Regulation of fatty acid transport protein and fatty acid translocase mRNA levels by endotoxin and cytokines

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Memon, Riaz A., Kenneth R. Feingold, Arthur H. Moser, John Fuller, and Carl Grunfeld. Regulation of fatty acid transport protein and fatty acid translocase mRNA levels by endotoxin and cytokines. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E210–E217, 1998.—The cloning of two novel fatty acid (FA) transport proteins, FA transport protein (FATP) and FA translocase (FAT), has recently been reported; however, little is known about their in vivo regulation. Endotoxin (lipopolysaccharide (LPS)), tumor necrosis factor (TNF), and interleukin-1 (IL-1) stimulate adipose tissue lipolysis and enhance hepatic lipogenesis and reesterification while suppressing FA oxidation in multiple tissues. Hence, in this study we examined their effects on FATP and FAT mRNA levels in Syrian hamsters. Our results demonstrate that LPS decreased FATP and FAT mRNA expression in adipose tissue, heart, skeletal muscle, brain, spleen, and kidney tissues in which FA uptake and/or oxidation is decreased during sepsis. In the liver, where FA oxidation is decreased during sepsis but the uptake of peripherally derived FA is increased to support reesterification, LPS decreased FATP mRNA expression by 70–80% but increased FAT mRNA levels by four- to fivefold. The effects of LPS on FATP and FAT mRNA levels in liver were observed as early as 4 h after administration and were maximal by 16 h. TNF and IL-1 mimicked the effect of LPS on FATP and FAT mRNA levels in both liver and adipose tissue. These results indicate that the mRNAs for both transport proteins are downregulated by LPS in tissues in which FA uptake and/or oxidation are decreased during sepsis. On the other hand, differential regulation of FATP and FAT mRNA in liver raises the possibility that these proteins may be involved in transporting FA to different locations inside the cell. FATP may transport FA toward mitochondria for oxidation, which is decreased in sepsis, whereas FAT may transport FA to cytosol for reesterification, which is enhanced in sepsis.

sepsis; tumor necrosis factor; interleukin-1; fatty acid oxidation; reesterification

LONG-CHAIN FATTY ACIDS (LCFA) are essential components of living cells because they are required for a variety of diverse cellular processes, including energy metabolism, synthesis of membrane lipids, intracellular signaling, and posttranslational modification of proteins (33). Whereas most cells are capable of taking up LCFA, the mechanisms involved in the transport of LCFA across biological membranes are still poorly understood (4, 13, 46). On one hand, it is suggested that LCFA uptake is a passive process that is dependent on the rate of cellular metabolism (46). On the other hand, it is proposed that specific fatty acid (FA) transport proteins facilitate the transfer of LCFA across plasma membranes (13). This viewpoint is supported by several studies (2, 39, 41, 44) that demonstrate that LCFA uptake is a rapid and saturable process that is competitively inhibited by FA analogs, that prior protease treatment of cells reduces FA uptake, and that FA transport is blocked by antibodies to specific plasma membrane proteins.

Several putative FA transport proteins have been identified and characterized by different techniques over the last several years. Recently, two of them, FA transport protein (FATP) and FA translocase (FAT), have been cloned (1, 32). FATP is a novel 63-kDa plasma membrane protein, which, when expressed in cultured fibroblasts, enhances the uptake of LCFA by severalfold (32). FATP has six predicted transmembrane domains, and its mRNA is expressed in several mouse tissues, including adipose tissue, heart, skeletal muscle, liver, brain, and kidney (32). FATP expression increases with differentiation in 3T3-L1 adipocytes and is negatively regulated by insulin at the level of transcription (23).

FAT is an 88-kDa plasma membrane glycoprotein with two predicted transmembrane domains. FAT mRNA is expressed in many rat tissues, including adipose tissue, heart, skeletal muscle, intestine, and spleen (1). Like FATP, the expression of FAT in cultured fibroblasts enhances the uptake of LCFA (19). The sequence of FAT is 85% similar (79% identical) to that of human CD36, a cell surface antigen previously described in vascular endothelium and platelets (14). CD36 has also been implicated in a variety of interactions with lipids, including binding fatty acids (20) and acting as a receptor for oxidized low-density lipoprotein (6). Finally, a third protein, named plasma membrane fatty acid binding protein (FABP-pm) has also been well characterized (40). FABP-pm is biochemically and immunologically identical to mitochondrial aspartate aminotransferase (40, 42). However, it is not known how a predominantly mitochondrial matrix protein may contribute to FA transport across the plasma membrane. Although FAT and FATP have been shown to act as FA transporters in isolated or cultured adipocytes and are induced during adipocyte differentiation, very little is known about their in vivo regulation.

The host response to infection and inflammation is usually accompanied by several alterations in FA metabolism, such as increased adipose tissue lipolysis, enhanced hepatic FA synthesis, reesterification of FA in the liver, and inhibition of FA oxidation in multiple tissues, including liver, heart, and muscle (12, 22, 23, 34, 43). These metabolic changes can also be induced by administration of endotoxin [lipopolysaccharide (LPS)], which mimics gram-negative infections, and by cytokines, such as tumor necrosis factor (TNF) and interleu-
kin-1 (IL-1), which mediate many of the metabolic responses that occur during infection (15, 25, 26). The host response to LPS and cytokines is therefore a good model to study the in vivo regulation of FA transporters. Hence, in this study, we have examined the effects of endotoxin, TNF, and IL-1 on the mRNA expression of FATP and FAT in multiple tissues in Syrian hamsters.

MATERIALS AND METHODS

Materials. [α-32P]dCTP (3,000 Ci/mmol, 10 mCi/ml) was purchased from NEN (Boston, MA). Endotoxin (Escherichia coli 55:BS) was purchased from Difco Laboratories (Detroit, MI) and was freshly diluted to desired concentrations in pyrogen-free 0.9% saline (Kendall McGraw Laboratories, Irvine, CA). Human TNF-α with a specific activity of 5 × 10^7 U/mg was kindly provided by Genentech (South San Francisco, CA). Recombinant human IL-1β with a specific activity of 1 × 10^6 U/mg was generously 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. Multiprime DNA labeling system was purchased from Amersham International (Amersham, UK). Minispin G-50 columns were from Pharmacia LKB Biotechnology (Uppsala, Sweden). Nitrocellulose and Nytran were from Schleicher and Schuell (Keene, NH). Kodak XAR5 film was used for autoradiography. The cDNA for FATP was kindly provided by Dr. J. E. Schaffer of Washington University (St. Louis, MO), and the FAT cDNA was kindly provided by Dr. N. A. Abumrad of State University of New York (Stony Brook, NY).

Animal procedures. Male Syrian hamsters (160–180 g) were obtained from Simonsen Laboratories (Gilroy, CA). The animals were maintained on a normal light-dark cycle (6 AM to 6 PM light, 6 PM to 6 AM dark) and were provided with rodent chow (Simonsen Laboratories) and water ad libitum. Animals were injected intraperitoneally with LPS, TNF, IL-1, or TNF + IL-1 at the indicated doses in 0.5 ml of 0.9% saline or with saline alone. After the injection of LPS or cytokines, food was withdrawn from both control and treated animals because LPS and cytokines are known to induce anorexia (15, 34). Animals were studied between 2 and 24 h after LPS or 8 h after cytokine administration, as indicated in the text. The doses of LPS used (0.1–100 µg/100 g body wt) are far below the doses required to cause death in rodents in our laboratory (50% lethal dose ~5 mg/100 g body wt) but have significant effects on triglyceride and cholesterol metabolism in Syrian hamsters (9, 10, 16). Similarly, the doses of TNF and IL-1 used (17 and 1 µg/100 g body wt, respectively) have marked effects on lipid metabolism and reproduce many of the effects of LPS on lipid metabolism in Syrian hamsters (17, 18).

Isolation of RNA and Northern blotting. Total RNA was isolated by a variation of the guanidinium thiocyanate method (5) as described earlier (9). Total RNA from adipose tissue was used for Northern blotting, whereas poly(A)⁺ RNA from all other tissues was isolated using oligo(dT) cellulose. Total or poly(A)⁺ RNA was quantified by measuring absorption at 260 nm. Equal amounts of total or poly(A)⁺ RNA were loaded on 1% agarose-formaldehyde gels and electrophoresed. The uniformity of sample applications was checked by ultraviolet visualization of the acridine orange-stained gels before transfer to Nytran membranes. We and others have found that LPS increases actin mRNA levels in liver by two- to fivefold in rodents (9, 29). TNF and IL-1 produce a twofold increase in actin mRNA levels. LPS also produced a twofold increase in hepatic mRNA levels for glyceraldehyde-3-phosphate dehydrogenase (GADPH) and a 2.6-fold increase in cyclophilin mRNA. Therefore, the mRNA levels of actin, GADPH, and cyclophilin, which are widely used for normalizing data, cannot be used to study LPS or cytokine-induced regulation of proteins in liver. However, the differing directions of the changes in mRNA levels for specific proteins after LPS or cytokine administration (increased for some proteins, decreased for some proteins, and no changes for other proteins), the magnitude of the alterations (up to 30-fold increase and 90% decrease), and the relatively small standard error of the means make it unlikely that the changes observed are due to unequal loading of mRNA. cDNA probe hybridization was performed in 0.75 M sodium chloride, 0.075 M sodium citrate, 2% sodium doxyl sulfate (SDS), 10% dextran sulfate, 2× Denhardt’s solution, and 100 mg/ml sheared salmon sperm DNA at 65°C overnight. Blots were washed in 0.2× saline sodium citrate and 0.1% SDS at room temperature for 30 min and at 65°C for 1 h. The blots were exposed to X-ray films for various durations to ensure that measurements were done on the linear portion of the curve, and the bands were quantified by densitometry.

RESULTS

Effect of LPS and cytokines on FATP and FAT mRNA levels in liver. To investigate the effect of LPS on FATP and FAT mRNA levels in liver, Syrian hamsters were injected with LPS (100 µg/100 g body wt). Livers were obtained at various time points, and poly(A)⁺ RNA was isolated for Northern analysis. LPS significantly decreased FATP mRNA levels, whereas it produced a marked increase in FAT mRNA levels (Fig. 1). FATP mRNA levels were decreased by 40% at 4 h after LPS administration and by 70–80% by 8–16 h after LPS (Fig. 1A). At 24 h after LPS, FATP mRNA levels were 50% of the control values. In contrast to FATP, FAT mRNA levels began to increase at 4 h after similar doses of LPS and were increased by twofold at 8 h and four- to fivefold at 16–24 h after LPS administration (Fig. 1B). These data demonstrate that both FATP and FAT mRNA levels are regulated in liver in an in vivo model of sepsis, although in opposite directions.

We next determined the dose response of LPS-induced alterations in FATP and FAT mRNA levels at 16 h after LPS treatment. The data presented in Fig. 2 demonstrate that LPS doses as low as 1 µg/100 g body wt are sufficient to induce maximal changes in FATP and FAT mRNA levels in liver. The half-maximal dose for LPS-induced decrease in FATP mRNA is 0.3 µg/100 g body wt (Fig. 2A). Similarly, the half-maximal dose for LPS-induced increase in hepatic FAT mRNA levels is between 0.1 and 1 µg/100 g body wt (Fig. 2B).

We next compared the effect of LPS treatment on FATP and FAT mRNA levels in the liver to control animals that were either fasted for 24 h or had free access to lab chow. LPS-treated animals were also fasted for 24 h in parallel with the control fasted animals. The data presented in Fig. 3 show that hepatic FAT mRNA levels are higher in the fasting state.
compared with fed state, whereas FAT mRNA levels are higher in the fed state. In the same experiment, LPS produced a 50% decrease in FATP mRNA levels compared with the fasted group. On the other hand, FAT mRNA levels were 2.5- and 5-fold higher in the fed and LPS-treated groups, respectively, compared with fasted animals.

Our previous studies have shown that TNF and IL-1 mediate many of the metabolic effects of LPS, hence we next examined the ability of TNF (17 µg/100 g body wt) and IL-1 (1 µg/100 g body wt) to mimic the effects of LPS on FATP and FAT mRNA levels. The data presented in Fig. 4 show that 8 h after administration, TNF and IL-1 decreased FATP mRNA levels by 50 and 55%, respectively, whereas a combination of both cytokines produced a 75% decrease in hepatic FATP mRNA levels (Fig. 4A). On the other hand, TNF produced a 50% increase in FAT mRNA levels, whereas IL-1 either alone or in combination with TNF produced a twofold increase in hepatic FAT mRNA levels (Fig. 4B). These data indicate that, like LPS, TNF and IL-1 also have opposite effects on FATP and FAT mRNA levels in liver.

Effect of LPS and cytokines on FATP and FAT mRNA levels in adipose tissue. Because FATP and FAT are both abundantly expressed in adipose tissue and LPS is known to increase the mobilization of free fatty acids by inducing lipolysis, we next examined the effect of LPS on FATP and FAT mRNA levels in hamster adipose tissue. The data presented in Fig. 5 represent a dose response of LPS effect on FATP and FAT mRNA levels in adipose tissue. Whereas LPS had very little effect on FATP mRNA levels at lower doses (1 and 10 µg/100 g body wt), a higher dose of LPS (100 µg/100 g body wt) decreased FATP mRNA levels by 55% in adipose tissue.
In contrast to the findings with FATP, a smaller dose of LPS (1 µg/100 g body wt) was sufficient to decrease FAT mRNA levels by 60% in adipose tissue, whereas 10- and 100-µg LPS doses produced an 80% decrease in FAT mRNA levels.

We next examined the effects of fed and fasting state on FATP and FAT mRNA levels in adipose tissue and compared them with the effects of LPS treatment. Control animals had either free access to food or were fasted for 24 h, whereas LPS-treated animals were fasted for 24 h in parallel with control fasted animals. Both FATP and FAT mRNA levels were higher in adipose tissue in the fasting state compared with the fed state (Fig. 6). In the same experiment, LPS decreased FATP mRNA by 60% and FAT mRNA levels by 55% compared with fasting controls.

The data presented in Fig. 7 demonstrate the effect of cytokines on FATP and FAT mRNA levels in the adipose tissue. Eight hours after administration, TNF and IL-1 decreased FATP mRNA levels by 40 and 45%, respectively, whereas a combination of both cytokines produced a 50% decrease in FATP mRNA levels in adipose tissue. Similarly, TNF alone produced a 50% decrease in FAT mRNA levels in adipose tissue, whereas IL-1 either alone or in combination with TNF decreased FAT mRNA levels by 65%.

Effect of LPS on FATP and FAT mRNA levels in other tissues. Because FATP and FAT are also expressed in several other tissues that have the ability to take up and metabolize LCFA, we next examined the effect of high-dose LPS (100 µg/100 g body wt) on FATP and FAT mRNA expression in heart, skeletal muscle, spleen, kidney, and brain. LPS produced a significant decrease in FATP mRNA levels (Fig. 8A) in heart (45%), skeletal muscle (65%), spleen (65%), kidney (80%), and brain (35%). LPS also significantly decreased FAT mRNA expression (Fig. 8B) in skeletal muscle (70%) and spleen (70%) but had only a marginal effect in heart (20%). In contrast to FATP, FAT mRNA levels were not detectable in kidney and brain in both control and LPS-treated animals.

DISCUSSION

The regulation of FA transport across biological membranes is an essential process for the control of fuel homeostasis, because FAs are important oxidative fuels for skeletal muscle, heart, liver, and kidney (33). Furthermore, FA can be stored in adipocytes in the form of triglycerides during states of nutrient abundance or mobilized from adipose tissue during fasting or in pathological states such as sepsis and malignancies. These mobilized FA are either oxidized in different tissues to supply energy or reesterified in the liver to support triglyceride synthesis and very low density lipoprotein (VLDL) production. Because FATP and FAT
have been postulated to facilitate FA flux across plasma membranes in several tissues (1, 32), we hypothesized that these transport proteins would be regulated in vivo by endotoxin and cytokines in parallel to their known effects on FA metabolism.

The present study demonstrates that both FATP and FAT mRNA levels are downregulated by LPS in most tissues in which they are expressed, except liver, where they are differentially regulated. LPS produced a marked decrease in FATP mRNA levels in liver, whereas it increased hepatic FAT mRNA levels. The LPS-induced changes in hepatic FATP and FAT mRNA occur as early as 4 h after administration and are maximal by 16 h, suggesting that the effects of LPS on FA transport proteins are rapid and sustained. Our previous studies have shown that the effects of LPS on lipogenesis and ketogenesis are also maximal by 16 h (25, 26). The half-maximal doses for LPS effects on both FATP and FAT mRNA levels in liver are between 0.1 and 1 µg/100 g body wt. These doses of LPS are far below the doses that induce death but are quite similar to the doses that produce changes in lipid metabolism in hamsters (9, 10, 16), suggesting that the regulation of FA transport proteins is a very sensitive host response to LPS.

Our results demonstrate that in adipose tissue both FATP and FAT mRNA levels are downregulated by LPS. LPS decreased FATP mRNA levels only at a high dose (100 µg/100 g body wt), whereas a lower dose of LPS (1 µg/100 g body wt) produced a comparable decrease in FAT mRNA levels, suggesting that FAT may be more sensitive to LPS in adipose tissue. Moreover, higher doses of LPS decreased the mRNA expression of FATP and FAT in several tissues that are involved in the uptake and metabolism of LCFA. LPS decreased FATP mRNA levels in skeletal muscle, heart, kidney, spleen, and brain. LPS also produced a marked decrease in FAT mRNA levels in skeletal muscle and spleen while inducing a small but statistically significant decrease in heart. LPS-induced decreases in FATP and FAT mRNA levels may contribute to decreased uptake and/or oxidation of LCFA in these tissues, a phenomenon commonly observed during sepsis (23, 34, 43).

Infection and LPS administration stimulate the production of several cytokines, including TNF and IL-1, and these cytokines mediate many of the pathophysiological responses that occur during infection. TNF and
IL-1 increase serum triglyceride and cholesterol levels, stimulate hepatic lipogenesis, and enhance VLDL production (8, 11, 26). Moreover, both TNF and IL-1 decrease FA oxidation and ketone body production (25, 30). In the present study, we demonstrate that, like LPS, both TNF and IL-1 decreased FATP mRNA levels and increased FAT mRNA levels in the liver, whereas they decreased mRNA levels for both transport proteins in the adipose tissue. These results indicate that the effects of TNF and IL-1 on FA transporters in liver and adipose tissue closely resemble those of LPS and suggest that TNF and IL-1 may be involved in mediating the effects of LPS on FA transport proteins.

The data presented in our study demonstrate that both FATP and FAT are primarily regulated at the mRNA level by endotoxin and cytokines. We have not examined the effect of LPS or cytokines on FATP or FAT at the protein level due to the unavailability of specific antibodies. It is possible that FATP and/or FAT may also be regulated at posttranscriptional or translational levels under different conditions because changes in the mRNA levels do not always reflect changes in protein levels.

It is of interest that, although FATP and FAT are coordinately downregulated by LPS in adipose tissue, heart, skeletal muscle, and spleen, these proteins are differentially regulated in the liver, where FATP mRNA levels are downregulated and FAT mRNA levels are upregulated by LPS and cytokines. Studies in experimental models of sepsis have shown that on one hand there is decreased hepatic FA oxidation and ketone body production (23, 43), whereas on the other hand there is an increase in hepatic lipogenesis, reesterification, and VLDL production (12, 22, 34). The time course of this reciprocal regulation of FA oxidation and lipogenesis by LPS in the liver is very similar (12, 25, 26). It is important to note that both FA oxidation and reesterification are highly compartmentalized, with FA oxidation taking place in the mitochondria and reesterification occurring in the cytosol. It is well known that the activity of carnitine palmitoyltransferase I (CPT-I) is the rate-limiting step for mitochondrial FA oxidation and ketogenesis (24). CPT-I is allosterically inhibited by the intracellular levels of malonyl-CoA, which is the first committed intermediate in FA biosynthesis (24). The levels of malonyl-CoA fluctuate in parallel with the rates of lipogenesis. We have earlier shown that LPS and cytokines increase hepatic malonyl-CoA levels and decrease hepatic ketogenesis, a marker of hepatic FA oxidation (25). The differential regulation of FATP and FAT mRNA in the liver by LPS and cytokines raises the possibility that these proteins may be involved in transporting FA to different locations inside the cell. FATP, which is downregulated by LPS and cytokines, may transport FA toward mitochondria for oxidation, which is suppressed in sepsis. On the other hand, FAT, which is upregulated by LPS, may transport FA toward cytosol for reesterification, which is enhanced in sepsis. This concept is further supported by the observations that, in the fasting state, when hepatic FA oxidation is stimulated, FATP mRNA levels are higher compared with those in the fed state. Moreover, LPS treatment, which suppresses FA oxidation, also lowers FATP mRNA levels in the fasted animals. On the other hand, in the fed state, when hepatic reesterification is enhanced, FAT mRNA levels are higher compared with those in the fasting state, whereas LPS treatment, which enhances reesterification, further increases FAT mRNA levels in the fasted animals. Taken together, these results suggest that FA transport in the liver may be compartmentalized and that FATP may be involved in transporting FA toward mitochondria for oxidation, whereas FAT may transport FA toward cytosol for reesterification.

FA can be transported into the adipose tissue for storage during states of nutrient abundance or can be mobilized from the adipose tissue to support the energy demands of other tissues during states of nutrient...
deprivation. On the basis of the finding of higher FATP mRNA levels in mouse adipose tissue in the fasting state, it has been proposed that FATP may be involved in the efflux of FA from the adipose tissue (23). Our results demonstrate a similar trend for FATP and FAT mRNA levels in hamster adipose tissue with higher FATP and FAT mRNA levels in the fasting state and lower level in the fed state. However, the downregulation of both transport proteins by LPS and cytokines is not consistent with the hypothesis that FA transporters are key regulators of the efflux of FA from the adipose tissue. LPS and TNF have been previously shown to induce adipose tissue lipolysis and increase mobilization of fatty acids in rodents (8, 11, 12, 25). Thus, if FATP and FAT were essential only for the efflux of FA from the adipose tissue, then the mRNA levels of these proteins should increase in response to LPS and cytokine treatment rather than decrease, as shown in the present study. The reasons for this discrepancy in the mRNA expression of both transport proteins in adipose tissue during the fasting state and LPS treatment are not clear. However, it is likely that other factors, such as the activity and expression of fatty acyl-CoA synthase (FACS), could determine the ultimate fate of transported FA inside the cell. Although FA transport is a bidirectional process, FACS catalyzes the activation of LCFA, making the transport process unidirectional. Weiner et al. (45) have shown that TNF, a known mediator of the metabolic effects of LPS, downregulates FACS gene expression in 3T3-L1 adipocytes. Our recent studies indicate that LPS, TNF, and IL-1 also decrease FACS mRNA levels in adipose tissue in vivo (unpublished results), suggesting that a significant decrease in the expression of FACS in adipose tissue during infection or inflammation may prevent the activation and subsequent storage of FA in the adipose tissue while allowing the efflux of mobilized FA if adequate transporters are available.

It is well known that heart, skeletal muscle, liver, and renal cortex use FAs as their preferred fuel substrate. However, several studies have shown that during sepsis several organs switch their fuel preferences. For example, Spitzer et al. (35) have shown that in vivo myocardial uptake and oxidation of LCFA is markedly reduced after LPS treatment, whereas the uptake and utilization of lactate are significantly elevated, suggesting that there is a shift in utilization of fuel substrates by heart during sepsis. Romanosky et al. (31) have shown that the uptake and oxidation of LCFA by skeletal muscle are significantly reduced after LPS administration. An LPS-induced decrease in FATP and FAT mRNA levels could be a possible mechanism for the decreased uptake of LCFA in heart and muscle observed during sepsis.

Several in vivo studies in rodents have demonstrated that LPS or TNF administration increases the uptake and utilization of glucose in several organs, including liver, spleen, kidney, lung, intestine, muscle, and skin (7, 27, 28). The LPS-induced increase in glucose uptake and utilization is marked and prolonged in macrophage-rich tissues such as spleen and liver (27). After LPS treatment, the glucose is heavily used in the pentose cycle in Kupffer and endothelial cells in liver (36, 38). An increase in pentose cycle activity supports enhanced superoxide production, which could aid in host defense by protecting against free radical-induced injury during bacterial infections. Recent studies by the same group have shown the increased glucose uptake in liver is mediated by a selective increase in GLUT-1 protein content in hepatic parenchymal, Kupffer, and endothelial cells (37), although the predominant glucose transporter in liver is GLUT-2 (3), which is in fact decreased after LPS administration (37). Thus glucose transporters are also differentially regulated in liver after LPS treatment.

In summary, our results demonstrate that LPS or cytokine administration coordinately downregulates FATP and FAT mRNA expression in most tissues in which they are expressed except liver, where these proteins are differentially regulated. In the liver, LPS decreases FATP mRNA levels but increases FAT mRNA expression. The differential regulation of FATP and FAT in liver raises the possibility that these proteins may be involved in transporting FA to different locations inside the cell. FATP may transport FA toward mitochondria for oxidation, which is decreased in sepsis, whereas FAT may transport FA to cytosol for reesterification, which is enhanced in sepsis. Further studies are needed to explore the linkage between these transport proteins and specific intracellular metabolic pathways.

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