Endotoxin, TNF, and IL-1 decrease cholesterol 7α-hydroxylase mRNA levels and activity

Kenneth R. Feingold,[1] David K. Spady, Allan S. Pollock, Arthur H. Moser, and Carl Grunfeld

Department of Medicine, University of California, San Francisco, and Metabolism and Nephrology Sections, Medical Service, Department of Veterans Affairs Medical Center, San Francisco, CA 94121, and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75235

Abstract Endotoxin (LPS) and cytokines increase cholesterol synthesis and the secretion of lipoproteins by the liver in rodents resulting in hypercholesterolemia. Cholesterol 7α-hydroxylase (CAH) is the rate-limiting enzyme in the conversion of cholesterol to bile acids in the liver, the major regulated pathway by which cholesterol is eliminated from the body. Decreases in CAH would increase the quantity of cholesterol available for lipoprotein production. In the present study, we demonstrate that LPS, TNF, or IL-1 administration to Syrian hamsters produces a marked decrease in the levels of CAH mRNA in the liver. This marked decrease occurred even when the basal level of CAH expression was increased by feeding the bile acid sequestrant, colestipol. Additionally, a marked decrease was also observed when the animals were fed a cholesterol-enriched diet. Moreover, the decrease in CAH mRNA occurred very rapidly (decreased 66% by 90 min after LPS administration) and required relatively small doses of LPS (100 ng/100 g body weight). Lastly, the decrease in mRNA levels was accompanied by a decrease in CAH activity. This decrease in CAH could contribute to the increase in hepatic lipoprotein production induced by LPS and cytokines. CAH can be added to the growing list of proteins that regulate lipid metabolism and that are altered during the acute phase response.–**Feingold, K. R., D. K. Spady, A. S. Pollock, A. H. Moser, and C. Grunfeld.** Endotoxin, TNF, and IL-1 decrease cholesterol 7α-hydroxylase mRNA levels and activity. *J. Lipid Res.* 1996. **37:** 223–228.

Supplementary key words acute phase response • cholesterol feeding • colestipol feeding • bile acids

Endotoxin (LPS) or cytokine administration, which mimic infection, increase serum lipid and lipoprotein levels (1). Serum triglyceride levels rapidly rise due both to increased secretion of VLDL by the liver and delayed clearance of triglyceride-rich lipoproteins secondary to an inhibition of lipoprotein lipase activity in adipose tissue and muscle (1–8). LPS also raises serum cholesterol levels in rodents and recent studies from our laboratory have demonstrated that this is predominantly due to an increase in LDL cholesterol (1, 9–11). HDL cholesterol levels decrease after LPS administration (1, 11).

The mechanisms by which LPS increases LDL cholesterol levels are not totally defined. Enhanced secretion of VLDL could lead to increased LDL production. We have also shown that LPS treatment produces an increase in the transcription of hepatic HMG-CoA reductase mRNA leading to increased levels of HMG-CoA reductase mRNA, protein and enzyme activity (11, 12). As a consequence, there is an increase in hepatic cholesterol synthesis that could contribute to the hypercholesterolemia (11).

In contrast, LPS did not increase hepatic mRNA levels of the LDL receptor, HMG-CoA synthase, or farnesyl pyrophosphate synthase (12). As these three proteins and HMG-CoA reductase are coordinately regulated by sterols (13–17), the absence of an increase in the mRNA for these three proteins suggests that LPS treatment does not regulate HMG-CoA reductase expression by alterations in hepatic cholesterol content. Indeed, there was no change in hepatic cholesterol levels after LPS administration (12). Moreover, as both LDL receptor mRNA and protein levels were not significantly altered by LPS, this finding suggests that a decrease in hepatic clearance of LDL does not contribute to LPS-induced hypercholesterolemia (11, 12).

The increase in hepatic HMG-CoA reductase mRNA levels after LPS administration was seen not only in chow-fed animals but also in hamsters fed a cholesterol-enriched diet, which suppresses HMG-CoA reductase

Abbreviations: LPS, endotoxin; CAH, cholesterol 7α-hydroxylase; TNF, tumor necrosis factor; IL-1, interleukin-1; LDL, low density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; BW, body weight; HPLC, high performance liquid chromatography.

[1]To whom correspondence should be addressed.

mRNA levels, or a diet containing the bile acid sequestrant colestipol, which increases HMG-CoA reductase mRNA levels (12, 18, 19). Thus, LPS is capable of increasing HMG-CoA reductase mRNA levels over a wide range of basal levels of gene expression. Additionally, TNF and IL-1, cytokines that mediate many of the metabolic effects of infection, also increase hepatic cholesterol synthesis, HMG-CoA reductase activity, and HMG-CoA reductase mRNA levels (20).

The conversion of cholesterol to bile acids in the liver represents the major regulated catabolic pathway by which cholesterol is eliminated from the body. The rate-limiting enzyme in this process is cholesterol 7α-hydroxylase (CAH) (21). Studies have shown that the activity and mRNA levels for CAH are regulated by diet and hormones (21–25). Feeding either cholesterol or bile acid sequestrants has been shown to increase CAH activity and mRNA levels (21–24). Additionally, both glucocorticoids and thyroid hormone have been shown to increase CAH (21, 25).

If an important function of the liver during infection and inflammation is to synthesize more cholesterol to be utilized in the formation of lipoproteins, we would hypothesize that the administration of LPS or cytokines should reduce CAH levels and thereby increase the quantity of cholesterol available for lipoprotein synthesis. The aim of the present study was to determine the effect of LPS and cytokines on the mRNA levels and activity of CAH.

METHODS

Materials

α^{32}P dCTP (3,000 Ci/mmol, 10 mCi/ml) and α^{32}P UTP (800 Ci/mmol) were purchased from New England Nuclear (Boston, MA); LPS (*E. coli* 055:B5) was from Difco Laboratories (Detroit, MI) and was freshly diluted to desired concentrations in pyrogen-free 0.9% saline (Kendall McGraw Laboratories, Inc., Irvine, CA); multiprime DNA labeling system was from Amersham International (Amersham, United Kingdom); minispin columns (G50) were from Worthington Biochemical Corporation (Freehold, NJ); oligo (dt) cellulose, type 77F was from Pharmacia LKB Biotechnology AB (Upsala, Sweden); nitrocellulose was from Schleicher & Schuell (Keene, NH); Kodak XAR5 film was used for autoradiography. The cDNA for hamster CAH was prepared as described previously (26). Human TNF with a specific activity of 5×10^7 U/mg was kindly provided by Genentech, Inc. (South San Francisco, CA). Recombinant human interleukin 1β with a specific activity of 1×10^9 U/mg was kindly provided by Immunex (Seattle, WA). The cytokines were freshly diluted to desired concentrations in pyrogen-free 0.9% saline containing 0.1% human serum albumin.

Animal procedures

Male Syrian hamsters (approximately 100–120 g) were purchased from Simonsen Laboratories (Gilroy, CA). The animals were maintained in a normal light cycle room (6 AM to 6 PM light, 6 PM to 6 AM dark) and were provided with rodent chow (Simonsen Laboratories) and water ad libitum. Where indicated, cholesterol or colestipol (Upjohn, Kalamazoo, MI) was added to the chow diet (2% by weight) and the animals were fed 4 days prior to study. Anesthesia with isofluorane was induced and the animals were injected I.P. with low dose LPS (100 ng/100 g body weight), high dose LPS (100 μg/100 g BW), TNF (25 μg/150 g BW), IL-1 (0.75 μg/150 g BW), or saline alone. In selected experiments, animals were injected I.P. with LPS without anesthesia. Subsequently, food was withdrawn from both control and treated animals because LPS and cytokines can induce anorexia.

Isolation of RNA and Northern blotting

Total RNA was isolated by a variation of the guanidinium thiocyanate method as described previously (11). Northern blotting was performed as described previously (11). Blots were exposed to X-ray film and bands were quantified by densitometry. Duration of film exposure was varied to allow measurements on the linear portion of the curve.

Determination of hepatic cholesterol 7α-hydroxylase activity

Hepatic CAH activity was measured using an HPLC-spectrophotometric assay that quantifies the mass of 7α-hydroxycholesterol formed from endogenous microsomal cholesterol using cholesterol oxidase as described previously (26, 27).

Statistics

Statistical significance was determined using a two-tailed Student's *t* test.

RESULTS

The effect of LPS (100 μg/100 g BW) on CAH mRNA levels in the liver of chow-fed animals is shown in **Fig. 1.** Ninety minutes after LPS administration, CAH mRNA levels were 34% of control levels, while at 4 h and 16 h, mRNA levels were less than 5% of controls (Fig. 1A). At 16 h, low doses of LPS (100 ng/100 g BW) also markedly decreased CAH mRNA levels (27 ± 10% of controls, $P < 0.05$) (Fig. 1B). In these experiments, separate controls

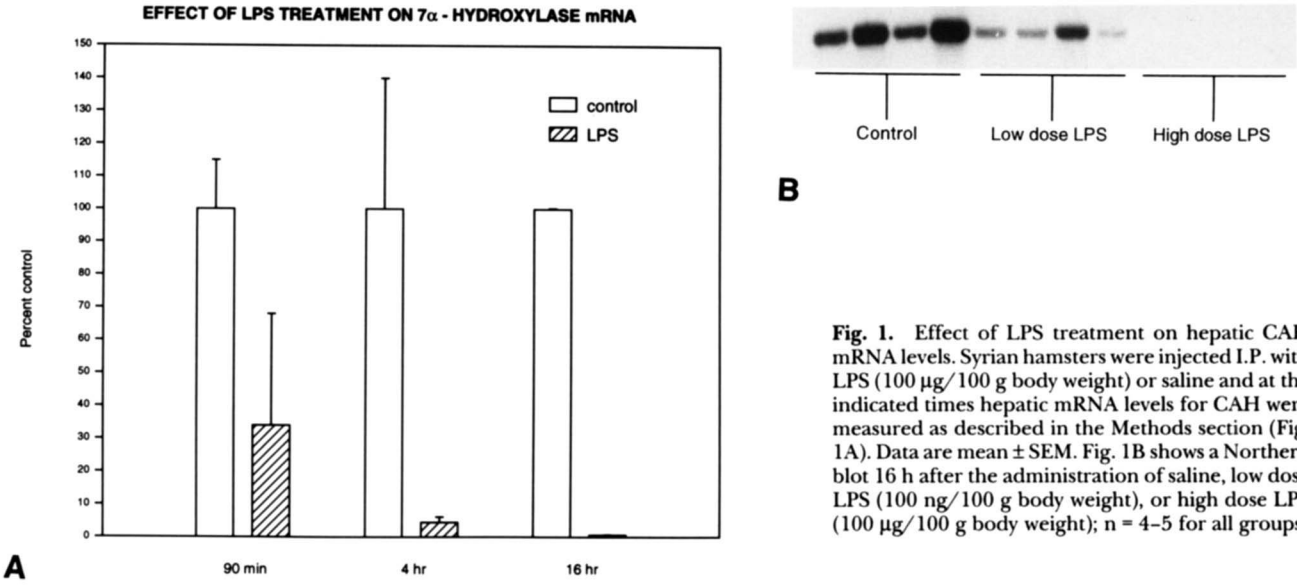


Fig. 1. Effect of LPS treatment on hepatic CAH mRNA levels. Syrian hamsters were injected I.P. with LPS (100 μg/100 g body weight) or saline and at the indicated times hepatic mRNA levels for CAH were measured as described in the Methods section (Fig. 1A). Data are mean ± SEM. Fig. 1B shows a Northern blot 16 h after the administration of saline, low dose LPS (100 ng/100 g body weight), or high dose LPS (100 μg/100 g body weight); n = 4–5 for all groups.

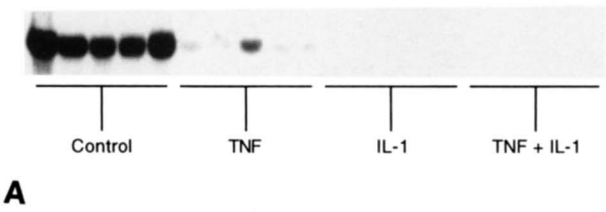
were carried out for each time point because animals were fasted after LPS administration and fasting could affect CAH mRNA levels. Both control and LPS-treated animals were fasted because LPS administration causes anorexia.

The effect of LPS (100 μg/100 g BW) on CAH mRNA levels in the liver was also determined in animals that were not anesthetized prior to LPS injection. A similar marked decrease in hepatic CAH mRNA levels was observed in unanesthetized animals (LPS < 5% of control), indicating that anesthesia does not account for these results.

The effect of TNF, IL-1, and the combination of TNF and IL-1 on CAH mRNA levels is shown in **Fig. 2.** Eight hours after cytokine administration, the levels of CAH mRNA in the liver were markedly reduced.

Studies by other investigators have shown that feeding cholesterol or bile acid sequestrants increased CAH mRNA levels (22–24). In our experiments, feeding a cholesterol-enriched diet resulted in a 26% increase in CAH mRNA levels in the liver that was not statistically significant. In contrast, colestipol feeding resulted in a 2.3-fold increase in hepatic CAH mRNA levels ($P < 0.01$). We next determined whether LPS treatment could reduce CAH mRNA levels under these dietary conditions. As shown in **Fig. 3,** LPS administration markedly decreased CAH mRNA in both cholesterol- and colestipol-fed animals.

We next determined whether this marked reduction in CAH mRNA levels after LPS treatment was paralleled



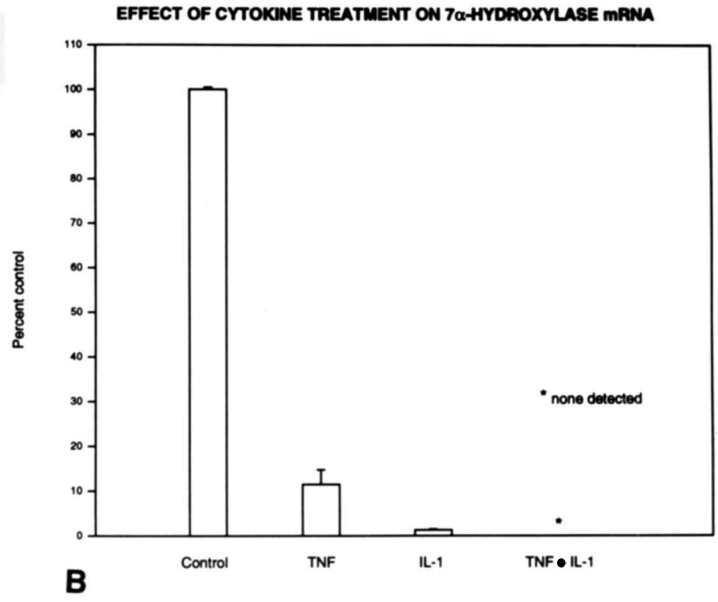


Fig. 2. Effect of cytokine treatment on hepatic CAH mRNA levels. Syrian hamsters were injected I.P. with saline, TNF (25 μg/150 g body weight), IL-1 (0.75 μg/150 g body weight), or the combination of TNF + IL-1. Eight hours after treatment, hepatic mRNA levels for CAH were measured as described in the Methods section. Fig. 2A shows the Northern blot while Fig. 2B depicts the quantitative analysis (mean ± SEM); n = 5 for all groups. The TNF, IL-1, and TNF + IL-1 groups are all significantly decreased compared to controls ($P < 0.001$).

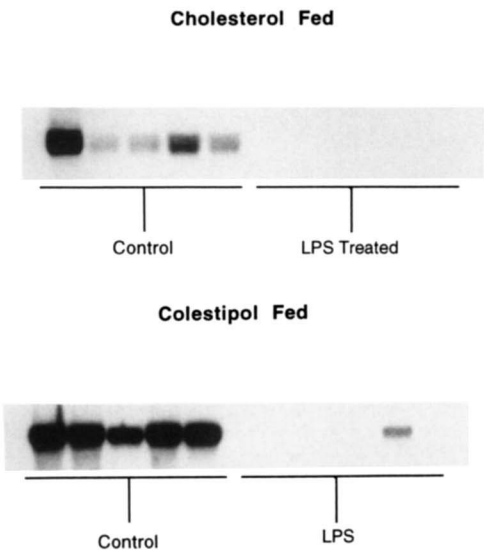


Fig. 3. Effect of LPS treatment on hepatic CAH mRNA levels in cholesterol- or colestipol-fed animals. Cholesterol or colestipol was added to the chow diet (2% by weight) for 4 days prior to study. The animals were injected I.P. with LPS (100 μg/100 g body weight) or saline and 16 h later hepatic mRNA was isolated as described in the Methods section. A Northern blot was made and probed for CAH as described in the Methods section. Top: cholesterol fed; bottom: colestipol fed; n = 5 for all groups.

by changes in CAH activity. As shown in **Fig. 4,** in colestipol-fed animals, LPS administration resulted in a 73% reduction in CAH activity within 16 h.

DISCUSSION

It is now well recognized that inflammation, infection, LPS, or cytokines increase serum lipid levels (1). This increase in serum lipid levels can be considered part of the acute phase response that results in marked changes in the levels of a large number of circulating proteins primarily due to alterations in their expression in the liver (28). The hepatic synthesis of certain proteins, such as fibrinogen and serum amyloid A, is increased (positive acute phase proteins), while the synthesis of other proteins, such as albumin and transferrin, is inhibited (negative acute phase proteins) (28).

The studies reported here demonstrate that regulation of CAH could play an important role in the changes in hepatic production of lipoproteins seen during the acute phase response. Recent studies have shown that the overexpression of CAH in the liver reduces plasma total and LDL cholesterol levels (29). The administration of LPS, TNF, or IL-1 resulted in a marked decrease in the levels of CAH mRNA in the liver. This marked decrease occurred even when the basal levels of CAH expression were increased by feeding the bile acid sequestrant, colestipol. Additionally, this decrease also occurred when the animals were fed a cholesterol-enriched diet. Moreover, the LPS-induced decrease in CAH mRNA levels occurred very rapidly (at 90 min levels were decreased 66%) and required relatively small doses of LPS (100 ng/100 g BW). Lastly, the decrease in mRNA levels was accompanied by a decrease in CAH activity. Thus, CAH can be considered a negative acute phase protein. A decrease in CAH could contribute to the increase in serum cholesterol levels seen after LPS or cytokine administration.

CAH is a member of a group of microsomal monooxygenases that consist of a specific cytochrome P450 and an NADPH-cytochrome P450 reductase (21). Studies have shown that during infection, inflammation, or cytokine administration, the activity of other cytochrome P450 enzymes is suppressed (30–35). Moreover, the suppression of cytochrome P450 enzymes has been shown to be achieved primarily at the level of gene transcription (33, 34). Thus, the inhibition of CAH reported here can be considered to be part of a negative acute phase response that effects the cytochrome P450 super family of monooxygenases.

CAH mRNA contains several AUUUA, AAU, or UAA motifs in its 3′ untranslated region that are characteristic of rapidly degraded mRNAs (23). In fact, the half-life of CAH mRNA is only 30 min in the rat (23, 25). Thus, the marked decrease in mRNA after LPS and cytokine administration seen in the present studies is probably

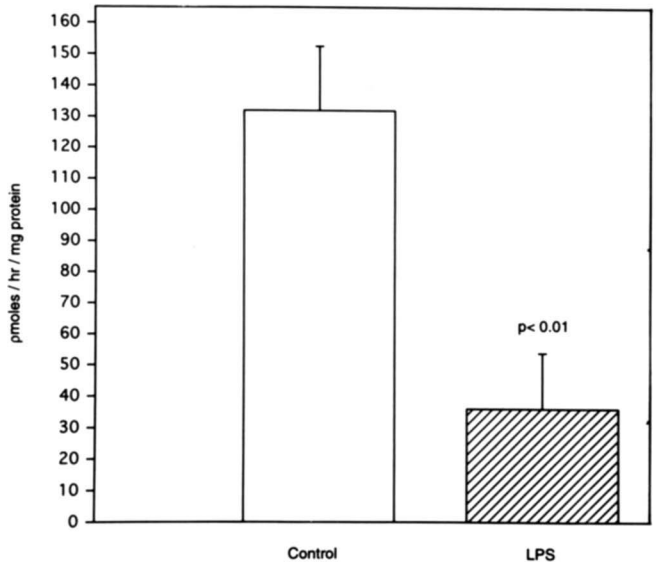


Fig. 4. Effect of LPS treatment on hepatic CAH activity. Colestipol was added to the chow (2% by weight) for 4 days prior to study. The animals were injected I.P. with LPS (100 μg/100 g body weight) or saline and 16 h later CAH activity was measured as described in the Methods section; n = 5 for control and LPS-treated animals. Data are presented as mean ± SEM and represent the pmol/h per mg protein 7α-hydroxycholesterol formed.

due to an inhibition of gene transcription. However, we were unable to assay CAH transcription in the hamster with our currently available probes.

It is believed that the hepatic changes in gene expression that occur during the acute phase response play an important role in host defense (28). For example, the increase in circulating C-reactive protein may assist in the opsinization of bacteria, immune complexes, and foreign particles (36). CAH is the rate-limiting enzyme in bile acid production and a decrease in this enzyme could result in an increase in the pool of cholesterol in the liver available for lipoprotein production (21). Previous studies by our and other laboratories have shown that LPS or cytokine administration in rodents produces an increase in serum triglyceride and cholesterol levels that is due in part to an increase in hepatic lipoprotein secretion (1). This increase in serum lipids and lipoproteins may be beneficial. An increase in serum lipids may result in an enhanced delivery of lipids to cells that are activated during the immune response and to cells involved in tissue repair. Moreover, studies have shown that all classes of lipoproteins bind LPS and this binding can protect from the toxic effects of LPS, including mortality (37–42). Additionally, lipoproteins also bind a variety of viruses, blocking their cytopathic effects (43–47). Thus, the decrease in CAH may play a role in facilitating the formation and secretion of lipoproteins in the liver thereby contributing to host defense.

In summary, the present study demonstrates that LPS, TNF, and IL-1 result in a marked decrease in CAH activity and mRNA levels. The decrease in CAH could contribute to the increase in hepatic lipoprotein production induced by the acute phase response. Thus, CAH can be added to the growing list of proteins that regulate lipid metabolism and that are altered during the acute phase response.

This work was supported by grants from the Research Services of the Department of Veterans Affairs and the National Institutes of Health (DK-40990, HL-38049 and HL-47551). We appreciate the excellent secretarial assistance of Pamela Herranz and the technical assistance of Wendy Williams.

Manuscript received 9 March 1995 and in revised form 24 October 1995.

REFERENCES

1. Hardardottir, I., C. Grunfeld, and K. R. Feingold. 1994. Effects of endotoxin and cytokines on lipid metabolism. *Curr. Opin. Lipidol.* **5:** 207–215.
2. Kaufmann, R. L., C. F. Matson, A. H. Rowberg, and W. R. Beisel. 1976. Defective lipid disposal mechanisms during bacterial infection in rhesus monkeys. *Metabolism.* **25:** 615–624.
3. Lanza-Jacoby, S., S. C. Lansey, M. P. Cleary, and F. E. Rosato. 1982. Alterations in lipogenic enzymes and lipoprotein lipase activity during gram negative sepsis in the rat. *Arch. Surg.* **117:** 144–147.
4. Scholl, R. A., C. H. Lang, and G. J. Bagby. 1984. Hypertriglyceridemia and its relation to tissue lipoprotein lipase activity in endotoxemia, *Escherichia coli* and polymicrobial septic rats. *J. Surg. Res.* **37:** 394–401.
5. Lanza-Jacoby, S., and A. Tabares. 1990. Triglyceride kinetics, tissue lipoprotein lipase and liver lipogenesis in septic rats. *Am. J. Physiol.* **258:** E678–E685.
6. Wolfe, R. R., J. H. F. Shaw, and M. J. Durkot. 1985. Effect of sepsis on VLDL kinetics: response in basal state and during glucose infusion. *Am. J. Physiol.* **248:** E732–E740.
7. Feingold, K. R., I. Staprans, R. Memon, A. H. Moser, J. K. Shigenaga, W. Doerrler, C. A. Dinarello, and C. Grunfeld. 1992. Endotoxin rapidly induces changes in lipid metabolism that produce hyperlipidemia: low doses stimulates heptic triglyceride production while high doses inhibit clearance. *J. Lipid Res.* **33:** 1765–1776.
8. Feingold, K. R., M. Marshall, R. Gulli, A. H. Moser, and C. Grunfeld. 1994. The effect of endotoxin and cytokines on lipoprotein lipase activity in mice. *Arterioscler. Thromb.* **14:** 1866–1872.
9. Lequire, V. S., J. D. Hutcherson, R. L. Hamilton, and M. E. Gray. 1959. Effects of bacterial endotoxin on lipid metabolism. *J. Exp. Med.* **110:** 293–309.
10. Hirsch, R. L., D. G. McKay, R. I. Travers, and R. K. Skraly. 1964. Hyperlipidemia, fatty liver and bromsulfophthalein retention in rabbits injected intravenously with bacterial endotoxin. *J. Lipid Res.* **5:** 563–568.
11. Feingold, K. R., I. Hardardottir, R. Memon, E. J. T. Krul, A. H. Moser, J. M. Taylor, and C. Grunfeld. 1993. Effect of endotoxin on cholesterol biosynthesis and distribution in serum lipoproteins in Syrian hamsters. *J. Lipid Res.* **34:** 2147–2158.
12. Feingold, K. R., A. J. Pollock, A. H. Moser, J. K. Shigenaga, and C. Grunfeld. 1995. Discordant regulation of proteins of cholesterol metabolism during the acute phase response. *J. Lipid Res.* **36:** 1474–1482.
13. Gil, G., J. L. Goldstein, C. A. Slaughter, and M. S. Brown. 1986. Cytoplasmic 3-hydroxy-3-methylglutaryl coenzyme A synthase from the hamster. *J. Biol. Chem.* **261:** 3710–3716.
14. Mehrabian, M., K. A. Callaway, C. F. Clarke, R. D. Tanaka, M. Greenspan, A. J. Lusis, R. S. Sparkes, T. Mohandas, J. Edmond, A. M. Fogelman, et al. 1986. Regulation of rat liver 3-hydroxy-3-methyl coenzyme A synthase and the chromosomal localization of the human gene. *J. Biol. Chem.* **261:** 16249–16255.
15. Ashby, M. N., and P. A. Edwards. 1989. Identification and regulation of a rat liver cDNA encoding farnesyl pyrophosphate synthetase. *J. Biol. Chem.* **264:** 635–640.
16. Rosser, D. S., M. N. Ashby, J. L. Ellis, and P. A. Edwards. 1989. Coordinate regulation of 3-hydroxy-3-methylglutaryl-coenzyme A synthase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and prenyltransferase synthesis but not degradation in HepG2 cells. *J. Biol. Chem.* **264:** 12653–12656.
17. Molowa, D. T., and G. M. Cimis. 1989. Coordinate regulation of low density lipoprotein receptor and 3-hydroxy-3-methylglutaryl CoA reductase and synthase gene expression in HepG2 cells. *Biochem. J.* **260:** 731–736.
18. Clarke, C. F., A. M. Fogelman, and P. A. Edwards. 1984. Diurnal rhythm of rat liver mRNAs encoding 3-hydroxy-3-methylglutaryl coenzyme A reductase. *J. Biol. Chem.* **259:**

10439–10447.
19. Duckworth, P. F., Z. R. Vlahcevic, E. J. Studer, E. C. Gurley, D. M. Heuman, Z. H. Beg, and P. B. Hylemon. 1991. Effect of hydrophobic bile acids on 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and mRNA levels in the rat. *J. Biol. Chem.* **266:** 9413–9418.
20. Hardardottir, I., A. H. Moser, R. A. Memon, C. Grunfeld, and K. R. Feingold. 1994. Effects of TNF, IL-1 and the combination of both cytokines on cholesterol metabolism in Syrian hamsters. *Lymphokine Cytokine Res.* **13:** 161–166.
21. Myant, N. B., and K. A. Mitropoulos. 1977. Cholesterol 7α-hydroxylase. *J. Lipid Res.* **18:** 135–153.
22. Jelinek, D. F., A. Andersson, C. A. Slaughter, and D. W. Russell. 1990. Cloning and regulation of cholesterol 7α-hydroxylase, the rate limiting enzyme in bile acid synthesis. *J. Biol. Chem.* **265:** 8190–8197.
23. Noshiro, M., M. Nishimoto, and K. Okuda. 1990. Rat liver cholesterol 7α-hydroxylase. Pretranslational regulation for circadian rhythm. *J. Biol. Chem.* **265:** 10036–10041.
24. Li, Y. C., D. P. Wang, and J. Y. Chiang. 1990. Regulation of cholesterol 7α-hydroxylase in the liver. Cloning, sequencing and regulation of cholesterol 7α-hydroxylase mRNA. *J. Biol. Chem.* **256:** 12012–12019.
25. Ness, G. C., L. C. Pendleton, and Z. Zhao. 1994. Thyroid hormone rapidly increases cholesterol 7α-hydroxylase mRNA levels in hypophysectomized rats. *Biochim. Biophys. Acta.* **1214:** 229–233.
26. Horton, J. D., J. Cuthbert, and D. K. Spady. 1994. Regulation of hepatic 7α-hydroxylase expression by dietary psyllium in the hamster. *J. Clin. Invest.* **93:** 2084–2092.
27. Chiang, J. Y. L. 1991. Reversed-phase high performance liquid chromatography assay of cholesterol 7α-hydroxylase. *Methods Enzymol.* **206:** 483–491.
28. Macliewicz, A., I. Kushner, and H. Baumann, editors. 1993. Acute Phase Proteins, Molecular Biology, Biochemistry and Clinical Applications. CRC Press, Boca Raton, FL.
29. Spady, D. K., J. A. Cuthbert, M. N. Willard, and R. S. Meidell. 1995. Adenovirus-mediated transfer of a gene encoding cholesterol 7α-hydroxylase into hamsters increases hepatic enzyme activity and reduces plasma total and low density lipoprotein cholesterol. *J. Clin. Invest.* **96:** 700–709.
30. Morgan, E. T. 1989. Suppression of constitutive cytochrome P450 gene expression in livers of rats undergoing an acute phase response to endotoxin. *Mol. Pharmacol.* **36:** 699–707.
31. Wright, K., and E. T. Morgan. 1991. Regulation of cytochrome P450 II C12 expression by interleukin-1α, interleukin-6 and dexamethasone. *Mol. Pharmacol.* **39:** 468–474.
32. Chen, Y. L., I. Florentin, A. M. Batt, L. Ferrari, J. P. Giroud, and L. Chauvelot-Moachon. 1992. Effects of interleukin-6 on cytochrome P450 dependent mixed function oxidases in the rat. *Biochem. Pharmacol.* **44:** 137–148.
33. Barker, C. W., J. B. Fagan, and D. S. Pasco. 1992. Interleukin-1β suppresses the induction of P4501 A1 and P451A2 mRNAs in isolated hepatocytes. *J. Biol. Chem.* **267:** 8050–8055.
34. Wright, K., and E. T. Morgan. 1990. Transcriptional and post-transcriptional suppression of P450 II C11 and P450 II C12 by inflammation. *FEBS Lett.* **271:** 59–61.
35. Abdel-Razzak, Z., P. Loyer, A. Fautrel, J. C. Gautier, L. Corcos, B. Turlin, P. Beaune, and A. Guillouzo. 1993. Cytokines down-regulate expression of major cytochrome P450 enzymes in adult human hepatocytes in primary culture. *Mol. Pharmacol.* **44:** 707–715.
36. Richards, C., J. Gauldie, and H. Baumann. 1991. Cytokine control of acute phase protein expression. *Eur. Cytokine Net.* **2:** 89–98.
37. Ulevitch, R. J., A. R. Johnston, and D. B. Weinstein. 1979. New function for high density lipoproteins: their participation in intravascular reactions of bacterial lipopolysaccharides. *J. Clin. Invest.* **64:** 1516–1524.
38. Ulevitch, R. J., A. R. Johnston, and D. B. Weinstein. 1981. New function for high density lipoproteins: isolation and characterization of a bacterial lipopolysaccharide–high density lipoprotein complex formed in rabbit plasma. *J. Clin. Invest.* **67:** 827–837.
39. Munford, R. S., C. L. Hall, J. M. Lipton, and J. M. Dietschy. 1982. Biological activity, lipoprotein binding behavior and in vivo disposition of extracted and native forms of *Salmonella typhimurium* lipopolysaccharides. *J. Clin. Invest.* **70:** 877–888.
40. Van Lenten, B. J., A. M. Fogelman, M. E. Haberland, and P. A. Edwards. 1986. The role of lipoproteins and receptor-mediated endocytosis in the transport of bacterial lipopolysaccharide. *Proc. Natl. Acad. Sci. USA.* **83:** 2704–2708.
41. Warren, H. S., C. V. Knights, and G. R. Siber. 1986. Neutralization and lipoprotein binding of lipopolysaccharides in tolerant rabbit serum. *J. Infect. Dis.* **154:** 784–791.
42. Harris, H. W., C. Grunfeld, K. R. Feingold, and J. H. Rapp. 1990. Human VLDL and chylomicrons can protect against endotoxin-induced death in mice. *J. Clin. Invest.* **86:** 696–702.
43. Shortridge, K. R., W. K. Ho, A. Oya, and M. Kobayashi. 1975. Studies on the inhibitory activities of human serum lipoproteins for Japanese encephalitis virus. *Southeast Asian J. Trop. Med. Public Health.* **6:** 461–466.
44. Leong, J. C., J. P. Kane, O. Oleszko, and J. A. Levy. 1977. Antigen specific nonimmunoglobulin factor that neutralizes xenotropic virus is associated with mouse serum lipoproteins. *Proc. Natl. Acad. Sci. USA.* **74:** 276–280.
45. Seganti, L., M. Grassi, P. Matromarino, A. Pana, F. Superti, and N. Orsi. 1983. Activity of human serum lipoproteins on the infectivity of rhabdoviruses. *Microbiology.* **6:** 91–99.
46. Sernatinger, J., A. Hoffman, D. Harmon, J. P. Kane, and J. A. Levy. 1988. Neutralization of mouse xenotropic virus by lipoproteins involves binding to virons. *J. Gen. Virol.* **69:** 2651–2661.
47. Heumer, H. P., H. J. Menzel, D. Potratz, B. Brake, D. Falke, G. Utermann, and M. P. Dierich. 1988. Herpes simplex virus binds to human serum lipoproteins. *Intervirology.* **29:** 68–76.