesterol in serum were measured by enzymatic methods (Boehringer Mannheim Diagnostics, Indianapolis, Ind.) as described previously (4). Tumor necrosis factor (TNF) (CLB, Amsterdam, The Netherlands), interleukin (IL)-1β, IL-6, IL-8, and soluble TNF receptors were measured in heparinized plasma by specific and sensitive enzyme-linked immunosorbent assays (ELISA) (15, 21, 24, 25). The reagents for the IL-1β ELISA were kindly provided by John S. Kenney; the reagents for the soluble TNF receptor ELISA were furnished by Wim A. Buurman. Leukocyte counts were determined in K_2-EDTA-anticoagulated blood by flow cytometry. Elastase-α_1-antitrypsin complexes and lactoferrin were measured in heparinized plasma by radioimmunoassay (28). C-reactive protein levels were determined by standard radial immunodiffusion (Behring Diagnostics, La Jolla, Calif.).

Statistical analysis. All values are given as means ± standard errors of the means. Changes within and among groups were analyzed by analysis of variance (ANOVA) and the Newman-Keuls test. The comparison of C-reactive protein levels measured after 24 h was done by unpaired *t* test. A probability of ≤0.05 was considered to represent a statistically significant difference.

RESULTS

Whole blood stimulation. First we assessed whether Intralipid resembles endogenous lipoproteins with respect to their capacity to reduce endotoxin-induced cytokine production. For this purpose, we utilized the well-characterized in vitro system of human whole blood (3, 32). In the absence of LPS, no TNF, IL-1β, or IL-6 was detectable in any of the recovered plasma samples. As shown in Fig. 1, Intralipid caused a dose-dependent decrease in the production of TNF ($P = 0.0007$ versus with LPS alone), IL-1β ($P = 0.0002$), and IL-6 ($P = 0.01$) in whole blood stimulated with LPS. Maximal inhibition by Intralipid was achieved at a concentration of 10 g/liter, which reduced TNF levels to 65.4% ± 6.3% of the TNF levels after stimulation with LPS alone, IL-1β levels to 29.2% ± 2.7%, and IL-6 levels to 49.5% ± 8.9%. Since especially the production of IL-1β and IL-6 in endotoxin-stimulated whole blood peaks after incubations longer than 4 h, we next assessed the effect of Intralipid (10 g/liter) on endotoxin-induced cytokine production after 8- and 12-h incubations. As shown in Fig. 2, Intralipid also reduced the levels of TNF, IL-1β, and IL-6

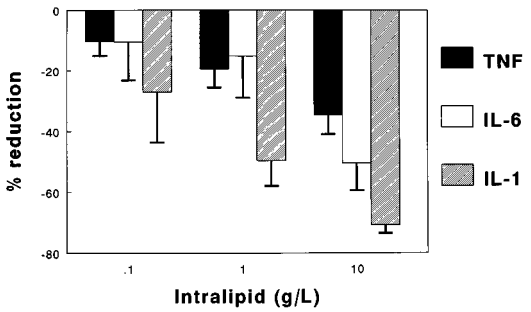

FIG. 1. Intralipid inhibits LPS-induced TNF, IL-1β, and IL-6 production in human whole blood in a dose-dependent manner. Mean ± standard error percent inhibitions of cytokine production in human whole blood by increasing concentrations of Intralipid are shown (the data are relative to cytokine levels measured after incubation with LPS only). Whole blood from six healthy volunteers was incubated for 4 h at 37°C with LPS (10 ng/ml) in the absence or presence of Intralipid. Mean ± standard error levels of cytokines after stimulation with endotoxin only were as follows: TNF, 3,368 ± 318 pg/ml; IL-1β, 907 ± 109 pg/ml; and IL-6, 6,915 ± 1,575 pg/ml.

after stimulation of whole blood for these longer time periods. Finally, we assessed whether Intralipid (10 g/liter) also inhibited the activity of the endotoxin to be used in the in vivo experiments (lot EC-5). This proved to be the case; i.e., Intralipid reduced TNF concentrations after an 8-h stimulation of whole blood with lot EC-5 endotoxin (10 ng/ml) from 9,518 ± 1,190 to 3,540 ± 695 pg/ml (a reduction of 63.5% ± 3.3% [$P < 0.05$]).

Endotoxemia in normal humans. We next assessed whether infusion-induced hypertriglyceridemia attenuates endotoxin responses in humans in vivo. The infusion regimen of 20% Intralipid was based on preliminary investigations (data not shown) in which we sought to achieve triglyceride levels in serum of approximately 10 g/liter at 2 h after the initiation of the infusion (i.e., triglyceride concentrations within the range that caused important inhibition of endotoxin-induced cytokine production in whole blood in vitro).

(i) Lipid levels. Injection of endotoxin alone did not induce changes in triglyceride concentrations compared with the baseline (Table 1). Infusion of Intralipid was associated with significant rises in triglyceride levels, which reached a peak at the end of the infusion (Table 1). Directly before the injection of endotoxin, triglyceride levels in serum were 818 ± 135 mg/dl.

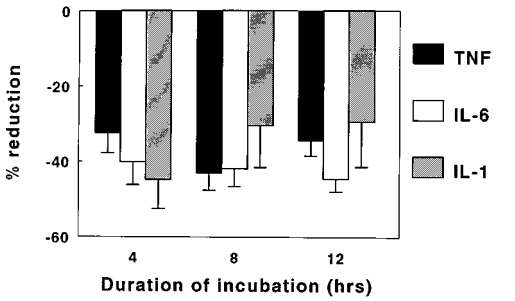

FIG. 2. Mean ± standard error percent inhibitions of cytokine production in human whole blood by Intralipid (the data are relative to cytokine levels measured after incubation with LPS only). Whole blood from six healthy volunteers was incubated for 4, 8, or 12 h at 37°C with LPS (10 ng/ml) in the absence or presence of Intralipid (10 g/liter). Mean ± standard error levels of cytokines after stimulation with endotoxin only were as follows: TNF, 4,295 ± 398 (4 h), 5,063 ± 669 (8 h), and 4,098 ± 629 pg/ml (12 h); IL-1β, 444 ± 136 (4 h), 1,143 ± 205 (8 h), and 1,352 ± 223 pg/ml (12 h); and IL-6, 6,967 ± 979 (4 h), 11,446 ± 1,140 (8 h), and 11,605 ± 995 pg/ml (12 h).

TABLE 1. Mean ± standard error triglyceride concentrations in serum after injection of endotoxin with or without an intravenous infusion of Intralipid[a]

Time (h)	Amt of triglycerides (mg/dl) with:	
	LPS	LPS and Intralipid
−2	113 ± 13	95 ± 16
0	104 ± 9	818 ± 135[b]
2	97 ± 8	1,216 ± 271[b]
6	86 ± 9	492 ± 285
24	103 ± 5	96 ± 19

[a] A bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) was given at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (n = 5) or 20% Intralipid (n = 5).

[b] $P < 0.05$, by ANOVA and the Newman-Keuls test (for the difference from the baseline value and from the corresponding value in the group treated with LPS only).

Cholesterol levels did not change in either treatment group (data not shown).

(ii) Clinical signs and symptoms. Injection of endotoxin elicited comparable influenza-like symptoms, such as headache, chills, and muscle aches, in the presence or absence of hypertriglyceridemia. In addition, intravenous endotoxin induced a similar rise in body temperature in both treatment groups, peaking after 4 h (Fig. 3). The maximum temperature after endotoxin alone was 38.2 ± 0.2°C ($P < 0.0001$ versus the baseline); after endotoxin with Intralipid, it was 38.5 ± 0.1°C ($P < 0.0001$ versus the baseline; $P = 0.12$ for the difference between the two groups). Mean arterial blood pressure did not change in either group (data not shown). Pulse rates increased from 62 ± 2 to 88 ± 7 beats per min 3 h after the administration of endotoxin only and from 57 ± 4 to 84 ± 5 beats per min 3 h after administration of endotoxin to the hypertriglyceridemic subjects ($P < 0.0001$ versus the baseline for both groups; $P = 0.87$ for the difference between the groups). Vital signs did not change after infusion of Intralipid only (i.e., without LPS).

(iii) Cytokines. Endotoxin elicited significant increases in the concentrations of TNF, IL-6, and IL-8 in plasma ($P < 0.0001$ for all three cytokines) (Fig. 4 and 5). TNF reached peak concentrations after 1.5 h (212 ± 69 pg/ml), IL-6 peaked after 2 h (162 ± 45 pg/ml), and IL-8 peaked after 2 h (171 ± 67 pg/ml). Hypertriglyceridemia did not affect endotoxin-induced TNF release (peak concentration, 265 ± 70 pg/ml) but did enhance the endotoxin-induced appearance of IL-6 and IL-8 (both $P = 0.05$), which was associated with more prolonged responses compared with the responses found after administration of endotoxin alone. The peak concentrations of IL-6 and IL-8 in hypertriglyceridemic subjects injected with endotoxin were 315 ± 134 and 277 ± 53 pg/ml, respectively. IL-1β remained undetectable in all study subjects. Endotoxin induced transient increases in the levels of soluble TNF receptor types I and II in plasma ($P < 0.0001$ for both). These changes were not influenced by concurrent hypertriglyceridemia (Fig. 4). Infusion of Intralipid alone did not result in significant changes in the levels of cytokines or soluble receptors (data not shown).

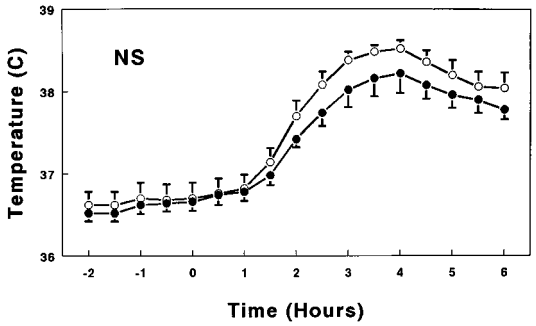

FIG. 3. Mean ± standard error rectal temperatures before and after a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (solid circles; n = 5) or 20% Intralipid (open circles; n = 5). NS, nonsignificant (for the difference between the two treatment groups by ANOVA).

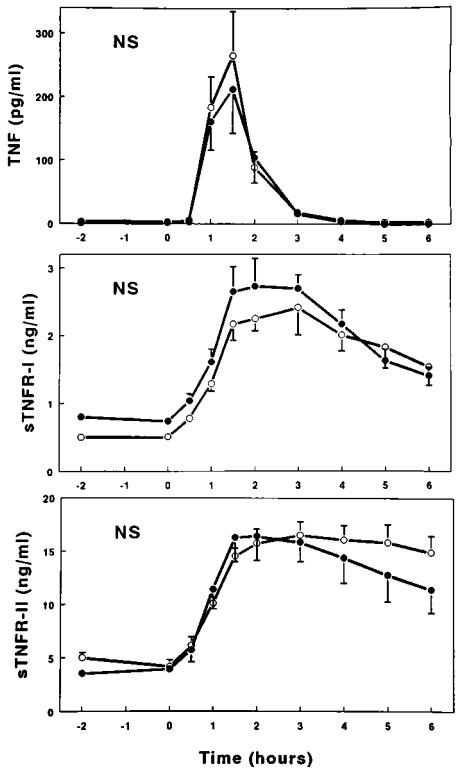

FIG. 4. Mean ± standard error concentrations of TNF and soluble TNF receptors in plasma after a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (solid circles; n = 5) or 20% Intralipid (open circles; n = 5). NS, nonsignificant (for the difference between the two treatment groups by ANOVA). sTNFR-I, soluble TNF receptor I; sTNFR-II, soluble TNF receptor II.

(iv) Leukocytes. Endotoxin induced a biphasic change in leukocyte and neutrophil counts which involved initial leukopenia (neutropenia) followed by leukocytosis (neutrophilia) and which was not influenced by concurrent hypertriglyceridemia (shown for total leukocyte counts in Fig. 6). Likewise, endotoxin-induced monocytopenia and lymphocytopenia were not affected by Intralipid (data not shown). Endotoxin administration was associated with an increase in the levels of elastase-α_1-antitrypsin complexes and lactoferrin in plasma, which is indicative for neutrophil degranulation and which peaked after 3 h (243 ± 103 and 353 ± 44 ng/ml, respectively; for both, $P < 0.0001$ versus the baseline) (Fig. 7). Hypertriglyceridemia markedly potentiated this endotoxin-induced inflammatory response. In hypertriglyceridemic subjects, peak levels of elastase-α_1-antitrypsin complexes were 652 ± 156 ng/ml ($P < 0.0001$ versus with LPS only) and those of lactoferrin were 570 ± 101 ng/ml ($P < 0.001$). Infusion of Intralipid only was not associated with changes in any of these inflammatory parameters (data not shown).

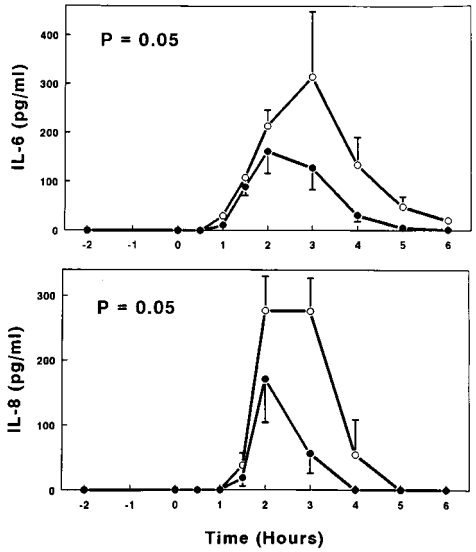

FIG. 5. Mean ± standard error concentrations of IL-6 and IL-8 in plasma after a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (solid circles; $n = 5$) or 20% Intralipid (open circles; $n = 5$). P values indicate the difference between the two treatment groups by ANOVA.

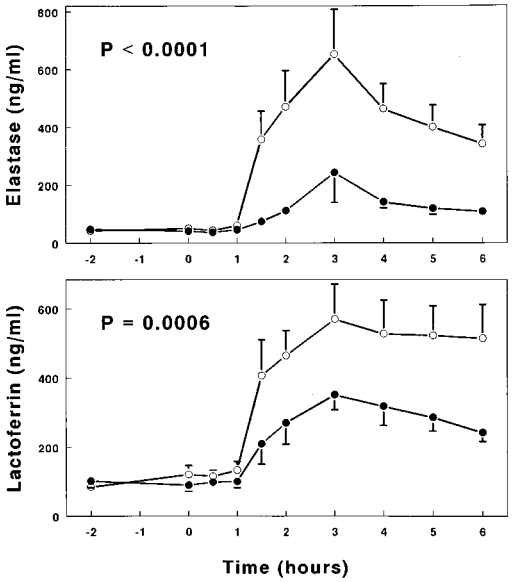

FIG. 7. Mean ± standard error concentrations of elastase-α_1-antitrypsin complexes and lactoferrin in plasma after a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (solid circles; $n = 5$) or 20% Intralipid (open circles; $n = 5$). P values indicate the difference between the two treatment groups by ANOVA.

(v) C-reactive protein. C-reactive protein levels in plasma were measured 24 h after the injection of endotoxin, and they tended to be higher in the hypertriglyceridemic subjects (5.5 ± 0.9 versus 3.9 ± 0.4 mg/dl; $P = 0.07$).

DISCUSSION

The LPS-inhibiting properties of triglyceride-rich lipoproteins in vivo have been demonstrated in rodents in several ways. Preincubation of LPS with either chylomicrons or very-low-density lipoproteins in the presence of lipoprotein-free plasma protected against LPS-induced death, which was associated with a reduced systemic TNF response (19, 20). Infusion of chylomicrons derived from mesenteric lymph directly before or 30 min after the administration of LPS also reduced mortality (20, 29). In contact with plasma, Intralipid resembles endogenous triglyceride-rich lipoproteins (1, 7, 13, 16–18, 30, 33). Accordingly, Intralipid improved survival after a lethal challenge with endotoxin in rats (29), and Soyacal, a highly similar fat emulsion, reduced LPS-induced death in mice as effectively as chylomicrons when preincubated in the presence of plasma (19).

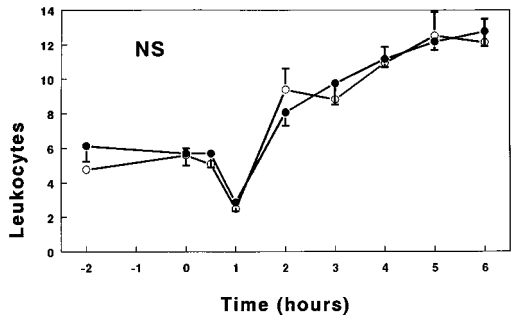

FIG. 6. Mean ± standard error leukocyte counts (10^9/liter) after a bolus intravenous injection of endotoxin (lot EC-5; 20 U/kg) at 0 h during a 4-h infusion (125 ml/h, starting at −2 h) of either 5% glucose (solid circles; $n = 5$) or 20% Intralipid (open circles; $n = 5$). NS, nonsignificant (for the difference between the two treatment groups by ANOVA).

In the present study, we first confirmed the ability of Intralipid to inhibit LPS activity in the human ex vivo system of whole blood. We then infused Intralipid at a quantity and rate that aimed to result in triglyceride concentrations in serum at the time endotoxin was administered within the range that caused important inhibition of LPS-induced cytokine production in whole blood. This goal was achieved, as triglyceride levels measured directly before endotoxin injection ranged from 590 to 1,270 mg/dl. It was therefore unexpected that this infusion-induced hypertriglyceridemia did not inhibit LPS-induced TNF production in humans in vivo and even potentiated IL-6 and IL-8 release. Hypertriglyceridemia also did not influence a number of other systemic inflammatory responses elicited by endotoxin, including fever and leukocytosis, while it strongly potentiated LPS-induced neutrophil degranulation. This latter finding contrasts with an earlier in vitro report demonstrating that Intralipid decreases neutrophil degranulation triggered by endotoxin (23).

We do not have a definite explanation for the differences between our in vivo data and results obtained with human whole blood and earlier with rats. Possibly, endotoxin in vivo acts on cytokine-producing cells absent from the bloodstream, for which Intralipid is not able to inhibit its activity. The possibility that preexposure of the volunteers to hypertriglyceridemia before the administration of endotoxin may have primed mononuclear cells is unlikely, considering the fact that preincubation of whole blood with Intralipid for up to 8 h did not affect the capacity of Intralipid to inhibit endotoxin-induced cytokine production (data not shown). One possible explanation may be that higher triglyceride concentrations are necessary in vivo to inhibit LPS activity. Indeed, in the above-cited rat study (20), triglyceride levels at the time of endotoxin administration were approximately six times higher than those in our study. However, it has to be taken into account that during a clinical gram-negative infection, such high triglyceride

levels are not found. They remain at around 400 mg/dl (i.e., 50% of the triglyceride concentrations that were measured in this study at the time of endotoxin administration) (11). Notably, in rats, chylomicrons or Intralipid was administered as a brief infusion directly before or after endotoxin (20, 29), whereas in our study, Intralipid was given as a constant intravenous infusion that continued after the injection of endotoxin. However, bolus injections of very large amounts of Intralipid or very-short-lasting endogenous production of triglyceride-rich lipoproteins is unlikely to occur in patients.

This study further suggests that in contrast to what has been reported for rodents, hypertriglyceridemia is not a sensitive response to systemic administration of endotoxin in humans. Indeed, in rats, endotoxin induces hypertriglyceridemia at very low doses, i.e., doses 2 logs lower than those required for a detectable TNF response (8). Our study demonstrates that a dose of endotoxin that induces a series of systemic inflammatory responses in normal humans does not cause hypertriglyceridemia. A controlled study comparing fasting humans after injection of either endotoxin or saline seems warranted to assess the effect of endotoxin on lipoprotein metabolism in humans more carefully.

Hypertriglyceridemia is unable to reduce endotoxin responsiveness in humans. These results raise doubt about the hypothesis, mainly based on rodent and in vitro studies, that elevated concentrations of triglyceride-rich lipoproteins during a gram-negative infection have a role of importance in the human defense against endotoxin-induced injury.

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