Discordant regulation of proteins of cholesterol metabolism during the acute phase response

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Abstract Recent studies have shown that the administration of endotoxin (LPS) and cytokines to Syrian hamsters increases serum cholesterol levels, hepatic cholesterol synthesis, and the activity, protein levels, and mRNA levels of hepatic HMG-CoA reductase. Despite the greater than 10-fold increase in HMG-CoA reductase mRNA levels, LPS had only minimal effects on hepatic LDL receptor mRNA levels. In the present study, we demonstrate that LPS increases the transcription rate in the liver of HMG-CoA reductase mRNA approximately 4- to 5-fold without affecting LDL receptor mRNA transcription. Most stimuli that regulate HMG-CoA reductase and LDL receptor mRNA levels also regulate, in parallel, HMG-CoA synthase and farnesyl pyrophosphate (FPP) synthetase. However, in chow-fed animals, LPS and cytokines (TNF, IL-1, TNF + IL-1) increased hepatic HMG-CoA reductase mRNA levels without increasing LDL receptor, HMG-CoA synthase, or FPP synthetase mRNA levels. The feeding of cholesterol or bile resin binders regulates the mRNA levels of HMG-CoA reductase, LDL receptor, HMG-CoA synthase, and FPP synthetase. In both cholesterol- and colestipol-fed animals, LPS increased HMG-CoA reductase mRNA levels while either decreasing or causing minimal increases in the mRNA levels of the other proteins. The present study demonstrates *1)* that the LPS-induced increase in hepatic HMG-CoA reductase mRNA levels is at least partially accounted for by an increase in gene transcription; *2)* that LPS and cytokines specifically increase HMG-CoA reductase mRNA levels without increasing the mRNA levels of other proteins that are usually coordinately regulated with HMG-CoA reductase; and *3)* that LPS is capable of increasing HMG-CoA reductase mRNA over a wide range of basal levels of expression. HMG-CoA reductase can be added to the list of proteins whose transcription is increased during the acute phase response.—**Feingold, K. R., A. S. Pollock, A. H. Moser, J. K. Shigenaga, and C. Grunfeld.** Discordant regulation of proteins of cholesterol metabolism during the acute phase response. *J. Lipid Res.* 1995. **36:** 1474–1482.

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Infection, in addition to increasing serum triglyceride levels, also produces increases in serum cholesterol levels in rodents and rabbits (1). An increase in hepatic cholesterol synthesis and/or HMG-CoA reductase activity has been shown in several different animal infections (2–4). These changes in lipid metabolism can also be induced by administration of endotoxin (LPS) which mimics gram negative infections. For example, recent studies by our laboratory have demonstrated that in Syrian hamsters, LPS administration produces an increase in serum cholesterol levels that was primarily due to an increase in LDL cholesterol (5). An increase in both hepatic cholesterol synthesis and HMG-CoA reductase activity also occurs in Syrian hamsters 16 h after treatment with LPS (5). Moreover, LPS increased hepatic HMG-CoA reductase mRNA levels greater than 10-fold (5). The increase in hepatic HMG-CoA reductase mRNA levels was seen as early as 4 h after LPS administration and persisted for at least 24 h.

In contrast to the changes in HMG-CoA reductase, LPS had only minimal effects on hepatic LDL receptor protein and mRNA levels (5). In most circumstances, HMG-CoA reductase and LDL receptor mRNA levels are coordinately regulated with parallel increases or decreases in mRNA levels in response to stimuli (6). However, our studies suggest that LPS treatment results in discordant regulation of the mRNAs for HMG-CoA reductase and LDL receptor.

Infection or LPS administration stimulates the production of the cytokines TNF and IL-1 which mediate many of the metabolic effects that occur during infection (7–9). Recent studies have demonstrated that TNF or IL-1 administration also increase hepatic HMG-CoA

Abbreviations: LPS, endotoxin; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low density lipoprotein; FPP, farnesyl pyrophosphate; TNF, tumor necrosis factor; IL, interleukin; BW, body weight.

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reductase mRNA levels without greatly affecting LDL receptor mRNA levels (10). Furthermore, studies in mice have shown that preadministration of antibodies that neutralize TNF activity can inhibit the increase in serum cholesterol levels, hepatic cholesterol synthesis, and HMG-CoA reductase activity that are induced by LPS administration, suggesting that TNF plays an important role in mediating these changes (11).

The aims of the present study were 3-fold: first, to determine whether the increase in hepatic HMG-CoA reductase mRNA levels after LPS administration was due to increased transcription; second, to determine whether hepatic mRNA levels of other enzymes in the cholesterol biosynthetic pathway that are coordinately regulated with the HMG-CoA reductase and LDL receptor, such as HMG-CoA synthase and farnesyl pyrophosphate (FPP) synthetase, are increased by LPS and cytokine treatment (12–16); and third, to determine whether dietary manipulations that regulate HMG-CoA reductase mRNA levels in liver, such as feeding cholesterol or bile resin binders (12, 13, 17, 18), alter the ability of LPS to increase hepatic HMG-CoA reductase mRNA levels.

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 HMG-CoA reductase and for the LDL receptor were from the American Tissue Type Culture Collection (Rockville, MD), clone name PH Red-102 ATTC #57042 and clone name PLDLR3 ATTC #57004, respectively. The cDNA for FPP synthetase and HMG-CoA synthase was kindly provided by Dr. Peter Edwards (UCLA, Los Angeles, CA). 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.

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 7 days prior to study. Anesthesia with isofluorane was induced and the animals were injected I.P. with LPS (100 μg/100 g BW), TNF (25 μg/150 g BW), IL-1 (0.75 μg/150 g BW) or saline alone. 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 (5, 10). Northern blotting was performed as described previously (5, 10). 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.

Measurement of transcription

Nuclei were isolated from hamster liver using the homogenization procedure described by Clarke, Fogelman, and Edwards (19). The isolated nuclei (about 200 μg DNA equivalent) were incubated in a 100 μl reaction mixture containing 20 mM Tris, pH 7.0, 30% glycerol, 140 mM β-mercaptoethanol, 1 mM each ATP, CTP, and GTP, and 250 μCi of [α-^{32}P]UTP for 20 min at 30°C. After the addition of 100 μg carrier yeast RNA, total RNA was purified by the acid guanidinium thiocyanate method. Plasmid DNA was boiled for 5 min in 0.1 N NaOH and bound to nylon filters with a 96-well dot blot manifold (10 μg DNA per dot). Hybridization was carried out in 5 × SSC, 50% formamide at 42°C for 40 h. Carrier yeast RNA (200 μg/ml) and salmon sperm DNA (25 μg/ml) were added to the hybridization buffers. After hybridization, the filters were washed in 2 × SSC, 0.1% SDS at room temperature, followed by a second wash in the same buffer at 42°C. The filters were treated with RNAse A (10 μg/ml) in 2 × SSC at 37°C for 30 min. The filters were then washed for 30 min in 2 × SSC, 0.1% SDS at 65°C. Radioactive RNA bound to the various filters were quantified by liquid scintillation counting.

Statistics

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

RESULTS

Role of transcription in increasing hepatic HMG-CoA reductase mRNA levels

Previous studies have shown that the administration of LPS to Syrian hamsters results in a large increase in HMG-CoA reductase mRNA levels in the liver without affecting LDL receptor mRNA levels (5). The results shown in **Fig. 1** demonstrate that LPS treatment increases the transcription rate of HMG-CoA reductase mRNA approximately 4- to 5-fold but has no effect on the transcription rate of LDL receptor mRNA. These data indicate that the stimulation of transcription plays an important role in the LPS-induced increase in HMG-CoA reductase mRNA levels.

Specificity of the increase in HMG-CoA reductase mRNA levels

It is well recognized that many of the stimuli that coordinately regulate HMG-CoA reductase and LDL receptor mRNA levels also regulate mRNA levels of other proteins essential in cholesterol metabolism. Specifically, studies have shown that both HMG-CoA synthase and FPP synthetase are coordinately regulated in parallel with HMG-CoA reductase and LDL receptors (6, 12–16). The effects of LPS on mRNA levels of HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor in the liver are shown in **Fig. 2A.** As seen in our previous studies, LPS administration (100 μg/100 g body weight) results in a marked increase in hepatic HMG-CoA reductase mRNA levels (8 h, 11.7-fold and 16 h, 14.2-fold). Additionally, as shown in Fig. 2B, low dose LPS (100 ng/100 g body weight) also increases hepatic HMG-CoA reductase mRNA levels 16 h after treatment. In contrast, LPS treatment does not increase HMG-CoA synthase, FPP synthetase, or LDL receptor mRNA levels in the liver (Fig. 2A). In fact, HMG-CoA synthase and FPP synthetase mRNA levels are significantly decreased 16 h after LPS treatment. The concentration of cholesterol in the liver was similar in control and LPS-treated animals (control 1.85 ± 0.078 vs. LPS 1.94 ± 0.191 mg/g). Thus, the increase in HMG-CoA reductase mRNA levels induced by LPS is specific; LPS does not increase mRNA levels of three other proteins that have important roles in cholesterol metabolism.

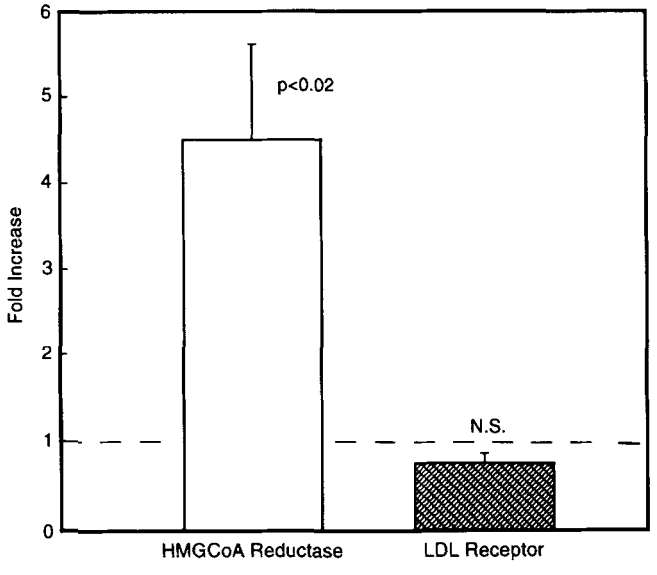


Fig. 1. Effect of LPS on HMG-CoA reductase and LDL receptor transcription. Animals were injected I.P. with either saline or 100 μg/100 g body weight LPS. Sixteen hours later the animals were killed, the livers were removed, nuclei were isolated, and transcription rates were assayed as described in Methods. Transcription rates in controls = 1. Data are presented as mean ± SEM; n = 6 for HMG-CoA reductase and n = 11 for LDL receptor for both control and LPS-treated animals.

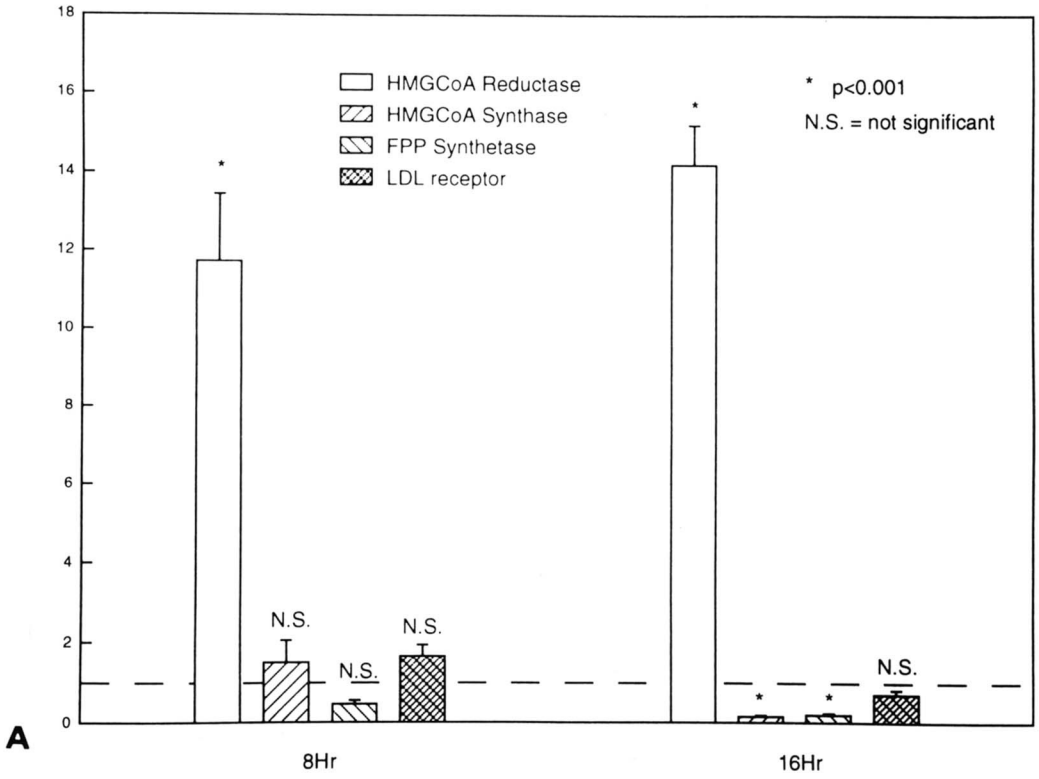
The effect of cytokines on mRNA levels of HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor in the liver are shown in **Fig. 3.** As seen in previous studies (10), 8 h after TNF, IL-1, and the combination of TNF and IL-1 there is a 1.5- to 4-fold increase in hepatic HMG-CoA reductase mRNA levels. HMG-CoA synthase, FPP synthetase and LDL receptor mRNA levels are not increased and in many instances are significantly decreased after TNF, IL-1, or TNF plus IL-1 administration. These results indicate that, similar to LPS, cytokines induce a specific increase in HMG-CoA reductase mRNA levels in the liver.

Effect of dietary manipulations on the stimulation of hepatic HMG-CoA reductase mRNA levels

Studies by other investigators have shown that feeding bile resin binders increases hepatic mRNA levels of HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and the LDL receptor (13, 14, 17, 18, 20). LPS administration to colestipol-fed animals produces an increase in hepatic HMG-CoA reductase mRNA levels (**Fig. 4**). In contrast, LPS induced marked decreases in HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels (Fig. 4).

Cholesterol feeding decreases mRNA levels of HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and the LDL receptor in the liver (12–14, 18, 20, 21). The effect of LPS on the levels of these mRNAs in the liver of animals fed a 2% cholesterol diet for 7 days is shown in **Fig. 5.** LPS administration increases HMG-CoA reductase mRNA levels almost 20-fold while increasing HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels less than 1.7-fold.

We next compared HMG-CoA reductase mRNA levels in control (chow-fed), cholesterol-fed, colestipol-fed, and chow-fed animals treated with LPS (**Fig. 6**). Cholesterol feeding decreased HMG-CoA reductase mRNA



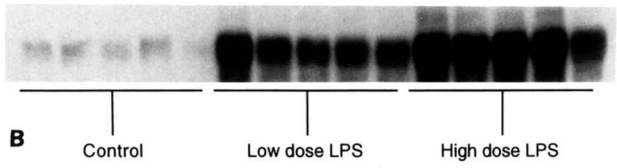


Fig. 2. Effect of LPS on hepatic mRNA levels. A: Animals were injected I.P. with either saline or 100 μg/100 g body weight LPS. Eight hours or 16 h later animals were killed, the livers were removed, and hepatic HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels were determined as described in Methods. mRNA levels in controls = 1. Data are presented as mean ± SEM; 8 h, n = 8–10; 16 h, n = 8, 9. B: Animals were injected I.P. with either saline, low dose LPS (100 ng/100 g body weight) or high dose LPS (100 μg/100 g body weight). Sixteen hours later the animals were killed, the livers were removed, and Northern blots were probed for HMG-CoA reductase mRNA as described in Methods.

levels 66% while colestipol feeding increased mRNA levels 83%. In the colestipol-fed animals HMG-CoA reductase mRNA levels were 5.4-fold greater than in cholesterol-fed animals, indicating that these different diets induced a wide range of basal levels of HMG-CoA reductase mRNA. As described earlier, LPS administration in chow-fed animals increased HMG-CoA reductase mRNA levels 9.4-fold. The increase in HMG-CoA reductase mRNA levels induced by LPS is much greater than the increase induced by colestipol feeding. Together these results indicate that LPS is capable of increasing hepatic HMG-CoA reductase mRNA levels over a wide range of basal expression and that the magnitude of the LPS-induced increase is relatively large compared to dietary manipulations.

DISCUSSION

Infection, inflammation, or trauma stimulate the production of a wide variety of cytokines, including TNF and IL-1, that induce marked changes in the transcription of a large number of different genes in the liver (acute phase response) (22). 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) (23). The results of this and previous studies (5) demonstrate that HMG-CoA reductase mRNA and protein levels are increased in the liver during the acute phase response indicating that HMG-CoA reductase is a positive acute

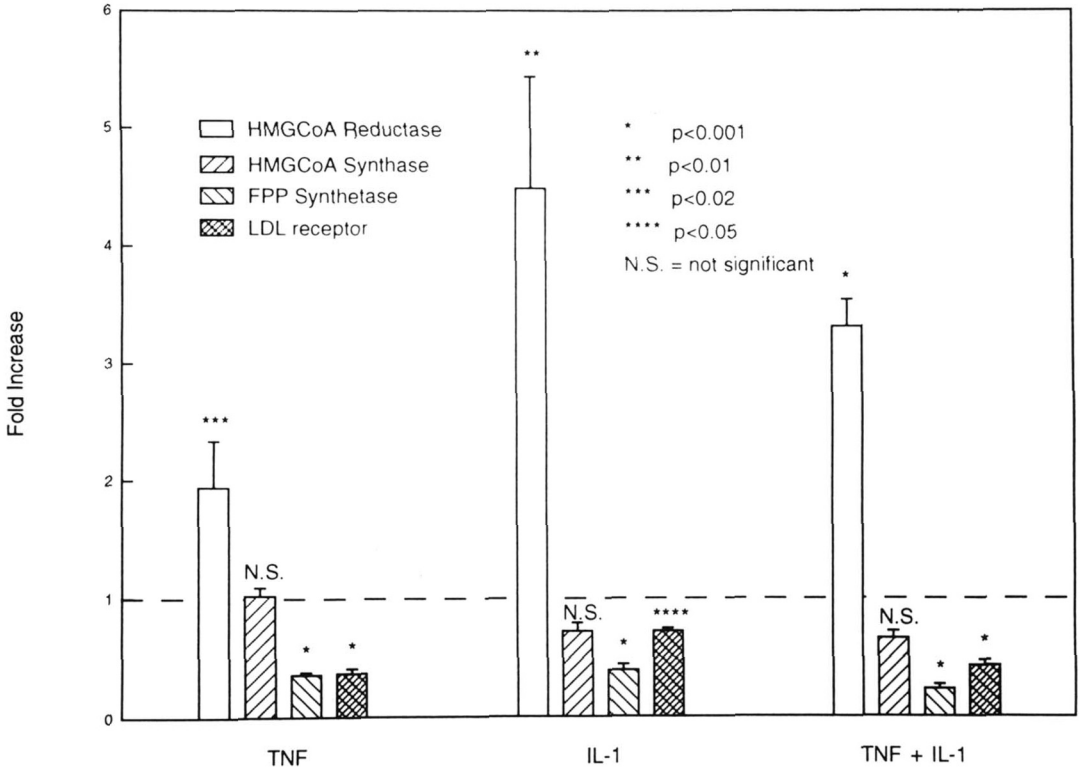
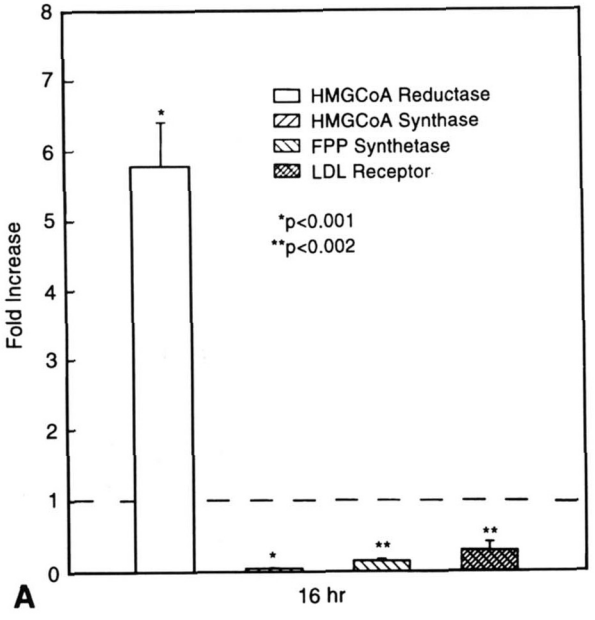


Fig. 3. Effect of cytokines on hepatic mRNA levels. Animals were injected I.P. with either saline or TNF (25 μg/150 g BW), IL-1 (0.75 μg/150 g BW), or TNF + IL-1. Eight hours later animals were killed, the livers were removed, and hepatic HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels were determined as described in Methods. mRNA levels in controls = 1. Data are presented as mean ± SEM; n = 5 for all groups of animals.



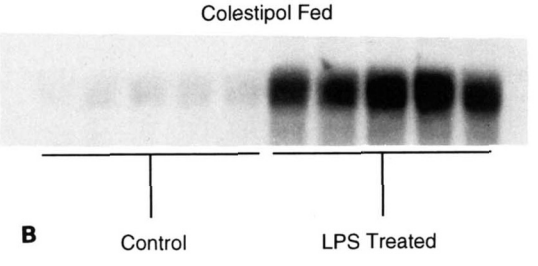
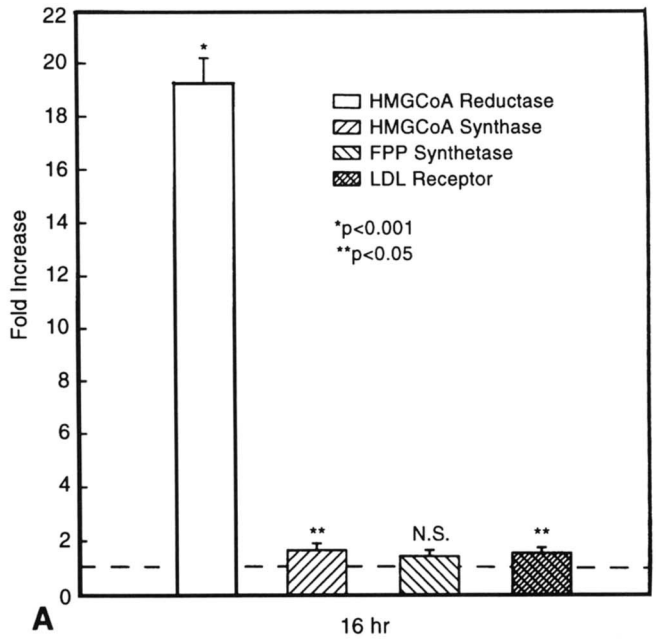


Fig. 4. Effect of LPS on hepatic mRNA levels in colestipol-fed animals. A: Colestipol (2% by weight) was added to the diet and the animals were fed for 7 days. Animals were injected I.P. with either saline or 100 μg/100 g body weight LPS. Sixteen hours later animals were killed, the livers were removed, and hepatic HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels were determined as described in Methods. mRNA levels in controls = 1. Data are presented as mean ± SEM; n = 5 for all groups. B: Northern blot probed for HMG-CoA reductase mRNA.



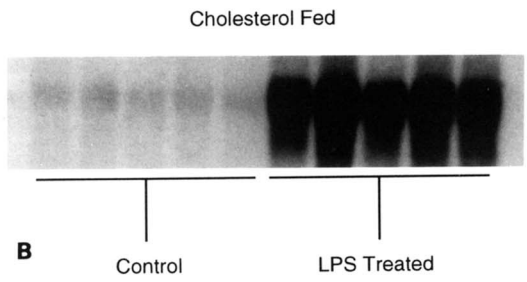
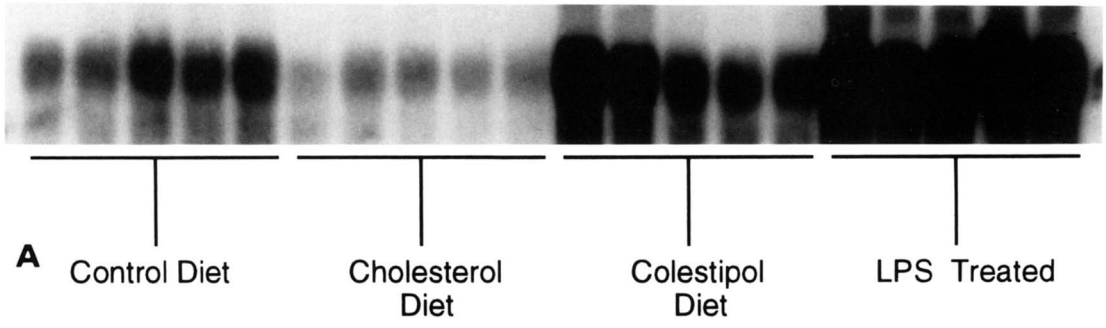


Fig. 5. Effect of LPS on hepatic mRNA levels in cholesterol-fed animals. A: Cholesterol (2% by weight) was added to the diet and the animals were fed for 7 days. Animals were injected I.P. with either saline or 100 μg/100 g body weight LPS. Sixteen hours later animals were killed, the livers were removed, and hepatic HMG-CoA reductase, HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels were determined as described in Methods. mRNA levels in controls = 1. Data are presented as mean ± SEM; n = 5 for all groups. B: Northern blot probed for HMG-CoA reductase mRNA.



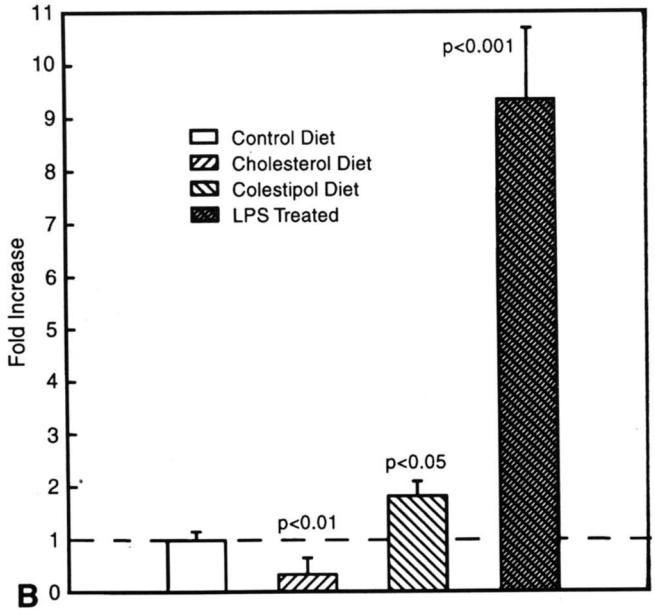


Fig. 6. Effect of diet and LPS on hepatic HMG-CoA reductase mRNA levels. Animals were fed either rodent chow alone or rodent chow containing 2% by weight cholesterol or colestipol for 7 days. A group of animals fed rodent chow alone were injected I.P. with 100 μg/100 g body weight LPS 16 h prior to study. The animals were killed, the livers were removed, and hepatic HMG-CoA reductase mRNA levels were determined as described in Methods. A: The Northern blot is shown. B: Data are presented as mean ± SEM, mRNA levels in controls = 1.

phase protein. The increase in HMG-CoA reductase mRNA levels is at least partially accounted for by an increase in transcription. Whether HMG-CoA reductase mRNA degradation is also altered during the acute phase response is unknown and very difficult to evaluate in an in vivo animal model.

Several other proteins that are important in cholesterol metabolism, such as the LDL receptor, HMG-CoA synthase, and FPP synthetase, are usually coordinately regulated with HMG-CoA reductase (6, 12–16). However, the present study demonstrates that LPS and cytokine administration specifically increase hepatic HMG-CoA reductase mRNA levels without also increasing the mRNA levels of LDL receptor, HMG-CoA synthase, or FPP synthetase. In fact, HMG-CoA synthase and FPP synthetase mRNA levels are significantly decreased 16 h after LPS administration under most conditions. Thus, after LPS administration, there is discordant regulation of HMG-CoA reductase and several other proteins that are important in cholesterol homeostasis. Recently, discordant regulation of HMG-CoA reductase and LDL receptor mRNA levels has been reported in lymphocytes after mitogen stimulation (23).

Dietary conditions are well recognized to be important regulators of the levels of these mRNAs in the liver (12–14, 17, 18, 20, 21). Cholesterol feeding coordinately suppresses HMG-CoA reductase, LDL receptor, HMG-CoA synthase, and FPP synthetase mRNA levels while bile resin binders increase these mRNA levels (12–14, 17, 18, 20, 21). In the present study, we demonstrate that in both cholesterol-fed and colestipol-fed animals, LPS administration increases hepatic HMG-CoA reductase mRNA levels. In contrast, in colestipol-fed animals, LPS markedly decreases HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA levels. In cholesterol-fed animals, LPS treatment results in a relatively small increase (less than 1.7-fold) in HMG-CoA synthase, FPP synthetase, and LDL receptor mRNA compared to the approximately 20-fold increase in HMG-CoA reductase mRNA levels. These results indicate that LPS is capable of increasing HMG-CoA reductase mRNA levels over a wide range of basal levels of expression (in the present study, we observed that HMG-CoA reductase mRNA levels were 5.4-fold greater in colestipol-fed animals than in cholesterol-fed animals).

It is believed that the changes in gene expression in the liver that occur during the acute phase response play an important homeostatic role in host defense (22). The beneficial properties have been elucidated for some of these proteins. For example, complement 3 and C reactive protein help in the opsinization of bacteria, immune complexes, and foreign particles (24). It is likely that the increase in hepatic cholesterol synthesis, which is mediated by an increase in HMG-CoA reductase, also plays a beneficial role. Previous studies, by our and other laboratories have shown in rodents that infection, LPS administration, or cytokine treatment produces an increase in serum levels of triglycerides and cholesterol that are due in part to an increase in hepatic lipoprotein secretion (1, 25). This increase in serum lipids may result in the enhanced delivery of lipids to cells that are activated during the immune response and to cells involved in tissue repair. Moreover, experiments have demonstrated that all classes of lipoproteins bind LPS and this binding can protect the animal from the toxic effects of LPS, including mortality (26–31). Additionally, lipoproteins also bind a variety of viruses, blocking their cytopathic effects (32–36). Thus, the increase in HMG-CoA reductase will lead to an increase in hepatic cholesterol synthesis which may play a role in facilitating hepatic lipoprotein secretion, thereby contributing to host defense.

The regulation of gene expression during the acute phase response is very complex (22). A number of different response elements interacting with several different *trans*-activating factors, either singly or in combination, are believed to be responsible for the alterations in gene expression. The major *trans*-activating factors mediating the acute phase response are NF-kB and members of the C/EBP family including NF-IL-6, IL-6 DBP, and AGP/EBP (22). Analysis of the 292 base pair region 5′ from the transcription start site of the hamster HMG-CoA reductase gene did not reveal any regulatory elements that could account for the increase in HMG-CoA reductase transcription during the acute phase. Thus, the exact mechanism by which the acute phase response leads to a specific increase in HMG-CoA reductase expression is not known. However, one can speculate that a combination of cytokines that are produced during the acute phase response activate *trans*-activating factors that interact with another class(es) of regulatory element or that the regulatory element falls outside of the sequences from −292 to the start site of the hamster HMG-CoA reductase gene.

The present study demonstrates that HMG-CoA reductase can be added to the list of genes in the liver whose transcription is increased during the acute phase response. Moreover, the resultant increase in cholesterol synthesis in the liver may play a crucial role in facilitating the increase in hepatic lipoprotein secretion and the hyperlipidemia observed during the acute phase response.

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