



Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2016 March ; 12(3): 245–251. doi:10.1517/17425255.2016.1139574.

Regulation of drug-metabolizing enzymes by local and systemic liver injuries

Yan Guo^{a,b,†}, Bingfang Hu^{a,c,†}, Yang Xie^a, Timothy R. Billiar^d, Jason L. Sperry^d, Min Huang^c, and Wen Xie^a

^aCenter for Pharmacogenetics and Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA, USA

^bDepartment of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

^cInstitute of Clinical Pharmacology, Sun Yat-Sen University, Guangzhou, China

^dDepartment of Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Introduction—Drug metabolism and disposition are critical in maintaining the chemical and functional homeostasis of xenobiotics/drugs and endobiotics. The liver plays an essential role in drug metabolism and disposition due to its abundant expression of drug-metabolizing enzymes (DMEs) and transporters. There is growing evidence to suggest that many hepatic and systemic diseases can affect drug metabolism and disposition by regulating the expression and/or activity of DMEs and transporters in the liver.

Areas covered—This review focuses on the recent progress on the regulation of DMEs by local and systemic liver injuries. Liver ischemia and reperfusion (I/R) and sepsis are used as examples of local and systemic injury, respectively. The reciprocal effect of the expression and activity of DMEs on animals' sensitivity to local and systemic liver injuries is also discussed.

Expert opinion—Local and systemic liver injuries have a major effect on the expression and activity of DMEs in the liver. Understanding the disease effect on DMEs is clinically important due to the concern of disease-drug interactions. Future studies are necessary to understand the mechanism by which liver injury regulates DMEs. Human studies are also urgently needed in order to determine whether the results in animals can be replicated in human patients.

Keywords

Animal models; drug-metabolizing enzyme; ischemia and reperfusion; sepsis

Contact Wen Xie wex6@pitt.edu University of Pittsburgh, 306 Salk Pavilion, 335 Sutherland Drive, Pittsburgh, PA 15261, USA.

[†]These two authors contributed equally to the writing of this article.

Declaration of interest: The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction

Hepatic injuries can be caused by infections, microbial toxins, tissue necrosis associated with ischemia, trauma, physical or chemical injury, and immune reactions. Severe injury may lead to the release of pro-inflammatory cytokines and increased risk for the development of multiple organ dysfunction syndrome, which contributes to poor prognosis and increased morbidity and mortality.[1] Hepatic dysfunction is recognized as an important component of multiple organ dysfunction syndrome,[2] and is related to the increased risk of death in patients with sepsis and trauma.[3,4] It has also been reported that the liver is central for the post burn outcome through the regulation of metabolic responses, the hormonal system, and the biliary system.[5,6]

Facilitated by a series of drug-metabolizing enzymes (DMEs) and transporters, drug metabolism and disposition are critical in maintaining the chemical and functional homeostasis of both xenobiotics, such as clinical drugs, as well as endobiotics, such as the sex hormones and bile acids. The liver plays an essential role in drug metabolism and disposition not only because of its large size, but also due to its abundant expression of DMEs and transporters. The expression of DMEs and transporters is subjected to transcriptional regulation by inflammation and by liver-enriched xenobiotic receptors such as the pregnane X receptor (PXR), constitutive androstane receptor (CAR), and aryl hydrocarbon receptor (AhR).[7,8] Hepatic dysfunction and inflammation caused by various liver injuries can influence the expression and activities of DMEs in the liver, impacting the absorption, distribution, and metabolism of drugs and other xenobiotic substances, [9] and may alter the drug pharmacokinetics, leading to unexpected failures of drug therapies and adverse side effects.[10–12] As such, it is imperative to understand the regulation of hepatic drug metabolism by hepatic injury caused by local insults such as the liver ischemia and reperfusion (I/R), as well as by certain systemic diseases such as the inflammation-prone sepsis.

Animal models have been used to study liver injury and inflammation for more than 80 years.[13] Previous studies demonstrated that inflammation-associated models can induce alternations in drug metabolism, [14] which resulted from altered expression of hepatic DMEs, including phase I enzymes cytochrome P450s (CYPs),[15–18] phase II conjugating enzymes UDP-glucuronosyltransferases (UGTs),[19] glutathione *S*-transferases (GSTs), and sulfotransferases (SULTs).[20] It is worth emphasizing that the CYP superfamily is among the most abundant and important DMEs that play key roles in the activation and deactivation of clinical drugs.[21,22] Phase II enzymes are responsible for the conjugation of estrogens, fatty acids, cholesterol,[23] bile acids, [24] and certain aromatic carcinogens,[25] altering both the biological activities and elimination dynamics of these endogenous and exogenous chemicals. It is also noted that the evaluation of the disease effect on drug metabolism has largely relied on the animal models, while there is an imperative need to validate these effects in human patients. In this review, we will use liver I/R and sepsis as typical examples of hepatic injuries caused by local and systemic diseases and discuss the regulation of DMEs by these disease conditions.

2. Regulation of hepatic drug metabolism by liver I/R

2.1. Liver I/R injury

Hepatic I/R injury is a major cause of liver damage associated with liver resection, solid organ transplantation, cardiac and vascular surgery, multiple trauma, and hemorrhagic and septic shock. It contributes significantly to multiple organ failure.[26] The pathogenesis of hepatic I/R injury is a dynamic process including the deprivation of blood and oxygen supply during the ischemic phase, followed by their restoration during the reperfusion phase. The pathological events associated with I/R include a direct hypoxic damage as a result of ischemia, as well as a delayed and more severe oxidative damage that eventually leads to the activation of inflammatory pathways.[7] During the hypoxic phase, sublethal cellular damage leads to the release of reactive oxygen species (ROS) and damage-associated molecular pattern molecules (DAMPs) from necrotic or activated macrophages and hepatocytes. Reperfusion of the ischemic tissue is essential for survival. However, reperfusion also augments the injury by triggering the sterile inflammatory responses, causing irreversible liver damage through the generation of mitochondrial ROS.[27] Mitochondrial ROS production has been considered a nonspecific consequence of the interaction of a dysfunctional respiratory chain with oxygen during reperfusion. Recent reports by Chouchani and colleagues suggested that selective accumulation of the citric acid cycle intermediate succinate is a universal metabolic signature of ischemia in a range of tissues and is responsible for mitochondrial ROS production during reperfusion.[28,29] Meanwhile, a series of protective pathways are also activated and as such, the extent of organ damage is determined by the balance between these two systems. During I/R, two transcriptional factors, the hypoxia inducible factor-1 (HIF-1) and nuclear factor erythroid 2-related factor 2 (Nrf2), play important roles in protecting the liver from I/R injury. Stabilization and accumulation of HIF-1 or Nrf2 lead to the activation of an array of genes to adapt the cells to hypoxic or oxidative damages, and thus affect numerous cellular functions, such as cell apoptosis, proliferation, survival, metabolism, and angiogenesis.[7,30]

2.2. Regulation of drug metabolism by liver I/R injury

2.2.1. Regulation of Phase I CYP enzymes by liver I/R—Accumulating evidence demonstrated that liver I/R can effectively alter DME levels, and enzymes such as the CYPs can in turn mediate ROS production,[31] which is a key factor in I/R-induced tissue changes. Using DNA microarray, Takahashi and colleagues [32] examined the hepatic expression of 50 CYP genes in Wistar-Kyoto rats that have been subjected to 15 min of ischemia and different periods of reperfusion. The authors showed a significant downregulation of eight CYP genes at 16 h after reperfusion, including CYP2C23, 2D3, 2J3, 3A18, 4A1, 4A10, and 4F4/27. Moreover, the mRNA reduction of these genes showed excellent correlation with the reperfusion time. In contrast, the mRNA expression of CYP2C12, 7B1, and CYP51 was induced after 16 h of reperfusion. In an independent study, Eum and Lee showed that a prolonged ischemia time (60 min) resulted in a different profile of CYP regulation in the rat liver.[33] After 24 h of reperfusion, the expression and/or activity of CYP1A1 and 1A2 were decreased. However, after 5 h of reperfusion, the expression of CYP2B1 and CYP2E1 was decreased and increased, respectively. In a third rat study, it was shown that the enzymatic

activities of CYP1A2, CYP2C9, CYP2E1, CYP2D6, and CYP3A4 were decreased upon liver I/R.[34]

2.2.2. Regulation of Phase II estrogen SULT (EST or SULT1E1) by liver I/R—

Liver I/R also affects the expression of Phase II enzymes, such as the SULTs. Svetlov and colleagues reported that liver I/R influenced the expression of EST/SULT1E1 in rats. [35] After 30 min of total hepatic ischemia and 3 h of reperfusion, EST appeared in blood and climbed to top within 1 h followed by a decline at 3 h of reperfusion. More recently, we reported a systemic analysis of the effect of liver I/R on the expression of EST. We showed that the expression of EST was markedly induced by I/R in both male and female mice in a time-dependent manner.[36] Mechanistically, oxidative stress-induced activation of Nrf2 was responsible for EST induction, which was abolished in the Nrf2^{-/-} mice. We identified two Nrf2 binding sites, the antioxidant response element (ARE), in the mouse EST gene promoter and established EST as a direct transcriptional target of Nrf2. The primary function of EST is to sulfonate and deactivate estrogens, because sulfonated estrogens cannot bind to and activate the estrogen receptor (ER), thus losing their hormonal activities.[37] Consistent with the estrogen-deactivating activity of EST, the I/R-responsive induction of EST compromised estrogen activity. We went on to show that EST ablation attenuated I/R injury in female mice as a result of decreased estrogen deprivation, whereas this benefit was abolished upon ovariectomy. Surprisingly, the effect of EST ablation was sex-specific, because the EST^{-/-} males showed heightened I/R injury. The detailed mechanism for the sex-specificity of EST ablation remains to be understood. Reciprocally, both estrogens and EST regulate the expression and activity of Nrf2. Estrogen deprivation by ovariectomy abolished the I/R-responsive Nrf2 accumulation, whereas the compromised estrogen deprivation in EST^{-/-} mice was associated with an increased Nrf2 accumulation. Our results suggested a novel I/R-responsive feedback mechanism to limit the activity of Nrf2, in which Nrf2 induces the expression of EST, which subsequently increases estrogen deactivation and limits the estrogen-responsive activation of Nrf2. Based on these results, we proposed that inhibition of EST, at least in females, may represent an effective approach to manage hepatic I/R injury.[36]

2.2.3. Regulation of hepatobiliary transporters by liver I/R—

A body of animal studies showed that liver ischemia might have contributed to hepatobiliary dysfunction. However, the mechanisms that account for cholestasis induced by liver ischemia are not well understood. [38,39] Iwashyna and colleagues reported that cholestasis was induced by acute liver ischemia.[40] Fouassier and colleagues examined the expression of hepatobiliary transporter genes, such as the Na⁺-transporting polypeptide (NTCP, also called Slc10a1), the bile salt export pump (BSEP), and the multidrug resistance-associated protein MRP2 (also called ABCC2), which are important for bile formation in the liver of rats 24 h after arterial deprivation. Their results showed that the mRNA levels of Ntcp, Bsep, and Mrp2 were markedly decreased upon liver ischemia when compared to the sham controls.[41]

3. Regulation of hepatic drug metabolism by sepsis

3.1. Sepsis and animal models of sepsis

Sepsis is the host's deleterious systemic inflammatory response to microbial infections. Despite the improvement of management and therapeutic advances, multiple organ dysfunction syndrome, sepsis, and septic shock are still the most common cause of morbidity and mortality in intensive care units.[42] Hepatic failure, including hyperbilirubinemia, hypoglycemia, encephalopathy, and coagulopathy, is typically considered to be a late complication of sepsis. Bacterial lipopolysaccharide (LPS) treatment and cecal ligation and puncture (CLP) are two widely used animal models of sepsis. LPS, or endotoxin, is a typical pattern recognition molecule and a model compound to trigger inflammatory response.[43] LPS is known to elicit its inflammatory actions through the toll-like receptor 4 (TLR4), a member of the pattern recognition receptor family, which mediates innate and adaptive immune response.[44] LPS infusion/injection model has been long recognized as an effective animal model in establishing infection-induced inflammation and chronic inflammation [45,46] and has been widely used for sepsis studies. LPS administration can activate Kupffer cells to generate immune pro-inflammatory cytokines (such as interleukin-1 β , interleukin-6, and tumor necrosis factor- α) as well as ROS and activate pro-inflammatory transcriptional factors such as NF- κ B, and finally elicit strong immune responses.[47] Mitochondrial respiration can be impaired by an exaggerated inflammatory response through impaired perfusion early in the septic process and by generation of excess amounts of nitric monoxide, carbon monoxide, hydrogen sulfide, and other ROS. Reciprocally, a hormone alteration may impact mitochondrial activity.[48] In the CLP model, sepsis originates from a polymicrobial infection within the abdominal cavity, followed by bacterial translocation into the blood, which then triggers a system inflammatory response.[49] CLP was considered as a reliable polymicrobial sepsis model to mimic various features of clinical sepsis-peritonitis.[50] It has been reported that TLR4 contributes to bacterial clearance and host inflammatory response in the setting of Gram-negative bacterial infection.[51,52]

3.2. Regulation of hepatobiliary transporters by sepsis

In the past 20 years, a body of studies have shown that hepatic dysfunction in sepsis is characterized by hyperbilirubinemia and intrahepatic cholestasis. In clinical studies, cholestatic jaundice associated with bacteremia can occur from 1 to 9 days before the initial positive blood culture in more than a third of the patients.[53] In a rat model of sepsis induced by CLP, it was reported that the hepatic mRNA expression of Ntcp and Mrp2 decreased rapidly upon CLP.[54]

3.3. Regulation of drug metabolism by LPS

LPS has been shown to suppress the expression of many CYPs *in vitro* and *in vivo*. Among the *in vivo* examples, Khatsenko and colleagues reported that treatment of rats with LPS inhibited the hepatic expression and activity of CYP2C11, 3A2, 1A2, and 2B1/2.[55] In an independent study, Yang and Lee showed that LPS affected the expression of CYPs in an isoform-dependent manner in rat livers.[56] Specifically, the expression of CYP1A1, 1A2, 2C6, 2C7, 2C11, 2C12, 2E1, 3A1/23, 3A2, and 4A1/2 was time-dependently reduced after

LPS injection. In contrast, the expression of CYP4A1, 4A2, and 4A3 was induced after 24 h of LPS challenge. In mice, treatment with LPS suppressed the phenobarbital-induced induction of CYP2B10 and CYP2B9 at both mRNA and protein levels.[45]

The expression of CYPs is under the transcriptional control of xenobiotic receptors, such as PXR, CAR, and AhR. LPS has been shown to suppress the xenobiotic receptor-responsive regulation of CYPs. For example, Moriya and colleagues showed that pretreatment of mice with LPS attenuated the PCN (a PXR agonist)-, TCPOBOP (a CAR agonist)- and B(a)P (an AhR agonist)-induced expression and activity of Cyp3a11, 2c29, 2c55, and 1a2.[57]

LPS administration in pregnant mice has been used to investigate its impact on CYPs in the fetal liver.[58] LPS exposure increased the TNF α protein level in the fetal liver, leading to the downregulation of Cyp3a11 mRNA and protein levels. Interestingly, in the same study, it was reported that a low dose of LPS pretreatment alleviated the LPS-induced increase in TNF α and downregulation of PXR in the fetal liver, which protected fetuses from the LPS-induced decrease of hepatic Cyp3a11 gene expression.[58]

LPS also has a major effect on the expression of the phase II enzymes. The hepatic expression of UGT1A1 (38% of control), 1A9 (25% of control), and 2B5 (46% of control) was significantly decreased in mice treated with LPS, compared to their vehicle-treated counterparts, whereas the expression of UGT1A2 and 1A6 mRNA was not affected. The protein levels of UGT1A and 2B were also reduced to 50–60% of the control, following their mRNA trends.[19] In rats, treatment with LPS can dramatically downregulate the metabolic ability of UGT1A6 and 2B3 to 70–80% of the control.[59] The LPS-induced acute phase response was also shown to decrease the expression and activity of the hydroxysteroid SULT (Sult2a1) in a dose- and time-dependent manner.[20]

Interestingly, the effect of LPS on the expression of SULTs appears to be isoform-specific. A recent report from our group showed that the hepatic expression of EST/SULT1E1 was markedly induced by LPS in a liver-specific manner. Treatment of 4-week-old intact virgin female mice with LPS resulted in a significantly reduced circulating estradiol level while increasing the urinary output of estrogen sulfate as a result of increased EST expression. We also showed that Kupffer cells were required for the optimal induction of EST. Treatment of Kupffer cells with LPS induced the expression of EST, while *in vivo* depletion of Kupffer cells by treating mice with gadolinium chloride attenuated the LPS-responsive induction of EST. In understanding the mechanism by which LPS induces EST, a putative NF- κ B-binding site was bioinformatically predicted in the mouse EST gene promoter, and its binding to p65, a major subunit of NF- κ B, was confirmed by electrophoretic mobility shift assay (EMSA). Luciferase reporter gene assay in HepG2 cells and chromatin immunoprecipitation (ChIP) assay on the liver of LPS-treated mice also demonstrated that EST is a transcriptional target of NF- κ B.[60]

3.4. Regulation of drug metabolism by CLP

CLP is a typical and faithful model of sepsis. It has become clear that in addition to its effect in inducing inflammation and multiple organ failures, CLP also has major effects on the expression and activity of DMEs, which in turn may affect the pharmacokinetics of drugs.

[61] A study using the Sprague Dawley rat CLP model showed a decrease of total CYP content in the liver 24 h after surgery. The expression and activity of CYP1A1 and CYP1A2 were found to be reduced in the same group of mice.[61] These results were confirmed in a study by Kim and colleagues, in which the authors also demonstrated the role of Kupffer cells in CLP-induced downregulation of CYPs.[62] Besides CYP1A, the expression and activity of CYP2E1 mRNA were also suppressed by CLP.[63,64] There were limited reports on the effect of CLP on the expression of Phase II conjugating enzymes. Recently, we reported that, similar to the LPS model of sepsis, CLP also induced the expression of EST and compromised the activity of estrogen. Interestingly and surprisingly, EST ablation markedly sensitized both female and male mice to CLP-induced death. These results indicated a crucial role of EST in the yet-to-be-explored mechanism of endocrine regulation of inflammation, which has an impact on the clinical outcome of sepsis.[60]

4. Conclusions and perspectives

As discussed above, both liver I/R and sepsis have a major effect on the expression and activity of DMEs in the liver. It appears that the regulation can be enzyme specific. Changes in key DMEs during injury and inflammation are highly relevant to the care and treatment of critically ill patients. Seriously injured trauma patients or patients of sepsis are uniformly prescribed multiple medications. The regulation of DMEs by I/R and sepsis has a potential to affect the absorption and disposition of drugs (pharmacokinetics or PK) as well as their efficacy and safety (pharmacodynamics or PD). For future studies, it remains to be seen whether the disease regulation of DMEs is conserved in rodents and humans. The mechanisms for the I/R- and sepsis-responsive regulation of DMEs remain to be better defined. Finally, having shown that I/R and sepsis can regulate DMEs, it is interesting to know whether the expression and activity of DMEs can in return alter the clinical outcome of these disease conditions.

5. Expert opinion

Hepatic injuries result from various pathological factors, including infections, microbial toxins, tissue necrosis associated with ischemia, trauma physical or chemical injury, and immune reactions.

Accumulating clinical and preclinical studies show that the expression and/or activity of DMEs and transporters can be markedly influenced by hepatic dysfunction and inflammation. The key findings of these studies are that diseases or disease conditions, such as liver I/R and sepsis, can have a major effect on the expression and activity of DMEs in the liver. Despite the progress, it has been recognized that more studies in this area are warranted. Among the weaknesses of existing studies, it is unclear whether the disease-responsive regulation of DMEs can affect the PK and PD behavior of clinical drugs *in vivo* in animal models or in human patients. In addition, the mechanisms for the I/R- and sepsis-responsive regulation of DMEs remain to be better defined.

Understanding the disease effect on DMEs and transporters is of great clinical significance. Among the outstanding questions, will the disease status affect the absorption, distribution,

metabolism and elimination of clinically used drugs? Will the disease status influence the effectiveness and toxicity of drugs? Will the disease status alter the behavior of drug–drug interactions, especially for drugs with narrow therapeutic windows? Answers to these questions are expected to contribute to the establishment of specific therapeutic strategies for certain disease populations. The ultimate goal for this field of study is to improve the clinical outcome of hepatic injury associated with various systemic or local diseases. Although the current studies have been focusing on the phenotypic characterization and preliminary mechanistic studies, they still hold the potential to translate the findings in DME regulation by systemic or local diseases from bench to the bedside.

Since most of the previous work has been descriptive, and the evaluation of the drug metabolism has largely relied on *in vitro* assays, future directions are to use genetic and pharmacological models to understand the mechanisms by which I/R and sepsis regulate DMEs. The effect of diseases on PK has to be validated *in vivo* in animal models or in human patients. Mouse models are invaluable in dissecting the genetic mechanisms by which diseases affect drug metabolism because of the availability of transgenic and gene knockout mice. However, mice also represent a challenging model for PK study due to their rapid rate of drug metabolism, which makes it hard to extrapolate the mouse results to humans, as well as their small body size and blood volume. As such, human studies are urgently needed in order to determine whether the animal results will be recapitulated in human patients.

Acknowledgments

The authors were supported in part by the National Institute of Health (NIH grant ES023438).

References

Papers of special note have been highlighted as either “of interest” (•) or “of considerable interest” (••) to readers.

1. Sauaia A, Moore FA, Moore EE, et al. Early predictors of postinjury multiple organ failure. *Arch Surg.* 1994; 129:39–45. [PubMed: 8279939]
2. Fry DE, Pearlstein L, Fulton RL, et al. Multiple system organ failure. The role of uncontrolled infection. *Arch Surg.* 1980; 115:136–140. [PubMed: 6965449]
3. Hebert PC, Drummond AJ, Singer J, et al. A simple multiple system organ failure scoring system predicts mortality of patients who have sepsis syndrome. *Chest.* 1993; 104:230–235. [PubMed: 8325076]
4. Harbrecht BG, Doyle HR, Clancy KD, et al. The impact of liver dysfunction on outcome in patients with multiple injuries. *Am Surg.* 2001; 67:122–126. [PubMed: 11243533]
5. Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med.* 2009; 15:337–351. [PubMed: 19603107]
6. Zheng H, Chen XL, Han ZX, et al. Effect of ligustrazine on liver injury after burn trauma. *Burns.* 2006; 32:328–334. [PubMed: 16529867]
- 7•. Zhai Y, Busuttill RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant.* 2011; 11:1563–1569. This is a comprehensive review on the effects of liver ischemia and reperfusion injury on the expression of drug metabolism enzymes and transporters. [PubMed: 21668640]

8. Timsit YE, Negishi M. CAR and PXR: the xenobiotic-sensing receptors. *Steroids*. 2007; 72:231–246. This is a comprehensive review on the regulation of drug metabolism enzymes by nuclear receptors CAR and PXR. [PubMed: 17284330]
9. Rieger JK, Reutter S, Hofmann U, et al. Inflammation-associated microRNA-130b downregulates cytochrome P450 activities and directly targets CYP2C9. *Drug Metab Dispos*. 2015; 43:884–888. [PubMed: 25802328]
10. Sewer MB, Morgan ET. Nitric oxide-independent suppression of P450 2C11 expression by interleukin-1beta and endotoxin in primary rat hepatocytes. *Biochem Pharmacol*. 1997; 54:729–737. [PubMed: 9310350]
11. Siewert E, Bort R, Kluge R, et al. Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. *Hepatology*. 2000; 32:49–55. [PubMed: 10869288]
12. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007; 56:1761–1772. [PubMed: 17456850]
13. Webb DR. Animal models of human disease: inflammation. *Biochem Pharmacol*. 2014; 87:121–130. [PubMed: 23811309]
14. Sewer MB, Koop DR, Morgan ET. Endotoxemia in rats is associated with induction of the P4504A subfamily and suppression of several other forms of cytochrome P450. *Drug Metab Dispos*. 1996; 24:401–407. [PubMed: 8801054]
15. Abdel-Razzak Z, Loyer P, Fautrel A, et al. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. *Mol Pharmacol*. 1993; 44:707–715. [PubMed: 8232220]
16. Barclay TB, Peters JM, Sewer MB, et al. Modulation of cytochrome P-450 gene expression in endotoxemic mice is tissue specific and peroxisome proliferator-activated receptor-alpha dependent. *J Pharmacol Exp Ther*. 1999; 290:1250–1257. [PubMed: 10454501]
17. Morgan ET, Thomas KB, Swanson R, et al. Selective suppression of cytochrome P-450 gene expression by interleukins 1 and 6 in rat liver. *Biochim Biophys Acta*. 1994; 1219:475–483. [PubMed: 7918645]
18. Waxman DJ. P450 gene induction by structurally diverse xenochemicals: central role of nuclear receptors CAR, PXR, and PPAR. *Arch Biochem Biophys*. 1999; 369:11–23. [PubMed: 10462436]
19. Richardson TA, Sherman M, Kalman D, et al. Expression of UDP-glucuronosyltransferase isoform mRNAs during inflammation and infection in mouse liver and kidney. *Drug Metab Dispos*. 2006; 34:351–353. [PubMed: 16339353]
20. Kim MS, Shigenaga J, Moser A, et al. Suppression of DHEA sulfotransferase (Sult2A1) during the acute-phase response. *Am J Physiol Endocrinol Metab*. 2004; 287:E731–E738. [PubMed: 15198932]
21. Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol*. 2001; 52:349–355. [PubMed: 11678778]
22. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. *Drug Metab Rev*. 1997; 29:413–580. [PubMed: 9187528]
23. Javitt NB, Lee YC, Shimizu C, et al. Cholesterol and hydroxycholesterol sulfotransferases: identification, distinction from dehydroepiandrosterone sulfotransferase, and differential tissue expression. *Endocrinology*. 2001; 142:2978–2984. [PubMed: 11416019]
24. Radomska A, Comer KA, Zimniak P, et al. Human liver steroid sulphotransferase sulphates bile acids. *Biochem J*. 1990; 272:597–604. [PubMed: 2268288]
25. Otterness DM, Wieben ED, Wood TC, et al. Human liver dehydroepiandrosterone sulfotransferase: molecular cloning and expression of cDNA. *Mol Pharmacol*. 1992; 41:865–872. [PubMed: 1588921]
26. Verweij M, Van Ginhoven TM, Mitchell JR, et al. Preoperative fasting protects mice against hepatic ischemia/reperfusion injury: mechanisms and effects on liver regeneration. *Liver Transpl*. 2011; 17:695–704. [PubMed: 21618690]

27. Klune JR, Tsung A. Molecular biology of liver ischemia/reperfusion injury: established mechanisms and recent advancements. *Surg Clin North Am.* 2010; 90:665–677. [PubMed: 20637940]
28. Chouchani ET, Pell VR, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature.* 2014; 515:431–435. [PubMed: 25383517]
29. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. *Nat Med.* 2011; 17:1391–1401. [PubMed: 22064429]
30. Dery MA, Michaud MD, Richard DE. Hypoxia-inducible factor 1: regulation by hypoxic and non-hypoxic activators. *Int J Biochem Cell Biol.* 2005; 37:535–540. [PubMed: 15618010]
31. Gottlieb RA. Cytochrome P450: major player in reperfusion injury. *Arch Biochem Biophys.* 2003; 420:262–267. [PubMed: 14654065]
32. Takahashi Y, Nishida Y, Ishii Y, et al. Monitoring expression of cytochrome P450 genes during postischemic rat liver reperfusion using DNA microarrays. *J Pharmacol Sci.* 2005; 97:153–156. [PubMed: 15655285]
33. Eum HA, Lee SM. Effects of Trolox on the activity and gene expression of cytochrome P450 in hepatic ischemia/reperfusion. *Br J Pharmacol.* 2004; 142:35–42. [PubMed: 15051625]
34. Li Q, Liu Y, Jiao J, et al. Assessment of effects of IR and IPC on activities of cytochrome P450 isozymes in rats by a five-drug cocktail approach. *Drug Dev Ind Pharm.* 2014; 40:157–162. [PubMed: 23339682]
35. Svetlov SI, Xiang Y, Oli MW, et al. Identification and preliminary validation of novel biomarkers of acute hepatic ischaemia/reperfusion injury using dual-platform proteomic/degradomic approaches. *Biomarkers.* 2006; 11:355–369. [PubMed: 16908442]
- 36•• Guo Y, Hu B, Huang H, et al. Estrogen sulfotransferase is an oxidative stress responsive gene that gender-specifically affects liver ischemia/reperfusion injury. *J Biol Chem.* 2015; 290:14754–14764. This is the first report on the regulation of sulfotransferases by liver ischemia and reperfusion injury. [PubMed: 25922074]
37. Song WC. Biochemistry and reproductive endocrinology of estrogen sulfotransferase. *Ann N Y Acad Sci.* 2001; 948:43–50. [PubMed: 11795394]
38. Schmittinger CA, Dunser MW, Torgersen C, et al. Histologic pathologies of the myocardium in septic shock: a prospective observational study. *Shock.* 2013; 39:329–335. [PubMed: 23376953]
39. Boekstegers P, Weidenhofer S, Pilz G, et al. Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. *Infection.* 1991; 19:317–323. [PubMed: 1800370]
40. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA.* 2010; 304:1787–1794. [PubMed: 20978258]
41. Fouassier L, Beaussier M, Schiffer E, et al. Hypoxia-induced changes in the expression of rat hepatobiliary transporter genes. *Am J Physiol Gastrointest Liver Physiol.* 2007; 293:G25–G35. [PubMed: 17615179]
42. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock.* 1998; 10:79–89. [PubMed: 9721973]
43. Ulevitch RJ, Tobias PS. Receptor-dependent mechanisms of cell stimulation by bacterial endotoxin. *Annu Rev Immunol.* 1995; 13:437–457. [PubMed: 7542010]
44. Poltorak A, He X, Smirnova I, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science.* 1998; 282:2085–2088. [PubMed: 9851930]
45. Li-Masters T, Morgan ET. Effects of bacterial lipopolysaccharide on phenobarbital-induced CYP2B expression in mice. *Drug Metab Dispos.* 2001; 29:252–257. [PubMed: 11181491]
46. Yu SC, Li XY. Effect of ginsenoside on IL-1 beta and IL-6 mRNA expression in hippocampal neurons in chronic inflammation model of aged rats. *Acta Pharmacol Sin.* 2000; 21:915–918. [PubMed: 11501043]
47. Rietschel ET, Kirikae T, Schade FU, et al. Bacterial endotoxin: molecular relationships of structure to activity and function. *Faseb J.* 1994; 8:217–225. [PubMed: 8119492]
48. Singer M. The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence.* 2014; 5:66–72. [PubMed: 24185508]

49. Rittirsch D, Huber-Lang MS, Flierl MA, et al. Immunodesign of experimental sepsis by cecal ligation and puncture. *Nat Protoc.* 2009; 4:31–36. [PubMed: 19131954]
50. Wang P, Chaudry IH. A single hit model of polymicrobial sepsis: cecal ligation and puncture. *Sepsis.* 1998; 2:227–233. This is the first report of single hit model of polymicrobial sepsis by cecal ligation and puncture.
51. Tsai TH, Chen SF, Huang TY, et al. Impaired Cd14 and Cd36 expression, bacterial clearance, and toll-like receptor 4-Myd88 signaling in caveolin-1-deleted macrophages and mice. *Shock.* 2011; 35:92–99. [PubMed: 20601931]
52. Cai S, Batra S, Shen L, et al. Both TRIF- and MyD88-dependent signaling contribute to host defense against pulmonary *Klebsiella* infection. *J Immunol.* 2009; 183:6629–6638. [PubMed: 19846873]
53. Franson TR, Hierholzer WJ Jr, LaBrecque DR. Frequency and characteristics of hyperbilirubinemia associated with bacteremia. *Rev Infect Dis.* 1985; 7:1–9. [PubMed: 3983523]
54. Kim PK, Chen J, Andrejko KM, et al. Intraabdominal sepsis down-regulates transcription of sodium taurocholate cotransporter and multidrug resistance-associated protein in rats. *Shock.* 2000; 14:176–181. [PubMed: 10947163]
55. Khatsenko O, Kikkawa Y. Nitric oxide differentially affects constitutive cytochrome P450 isoforms in rat liver. *J Pharmacol Exp Ther.* 1997; 280:1463–1470. [PubMed: 9067336]
56. Yang KH, Lee MG. Effects of endotoxin derived from *Escherichia coli* lipopolysaccharide on the pharmacokinetics of drugs. *Arch Pharm Res.* 2008; 31:1073–1086. [PubMed: 18806948]
57. Moriya N, Kataoka H, Fujino H, et al. Effect of lipopolysaccharide on the xenobiotic-induced expression and activity of hepatic cytochrome P450 in mice. *Biol Pharm Bull.* 2012; 35:473–480. [PubMed: 22466549]
58. Li XY, Zhang C, Wang H, et al. Tumor necrosis factor alpha partially contributes to lipopolysaccharide-induced downregulation of CYP3A in fetal liver: its repression by a low dose LPS pretreatment. *Toxicol Lett.* 2008; 179:71–77. [PubMed: 18501536]
59. Chen YL, Florentin I, Batt AM, et al. Effects of interleukin-6 on cytochrome P450-dependent mixed-function oxidases in the rat. *Biochem Pharmacol.* 1992; 44:137–148. [PubMed: 1632828]
60. Chai X, Guo Y, Jiang M, et al. Oestrogen sulfotransferase ablation sensitizes mice to sepsis. *Nat Commun.* 2015; 6:7979. This is the first report on the regulation of sulfotransferases by sepsis. [PubMed: 26259151]
61. Lee SH, Lee SM. Suppression of hepatic cytochrome p450-mediated drug metabolism during the late stage of sepsis in rats. *Shock.* 2005; 23:144–149. [PubMed: 15665729]
62. Kim TH, Lee SH, Lee SM. Role of Kupffer cells in pathogenesis of sepsis-induced drug metabolizing dysfunction. *Febs J.* 2011; 278:2307–2317. [PubMed: 21535472]
63. Eum HA, Yeom DH, Lee SM. Role of nitric oxide in the inhibition of liver cytochrome P450 during sepsis. *Nitric Oxide.* 2006; 15:423–431. [PubMed: 16884934]
64. Kim JY, Lee SM. Vitamins C and E protect hepatic cytochrome P450 dysfunction induced by polymicrobial sepsis. *Eur J Pharmacol.* 2006; 534:202–209. [PubMed: 16483564]

Article highlights

- Liver is an essential organ for drug metabolism and disposition.
- Drug metabolism and disposition are facilitated by drug-metabolizing enzymes (DMEs) and transporters, which are highly enriched in the liver.
- Hepatic and systemic diseases can potentially affect drug metabolism and disposition by regulating the expression and/or activity of DMEs and transporters in the liver.
- Understanding the disease effect on DMEs is clinically important, because the changes in the expression and activity of DMEs may affect the pharmacokinetics and pharmacodynamics of clinical drugs.