Continuous Infusion of Interleukin-1β in Rats Induces a Profound Fall in Plasma Levels of Cholesterol and Triglycerides

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During infectious diseases, striking alterations in plasma concentrations of cholesterol (hypcholesterolemia) and triglycerides (hypertriglyceridemia) may occur. It has been suggested that interleukin-1 is a mediator of these alterations. We studied the effects of continuous administration of recombinant human interleukin-1β (rhIL-1β) on plasma levels of cholesterol and triglycerides. A total of 42 rats were equipped with minipumps loaded with either rhIL-1β (delivery rate of 0.5, 2.0, or 4.0 μg/day i.p. for 1 week) or saline. After 1 day of treatment with rhIL-1β, plasma cholesterol levels had not changed. On day 2 a remarkable decrease of plasma cholesterol levels was observed in rats treated with 2.0 μg rhIL-1β/day (1.49±0.13 versus 2.23±0.08 mmol/l, p<0.005; rhIL-1β versus saline) or 4.0 μg rhIL-1β/day (1.46±0.04 versus 2.18±0.04 mmol/l, p<0.0005). This decrease persisted until the end of the experiment and occurred in all major lipoprotein fractions. Triglycerides in plasma (and in very low density lipoprotein) decreased almost concomitantly with plasma cholesterol, although to a lesser degree. Infusion of 2.0 μg rhIL-1β/day did not affect either cholesterol esterification or total postheparin lipolytic activity in plasma. Long-term infusion with 4.0 μg rhIL-1β/day induced prolonged fever, whereas at the lower doses temperatures were elevated only the first 2 days. rhIL-1β at a dose of 2.0 and 4.0 μg/day induced a transient decrease of food intake and a suppression of body weight gain. Restriction of food consumption to the level observed in the 2.0 μg rhIL-1β experiment caused only a small decrease of plasma cholesterol level and had no effects on plasma concentrations of triglycerides. Therefore, it is unlikely that the decline in triglyceride levels during rhIL-1β infusion was caused by a decrease in food intake. Diminished food consumption also cannot completely explain the profound decline of cholesterol levels during rhIL-1β administration. Whether IL-1 plays a role as a mediator of the lowering of plasma cholesterol levels during infections remains to be determined. (Arteriosclerosis and Thrombosis 1992;12:1036–1043)

Key Words • interleukin-1 • cholesterol • triglycerides • lipids • rats

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Other studies have emphasized the role of increased hepatic synthesis of such particles during infection.14,15 Cerami and coworkers (Kawakami and Cerami16 and Kawakami et al17) were the first to suggest that macrophage factors are important mediators of the hypertriglyceridemia of infection. Their hypothesis was based on the observation that endotoxin-stimulated mouse macrophages secrete a factor that decreases the activity of adipose tissue lipoprotein lipase (LPL) as well as the synthesis and storage of lipids in cultured fat cells.16,17 In later studies this macrophage factor was identified as tumor necrosis factor (TNF).18 Further indirect evidence for the concept that TNF is an important mediator of the hypertriglyceridemia of infection came from a series of studies conducted by Feingold and Grunfeld. These researchers showed that administration of TNF to rodents produces hypertriglyceridemia mainly by increased hepatic synthesis of triglyceride-rich lipoproteins.19–23 Interleukin-1 (IL-1) is a cytokine that shares with TNF a variety of important biological effects.24 Increased levels of both cytokines have been measured in biological fluids of patients suffering from infections.25,26 Although the effects of TNF have been extensively studied, only a few reports have focused on the effects of IL-1 on lipid metabolism. Recently it was demonstrated

D during infectious diseases, striking alterations in the plasma concentrations of cholesterol and triglycerides may occur in both humans and laboratory animals. Except for studies of rabbits,1,2 most reports show that plasma cholesterol levels are decreased during the febrile phase of bacterial infections.3–8 The mechanism causing hypocholesterolemia during infectious diseases is unknown. In contrast, plasma levels of triglycerides are usually elevated in bacterial, viral, and parasitic infections, particularly during recovery.8–12 In animal models of infection a decrease in the catabolism of circulating triglyceride-rich lipoproteins has been observed.13
that a single bolus injection of IL-1 causes hypertriglycerideremia in rats.\textsuperscript{27-28} These short-term studies demonstrate that IL-1, like TNF, is a potential mediator of the hypertriglycerideremia of infection. Until now no data have been available with respect to the effects of long-term administration of IL-1 on plasma cholesterol and triglyceride levels in rats. Although IL-1 is likely released in a pulsatile fashion during most infections, long-term administration of IL-1 is of interest because in some infections and especially in chronic inflammation, IL-1 may be released in a more continuous fashion. Such a long-term study is also relevant because rapid development of tolerance with respect to a number of biological effects of IL-1 occurs during long-term administration of this peptide.\textsuperscript{29-30} In this study we show that long-term intraperitoneal administration of relatively low doses of IL-1 to rats for 1 week caused a profound decline of plasma cholesterol levels as well as a moderate decline in triglyceride levels.

**Methods**

**Test Materials**

Recombinant human IL-1\(\beta\) (rhIL-1\(\beta\)) was kindly provided by Dr. D. Boraschi (Sclavo, Siena, Italy). The preparation had a specific activity of 10\(^6\) units/mg protein on D10.G4.1 cells, corresponding to an activity of 10 units/\(\mu\)g versus the interim IL-1\(\beta\) reference reagent 80552. According to the specifications of the suppliers, endotoxin contamination was negligible (<1.2 ng lipopolysaccharide/mg IL-1). rhIL-1\(\beta\) was diluted in sterile pyrogen-free saline.

**Animals**

Male albino Wistar rats (Cpb:WU) were obtained from a local breeding facility. They were housed in an artificially lighted room (lights on at 7 AM and off at 7 PM) in individual Plexiglas cages. Rats were fed with commercial rat chow (RMH-TM, Hope Farms, Woerden, The Netherlands) and tap water ad libitum. The diet contained 22% protein, 4.8% fat, 5.1% fiber, and 61.7% other carbohydrates. At the start of the experiments rats were 10 weeks old and weighed 200–220 g. All experimental procedures were in accordance with institutional guidelines concerning the care and use of laboratory animals.

**Experimental Protocols**

**Long-term administration of rhIL-1\(\beta\).** To accommodate the animals to the stress of the experimental procedures, they were handled daily by the experimenter starting 1 week before venous cannulation. Body weight was measured daily at 8 AM, and food and water intake was recorded by weighing the residual food and water for individual cages. Body temperature was measured serially two times a day between 8:30 and 9 AM and between 1 and 2:30 PM in conscious hand-held rats by insertion of a thermal probe into the rectum. The probe was connected to a digital temperature monitor (Digital DT100, Elbatron, Kerkdriel, The Netherlands). Mean daily temperature for each rat was determined by averaging the morning and afternoon rectal temperatures. Blood was collected from freely moving rats by means of an indwelling cannula. Rats were cannulated as described by Steffens.\textsuperscript{31} Under anesthesia with pen-
experiments but without implantation of osmotic minipumps. One group of animals (n=6) received food ad libitum, whereas another group (n=7) was fed daily with the same amount of food that had been consumed on that particular day of the experiment by rats treated with 2.0 \( \mu \)g rhIL-1/β/day (food-restricted group). Plasma levels of cholesterol and triglycerides as well as food intake and body weight were measured daily for 1 week.

**Analytical Methods**

Plasma levels of triglycerides and cholesterol were determined by enzymatic methods using a BM/Hitachi 717 automatic analyzer system and Boehringer Mannheim (Mannheim, FRG) diagnostic kits No. 1058550 (for triglycerides) and 1040839 (for cholesterol). The very low density lipoprotein (VLDL) plus intermediate density lipoprotein (IDL) \((d<1.019 \text{ g/ml})\), low density lipoprotein (LDL, \(1.019<d<1.070 \text{ g/ml}\)), and high density lipoprotein (HDL, \(d>1.070 \text{ g/ml}\)) fractions were isolated by sequential ultracentrifugation for 18 hours at 168,000g. By previous density gradient ultracentrifugation and electrophoretic studies, the density of 1.070 g/ml was found to give an accurate separation of LDL from HDL in rat plasma. LPL and hepatic lipase (HL) in postheparin plasma samples were measured selectively by a method that uses a gum arabic-stabilized emulsion of triolein and \[^3\text{H}\]tri olein.32 With the substrate containing 0.1 M NaCl and an optimal amount of dialyzed human serum to provide activating apolipoprotein C-II, total triglyceride lipase activity (LPL+HL) was measured. HL was determined in the same substrate at a sodium chloride concentration of 1 M with omission of the serum activator. LPL was determined by subtraction. The assays were performed by incubating 10 \( \mu \)l postheparin plasma with 250 \( \mu \)l of either substrate for 30 minutes at 37°C. The rate of cholesterol esterification by lecithin:cholesterol acyltransferase (LCAT) was measured by estimating the decrease in unesterified cholesterol during incubation of plasma at 37°C for 1 and 3 hours.33 Plasma unesterified cholesterol was measured by an enzymatic method with diagnostic kit No. 310328 from Boehringer Mannheim. All incubations were performed in duplicate with undiluted plasma.

**Statistical Analysis**

In each experiment a few rats had to be excluded because of blood clotting within the cannula. All data are presented as \( \text{mean} \pm \text{SEM}\) of five to seven rats. Comparisons between treatment groups were made by analysis of variance (ANOVA) with repeated measurements to analyze the effects of the treatment course. Only when the ANOVA revealed a significant difference between both groups was a comparison of the groups at specific time points evaluated further by Student’s \( t \) test for unpaired observations.

**Results**

**Results of Long-term Treatment of Rats With rhIL-1/β**

**Physical discomfort.** Signs of physical discomfort including piloerection and decreased physical activity were observed in animals infused with 4.0 \( \mu \)g rhIL-1/β/day starting a few hours after implantation of the pumps. This visually observed uneasiness gradually diminished during the first day of the treatment period and had disappeared by the end of day 1. Infusion with 2.0 \( \mu \)g rhIL-1/β/day also induced signs of discomfort that were less pronounced than those induced by the 4.0 \( \mu \)g rhIL-1/β dose. Treatment of rats with 0.5 \( \mu \)g rhIL-1/β/day or with saline did not perceptibly distress the animals.

**Plasma levels of cholesterol and triglycerides** (Figure 1). Figure 1A shows that from day 2 after implantation of the minipumps, plasma cholesterol levels in rats treated with 0.5 \( \mu \)g rhIL-1/β/day were slightly but not significantly lower than those in rats treated with saline. After 1 day of treatment with 2.0 or 4.0 \( \mu \)g rhIL-1/β/day, plasma cholesterol levels had not changed. From day 2 onward a remarkable decrease in plasma cholesterol levels was observed in rhIL-1/β-treated rats, which persisted until the end of the experiment (Figures 1C and 1E; ANOVA days 2–7, 2.0 \( \mu \)g rhIL-1/β experiment, \( p<0.0005\); 4.0 \( \mu \)g rhIL-1/β experiment, \( p<0.0005\)). Plasma cholesterol levels in rhIL-1/β-treated rats were significantly decreased from day 2 (2.0 \( \mu \)g rhIL-1/β experiment, 1.49±0.13 versus 2.23±0.08 mmol/l, \( p<0.0005\); 4.0 \( \mu \)g rhIL-1/β experiment, 1.46±0.04 versus 2.18±0.04 mmol/l, \( p<0.0005\); rhIL-1/β versus saline) up to and including day 7 (2.0 \( \mu \)g rhIL-1/β experiment, 1.71±0.07 versus 2.09±0.04 mmol/l, \( p<0.005\); 4.0 \( \mu \)g rhIL-1/β experiment, 1.57±0.05 versus 2.15±0.03 mmol/l, \( p<0.0005\); rhIL-1/β versus saline).

Treatment with rhIL-1/β also induced a decrease in plasma levels of triglycerides (Figures 1B, 1D, and 1F; ANOVA days 1–7, 0.5 \( \mu \)g rhIL-1/β, \( p<0.10\); 2.0 \( \mu \)g rhIL-1/β, \( p<0.05\); 4.0 \( \mu \)g rhIL-1/β, \( p<0.05\)). In contrast with the decrease in cholesterol level, which persisted until the end of the infusion, the decline in triglyceride levels was diminishing at the end of the infusion period. Statistically significant differences in plasma levels of triglycerides were observed on days 1–4 during treatment with 2.0 \( \mu \)g rhIL-1/β/day and on days 1–3 and 5–7 during treatment with 4.0 \( \mu \)g rhIL-1/β/day. Although blood samples were not taken from previously fasted rats, chylomicrons appeared to be absent, as evidenced by agarose gel electrophoresis (data not shown).

**Suppression of food intake and daily body weight change** (Figure 2). In saline-treated rats there was a slight reduction in food intake 1 day after implantation of the minipumps. Long-term treatment of rats with 0.5 \( \mu \)g rhIL-1/β/day did not affect daily food intake. Analysis of repeated measures (days 1–7) revealed a depressive effect on food consumption associated with treatment with the higher doses of rhIL-1/β (2.0 \( \mu \)g rhIL-1/β, \( p<0.05\); 4.0 \( \mu \)g rhIL-1/β, \( p<0.0005\)). One day after implantation of the pumps, the decrease in food intake was maximal (2.0 \( \mu \)g rhIL-1/β, 4.4±1.6 versus 11.6±1.7 g, rhIL-1/β versus saline, \( p<0.05\); 4.0 \( \mu \)g rhIL-1/β, 5.5±0.9 versus 13.7±0.9 g, \( p<0.0005\)). Food intake remained significantly lower in rhIL-1/β-treated than in control animals up to and including days 3 (2.0 \( \mu \)g) and 5 (4.0 \( \mu \)g).

There was only a small (0.5 \( \mu \)g rhIL-1/β, −3.4±1.8 g; 2.0 \( \mu \)g rhIL-1/β, −7.1±1.9 g) or no (4.0 \( \mu \)g rhIL-1/β) decrease in body weight on the first day of saline infusion (Figure 2). Infusion of rats with 0.5 \( \mu \)g rhIL-1/β/day did not notably affect daily body weight change compared with saline infusion. Continuous infusion of...
2.0 or 4.0 μg rhIL-1β/day reduced body weight gain (ANOVA days 1–7, 2.0 μg, p<0.0005; 4.0 μg, p<0.05). Weight loss was already maximal on the first day of infusion. Daily body weight change in rhIL-1β-treated rats reached approximately initial levels by the third day of infusion. Thereafter the rate of daily body weight increase was essentially the same for both rhIL-1β- and saline-treated groups of animals. Continuous infusion of rhIL-1β at doses of 0.5, 2.0, and 4.0 μg/day into rats had no effect on total daily fluid intake (data not shown).

Rectal temperature changes (Figure 3). Saline-treated rats maintained a virtually constant rectal temperature throughout the entire infusion period. Infusion of rhIL-1β produced an increase in rectal temperature (ANOVA days 1–7, 0.5 μg, p<0.005; 2.0 μg, p<0.05; 4.0 μg, p<0.05). Temperature peaked 1 day after implantation of pumps infusing rhIL-1β at a rate of 0.5 and 2.0 μg/day but had returned to values of saline-infused rats on day 3. From then on values of rhIL-1β–treated rats and saline-treated rats were similar. The mean maximal increase in temperature induced by 2.0 μg rhIL-1β/day (+1.7°C) was significantly greater (p<0.05) than that induced by infusion of 0.5 μg rhIL-1β/day (+0.9°C). At a dose of 4.0 μg rhIL-1β/day, rectal temperature also peaked on day 1 (+1.3°C) and then gradually declined but remained elevated throughout the whole experimental period. Post hoc analysis of the individual groups in this experiment revealed that rectal temperatures were significantly elevated on days 1, 2, 3, 4, and 7.

Lipoprotein analysis. Figure 4 shows the lipoprotein profile in plasma on day 5 of treatment with 2.0 μg rhIL-1β/day or saline. The decrease in total plasma cholesterol (−32.8%) was accounted for by a decrease of cholesterol in all major lipoprotein fractions (VLDL+IDL, 0.13±0.02 versus 0.25±0.04 mmol/l, p<0.05; LDL, 0.36±0.04 versus 0.54±0.03 mmol/l, p<0.005; and HDL, 0.38±0.01 versus 0.56±0.02 mmol/l, p<0.0005; rhIL-1β versus saline). The decrease in plasma levels of triglycerides was reflected by a decrease in VLDL+IDL triglycerides.

Determination of cholesterol esterification rate. The percentage of unesterified cholesterol to total cholesterol in plasma was not different between rats treated with 2.0 μg rhIL-1β/day or saline (32.6±1.9%). The cholesterol esterification rate measured during incubation of plasma for 1 and 3 hours also did not differ significantly between both groups: at 1 hour the rate of cholesterol esterification was 0.060±0.010 mmol/l·hr⁻¹ in the rhIL-1β group and 0.057±0.007 mmol/l·hr⁻¹ in the control group; at 3 hours these values were 0.080±0.010 and 0.065±0.012 mmol/l·hr⁻¹, respectively.

Total lipolytic, HL, and LPL activities in postheparin plasma samples. On day 7 of the 2.0 μg rhIL-1β exper-
Effects of Food Restriction on Plasma Levels of Cholesterol and Triglycerides

As expected, the food intake of the food-restricted rats mimicked that of the rats given 2.0 μg rhIL-1β/day (Figure 5A). Rats that were fed the same amount of food as that consumed by rhIL-1β–treated rats showed a significantly different pattern of body weight change in comparison with control rats fed ad libitum (Figure 5B; ANOVA days 1–7; p<0.0005). On day 1 food-restricted rats showed a body weight decrease of 16.4±1.5 g while control rats fed ad libitum lost 3.0±2.0 g (food-restricted versus control rats, p<0.0005). On day 2 food-restricted rats lost 5.7±1.0 g and control rats gained 2.8±1.1 g (p<0.0005). Thereafter, daily body weight gain was no longer decreased in the food-restricted rats. Food restriction induced a slight but significant decrease in plasma cholesterol levels compared with values in rats fed ad libitum (ANOVA days 1–7, p<0.05; Figure 5C). Statistically significant differences in plasma cholesterol levels between both groups of rats were observed on day 3 (1.62±0.04 versus 1.88±0.06 mmol/l, rhIL-1β versus saline, p<0.05) and day 4 (1.62±0.06 versus 1.89±0.05 mmol/l, rhIL-1β versus saline, p<0.05). Restriction of food intake had no effects on plasma concentrations of triglycerides (Figure 5D).

Discussion

The present study demonstrates that continuous infusion of rhIL-1β in doses as low as 2.0 and 4.0 μg/day profoundly lowers plasma cholesterol concentrations in rats. Infusion of 0.5 μg rhIL-1β/day did not significantly change plasma cholesterol levels. rhIL-1β was infused for 7 days by osmotic minipumps implanted in the peritoneal cavity. Previously it has been shown that under these conditions IL-1 remains bioactive and bioavailable for at least 1 week. The cholesterol-lowering effect of the higher doses of IL-1 persisted until the end of the study. Interestingly, the decrease in plasma cholesterol levels was not observed before the second day of treatment with IL-1. Lipoprotein analysis on day 5 of the 2.0 μg rhIL-1β experiment revealed that the decrease in the total plasma cholesterol level was due to a decrease in cholesterol levels in all lipoprotein fractions.

Our study also shows that triglyceride levels in plasma obtained from nonfasted rats were significantly decreased during long-term administration of 2.0 and 4.0 μg rhIL-1β/day and that at the end of the infusion
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0.5 µg IL-1

2.0 µg IL-1

4.0 µg IL-1

Line plots showing effects of continuous infusion of recombinant human interleukin-1β (IL1) (●) or saline (○) for 1 week on rectal temperature of rats. Asterisks mark significant differences between IL1- and saline-treated rats: *p<0.05, **p<0.005, ***p<0.0005 by Student’s t test.

FIGURE 3. Line plots showing effects of continuous infusion of recombinant human interleukin-1β (IL1) (●) or saline (○) for 1 week on rectal temperature of rats. Asterisks mark significant differences between IL1- and saline-treated rats: *p<0.05, **p<0.005, ***p<0.0005 by Student’s t test.

FIGURE 4. Lipoprotein profile in rats on day 5 of treatment with 2.0 µg recombinant human interleukin-1β (IL1)/day (●) or saline (○). Asterisks mark significant differences between IL1- and saline-treated rats: *p<0.05, **p<0.005, ***p<0.0005 by Student’s t test. VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; LDL, low density lipoprotein.

Besedovsky et al. found that injection of 0.25 µg IL-1 in diabetic mice caused a marked reduction in serum triglyceride levels.

We confirm previous findings that administration of IL-1 induces dose-dependent fever in rats. In our study, infusion of rats with 4.0 µg rhIL-1β/day induced prolonged fever, whereas at the lower doses of rhIL-1β (2.0 and 0.5 µg/day) temperatures were elevated only on the first 2 days of infusion. rhIL-1β treatment was also associated with a decrease in food intake and body weight gain, which is in good agreement with previous reports. The effect of rhIL-1β on body weight gain was present during the first 2 days of infusion but had been lost by day 3 of treatment. This is in line with studies demonstrating that tolerance to the anorectic effects of IL-1 develops within a few days.

In fasting rats plasma cholesterol and triglyceride levels are lower than in rats with unrestricted access to food. To clarify whether the effects of IL-1 on plasma cholesterol and triglyceride levels could be explained solely by the reduction of food intake during rhIL-1β treatment, we investigated the effects of food consumption restricted to the same level as in the 2.0 µg rhIL-1β experiment on plasma cholesterol and triglyceride concentrations. This experiment revealed that such a reduction of food intake had no effect on plasma triglyceride concentrations, whereas plasma cholesterol levels were moderately lowered. Therefore, it can be concluded that it is highly unlikely that the decrease in plasma triglyceride levels observed during long-term IL-1 infusion is caused by decreased food intake and that the observed decrease in food intake cannot completely explain the profound decrease of plasma cholesterol levels during IL-1 administration.

Intravenous injection of lipopolysaccharide or TNF causes a decrease in the activity of the LCAT enzyme in nonhuman primates. It has been suggested that this decrease in LCAT activity after TNF administration is causally related to the occurrence of hypocholesterolemia after injection of this cytokine in nonhuman primates. However, it is unlikely that in our study a decrease in LCAT activity was the cause of the hypocholesterolemia during IL-1 treatment because the ra-
The mechanism of the hypocholesterolemia observed during treatment with granulocyte-macrophage colony-stimulating factor (GM-CSF) is also observed during treatment with granulocyte colony-stimulating factor. In humans treated after administration of these hematopoietic growth factors, the decrease in plasma cholesterol levels is due to a diminished secretion of nascent VLDL. We suggest that the decrease in plasma cholesterol levels observed during treatment with GM-CSF is caused by (intrahepatic) release of GM-CSF. Therefore it might be that hypocholesterolemia during long-term IL-1 treatment is caused by impaired secretion of apolipoprotein B by hepatocytes. With respect to the metabolism of triglycerides, we found that although small reciprocal changes were observed in the activities of LPL and HL, the total postheparin lipolytic activity in triglyceride-rich lipoproteins. We suggest that the decrease in plasma cholesterol levels observed during treatment with GM-CSF is caused by (intrahepatic) release of IL-1. Alternatively, because IL-1 induces GM-CSF secretion, it might be that IL-1 causes hypocholesterolemia by inducing GM-CSF secretion.

Hypertriglyceridemia is frequently present during infection in both humans and laboratory animals. There are as yet no convincing data that IL-1 does mediate the hypertriglyceridemia of infection. Except for studies of rabbits, most reports of cholesterol metabolism during bacterial infections agree that plasma cholesterol levels are decreased during the febrile phase of bacterial infections. Whether IL-1 released from the inflammatory site or produced locally by endotoxin-stimulated Kupffer cells plays a role as a mediator in the lowering of plasma cholesterol levels during infections remains to be investigated.

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