Infection and Inflammation Induce LDL Oxidation In Vivo

Riaz A. Memon, Ilona Staprans, Mustafa Noor, Walter M. Holleran, Yoshikazu Uchida, Arthur H. Moser, Kenneth R. Feingold, Carl Grunfeld

Abstract—Epidemiological studies have shown an increased incidence of coronary artery disease in patients with chronic infections and inflammatory disorders. Because oxidative modification of lipoproteins plays a major role in atherosclerosis, the present study was designed to test the hypothesis that the host response to infection and inflammation induces lipoprotein oxidation in vivo. Lipoprotein oxidation was measured in 3 distinct models of infection and inflammation. Syrian hamsters were injected with bacterial lipopolysaccharide (LPS), zymosan, or turpentine to mimic acute infection, acute systemic inflammation, and acute localized inflammation, respectively. Levels of oxidized fatty acids in serum and lipoprotein fractions were measured by determining levels of conjugated dienes, thiobarbituric acid–reactive substances, and lipid hydroperoxides. Our results demonstrate a significant increase in conjugated dienes and thiobarbituric acid–reactive substances in serum in all 3 models. Moreover, LPS and zymosan produced a 4-fold to 6-fold increase in conjugated diene and lipid hydroperoxide levels in LDL fraction. LPS also produced a 17-fold increase in LDL content of lysophosphatidylcholine that is formed during the oxidative modification of LDL. Finally, LDL isolated from animals treated with LPS was significantly more susceptible to ex vivo oxidation with copper than LDL isolated from saline-treated animals, and a 3-fold decrease occurred in the lag phase of oxidation. These results demonstrate that the host response to infection and inflammation increases oxidized lipids in serum and induces LDL oxidation in vivo. Increased LDL oxidation during infection and inflammation may promote atherogenesis and could be a mechanism for increased incidence of coronary artery disease in patients with chronic infections and inflammatory disorders. (***Arterioscler Thromb Vasc Biol*****. 2000;20:1536-1542.)**

Key Words: lipoproteins ■ atherosclerosis ■ infection ■ inflammation

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Recent epidemiological studies have suggested a link between atherosclerosis and infection and inflammation. For example, a higher incidence of coronary artery disease (CAD) occurs in patients with *Chlamydia pneumoniae* and cytomegalovirus infections, and these microorganisms have been detected in atherosclerotic plaques.[1–3] However, an increased incidence of CAD also occurs in patients with *Helicobacter pylori* infections, chronic dental infections, and chronic bronchitis, infections in which microorganisms are not localized to the vessel wall.[4–6] Moreover, an increased incidence of CAD exists in patients with local inflammatory diseases such as rheumatoid arthritis and psoriasis.[7,8] Although some studies have suggested that specific infectious agents play a direct role in the vessel wall in the formation of atherosclerotic lesions,[1–3] both infection and inflammation are accompanied by a systemic host response known as the acute-phase response (APR). Changes associated with APR could also be a mechanism for enhanced susceptibility to atherogenesis.

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APR represents a complex reaction of the host that is characterized by changes in serum levels of specific proteins such as C-reactive protein and serum amyloid A.[9] APR is accompanied by alterations in lipid metabolism that include increased serum triglycerides and decreased HDL levels.[10] These changes also can be produced by administration of endotoxin (lipopolysaccharide [LPS]), a well-characterized inducer of APR. LPS rapidly increases serum triglyceride levels by stimulating hepatic VLDL production and by decreasing triglyceride clearance.[11] In rodents, LPS increases serum cholesterol levels by increasing LDL,[12] whereas in primates, LDL levels decrease during infection but an increase occurs in small, dense LDL.[13] Finally, LPS decreases HDL levels in both rodents and primates.[11–13] The increase in triglycerides and small, dense LDL and the decrease in HDL are proatherogenic.

Oxidative modification of lipoproteins plays a central role in the pathogenesis of atherosclerosis.[14,15] Oxidized LDL exerts several proatherogenic effects, which include increased synthesis and secretion of adhesion molecules, monocyte chemotaxis and adhesion, cytotoxicity to endothelial cells, enhanced foam cell formation, and increased smooth muscle cell proliferation.[14,15] Moreover, lipoproteins with oxidative

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From the Departments of Medicine (R.A.M., M.N., A.H.M., K.R.F., C.G.), Surgery (I.S.) and Dermatology (W.M.H., Y.U.), University of California San Francisco, Calif, and Metabolism Section (R.A.M., M.N., A.H.M., K.R.F., C.G.), Medical Service, Department of Veterans Affairs Medical Center, San Francisco, Calif.

Correspondence to Riaz A. Memon, PhD, Department of Veterans Affairs Medical Center, Metabolism Section (111F), 4150 Clement St, San Francisco, CA 94121. E-mail rmemon@itsa.ucsf.edu

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damage and lipid peroxidation products have been detected in atherosclerotic lesions.[14,15] Finally, several structurally unrelated antioxidants slow the progression of atherosclerosis[14,15]; whereas oxidized lipids in the diet enhance atherosclerosis.[16,17] Although these studies support a role for oxidized lipoproteins in atherogenesis, the mechanisms by which lipoproteins are oxidized in vivo are unknown. Moreover, the pathogenic stimuli that induce lipoprotein oxidation in vivo have not been identified. Under normal circumstances, circulating LDL is protected from oxidative stress by HDL-associated enzymes, particularly paraoxonase, which destroys biologically active oxidized phospholipids.[18]

Van Lenten et al[19] have shown that serum paraoxonase activity is decreased in rabbits after croton oil administration, and paraoxonase depleted HDL is unable to protect LDL from oxidation in vitro. We have recently reported that LPS, tumor necrosis factor, and interleukin-1 decrease serum paraoxonase activity and hepatic paraoxonase mRNA levels in Syrian hamsters in vivo,[20] which suggests that the decrease in paraoxonase is a feature of APR. Because reactive oxygen is generated as part of host defense[9] and paraoxonase protects LDL from oxidative stress, we postulated that APR may increase LDL oxidation in vivo. We have now examined this hypothesis in 3 distinct models of infection and inflammation, which are produced by administration of LPS (acute systemic infection), zymosan (acute noninfectious systemic inflammation), and turpentine (acute localized sterile inflammation). Each of these stimuli is a well-characterized inducer of APR.[11,21,22]

Methods

Materials

Endotoxin (*E coli* 55:B5) was purchased from Difco Laboratories and freshly diluted to desired concentrations in pyrogen-free 0.9% saline (Kendall McGraw Laboratories Inc). Oil of turpentine (microscopic grade) was purchased from BDH Laboratories; zymosan and other chemicals were from Sigma Chemical Co.

Animal Procedures

Male Syrian hamsters (≈140 to 160 g) were purchased from Charles River Laboratories (Wilmington, Mass). We chose Syrian hamsters because compared with that in mice and rats, lipoprotein metabolism in Syrian hamsters closely resembles that in humans. For example, Syrian hamsters have substantial plasma LDL, and the LDL levels change in response to dietary manipulations in a fashion similar to humans.[23] Animals were kept on a normal light cycle and provided with rodent chow and water ad libitum. The Syrian hamsters were injected either with LPS (0.1 to 100 μg per 100 g body weight [BW] IP), zymosan (10 mg per 100 g BW IP), turpentine (0.5 mL/100 g BW SC), or saline. Subsequently, food was withdrawn from both control and treated animals because APR induces anorexia.[11,22] Animals were studied between 4 and 48 hours after LPS treatment and 24 hours after zymosan or turpentine. Doses of LPS used here are much lower than the doses that induce lethality in rodents (LD_{50}, ≈5 mg per 100 g BW) but have significant effects on lipoprotein metabolism in Syrian hamsters.[12] Similarly, doses of zymosan and turpentine used have been shown to induce APR.[21,22]

Isolation of Lipoproteins and Measurement of Lipoprotein Oxidation

At indicated times after LPS, turpentine, or zymosan treatment, animals were anesthetized with isoflurane and their blood was obtained. Samples were processed immediately. Lipoproteins were isolated by use of density-gradient ultracentrifugation.[24] Butylated hydroxytoluene (final concentration, 5 μmol/L) was added to all lipoprotein fractions to prevent further oxidation. Lipid peroxidation products in serum and lipoprotein fractions were measured by use of several methods. Conjugated diene content was measured by the second-derivative UV spectroscopy method[25] as described earlier.[26] Lipid peroxide levels were measured by the method of Ohishi et al.[27] Lipid peroxide decomposition products, which consist of a variety of aldehydes, were measured as thiobarbituric acid–reactive substances (TBARS) as described by Morel et al.[28] Lysophosphatidylcholine (LPC) content in lipoprotein fractions was measured by the method of Quinn et al.[29] The LPC band on silica-gel plates was identified by comigration with standard, scraped, and assayed for phosphorus content as described.[30]

LDL Oxidation Ex Vivo

Susceptibility of LDL to ex vivo oxidation was determined by continuous monitoring (every 15 minutes for 4 hours at 37°C) of conjugated diene production[31] as described previously.[26] Susceptibility to oxidation is expressed as the "lag time" and is determined from an intercept of lines drawn through the linear portion of lag and propagation phases for each sample. At the end of incubation, the levels of TBARS formed were also measured.[28]

Statistics

Results are presented as mean±SEM. Statistical significance between 2 groups was determined by use of Student's *t* test. Comparison among >2 groups was done by ANOVA with statistical significance calculated with Bonferroni's multiple-comparison test.

Results

Infection and Inflammation Increase Lipid Oxidation Products in Serum

We initially examined the effect of LPS on lipid peroxidation products in serum. Syrian hamsters were injected with LPS (100 μg per 100 g BW) or saline and conjugated dienes, and TBARS were measured at different time points. A 2.2-fold increase occurred in serum-conjugated dienes 24 hours after LPS administration (Figure 1A). This effect of LPS was sustained for ≥48 hours (2-fold increase compared with controls). LPS had no significant effect on conjugated dienes at earlier time points. LPS also produced a 62% and 83% increase in serum TBARS after 24 and 48 hours of administration, respectively (Figure 1B). The dose-response curve for the LPS effect on serum-conjugated dienes is presented in Figure 2. The data demonstrate that the effect of LPS on serum-conjugated dienes is a sensitive and dose-dependent response. Doses as low as 1 μg per 100 g BW produced a 66% increase, whereas a 2.6-fold increase in conjugated dienes was seen with a dose of 100 μg per 100 g BW.

To determine whether the increase in lipid oxidation products is limited to LPS or is seen with other APR inducers, we examined the effect of zymosan (a model for acute systemic inflammation) and turpentine (a model for acute localized inflammation) on serum-conjugated dienes and TBARS. Because the baseline levels of conjugated dienes and TBARS may vary between animal groups depending on their antioxidant status, each experimental group was compared with its own control group from the same set of animals. Zymosan 10 mg per 100 g BW IP produced a 2.2 fold increase in serum-conjugated dienes, whereas turpentine 0.5 mL per 100 g BW SC increased conjugated dienes by 52% (Figure 3A). Similarly, zymosan and turpentine increased serum TBARS by 61% and 72%, respectively (Figure 3B), which demonstrated that serum lipid peroxidation products

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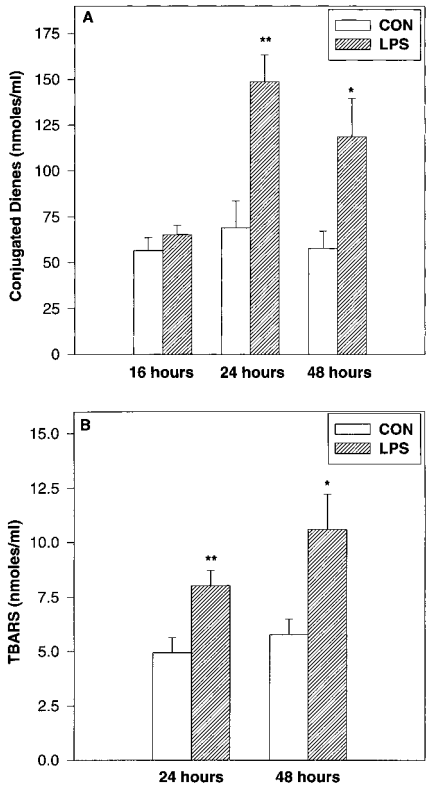

Figure 1. Effect of LPS on serum-conjugated dienes (A) and TBARS (B). Syrian hamsters were injected intraperitoneally with saline or LPS (100 μg per 100 g BW), and blood was obtained at different time points. Conjugated dienes and TBARS in serum were measured as described in Methods. Data are presented as mean±SEM; n=5 for both groups. A, *P<0.05, **P<0.005; B, *P<0.02, **P<0.005.

are increased in several distinct models of infection and inflammation.

Infection and Inflammation Increase Lipoprotein Oxidation In Vivo

We next examined the effect of treatment with LPS and zymosan on conjugated dienes, lipid hydroperoxides, and

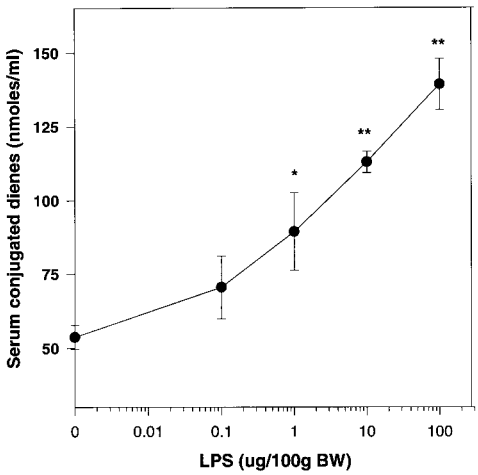

Figure 2. Dose-response of LPS effect on serum-conjugated diene levels. Syrian hamsters were injected intraperitoneally either with saline or LPS doses, indicated on x axis. Blood was obtained 24 hours later, and serum-conjugated dienes were measured as described in Methods. Data are presented as mean±SEM; n=4 for each dose. *P<0.05; **P<0.001.

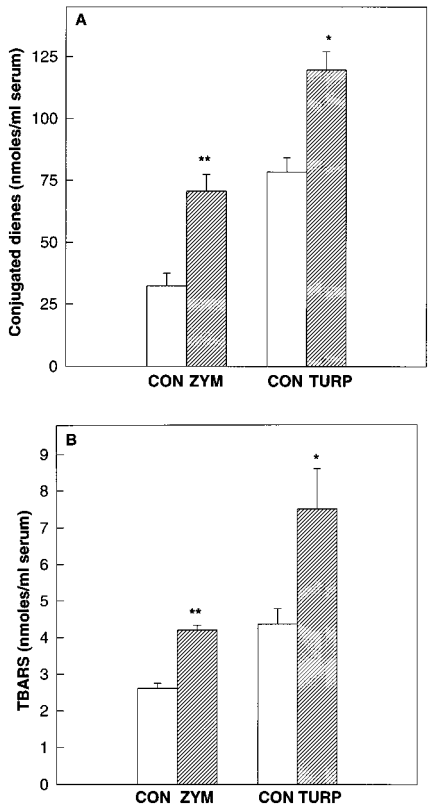

Figure 3. Effects of zymosan (ZYM) and turpentine (TURP) on serum-conjugated dienes (A) and TBARS (B). Syrian hamsters were injected with saline and zymosan (10 mg per 100 g BW IP) or turpentine (0.5 mL per 100 g BW SC), and 24 hours later blood was obtained. Serum-conjugated dienes and TBARS were measured as described in Methods. Data are presented as mean±SEM; n=5 for all groups. A, *P<0.05, **P<0.002; B, *P<0.05, **P<0.005.

TBARS in lipoprotein fractions. TBARS were not detectable in any fraction. Basal levels of conjugated dienes and lipid hydroperoxides were low in lipoprotein fractions from saline-treated animals. LPS produced a 7-fold increase in conjugated diene content in the LDL fraction when presented as nanomoles per milligram LDL protein (Figure 4A). Similarly, zymosan produced a 4.8-fold increase in conjugated diene content (nanomoles per milligram protein) in the LDL fraction (Figure 4A). Levels of conjugated dienes in the LDL fraction from LPS-treated animals were 3.9-fold higher when expressed as nanomoles per milligram LDL triglycerides and 8.1-fold higher when presented as nanomoles per milligram LDL cholesterol. Similarly, levels of conjugated dienes in the LDL fraction from zymosan-treated animals were 6.1-fold higher when expressed as nanomoles per milligram LDL triglycerides and 6.3-fold higher when presented as nanomoles per milligram LDL cholesterol. No significant effect of LPS or zymosan was seen on conjugated diene content of VLDL and HDL fractions when adjusted for protein, triglyceride, or cholesterol content (data not shown).

Both LPS and zymosan increased lipid hydroperoxides (nanomoles per milligram protein) in the LDL fraction by 4.3-fold and 2.9-fold, respectively (Figure 4B). Increases in hydroperoxides were also significant when expressed as nanomoles per milligram LDL triglycerides (3.9-fold for LPS and 3.8-fold for zymosan) or as nanomoles per milligram

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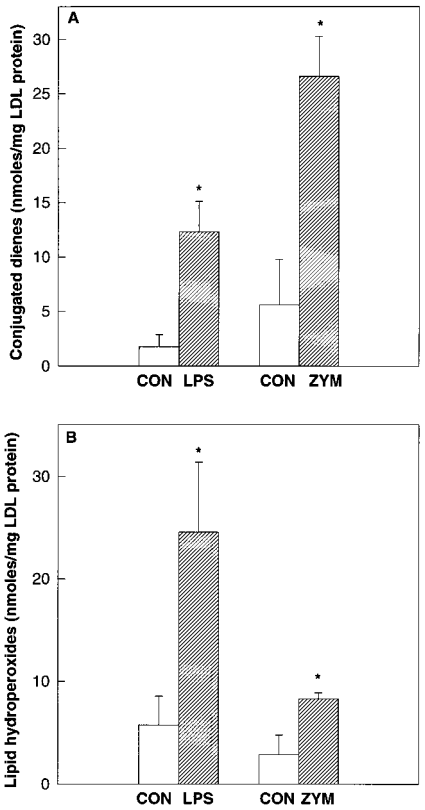

Figure 4. Effect of LPS and zymosan on conjugated dienes (A) and lipid hydroperoxides (B) in LDL. Syrian hamsters were injected with LPS (100 μg per 100 g BW IP), zymosan (10 mg per 100 g BW IP), or saline. Blood was obtained 24 hours later, and lipoproteins were isolated. Levels of conjugated dienes and lipid hydroperoxides in LDL were measured as described in Methods and normalized to LDL protein content. Data are presented as mean±SEM; n=10 for LPS group and 5 for zymosan group. Abbreviations are as in Figure 3. A, *$P<0.01$; B, *$P<0.05$.

LDL cholesterol (5.5-fold for LPS and 5.1-fold for zymosan). Neither LPS nor zymosan altered hydroperoxide levels in VLDL or HDL fraction when adjusted for protein, triglyceride, or cholesterol content (data not shown).

Susceptibility of LDL to Ex Vivo Oxidation

We next determined whether LDL oxidized in vivo during the host response to infection or inflammation is more susceptible to further oxidation ex vivo. To address this question, we isolated LDL from hamsters treated with LPS (100 μg per 100 g BW; 24-hour treatment) or saline and examined its susceptibility to ex vivo oxidation with copper sulfate (1.67 μmol/L) by monitoring the formation of conjugated dienes every 15 minutes for 4 hours at 37°C. LDL obtained from LPS-treated animals was significantly more susceptible to ex vivo oxidation at every time point (Figure 5). LDL obtained from LPS-treated hamsters had a shorter lag phase followed by a propagation phase that reached plateau by 4 hours, whereas LDL obtained from controls had a longer lag phase, and in some samples the propagation phase was not generated after 4 hours. Mean lag time for the onset of oxidation was significantly shorter for the LDL obtained from LPS-treated hamsters (control 92.5±10.3 minutes versus LPS 31.2±4.7 minutes; $P<0.001$). Moreover, at the end of the 4-hour reaction, a 3.2-fold increase occurred in TBARS in the incubation medium that contained LDL isolated from LPS-

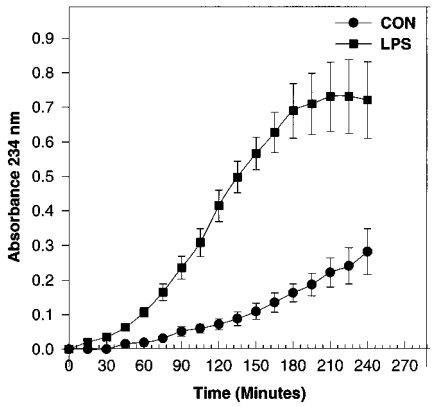

Figure 5. Susceptibility of acute-phase LDL to ex vivo oxidation. Syrian hamsters were injected with saline or LPS (100 μg per 100 g BW IP) and 24 hours later lipoproteins were isolated. Susceptibility of LDL to ex vivo oxidation was determined by continuous monitoring of production of conjugated dienes for 4 hours as described in Methods. Lag time in each sample was determined from an intercept of lines drawn through the linear portion of lag and propagation phase for each sample. Data are presented as mean±SEM of absorbance at 234 nm for each time point; n=4 for each group.

treated animals (control 17±1.6 versus LPS 54±4.5 malondialdehyde equivalents per milligram LDL protein; $P<0.001$). These results indicate that the host response to infection produces LDL that not only contains more oxidized lipids, but is also more susceptible to further oxidation.

LPS Increases LPC Content in LDL

Oxidative modification of LDL is associated with increased formation of LPC, a product of phosphatidylcholine hydrolysis, and this reaction is primarily mediated by plasma-activating factor–acetylhydrolase (PAF-AH).[32] We have recently shown that LPS increases plasma PAF-AH activity in Syrian hamsters.[33] We therefore postulated that LPS should increase LPC content in the LDL fraction. As shown in Figure 6, basal levels of LPC are low in the LDL fraction and LPS treatment produces a 17-fold increase in LPC content in LDL. No significant effect of LPS existed on LPC content in VLDL or HDL (data not shown).

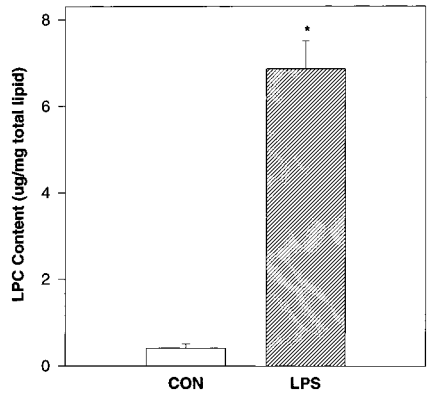

Figure 6. Effect of LPS on LPC levels in LDL. Syrian hamsters were injected with saline or LPS (100 μg per 100 g BW IP), and 24 hours later lipoproteins were isolated. Levels of LPC in LDL were determined as described in Methods. Data are presented as mean±SEM; n=5 for each group. *$P<0.002$.

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Discussion

Oxidative modification of lipoproteins is believed to play a central role in the pathogenesis of atherosclerosis.[14,15] Because plasma contains several antioxidants[34] and lipoproteins with oxidative damage have been isolated from atherosclerotic lesions,[14,15] lipoprotein oxidation generally is considered to occur in the vessel wall. Although lipid oxidation in the vessel wall is thought to occur as a result of a local deficiency of endogenous antioxidants or an excess of free metal ions, only limited data support these hypotheses. Research has recently shown that human atherosclerotic plaques contain massive amounts of lipid peroxidation products, despite the presence of large quantities of α-tocopherol and ascorbate.[35] Thus, it is unclear whether oxidized lipoproteins originate in the arterial wall or are produced in the circulation and then enter the intimal space.

The present study demonstrates that systemic oxidation of lipoprotein particles occurs as part of the host response to infection and inflammation. These conclusions are based on several observations. First, both serum-conjugated dienes (which measure the initial phase of lipid peroxidation) and TBARS (which measure the degradation phase of lipid peroxidation) are increased in Syrian hamsters after LPS administration. This increase in serum-oxidized lipids is a dose-dependent effect seen 24 hours after LPS administration and is sustained for at least 48 hours. The LPS-induced increase in serum triglycerides occurs within 90 minutes,[11] whereas changes in oxidized lipids are not seen until 24 hours after LPS treatment, which indicates that increase in oxidized lipids in serum is not simply a result of increased availability of fatty acid substrate. Second, serum-conjugated dienes and TBARS are increased in animals treated with either zymosan or turpentine, which produces systemic or localized inflammation, respectively.[21,22] Third, conjugated dienes and lipid hydroperoxides are markedly increased in circulating LDL from animals treated with either LPS or zymosan, which indicates that LDL oxidation occurs in 2 distinct models of acute infection and inflammation. The significant increase in conjugated dienes and lipid hydroperoxides in LDL persists when expressed as nanomoles per milligram protein, triglycerides, or cholesterol, which suggests that increased oxidation of LDL is not merely a result of changes in the composition of LDL during APR.[12] More-dramatic changes in the composition of VLDL and HDL occur during APR.[12] However, no change occurs in the oxidation status of these fractions when adjusted for triglyceride, cholesterol, or protein content. Fourth, LPC content, a marker for oxidative modification of LDL, is increased in circulating LDL after LPS treatment, which indicates that lipoprotein phospholipids are oxidized in vivo during APR. Fifth, LDL isolated from LPS-treated animals is more susceptible to ex vivo oxidation, which suggests that acute-phase LDL may be more susceptible to further oxidation in the vessel wall. Together, these results indicate that the host response to infection and inflammation is a potent stimulus for producing oxidation of serum lipids, including circulating LDL.

Several mechanisms could contribute to increased LDL oxidation during APR. Paraoxonase is a HDL-associated enzyme that protects LDL from oxidative stress by destroying biologically active phospholipids.[18] Van Lenten et al[19] have reported a decrease in serum paraoxonase activity both in rabbits after croton oil was administered and in humans postoperatively.[19] We have recently shown that LPS, tumor necrosis factor, and interleukin-1 decrease hepatic paraoxonase mRNA expression and serum paraoxonase activity in Syrian hamsters.[20] Castellani et al[36] have shown that depletion of paraoxonase results in the loss of the antioxidant function of HDL, and addition of paraoxonase to HDL restores the protective function of HDL. Moreover, Aviram et al[37] also reported that purified paraoxonase is a potent inhibitor of LDL and HDL oxidation in vitro. Finally, lipoproteins isolated from paraoxonase knockout mice are more susceptible to oxidation than lipoproteins isolated from their wild-type littermates,[38] and paraoxonase knockout mice on a high fat–high cholesterol diet are more susceptible to atherosclerosis.[38] These results suggest that paraoxonase may protect LDL from oxidation in vivo. Because the time course of increase in LDL oxidation in vivo during APR (in the present study) follows the time course of LPS-induced decrease in paraoxonase activity,[20] the decreased paraoxonase activity during APR is likely to be a potential mechanism for the increased oxidation of circulating LDL reported herein.

In addition to paraoxonase, other HDL-associated proteins also could contribute to increased LDL oxidation during the APR. Plasma ceruloplasmin levels are increased during APR,[39] and purified ceruloplasmin has been shown to increase oxidation of LDL in cell-free systems as well as in cultured endothelial, smooth muscle, and U937 monocytic cells.[40] Because both LPS and zymosan increase ceruloplasmin levels,[39,40] it is possible that an increase in ceruloplasmin during infection and inflammation could increase LDL oxidation.

Transferrin is another metal-binding protein associated with HDL.[41] Hepatic synthesis and serum levels of transferrin are decreased during APR.[42] Removal of HDL subpopulations that contain transferrin reduces the ability of HDL to protect against LDL oxidation in vitro.[41] Thus, a decrease in transferrin synthesis during APR may lead to less transferrin in HDL, which makes it less effective for protection of LDL against oxidation.

We also found increased LPC levels in circulating LDL after LPS treatment. LPC is known to exert several proatherogenic effects and is a marker for oxidative modification of LDL.[15] LPC is produced by hydrolysis of phosphatidylcholine, a reaction primarily mediated by plasma PAF-AH, an enzyme associated with lipoproteins.[32] Plasma PAF-AH activity is increased in Syrian hamsters, rats, and mice after LPS, zymosan, or turpentine treatment.[33] Plasma PAF-AH activity is also higher in patients with human immunodeficiency virus infection.[43] Because the time course of LPS-induced increase in LPC content in circulating LDL in Syrian hamsters follows that of lipid oxidation (reported in the present study) and plasma PAF-AH activity,[33] it is possible that the increase in LPC levels in LDL is secondary to an increase in plasma PAF-AH activity.

Several studies have shown that APR is accompanied by many proatherogenic changes in lipoprotein metabolism, such as a more-atherogenic lipoprotein profile that consists of increases in serum triglycerides and small, dense LDL and a decrease in HDL.[10–13] APR is also accompanied by decreases in mRNA levels and activity of lecithin-cholesterol acyltrans-

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ferase, cholesteryl ester transfer protein, and hepatic lipase (reviewed in reference 44). These decreases could decrease reverse-cholesterol transport. ApoA1 levels are also decreased during APR.[45] Because apoA1 prevents the aggregation of LDL,[46] decreased apoA1 during APR may facilitate LDL aggregation. Additionally, we have recently reported that lipoproteins isolated from Syrian hamsters treated with LPS are enriched in ceramides and sphingomyelin.[47] An increase in LDL ceramide facilitates LDL aggregation and enhances its uptake by macrophages, which leads to foam cell formation.[48] Finally, the present results demonstrate increased oxidized lipids in serum and circulating LDL during APR, which supports the hypothesis that the sustained host response to infection and inflammation may be proatherogenic, albeit through multiple mechanisms.

The present study raises a question as to why lipoprotein oxidation would occur during APR, a host reaction to infection and inflammation. The APR is thought to be a protective mechanism to prevent systemic injury and help the repair process. Lipoprotein oxidation during APR initially is likely to serve a beneficial purpose. Reactive oxygen species and free radicals are part of the local host defense mechanisms, given that they play a role in killing invading microorganisms and are induced by the same stimuli that induce APR.[9] Thus, lipoproteins may scavenge these free radicals to prevent systemic toxicity and membrane damage. However, in doing so, lipoproteins may get oxidized. One of the major enzymes that plays a key role in microbial killing, myeloperoxidase, is acutely released by activated neutrophils and monocytes in response to LPS and other inflammatory stimuli.[49] Myeloperoxidase also plays an important role in the oxidation of protein and lipid components of LDL and is expressed in atherosclerotic lesions.[50] Moreover, LPS acutely induces the expression of lipoxygenases[51] to increase the synthesis of prostaglandins and leukotrienes during the inflammatory response. Lipoxygenases also participate in LDL oxidation by oxidizing fatty acids, cholesteryl esters, and phospholipids.[52] Because the activation of myeloperoxidase and lipoxygenases after LPS administration or other inflammatory stimuli occurs rapidly[49,51] compared with LDL oxidation, which takes about 24 hours, it is unclear whether these enzymes participate in LDL oxidation during APR. Early activation of myeloperoxidase or lipoxygenase may initiate the oxidative process, which then accelerates after the depletion of paraoxonase or transferrin or after the upregulation of ceruloplasmin. Further studies are required to understand fully the metabolic changes that occur during APR and contribute to lipoprotein oxidation.

In summary, the present study demonstrates that the host response to infection and inflammation induces LDL oxidation in vivo. Moreover, the LDL that has been oxidized in vivo is more susceptible to further ex vivo oxidation and has a significantly shorter lag time. Increased LDL oxidation that occurs during infection and inflammation could be one of the mechanisms that promote atherosclerosis in patients with chronic infections and inflammatory diseases.

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