Suppression of estrogen-related receptor α and medium-chain acyl-coenzyme A dehydrogenase in the acute-phase response

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Abstract Fatty acid oxidation provides energy in tissues with high metabolic demands. During the acute-phase response (APR) induced by infection and inflammation, fatty acid oxidation is decreased associated with hypertriglyceridemia. Little is known about the mechanism by which the APR decreases fatty acid oxidation. Therefore, we investigated whether the APR affects the expression of medium-chain acyl-coenzyme A dehydrogenase (MCAD), its regulator the estrogen-related receptor α (ERRα), and a key coactivator of ERRα, the peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α). mRNA levels of PGC-1α, ERRα, and MCAD are markedly reduced in the liver, heart, and kidney of mice during the lipopolysaccharide (LPS)-induced APR. The decreases were rapid and occurred at very low doses of LPS. MCAD activity in liver was also reduced. Furthermore, binding of hepatic nuclear extracts to the ERRα response element found in the promoter region of MCAD was significantly decreased during the APR, suggesting the decreased transcription of the MCAD gene. The binding activity was identified as ERRα by supershift with antibody to ERRα. Similar decreases in mRNA levels of these genes occur during zymosan- and turpentine-induced inflammation, indicating that suppression of the PGC-1α, ERRα, and MCAD pathway is a general response during infection and inflammation. Our study provides a potential mechanism by which the APR decreases fatty acid oxidation.—Kim, M. S., J. K. Shigenaga, A. H. Moser, K. R. Feingold, and C. Grunfeld. **Suppression of estrogen-related receptor α and medium-chain acyl-coenzyme A dehydrogenase in the acute-phase response.** ***J. Lipid Res.*** **2005.** 46: **2282–2288.**

Supplementary key words peroxisome proliferator-activated receptor γ coactivator-1α • β-oxidation • fatty acid oxidation

Estrogen-related receptor α (ERRα) is a nuclear receptor that was initially cloned based on its homology to the estrogen receptor (1). ERRα is not activated by estrogen and is an orphan receptor whose ligand has not yet been defined. However, it can accentuate estrogen-dependent induction of the complex lactoferrin estrogen response element (2). It has also been shown that ERRα regulates the transcription of medium-chain acyl-coenzyme A dehydrogenase (MCAD), which mediates the initial step in the mitochondrial β-oxidation of fatty acids (3). Changes in the expression of MCAD modulate the rate of tissue fatty acid β-oxidation (4), and its deficiency has been linked to childhood nonketotic hypoglycemia, coma, or sudden death, which occurs with prolonged fasting or during intercurrent infection (4–6).

Infection, inflammation, and trauma induce the acute-phase response (APR) via the release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 (7). These cytokines, in turn, trigger signaling pathways and cause characteristic changes in lipid metabolism, including decreased hepatic fatty acid oxidation (7, 8). Our previous studies showed that the APR suppresses the nuclear hormone receptors retinoid X receptor α (RXR) and its heterodimeric partners retinoic acid receptor (RAR), liver X receptor, farnesoid X receptor, thyroid receptor, and peroxisome proliferator-activated receptor α (PPARα), which is associated with decreased expression of their target genes (9–11). Because PPARα target genes such as L-Carnitine palmitoyl transferase-Iα, acyl-CoA oxidase, and acyl-CoA synthase are involved in fatty acid metabolism, the APR-induced suppression of PPARα provides at least a partial explanation for the decreased fatty acid oxidation observed during the APR.

However, cooperative induction of PPARα target genes by peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) raises the possibility that PGC-1α may also play a role in the APR-induced suppression of fatty acid oxidation (12). PGC-1α is abundantly expressed in tissues reliant on oxidative metabolism, such as heart and brown adipose tissue, but it is also present in liver and kid-

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ney. During the APR, the mRNA level of PGC-1α is dramatically decreased in mouse heart (13). Overexpression of PGC-1α in hearts of transgenic mice leads to the transcriptional activation of genes encoding mitochondrial fatty acid oxidation enzymes, such as MCAD (14). A recent study by Huss, Kopp, and Kelly (15) demonstrated that PGC-1α interacts with and coactivates ERRα and enhances the transcriptional activation of MCAD by ERRα, suggesting the possibility that ERRα and the MCAD pathway are also suppressed during the APR.

In the present study, we hypothesized that decreased expression of PGC-1α downregulates the ERRα and MCAD pathway, which would provide an additional mechanism for the decreased fatty acid oxidation during infection and inflammation. We found that inflammation induced by lipopolysaccharide (LPS) decreases the expression of PGC-1α, ERRα, and MCAD in liver, heart, and kidney. In addition, zymosan and turpentine, which also induce inflammation, decrease PGC-1α, ERRα, and MCAD, indicating that this suppression is a general response to infection and inflammation. Results from the present study provide a potential mechanism for the APR-induced decrease in fatty acid oxidation, which could contribute to the hypertriglyceridemia characteristically observed during infection and inflammation.

METHODS

Animals

All animal experimentation described in the present study was conducted in accordance with accepted standards of humane animal care approved by an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) approved animal subcommittee. Eight week old female C57BL/6 mice were purchased from the Jackson Laboratory. Only female mice were used in the present study because they do not fight as much as males and fighting leads to an inflammatory response. The animals were maintained in a normal light cycle room and were provided with rodent chow and water ad libitum. Their weight was ∼20 g at the time of experiment. Anesthesia was induced with halothane. To determine the effect of the APR on PGC-1α, ERRα, and MCAD mRNA levels, mice were studied using three different protocols: intraperitoneal injection with 0.1–100 μg of LPS in saline or with saline alone; intraperitoneal injection with 80 mg/kg body weight zymosan A in saline or with saline alone; or subcutaneous injection of 100 μl of turpentine per mouse, or a similar volume of saline. Food was withdrawn at the time of injection, because LPS, zymosan, and turpentine induce anorexia in rodents (16). Organs were removed at the times indicated below after treatment. The doses of LPS used in this study have significant effects on triglyceride and cholesterol metabolism (17, 18) but are not lethal, as the LD_{50} for LPS in rodents is ∼5 mg/100 g body weight.

Materials

LPS (*Escherichia coli* 55:B5) was obtained from Difco Laboratories and freshly diluted to the desired concentration in pyrogen-free 0.9% saline. Turpentine was purchased from BDH. Zymosan A and Tri-Reagents were purchased from Sigma. Minimal essential medium was purchased from Fisher Scientific. [α-^{32}P]dCTP (3,000 Ci/mmol) and [γ-^{32}P]dATP (3,000 Ci/mmol) were purchased from NEN Life Science Products. Oligo(dT)-cellulose type 77F was from Amersham Pharmacia Biotech. Antibody to ERRα was from Affinity Bioreagents.

RNA isolation and Northern blot analysis

Total RNA from mouse was isolated from 300–400 mg of snap-frozen liver, heart, and kidney tissues using Tri-Reagent (Sigma). Poly(A)$^+$ RNA was subsequently purified using oligo(dT) cellulose. RNA was quantified by measuring absorption at 260 nm. Ten micrograms of poly(A)$^+$ was denatured and electrophoresed on a 1% agarose-formaldehyde gel. The uniformity of RNA loading was checked by ultraviolet visualization of 18S and 28S bands on the ethidium bromide-stained gel before electrotransfer to Nytran membrane (Schleicher and Schuell). Prehybridization, hybridization, and washing procedures were performed as described previously (19). Membranes were probed with [α-^{32}P] dCTP-labeled cDNAs using the random priming technique (Amersham Biosciences). mRNA levels were detected by exposure of the membrane to X-ray film and quantified by densitometry. Housekeeping genes such as GAPDH were used to confirm the equal amount of RNA loading. PGC-1α, ERRα, and MCAD probes were prepared by PCR using the following primers; PGC-1α, 5′-GACCACAAACGATGACCCTCC -3′ (upper), 5′-GCCTCCAAAG-TCTCTCTCAGG-3′ (lower); ERRα, 5′-GGGCATCGAGCCTCTC-TAC-3′ (upper), 5′-GCACTCCCTCCTTGAGCAT-3′ (lower); MCAD, 5′-GAACAGCAGAAAGAGTTTCAAGC-3′ (upper), 5′-GCTTCCA-CAATGAATCCAGTAA-3′ (lower).

Preparation of nuclear extracts

Nuclear extracts were prepared according to Neish et al. (20). Briefly, cells were disrupted in sucrose-HEPES buffer containing 0.5% Nonidet-P40 as a detergent, protease inhibitors, and DTT. After a 5 min incubation on ice, cells were centrifuged, then nuclear proteins were separated in NaCl-HEPES buffer and resuspended in glycerol-containing buffer. All of the procedures were carried out on ice. Protein quantification was determined by the Bradford assay (Bio-Rad), and yields were similar in control and LPS-treated groups.

Electrophoretic gel mobility shift assays

Double-stranded oligonucleotides were end-labeled with T_4-polynucleotide kinase in the presence of 50 μCi of [γ-^{32}P]dATP and purified on a Sephadex G-25 column (Amersham Pharmacia Biotech). Ten micrograms of crude nuclear extract was incubated on ice for 30 min with 6×10^4 cpm of ^{32}P-labeled oligonucleotides in 15 μl of binding buffer [20% glycerol, 25 mM Tris-HCl (pH 7.5), 40 mM KCl, 0.5 mM $MgCl_2$, 0.1 mM EDTA, and 1 mM dithiothreitol], 2 μg of poly(dI-dC), and 1 μg of salmon sperm DNA. DNA-protein complexes were separated by electrophoresis (constant voltage of 300 V) on a 5% nondenaturing polyacrylamide gel in 1× TBE at 4°C. The gel was dried, exposed to X-ray film, and quantified by densitometry. In the competition assay, a 100-fold molar excess of the specific or mutated unlabeled oligonucleotide was preincubated on ice for 1 h with 10 μg of nuclear extract from control mice in the binding buffer before adding the oligonucleotide probe. The following oligonucleotides were used: nuclear receptor response element 1 (NRRE1), 5′-GGG-TTTGACCTTTCTCTCCGGGTAAAGGTCAA-3′; estrogen response element consensus, 5′-GAGTTTTTCAAGGTCATGCTCATTT-3′ (21). In supershift studies, control nuclear extract was preincubated with 2 μl of ERR-α antibody (Affinity BioReagents) for 1 h at room temperature before the addition of the labeled probe.

Measurement of MCAD activity

Briefly, frozen liver samples (50 mg) were homogenized (20%, w/v) in ice-cold buffer containing 100 mM HEPES and 0.1 mM EDTA, pH 7.6, and then centrifuged at 700 *g*. MCAD activity was

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determined as described (22) by adding 20 μl of supernatant to 500 μl of reaction mixture containing 100 mM HEPES, pH 7.6, 0.1 mM EDTA, 200 μM ferricenium hexafluorophosphate, 0.5 mM sodium tetrathionate, and 50 μM octanoyl-CoA and incubated at 37°C. The decrease in ferricenium hexafluorophosphate absorption at 300 nm in the presence of supernatant was stable for at least 3 min; the results were calculated from the decrease observed over this period with correction by subtracting the absorbance of a tissue blank measured without the addition of octanoyl-CoA.

Statistical analysis

Data are expressed as means ± SEM of experiments from three to five animals or plates for each group or time point. The difference between two experimental groups was analyzed using Student's *t*-test. Differences among multiple groups were analyzed using one-way ANOVA with the Bonferroni post hoc test. $P < 0.05$ was considered significant.

RESULTS

mRNA levels of PGC-1α are decreased during the APR

To determine the effect of LPS on the mRNA levels of PGC-1α, mice were administered LPS intraperitoneally and tissues were collected after 16 h. Results from Northern analysis are shown in **Fig. 1** and demonstrate that LPS dramatically decreased mRNA levels of PGC-1α in liver, heart, and kidney. These results suggested that during the APR, oxidative metabolism that is dependent on the coactivator function of PGC-1α may be suppressed in these tissues.

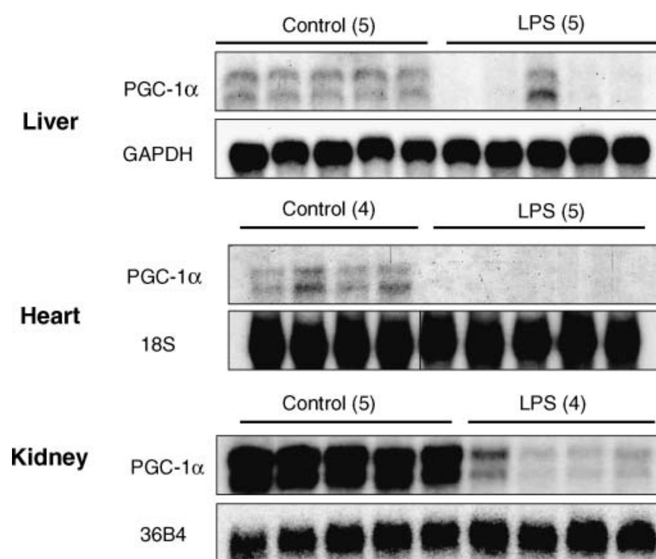

Fig. 1. mRNA levels of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) are decreased during the acute-phase response (APR). C57BL/6 mice were injected intraperitoneally with either saline or lipopolysaccharide (LPS; 100 μg per mouse), and the animals were euthanized 16 h later. Poly(A)$^+$ RNA was prepared from liver, heart, and kidney, and Northern blot analysis was carried out as described in Methods. GAPDH, 18S, and 36B4 were used as loading controls for the liver, heart, and kidney, respectively. For the liver, there were five control and five LPS animals; for the heart, there were four control and five LPS animals; for the kidney, there were five control and four LPS animals.

mRNA levels of ERRα are decreased during the APR

Having found that mRNA levels of PGC-1α are significantly reduced during the APR, we next determined the effect of the APR on the mRNA levels of ERRα, which has been shown to be activated by PGC-1α. Animals were administered 100 μg of LPS and euthanized after 16 h. RNA was isolated from liver, heart, and kidney, and Northern blot analysis was performed. LPS administration significantly decreased the ERRα mRNA levels in liver, heart, and kidney (**Fig. 2A**). Next, we determined the dose response for LPS suppression of ERRα mRNA levels in the liver. LPS administration of 0.1 μg of LPS per mouse caused a 50% decrease in the hepatic mRNA levels of ERRα (Fig. 2B), suggesting that ERRα transcription is a very sensitive response in the LPS-induced APR. Almost complete suppression of ERRα mRNA levels was observed at 100 μg of LPS per mouse. Next, we determined the time course of ERRα suppression by LPS at various times for a 24 h period. As shown in Fig. 2C, the mRNA level of ERRα was significantly decreased as early as 4 h after LPS administration, and the effect was sustained for up to 24 h. Together, these data indicate that the effect of LPS on ERRα is very rapid and sensitive.

mRNA levels and activity of MCAD are decreased during the APR

Having found that LPS-induced APR causes a significant reduction in the mRNA levels of both PGC-1α and ERRα, we next determined the effect of LPS administration on the mRNA levels of MCAD, a target gene for ERRα in the liver, heart, and kidney in mouse. As shown in **Fig. 3A**, LPS administration significantly decreased the mRNA level of MCAD in the liver, heart, and kidney (by ~90, ~60, and ~50%, respectively). LPS administration at 0.1 μg per mouse caused a 45% decrease in MCAD mRNA levels, and higher doses caused a further reduction, reaching a maximal effect at 100 μg per mouse (Fig. 3B), indicating that this hepatic response is very sensitive. Also, LPS administration caused a significant reduction in the mRNA levels of MCAD as early as 4 h after LPS administration, and the reduction was sustained for up to 24 h (Fig. 3C).

We then determined whether the decreases in MCAD mRNA led to decreases in MCAD activity. By 4 h after LPS administration, MCAD activity had decreased by only 23% (**Fig. 4**). However, by 16 h after LPS administration, MCAD activity had decreased by 83%. Thus, the decrease in MCAD mRNA precedes the decrease in MCAD activity.

Binding activity of hepatic nuclear extracts to ERRα response elements is significantly decreased during the APR

Characterization of the MCAD promoter demonstrated that it contains a response element designated NRRE1 that has been shown to interact with and is activated by ERRα. Using an NRRE1 sequence, we investigated the binding activity of hepatic nuclear extracts obtained from mouse liver treated with 100 μg of LPS for 16 h using an electromobility shift assay. As shown in **Fig. 5A**, NRRE1 binding activity of nuclear extracts from LPS-treated animals was dramatically decreased compared with that in the control

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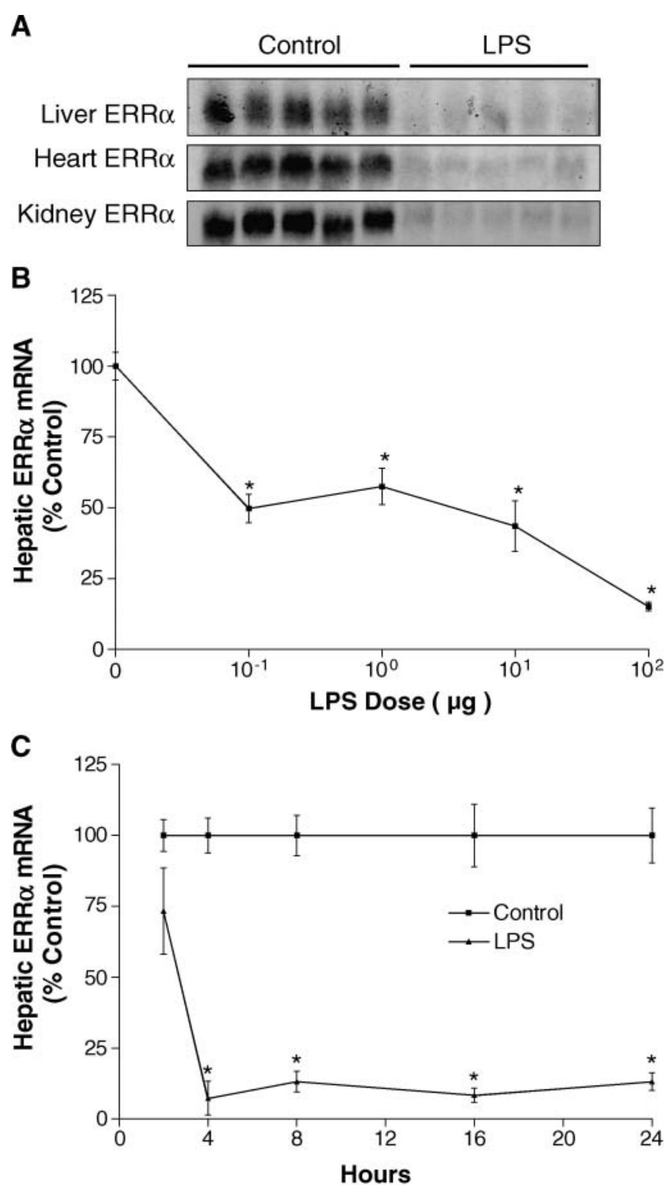

Fig. 2. mRNA levels of estrogen-related receptor α (ERRα) are decreased during the APR. A: mRNA levels of ERRα in the liver, heart, and kidney. Poly(A)$^+$ RNA was prepared from liver, heart, and kidney, and Northern blot analysis was carried out as described in Methods. B: Dose response in the liver. C57BL/6 mice were injected intraperitoneally with LPS at various concentrations as indicated, and animals were euthanized 16 h later. C: Time course in the liver. C57BL/6 mice were injected intraperitoneally with either saline or LPS (100 μg of LPS per mouse), and the animals were euthanized at the times indicated after injection. Data (means ± SEM, n = 4∼5) are expressed as a percentage of controls. * $P < 0.05$ versus control.

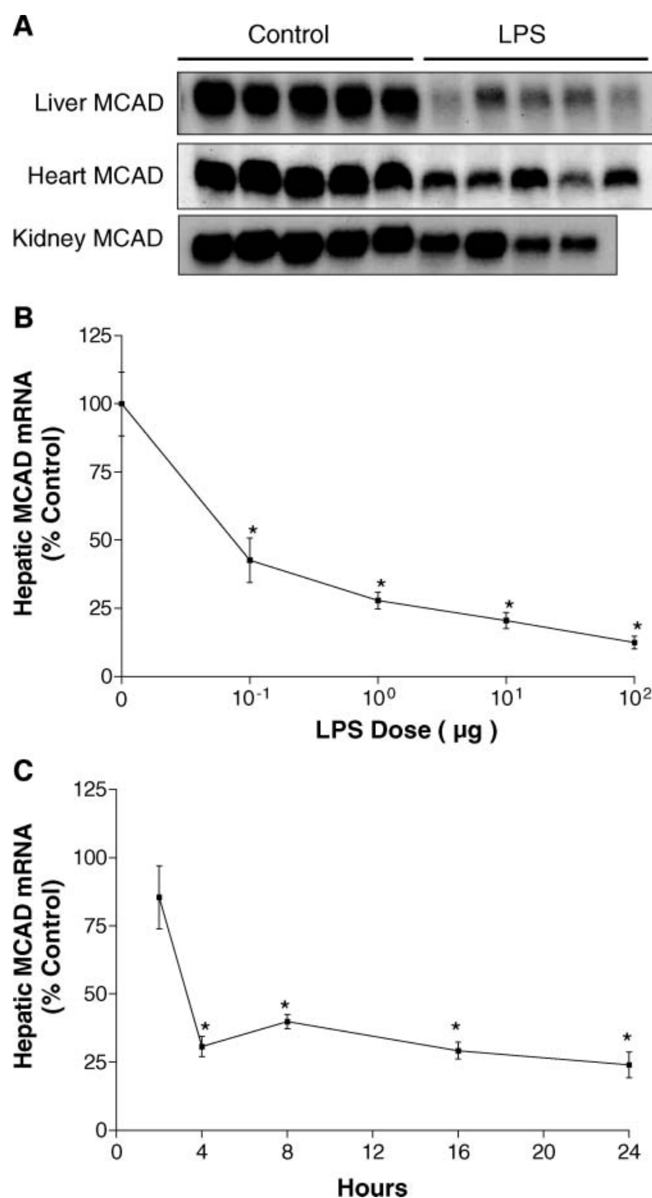

Fig. 3. mRNA levels of medium-chain acyl-coenzyme A dehydrogenase (MCAD) are decreased during the APR. A: mRNA levels of MCAD in the liver, heart, and kidney. Poly(A)$^+$ RNA was prepared from liver, heart, and kidney, and Northern blot analysis was carried out as described in Methods. B: Dose response in the liver. C57BL/6 mice were injected intraperitoneally with LPS at various concentrations as indicated, and animals were euthanized 16 h later. C: Time course in the liver. C57BL/6 mice were injected intraperitoneally with either saline or LPS (100 μg of LPS per mouse), and the animals were euthanized at the times indicated after injection. Data (means ± SEM, n = 4∼5) are expressed as a percentage of controls. * $P < 0.05$ versus control.

group. The average decrease in both bands was 52% ($P <$ 0.001 vs. control). Binding specificity was confirmed by competition between labeled NRRE1 and unlabeled wild-type NRRE1 in 100-fold excess. The presence of 100-fold excess of wild-type NRRE1 completely abolished the complex formation, whereas the presence of 100-fold excess of a nonspecific oligonucleotide did not.

In a similar experiment using an ERRα consensus sequence, we found that nuclear extracts from LPS-treated mice also had decreased binding in both complexes (Fig. 5B). The binding from LPS-treated animals was decreased by 63% in the higher molecular weight complex ($P = 0.034$). These results indicate that LPS-treated animals have a significant decrease in the binding activity of hepatic nuclear extracts against ERRα-specific response elements that may explain the decreased expression of MCAD during the APR.

We then identified the binding activity in these extracts

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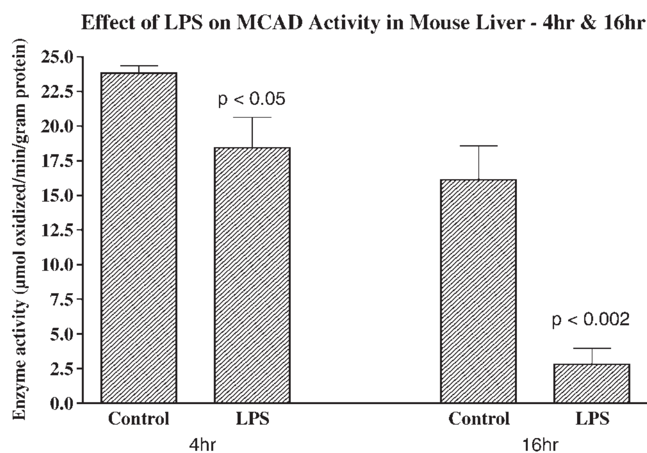

Fig. 4. MCAD activity is decreased during the APR. C57BL/6 mice were injected intraperitoneally with either saline (Control) or LPS (100 μg of LPS per mouse). Four and 16 h later, the animals were euthanized, and hepatic extracts were prepared as described in Methods. Data are means ± SEM of four to five animals for each condition.

as ERRα by a supershift experiment (Fig. 5C). Nearly all of the binding was shifted by an antibody to ERRα (lane 3 vs. lane 2). In contrast, control antibody produced no significant shift. Hence, the majority of binding in the nuclear extracts is mediated by a complex that includes ERRα.

Zymosan and turpentine suppress mRNA levels of PGC-1α, ERRα, and MCAD

Having found that LPS strongly suppresses the mRNA levels of PGC-1α, ERRα, and MCAD, we next determined the effect of weak inducers of inflammatory responses, such as zymosan and turpentine, on the hepatic expression of these genes. Whereas zymosan is a fungal product and signals through Toll-like receptor 2, causing systemic inflammation through the induction of TNF and IL-1, turpentine causes localized inflammation mediated by IL-1. As shown in **Fig. 6A**, zymosan decreased the mRNA levels of PGC-1α, ERRα, and MCAD by 44–58%. Also, turpentine caused a decrease in the mRNA levels of these genes to a similar extent (Fig. 6B). These data clearly demonstrate that expression of PGC-1α, ERRα, and MCAD is suppressed during the inflammatory response regardless of the types of inflammation.

DISCUSSION

MCAD plays a crucial role in cellular energy metabolism, and its activity is regulated by diverse metabolic and physiologic conditions. In the present study, we investigated whether the expression of MCAD and its regulator ERRα are altered during the APR, a condition that is accompanied by decreased fatty acid oxidation. We found that the LPS-induced APR induces a significant reduction in mRNA levels of MCAD in mouse liver, heart, and kidney. MCAD activity was also decreased at doses of LPS that previously had been shown to decrease ketogenesis (7, 8). The decrease was accompanied by a concomitant decrease

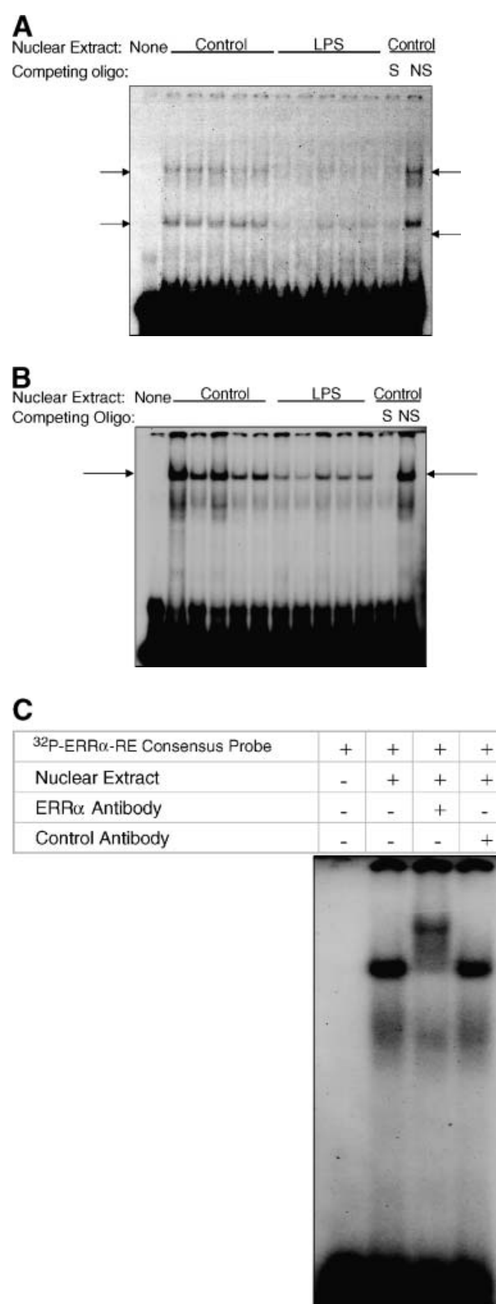

Fig. 5. Binding activity of hepatic nuclear extract to ERRα response elements is significantly decreased during the APR. C57BL/6 mice were injected intraperitoneally with either saline (Control) or LPS (100 μg of LPS per mouse). Sixteen hours later, the animals were euthanized, and hepatic nuclear extracts were prepared as described in Methods. Ten micrograms of nuclear extracts was incubated with radiolabeled oligonucleotides and run on gels. In some experiments, oligonucleotide (oligo) competition was performed. In others, antibody was used to induce shifts. A: Radiolabeled nuclear receptor response element 1 (NRRE1) was used as a binding site for ERRα. Arrows indicate the complex between nuclear protein and radiolabeled NRRE1. NS, competition with 100× unlabeled nonspecific DNA; S, competition with 100× unlabeled NRRE1. B: In a similar experiment, the consensus sequence for ERRα was used, and specific shifting was similarly shown. The data represent means ± SEM of four to five animals for each condition. C: The consensus sequence for ERRα was used as the probe. Antibody specific to ERRα was used to induce a supershift, which was not seen with control antibody. RE, response element.

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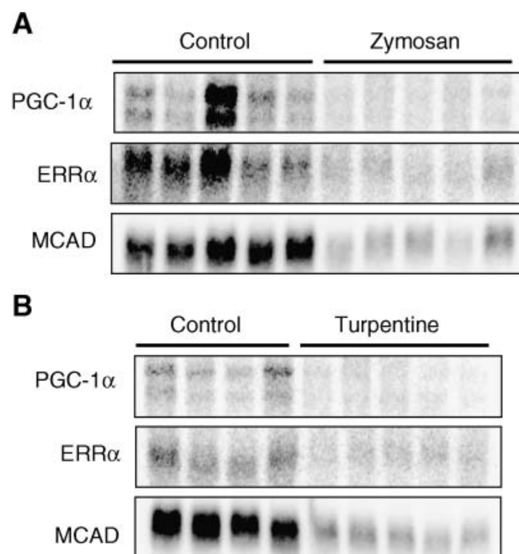

Fig. 6. mRNA levels of PGC-1α, ERRα, and MCAD are decreased during zymosan- and turpentine-induced inflammation. A: C57BL/6 mice were injected intraperitoneally with either saline or zymosan (80 mg/kg body weight), and the animals were euthanized 16 h later. B: C57BL/6 mice were injected subcutaneously with either saline or turpentine (100 μl), and the animals were euthanized 16 h later. Poly(A)$^+$ RNA was prepared from liver, heart, and kidney, and Northern blot analysis was carried out as described in Methods.

in mRNA levels of ERRα and its coactivator PGC-1α, which has been shown to increase the transcription of MCAD. We also found a decrease in the binding activity of hepatic nuclear extracts from LPS to two sequences containing ERRα elements, including NRRE1, which is found in the MCAD promoter. Furthermore, the binding activity in the nuclear extracts was shown to be dependent on ERRα, but antibody induced supershifts. These data suggest that the transcription of MCAD is decreased, possibly as a result of the decreased nuclear level of ERRα and PGC-1α.

Because MCAD mediates the initial step in mitochondrial fatty acid oxidation, these findings suggest that suppression of the PGC-1α, ERRα, and MCAD pathway could contribute to the decreased fatty acid oxidation observed during the APR. The hypertriglyceridemia of the APR is substrate-driven (7), and decreased fatty acid oxidation is one of several mechanisms that could provide increased fatty acid as substrate for VLDL production. Furthermore, the similar suppressive effects shown by zymosan and turpentine strongly indicate that suppression of this pathway is a universal inflammatory response.

The regulation of MCAD expression in vivo may involve not only ERRα but also other nuclear hormone receptors. DNase I footprinting assays demonstrate that the NRRE1 site in the MCAD promoter interacts with COUP (23), PPARα (24), RXR/RAR (25), and Hepatocyte Nuclear Factor-4 (HNF-4) (26). Whereas COUP functions as a *trans*-repressing regulatory element (23), RXR/RAR (25) or PPAR (23) can activate MCAD transcription via an NRRE1 site. Our previous studies found that the expression and activity of RXR/RAR and RXR/PPARα are downregulated during the APR (9). Therefore, it is possible that PPARα, RXR, and other nuclear receptors, in addition to ERRα, also play a role in regulating MCAD transcription. Results from the present study provide clear evidence for the downregulation of MCAD and its regulators, providing additional explanation for the altered fatty acid oxidation during the APR. The decrease in fatty acid oxidation, in turn, may contribute to the increase in triglycerides that accompanies the APR and potentially contributes to atherosclerosis.

We also found that the expression of PGC-1α is dramatically decreased in the liver, heart, and kidney. Considering the versatile role that PGC-1α plays (27), a significant decrease in PGC-1α expression could downregulate many biological functions that are important in the normal maintenance of metabolism. Microarray analysis revealed that PGC-1α-responsive genes are involved in oxidative phosphorylation and that their expression is downregulated in human diabetes. PGC-1α expression in human diabetes was reported to be decreased by 20% (28). However, in the present study, we report that the mRNA level of PGC-1α was decreased more dramatically, with levels that were barely detectable during the APR. This finding may imply that the disturbances in oxidative metabolism during the APR could be more detrimental. The decrease in fatty acid oxidation in various tissues likely provides fatty acids that contribute to the increase in triglycerides during infection and inflammation (7, 8), which in turn could contribute to the higher incidence of atherosclerosis among patients with infections and inflammatory diseases (7).

Hypertriglyceridemia is one of the components that constitute the metabolic syndrome, which is also associated with an increased risk of developing atherosclerosis (29, 30). Numerous studies have demonstrated that increased levels of the acute-phase protein C-reactive protein and the adipocyte-derived cytokines IL-6 and TNF are found in the metabolic syndrome (31–33). Thus, the metabolic syndrome is also a low-grade inflammatory state, but the underlying mechanisms by which inflammation may be linked to the features of the metabolic syndrome and ultimately the development of atherosclerosis have not been elucidated. The data from our group and others show that the changes in lipid profiles during the APR are similar to those in the metabolic syndrome, including hypertriglyceridemia and decreases in serum HDL cholesterol levels. Likewise, both states have increased mobilization of adipose tissue fatty acids and increased hepatic fatty acid synthesis, coupled with decreased hepatic fatty acid oxidation and ketogenesis (7). Whether the low-grade inflammation seen in the metabolic syndrome contributes to the changes in fatty acid metabolism, hypertriglyceridemia, and insulin resistance remains to be determined.

In summary, decreased fatty acid oxidation that results from the suppression of MCAD, possibly via decreases in PGC-1α, PPARα, and ERRα, reported herein could explain some of the changes in lipid metabolism that are observed during infection and inflammation.

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