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Reduction in cytochrome P-450 enzyme expression is associated with repression of CAR (constitutive androstane receptor) and PXR (pregnane X receptor) in mouse liver during the acute phase response☆

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Abstract

Expression of P-450 (Cyp) enzymes is reduced in liver during the acute phase response, contributing to the decrease in bile acid levels and drug metabolism during infection. Nuclear hormone receptors CAR and PXR are key transactivators of *Cyp2b* and *Cyp3a* genes, respectively. Injection of bacterial lipopolysaccharide (LPS) induced the expected reduction in Cyp2b10 and Cyp3a mRNA levels in mouse liver. These decreases were associated with a marked reduction in CAR and PXR mRNA levels within 4 h following treatment. LPS-induced CAR and PXR repression were dose-dependent and sustained for at least 16 h. LPS treatment also reversed the up-regulation of Cyp3a in mice pre-treated with PXR ligand RU486. In addition, we observed a concomitant decrease in RXR (retinoid X receptor) mRNA levels, the obligatory partner of both CAR and PXR for high affinity binding to DNA. These findings represent one possible molecular mechanism underlying sepsis-induced repression of Cyp enzymes.

Keywords: Infection; Endotoxin; Cholestasis; Drug metabolism; Bile acid metabolism

Infection, inflammation or trauma leads to a pathophysiological condition referred to as the acute phase response (APR) [1]. Induction of the APR by lipopolysaccharide (LPS) or pro-inflammatory cytokine administration is associated with the suppression of P-450 or Cyp enzyme activity [2–5] and expression [6–9] in the liver. Cyp isoforms constitute a superfamily of hemethiolate proteins, with functions ranging from the synthesis and degradation of endogenous steroid hormones, bile acids, vitamins, and fatty acid derivatives to the metabolism of foreign compounds such as drugs, environmental pollutants, and carcinogens (xenobiotics) [10].

Recently, two members of the nuclear hormone receptor superfamily of ligand-activated transcription factors, PXR and CAR, both of which are highly expressed in the liver [11,12], have been implicated in mediating the xenobiotic-induced increases in gene expression of rat *Cyp3a23* [13–15], mouse *Cyp2b10* [16–19], and human *CYP2B6* [17]. Furthermore, both dexamethasone and the glucocorticoid antagonist RU486 activate PXR [12,14,20] thereby increasing the expression of *CYP3A4* gene [20].

Both CAR and PXR must heterodimerize with the nuclear hormone receptor RXR for high affinity binding to their cognate DNA response elements [12,21]. We and others have shown that LPS or TNF (tumor necrosis factor) down-regulates the expression of RXR in ham-

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ster liver [22] and rat GH3 cells [23]. Previous studies in our laboratory indicate that the coordinate decrease in RXR and the nuclear hormone receptor LXR could represent one mechanism by which the expression of Cyp7a is suppressed during the APR in rodent liver [22,24]. Furthermore, it has recently been shown that interleukin (IL)-6 reduces CAR and PXR mRNA levels in human hepatocytes [25]. We therefore sought to determine whether the APR is associated with a reduction in PXR and CAR expression in vivo. To test this hypothesis we measured CAR, PXR, and RXR expression levels in mouse liver following LPS treatment.

Materials and methods

Animals. Six-week-old female C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were maintained in a normal-light-cycle room and were provided with rodent chow and water ad libitum. Anesthesia was induced with halothane. To determine the effect of the APR on CAR and PXR mRNA levels, mice were injected intraperitoneally (IP) with 0.1–100 μg of LPS (*Escherichia coli* 55:B5, Difco Laboratories, Detroit, MI) in saline or with saline alone. In all other experiments, mice were injected IP with 100 μg of LPS or with saline alone. To assess the effect of LPS treatment on PXR activation, mice were injected IP daily with RU486 (Sigma, St. Louis, MO) in olive oil at a dose of 50 mg/kg of body weight or with olive oil alone for 4 days. On the fourth day, 100 μg of LPS or saline alone was also administered IP. Food was withdrawn at the time of injection since LPS induces anorexia in rodents [26]. Livers were removed at the time indicated in the text after treatment. The doses of LPS used in this study were non-lethal since the LD_{50} for LPS in rodents is approximately 5 mg/100 g of body weight.

RNA isolation and Northern blot analysis. Total RNA was isolated from 300–400 mg of snap-frozen whole liver tissue using Tri-Reagent (Sigma, St. Louis, MO). Poly(A) + RNA was purified using oligo(dT) cellulose (Amersham Pharmacia Biotech, Piscataway, NJ). Ten micrograms of poly(A)+ or 30 μg total RNA was electrophoresed on a 1% agarose/formaldehyde gel, electrotransfered to Nytran membrane (Scleicher and Schuell, Keene, NH), and hybridized with [α-^{32}P] dCTP (NEN Life Science Products, Boston, MA) labeled cDNAs using the random priming technique. mRNA levels were detected by exposure of the membrane to X-ray film and quantified by densitometry. Human RARα, RARβ, RARγ, and RXRα cDNAs were a gift from Dr. D. Bikle (University of California, San Francisco). Mouse RXRβ and RXRγ cDNAs were provided by Dr. D. Mangelsdorf (University of Texas Southwestern Medical Center, Dallas). Mouse PXR cDNA was provided by Dr. T. Willson (Glaxo Smith Kline, Research Triangle Park, NC). All other cDNAs were generated by PCR amplification using the following primers: mouse CAR 5′-GAC CGC ACT CCC TAA TTC CT-3′ and 5′-CGG GTC TGTCAG GGG AGA AG-3′; mouse Cyp2b10 5′-TGT GCT GCT CCT CCT TGC TCT CC-3′ and 5′-GTA CTT GAG CAT GAG CAG GAA GCC ATA GTG-3′; human FXR 5′-CGT GAC TTGCGN CAA GTG ACC-3′ and 5′-CCA NGA CAT CAG CAT CTC AGC G-3′; mouse Oatp2 5′-TCT CCA CAG TGG CCA TCT CC-3′ and 5′-GGT GGG GCA TGC ACA ATT AAA-3′.

A rat cDNA library was used to amplify by PCR a rat Cyp3a23 cDNA using the following primers: 5′-GGA CCT GCT TTC AGC TCT CAC ACT GG-3′ and 5′-GAG AGC AAA CCT CAT GCC AAT GCA G-3′. We used this rat probe to study the effect of LPS on the Cyp3a subfamilly of Cytochrome P-450 in mouse liver.

Statistical analysis. Difference between two experimental groups was analyzed using the unpaired *t* test. Differences among multiple groups were analyzed using one-way ANOVA with Newman–Keuls' post test correction.

Results and discussion

The decreased metabolism of drugs in humans during infection is well documented [27]. Consistent with these data, our mouse model of LPS-induced acute inflammation resulted in the expected decrease in the expression of two classes of Cyp enzymes involved in drug metabolism [10]. As shown in Fig. 1, we observed an 80% decrease ($p < 0.01$) in Cyp2b10 mRNA levels as soon as 4 h after LPS administration. This effect on Cyp2b10 expression was sustained for at least 16 h with LPS treatment inducing a 95% decrease ($p < 0.01$) in Cyp2b10 mRNA levels at this time point. As described under Materials and methods, a rat Cyp3a23 probe was also used to measure Cyp3a mRNA levels in mouse liver following LPS treatment. This probe strongly bound to a single mRNA species in mouse liver. No significant effect on Cyp3a mRNA levels was observed 4 h after LPS injection, but by 16 h Cyp3a expression was markedly reduced by 99% ($p < 0.01$) in LPS-treated mice when compared to control mice (Fig. 1). Although an increase in RNA turnover cannot be excluded by our in vivo studies, the repression of Cyp enzymes during inflammation is thought to occur primarily at the transcriptional level [27]. The transcription factors implicated in this regulation have not been previously been identified.

Extensive studies of the molecular mechanisms underlying the up-regulation of positive acute phase proteins expression have revealed the importance of the activation of transcription factors, such as NFκB, C/EBP, and STAT, in this hepatic response to infection [28]. On the other hand, much less is known about the molecular mechanisms responsible for the down-regulation of negative acute phase proteins. Recent findings

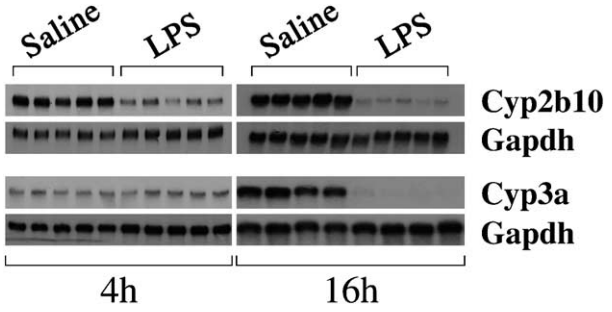

Fig. 1. Reduction in Cyp2b10 and Cyp3a mRNA levels in mouse liver following LPS treatment. Mice were injected IP with either saline or 100 μg LPS, and animals were sacrificed 4 and 16 h after treatment. Poly(A) + RNA were isolated, and Northern blot analysis was performed as described under Materials and methods. A Gapdh probe was used to check for RNA integrity.

have established that the nuclear hormone receptors CAR and PXR are key regulators of *Cyp2b* [18] and *Cyp3a* [15] gene expression, respectively. Thus, we sought to determine whether CAR and PXR levels are reduced during the APR. As shown in Fig. 2, CAR mRNA levels were reduced by 84% ($p < 0.001$) and 90% ($p < 0.001$) when compared to control levels, respectively, 4 and 16 h after injection of 100 μg of LPS. Furthermore, the inhibitory effect of LPS on CAR mRNA levels was dose-dependent and very sensitive, with a half-maximal effect occurring below 0.1 μg of LPS (data not shown). As shown in Fig. 2, LPS treatment was also associated with a marked decrease in PXR mRNA levels, with PXR mRNA levels being reduced by 96% ($p < 0.001$) and 76% ($p < 0.05$) when compared to control levels, at 4 and 16 h, respectively. This inhibition was dose-dependent and sensitive, with a half-maximal effect occurring at approximately 0.6 μg of LPS (data not shown). Therefore, very low doses of LPS (LD_{50} for LPS in rodents are approximately 5 mg/100 g of body weight) rapidly and dramatically reduce CAR and PXR expression levels in mouse liver.

In addition, this decrease in CAR and PXR levels was associated with a decrease in RXR, the obligatory partner of both CAR and PXR for high affinity binding to DNA [12,21]. As shown in Fig. 2, the expression of RXRα, the major isoform in the liver [29], was markedly reduced by 76% ($p < 0.001$) and by 81% ($p < 0.05$), respectively, 4 and 16 h after LPS treatment. This decrease in RXRa mRNA levels was not compensated by an up-regulation of the minor isoforms RXRβ and RXRγ. In fact, RXRβ expression level was reduced by 58% ($p < 0.01$) and 68% ($p < 0.05$) when compared to control levels 4 and 16 h after LPS administration (Fig. 2). Furthermore, RXRγ mRNA levels were transiently reduced by 78% ($p < 0.001$) when compared to control at 4 h, returning towards normal by 16 h after LPS injection (Fig. 2).

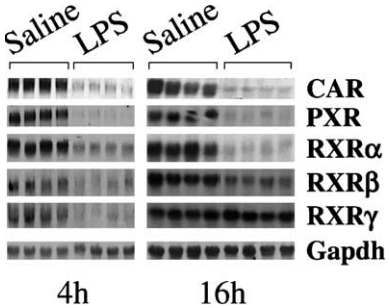

Fig. 2. Decrease in CAR, PXR, and RXR mRNA levels in mouse liver following LPS treatment. Mice were injected IP with either saline or 100 μg LPS. Animals were sacrificed 4 and 16 h after treatment. Poly(A) + RNA were isolated, and Northern blot analysis was performed as described under Materials and methods. A Gapdh probe was used to check for RNA integrity.

Several lines of evidence suggest that a reduction in CAR, PXR and RXR levels could play a role in the reduction in Cyp2b and Cyp3a levels during APR. First, in this study we show that the repression of PXR and RXR precedes the decrease in Cyp3a mRNA levels. Second, LPS administration blocks the induction of Cyp3a expression in the presence of PXR ligand, the glucocorticoid antagonist RU486. Indeed, a four-day treatment with RU486 resulted in a 5-fold increase in Cyp3a mRNA levels in mouse liver (Fig. 3). LPS administration reversed the stimulatory effect of the PXR ligand on Cyp3a expression, bringing Cyp3a mRNA levels in RU486 pre-treated mice down towards control levels (Fig. 3). Finally, it has been suggested that IL-6 might mediate the decrease in CYP2 and CYP3 mRNA levels in human hepatocytes by reducing the expression of CAR and PXR in these cells [25].

On the other hand, our results are in apparent contradiction with the observation that in CAR-null mice [19], and in PXR-null mice [30] the basal mRNA levels of, respectively, Cyp2b10 and Cyp3a11 are not decreased. However, since CAR and PXR response elements are quite similar, it is conceivable that these two nuclear hormone receptors can compensate for each other in maintaining the basal expression levels of their respective target genes.

In accordance with this hypothesis, it has been shown that CAR can transactivate the steroid/rifampicin-response element of the human *CYP3A4* gene in HepG2 cells [17]. Furthermore, during the APR, such a compensatory mechanism could not occur, since CAR, PXR, and RXR are all repressed following LPS treatment.

The sepsis-associated decrease in CAR, PXR, and RXR levels could represent a rapid and highly sensitive

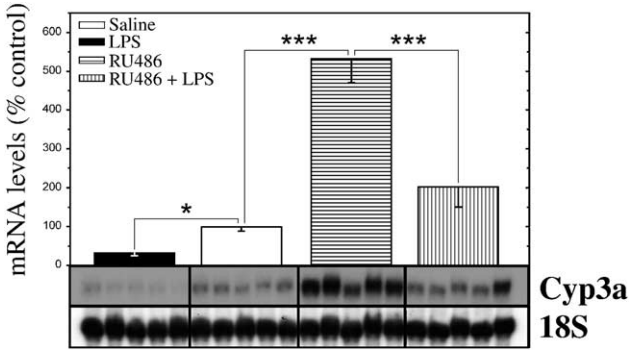

Fig. 3. LPS effect on Cyp3a expression after activation by a PXR ligand, the glucocorticoid antagonist RU486. Mice were pre-treated for 4 days with either olive oil or RU486 (50 mg/kg of body weight, IP), and on the fourth day, animals were injected IP with either saline or 100 μg LPS. Mice were sacrificed 16 h after LPS treatment. Total RNA was isolated from liver, and Northern blot analysis was performed as described under Materials and methods. Data (mean + SEM, $n = 5$) are expressed as percentage of control after normalization to the 18S signal. $^{*}p < 0.05$; $^{***}p < 0.001$.

molecular mechanism to repress Cyp2b and Cyp3a isoforms thereby decreasing the metabolism of a variety of lipophilic compounds. Aside from being responsible for the metabolism of many xenobiotics, Cyp3a enzymes also metabolize bile acids [10]. Interestingly, this reduction in Cyp3a levels during the APR is consistent with APR-associated changes in lipid metabolism including hypercholesterolemia and inhibition of bile acid synthesis and metabolism [31,32]. LPS administration in rodent leads to a rapid decrease in expression of Cyp7a, the rate-limiting enzyme for the classic bile acid biosynthesis [24]. Three nuclear hormone receptors have been shown to regulate the expression of the *Cyp7a* gene: LXR as a transactivator [14,33], FXR (farnesoid X receptor) and PXR as transcriptional repressers [30,34,35]. The data presented here and elsewhere suggest that repression of LXR during the APR [22] is most likely responsible for the LPS-induced repression of Cyp7a, rather than an up-regulation of the repressers PXR and/or FXR: (1) LPS was able to block the up-regulation of Cyp7a in hamsters fed a cholesterol-enriched diet [24]; (2) The present study demonstrates that PXR levels are actually decreased during the APR; (3) As shown in Fig. 4A, 4 h after LPS administration we observed a significant 47% ($p < 0.001$) decrease in FXR mRNA levels in mouse liver.

The physiopathology of sepsis-associated cholestasis also includes a decrease in bile acid transport [32,36]. In rodents, LPS treatment is associated with a marked reduction in expression of genes coding for transporters responsible for hepatocellular uptake of bile acids, such as *Oatpl* (Na^+-independent organic anion transporter protein 1) [36] and *Ntcp* (Na^+/taurocholate cotransporter) [37]. Moreover, studies in vitro have demonstrated that the repressing effect of LPS in vivo on Ntcp mRNA levels is mediated at least in part by IL-1, and that IL-1-induced Ntcp down-regulation results from a decreased RXR:RAR (retinoic acid receptor) binding activity to the *Ntcp* promoter [38]. Consistent with these data, the expression of all three RAR isoforms, RARα, RARβ, and RARγ, was decreased in mice liver by 92% ($p < 0.001$), 74% ($p < 0.001$), and 64% ($p < 0.001$) 4 h following LPS treatment, respectively (Fig. 4A). The decrease in RAR and RXR levels that occurs during the APR is most likely responsible for the reduction in RXR:RAR binding to the *Ntcp* promoter thereby resulting in reduced *Ntcp* gene transcription and inhibition of bile acid transport. In addition, PXR has recently been shown to regulate the expression of another member of the *Oatp* family of transporters, *Oatp2* [30]. As shown in Fig. 4B, LPS-induced PXR repression is associated with a 49% ($p < 0.001$) decrease in Oatp2 mRNA levels at 4 h. This inhibitory effect was maintained for at least 16 h, as we observed a similar 52% ($p < 0.005$) reduction in Oatp2 mRNA levels at this time point (Fig. 4B). The decrease in Oatp2 expression we observe in our model of acute inflammation is consistent with the repression in bile acid transport across the basolateral membrane associated with sepsis.

Unfortunately, using in vivo models such as ours, it is difficult to carry out studies to directly demonstrate that LPS decreases the expression of CAR and PXR target genes at the transcriptional level. Definitive studies of the molecular mechanisms by which CAR and PXR target genes, such as *Cyp2b10* and *Oatp2*, are down-regulated during the APR await the development of an in vitro model.

In summary, the present study demonstrates that the APR is associated with a marked and rapid decrease in CAR, PXR, and RXR mRNA levels in mouse liver. Whether the reduction in CAR and PXR levels is a protective or a pathological response to infection remains unclear. On one hand, the subsequent decrease in Cyp3a enzyme activity could cause the accumulation of toxic bile acids thereby resulting in liver damage. On the other hand, the decrease in Cyp activity could prevent the generation of other toxic metabolites, and more importantly increase the pool of cholesterol available for VLDL production and for cells involved in tissue repair.

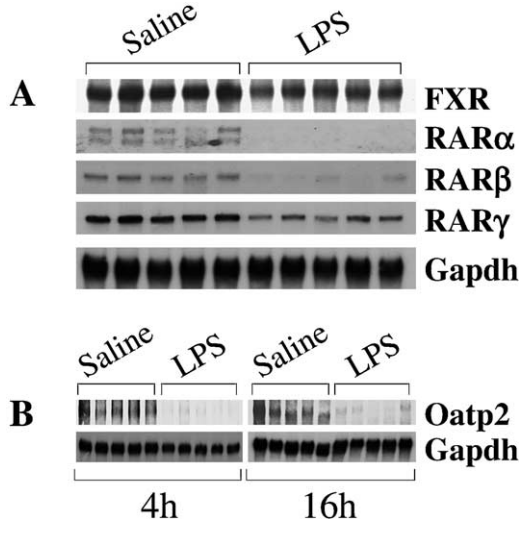

Fig. 4. Reduction in FXR, RAR, and Oatp2 mRNA levels in mouse liver following LPS treatment. Mice were injected IP with either saline or 100 μg LPS. Mice were sacrificed 4 h (A), and 4 and 16 h (B) after treatment. Poly(A) + RNA was isolated, and Northern blot analysis was performed as described under Materials and methods. A Gapdh probe was used to check for RNA integrity.

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