Published in final edited form as:

Dig Dis Sci. 2012 April ; 57(4): 918–924. doi:10.1007/s10620-012-2046-2.

Lipopolysaccharide Binding Protein is Down-regulated During Acute Liver Failure

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Abstract

Background and Aims—Lipopolysaccharide binding protein is involved in the modulation of acute liver injury and failure from acetaminophen. Although the biological activity of lipopolysaccharide binding protein is concentration dependent, little is known about its levels in acute liver failure.

Methods—Serum and hepatic lipopolysaccharide binding protein were measured in acute acetaminophen induced liver injury in mice. Serum lipopolysaccharide binding protein was measured in human acute liver failure patients with acetaminophen and non-acetaminophen causes.

Results—Interestingly, contrary to other diseases, serum and hepatic lipopolysaccharide binding protein levels decreased significantly in mice within 24 hours after acetaminophen induced injury compared to control. (1.6 ± 0.1 vs. 3.5 ± 1.6 ug/ml, acetaminophen vs. control, $p < 0.05$). Similar decreases were noted in another mouse model of acute liver injury due to carbon tetrachloride. Amongst patients with acute liver failure due to acetaminophen ($n=5$) and non-acetaminophen ($n=5$), admission lipopolysaccharide binding protein levels were decreased compared to those of healthy controls (5.4 ± 1.4 vs. 3.2 ± 0.2 ug/ml, normal vs. acute liver failure, $p = 0.07$) However, the levels were not associated with the etiology of acute liver failure or 3 week outcome.

Conclusions—Serum and hepatic lipopolysaccharide binding protein levels are significantly reduced early after induction of severe acute liver injury/failure due to acetaminophen and other liver injuries. This reduction in LBP production is specific to acute liver failure and may be important in developing future diagnostic and therapeutic approaches for patients with acute liver failure.

INTRODUCTION

Lipopolysaccharide binding protein (LBP) is an acute phase protein which plays an important role in lipopolysaccharide (LPS) signaling and innate immunity (1–3). A 60 kDa type I acute phase protein, LBP is produced predominantly by hepatocytes (4, 5). It is constitutively expressed and present in the serum at concentrations reported at 4–10 ug/ml using immunoassays but can increase 3 to 10 fold after an acute phase response (6). LBP binds with a high specificity and affinity ($K_d \approx 10^{-9}$) to the lipid A portion of bacterial lipopolysaccharides (7) to facilitate the transfer of LPS to cellular receptors such as CD14.

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Conflict of Interest: None

Early studies of LBP focused on its ability to augment LPS reactivity in monocytes (8) and Kupffer cells (9). In the presence of LBP, 1/100th to 1/1000th the concentration of LPS is needed to activate immune cells consistent with the amount of LPS needed to cause immune activation *in vivo*. Therefore, LBP acts as an immune system sensitizer to help detect and react to LPS and Gram negative bacteria.

The ability of LBP to act as a sentinel for LPS detection is likely the mechanism by which it protects against Gram negative infections. LBP has been shown to be protective in many different animal models of Gram negative infections including *Klebsiella pneumonia* (10, 11) and *Salmonella peritonitis* (12). The increased susceptibility of LBP KO mice to bacterial challenges and the ability of LBP repletion to correct these deficiencies support an important role for LBP in innate host immunity against common enteric pathogens (13). In contrast to its protective role in bacterial infections, we found that LBP can also be detrimental in acute liver injury due to acetaminophen. Specifically, LBP KO mice were protected against a lethal challenge of acetaminophen and administration of LBP inhibitory peptides protected mice from acetaminophen induced liver injury (14, 15). The mechanism by which LBP participates in liver injury is not clear but is associated with a diminished hepatic inflammatory response. Although much emphasis has been focused on the ability of LBP to augment inflammatory response to LPS, it is clear that LBP can have either activating or inhibitory actions depending on its concentration (16). At low concentrations, LBP augments activation by LPS but at normal or high concentrations, LBP can actually inhibit LPS activation (17). The level of LBP in acute liver injury and liver failure may significantly affect the physiological derangements that are observed in acute liver failure.

LBP levels have been studied in many clinical conditions including sepsis, multiorgan failure and acute pancreatitis (18, 19). LBP levels are increased in these inflammatory states and quantitative LBP levels have been proposed as a biomarker for infectious endocarditis and as a prognostic marker for patients with sepsis. In cirrhosis, LBP levels are also increased and associated with hyperdynamic circulation (20). High LBP levels have also been found to be predictive of severe bacterial infections in cirrhotic patients with ascites (21). However, there have been limited studies of the role of LBP in animal and human models of severe acute liver injury. The aims of our study were to first measure and characterize the role of LBP in two well-described models of severe acute liver injury and failure (APAP and CCL₄). We then set out to assess the role of LBP in human liver failure by measuring serum LBP levels from prospectively identified adult patients with acetaminophen and non-acetaminophen induced acute liver failure (ALF). Contrary to our initial expectations, mouse serum LBP levels are actually decreased after acute liver injury from acetaminophen. The decrease in serum LBP levels appears to be due to a reduction in LBP expression in the liver. In humans, we also confirmed a reduction in serum LBP levels in patients with ALF of varying etiology that was not related to the grade of encephalopathy or likelihood of recovery. These observations suggest that modulation of LBP expression may be of interest as a future therapeutic target in ALF.

MATERIAL AND METHODS

Animal Models

For all the experiments, age and sex matched 8–14 week old C57Bl/6 mice were used (Jackson Laboratories, Bar Harbor, ME). For the acetaminophen (APAP) induced liver injury and failure, mice were fasted for 16 hours prior to administration of a single intraperitoneal injection of either APAP (350 mg/kg in saline) or equal volume of saline (Saline). This dose after the 16 hour fast previously shown to lead to 100% mortality in this strain of mice by 72 hours post injection (15). Mice were euthanized at either 6 or 24 hours after APAP or 6 hours after saline. For the CCL₄ induced liver injury mice were given a single

intraperitoneal injection of carbon tetrachloride (100ul/kg diluted 1:10 in mineral oil) and euthanized at 1 day, 3 days or 5 days after injection. For the acute phase response model, mice were given a single hindlimb injection of turpentine (100ul/mouse) and sacrificed after 24 hours. Control mice (CTRL) were untreated and sacrificed at 24 hours. Experiments were performed in accordance with National Institute of Health guidelines and prior approval was obtained from the University of Michigan Animal Care and Use Committee.

Human Study

The serum samples were obtained from 5 adult acetaminophen and 5 non-acetaminophen patients enrolled in the US Acute Liver Failure Study Group (ALFSG) at the University of Michigan. The ALFSG is a consortium of 23 referral centers with a research interest in ALF. The group is carrying out a prospective observational study to determine the etiology, clinical features, and outcomes of adult patients with ALF. Enrollment criteria include the presence of coagulopathy with a INR ≥ 1.5 and any level of hepatic encephalopathy within 26 weeks of illness onset in a person with no underlying liver disease. Written informed consent was obtained from the patient's next of kin since all patients had an impaired mental status by definition and the study was approved by the local Institutional Review Board. The current study population comprised 10 consecutive adult ALF patients enrolled from January 1998 to May 2001 with adequate stored serum samples. Normal serum was obtained from healthy volunteers without known liver disease or active infection.

Serum LBP Levels

Serum levels of LBP were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) for detection of mouse and human LBP per manufacturer's instructions (Cell Sciences, Canton, MA).

Real time reverse transcription polymerase chain reaction (RT-PCR)

Total Liver RNA was isolated with the TRIzol reagent per manufacturer's instructions (Invitrogen, Carlsbad, CA). Reverse transcription was performed as previously described (14). To determine the relative amount of cytokine mRNA, amplification of sample cDNA was monitored using the Smart Cycler (Cepheid, Sunnyvale, CA) and the DNA fluorescent dye SYBR Green (Molecular Probes, Eugene OR). Primers were designed using reported sequences in Genbank. Primer sequences are as follows:

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LBP    5' ACTTCAAGATCAAGGCCGTGG
        3' CACCGATGGAAGAGTCAGAGA
Actin  5' TCTACG AGGGCTATGCTC TC
        3' AAGAAGGAAGGCTGGAAAAG
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Primers were designed to span at least one intron if possible to minimize risk of genomic amplification. The specificity of the primers was verified using analysis of PCR product on ethidium bromide stained agarose gel electrophoresis as well as direct sequencing of the PCR product. All real time PCR runs included a Melting Curve analysis to assure the specificity of the product with each PCR reaction. The validity of the semi-quantitative method is confirmed by a consistent log linear correlation of $r^2 > 0.95$ between starting template RNA concentration and threshold cycle. All the values were obtained by converting the threshold cycle of the sample to relative RNA concentration based on the calibrator RNA (a random RNA sample generating a standard curve for that specific amplicon). All values are expressed as a ratio of RNA concentration of target amplicon to the RNA concentration of a housekeeping gene (actin) to equalize for RNA concentrations between samples.

Statistical analysis

Analysis was performed using Statview software (SAS Institute, Cary, NC). Unless indicated otherwise, data are expressed as the mean $\pm$ standard error. Analysis was performed using Student's *t* test and analysis of variance (ANOVA) with Fisher's PLSD post-hoc analysis when more than two variables were compared. Statistical significance was assigned at *p* values <0.05 .

RESULTS

LBP levels are decreased in a mouse model of acetaminophen induced liver injury/failure

Serum LBP levels were measured in C57/BL6 mice 6 and 24 hours after a single dose of acetaminophen (Figure 1). Our prior studies have shown that these conditions led to acute liver failure with peak liver injury by 6 hours after acetaminophen (14). Control animals were fasted in a similar fashion and received an equal volume of saline i.p (Saline) and sacrificed at 6 hours. Serum LBP levels declined significantly by 6 hours and remained low at 24 hours after APAP as compared to saline injected mice. Of note, the levels of serum LBP in the saline treated mice were similar to those of normal untreated mice (approximately 4 ug/ml which is similar to that reported with this assay for normal mice levels (6)). All mice died by day 3 after acetaminophen consistent with this being a model of acute liver failure.

In order to assess whether this unexpected decline in LBP levels during the acute phase following liver injury was unique to acetaminophen, we utilized another animal model of hepatotoxicity that employed carbon tetrachloride. In this model also, serum LBP levels were significantly lower on day 1 and 3 after CCl₄ as compared to serum from normal untreated mice (CTRL). However, by day 5 after carbon tetrachloride, levels returned back to normal (Figure 2). The control mice were not fasted in this study since for the carbon tetrachloride model, mice were not fasted prior to injections.

To assure that the assay was accurate, we measured serum levels of LBP in a classic animal model of acute phase response (22). In this model, mice are given an injection of intramuscular turpentine (remote injury) and serum was obtained 24 hours after the insult. In contrast to the decline in LBP seen with acetaminophen and carbon tetrachloride induced liver injury, serum LBP levels increased sevenfold to 28 ± 2.1 ug/ml (*n* = 4 animals), 24 hours after turpentine injection. This is the anticipated level of rise for LBP after an acute phase response.

Steady state hepatic LBP RNA levels in acetaminophen induced liver failure

To determine if the decreased LBP levels was due to a decline in hepatic production, we examined the steady state RNA levels of LBP within the liver. We found that similar to the serum levels, LBP RNA levels were significantly decreased by 6 hours after acetaminophen with recovery by 24 hours. This suggests that the decline in levels was due to decreased intrahepatic production of LBP.

LBP levels are decreased in patients with acute liver failure

To further explore the role of LBP in human liver physiology, we examined ten patients from the US Acute Liver Failure Study Group enrolled at the University of Michigan. As noted in Table 1, there were 5 APAP hepatotoxicity patients with a mean age of 37 years and 5 Non-acetaminophen ALF patients with a mean age of 31. 90% of the patients were female and 90% were Caucasian. There was no distinct relationship discernable between the patient characteristics and LBP levels. However, there was a trend towards decreased levels in patients with acute liver failure (*p* = 0.07) as compared to normal volunteers (CTRL)

without significant difference between acetaminophen and non-acetaminophen causes (Figure 4).

DISCUSSION

Unlike other disease states where LBP levels were typically elevated, we found that LBP levels were decreased in acute liver failure patients compared to healthy volunteers. The decrease in LBP was associated with a reduction in steady state intrahepatic RNA levels suggesting diminished hepatic production. In mice, similar reductions in LBP levels were also seen in another toxic model of liver injury, carbon tetrachloride. By contrast, in the acute phase model of intramuscular turpentine, LBP levels were increased more than seven fold consistent with what has been seen clinically in other inflammatory states such as infections, sepsis, acute pancreatitis and Crohn's Disease (18, 19, 23–25). In fact, there have been many special situations such as cirrhosis, renal transplantation and neonates where increased LBP may be a predictor for the presence of bacterial infection (21, 26–28).

In our study, we found that LBP trended downward in acute liver failure due to multiple causes. There was no clear difference in the levels between different causes of acute liver failure (whether acetaminophen or non acetaminophen) but the number of patients studied was limited. Our observations are in contrast to other types of chronic liver disease including biliary obstruction and cirrhosis where LBP levels have been reported to be increased (20, 29, 30).

The decrease in LBP seen in acute liver failure is surprising. Generally, fulminant hepatic failure is associated with an acute phase response. Levels of acute phase reactants such as CRP and pro-inflammatory cytokines such as IL-6 are increased in acute liver failure (31). Similar to CRP, LBP production is upregulated by IL-6 as well as other pro-inflammatory cytokines (32). In most inflammatory states such as sepsis and multiple organ dysfunction syndrome (MODS), both LBP and CRP are increased (24, 33). The clinical significance of the decrease in LBP levels is not known. However, it is important to note that the levels detected in acute liver failure (2–3 ug/ml) are sufficient for the activating properties of LBP. In fact, very low concentrations of LBP are required for the LPS activating properties in contrast to inhibitory properties. In virtually all the *in vitro* studies describing the activities of LBP, the doses of LBP utilized are about 1 to 5% of serum (1). In contrast to the low concentrations of LBP needed to facilitate LPS activation, high levels of LBP as seen in sepsis may actually be inhibitory of LPS activation (16, 34). In *ex vivo* studies, sera from patients with SIRS had inhibited LPS activation of human monocytes. Studies using LBP depletion and addition of recombinant LBP confirmed that the critical protein responsible for inhibiting LPS activation was high levels of LBP (16). Biophysical studies suggested that intercalation of LBP into the membrane may be important for LBP-mediated activation while LBP-LPS complexation in serum may lead to neutralization, providing a potential mechanism for this disparate concentration dependent role of LBP (34). The dual role of LBP was confirmed with *in vivo* studies by Lamping et al who showed that administration of high doses of LBP was protective in mouse model of sepsis (17). Similar to monocytes, the effect of LBP on LPS activation of Kupffer cells is also dose dependent (30). Furthermore, we found that the concentration of LBP determining whether LBP was activating or inhibitory depended on the responding cell. Thus, Kupffer cells which were activated required more LBP to inhibit LPS activation than a resting Kupffer cell. Activated Kupffer cells isolated from animals with biliary obstruction required significantly higher concentrations of LBP to inhibit LPS mediated activation than Sham animals (30). Thus, we speculate that in acute liver failure, the low concentrations of LBP found enhance LPS activation and thus can contribute to the overall hyper-inflammatory state typically seen in

this clinical setting. As such, restoration or supplementation of LBP in this state may be potentially therapeutic and will require further study.

Acknowledgments

Financial Support: We gratefully acknowledge the support provided by the Acute Liver Failure Study Group which was funded by NIH grant DK U-01 58369 from the National Institute of Diabetes, Digestive and Kidney Disease and the Veteran's Administration Merit Award (G.L.S.).

List of Abbreviations

LBP LPS, CD14, KO, APAP, CCL4, ALF, CTRL, ALFSG, CRP, and MODS

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Table 1

Clinical features of 10 patients with acute liver failure

Patient No.	Gender	Age	Race	Cause of ALF	Day 1 ALT (IU/ml)	Day 1 Cr (mg/dl)	Day 1 Bilirubin (mg/dl)	3-week Outcome	N-Acetyl Cysteine	Serum LBP Levels (ug/ml)
4	F	30	C	Acetaminophen	3367	1	2	Alive	Yes	2.9
5	F	45	C	Acetaminophen	1621	4.3	5.5	Deceased	Yes	3.42
6	F	36	C	Acetaminophen	2690	0.6	6.6	Alive	Yes	2.86
9	F	33	C	Acetaminophen	1830	0.8	2.3	Alive (T)	Yes	3.91
10	F	41	C	Acetaminophen	2348	2.6	3.7	Alive (T)	Yes	2.48
Mean	100% F	37	100% C	--	2371	1.9	4.0	80% Alive		3.11
1	F	40	H	Idiosyncratic drug reaction	1785	1.0	18.3	Alive (T)	Yes	3.19
2	F	33	C	Ischemia	849	3.9	10.9	Deceased	No	3.30
3	F	46	C	Hepatitis A	5267	0.6	6.4	Alive	Yes	3.90
7	M	19	C	Indeterminate	2531	1.4	24.5	Deceased	No	2.78
8	F	17	C	Wilson's Disease	23	1.2	31.4	Alive (T)	No	2.78
Mean	80% F	31	80% C	--	2091	1.6	18.3	60% Alive		3.19

T= Transplanted C= Caucasian H= Hispanic