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Review Article

The role of hepatic cytochrome P-450 in sepsis

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Abstract: Severe sepsis is a common, expensive, and fatal condition with as many deaths annually as those from acute myocardial infarctions. The average cost per case seems to exceed $22,000. The increased morbidity and mortality attributed to sepsis could be due to the lack of our understanding of mediators and factors responsible for early cellular alterations and thus could not be intervened which result in progressive deterioration of cell and organ function and even death. It has been well documented that hepatocellular dysfunction occurs early in sepsis and it contributes to multiple organ failure and ultimately death; however the exact mechanism is poorly understood. We and others have shown that cytochrome P-450 (CYP) enzyme system, a superfamily of heme proteins responsible for the metabolism of a variety of endogenous and exogenous substances, plays a crucial role in the prevention of hepatocellular dysfunction in sepsis. In this review, we describe the alterations of CYP enzymes in the experimental model of sepsis and provide the limited information available in septic and severely injured patients. We also review the potential mechanism for the alterations of CYP enzymes in sepsis. Finally, we highlight the importance of future studies needed to understand the regulation of CYP isoforms to develop therapy for hepatocellular dysfunction in sepsis.

Key words: Cytochrome P-450, CYP enzymes, hepatic dysfunction, liver, sepsis

Introduction

The CYP enzyme system is a superfamily of heme proteins responsible for the metabolism of a vast array of endogenous and exogenous substances. To date, seventeen mammalian CYP gene families have been identified [1]. Within the CYP families, CYP isoforms 1-3 metabolize more than 90% of known drugs [2]. The CYP enzymes are generally found in the hepatocyte endoplasmic reticulum and microsomes while they exist in varying amounts in most extra-hepatic tissues. Environmental factors, foods, social habits and disease conditions are all known to alter CYP enzymes [3]. We [4-6] and others [7] have shown that CYP isoforms are significantly downregulated in sepsis and this decrease is due to the reduction of AhR and Arnt, two critical transcription factors involved in the regulation of CYP1A2 mRNA. Interestingly, our studies further showed that AhR and Arnt expressions were inversely correlated with pro-inflammatory cytokines in sepsis and that exposure of cells with such cytokines downregulated these transcription factors.

Liver dysfunction in sepsis

Sepsis and the ensuing septic shock and multiple organ failure continue to be the most common causes of death in surgical intensive care units [8-12]. Despite advances in the management of trauma victims, the incidence of sepsis and septic shock has increased significantly over the past two decades [11, 13-15]. It has been estimated that in the United States alone more than 750,000 patients develop sepsis and septic shock each year with an overall mortality of 28.6% [16]. Severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction. The average costs per case were $22,100, with annual total costs of more than $16 billion nationally [16]. The increased morbidity and mortality attributed to sepsis could be due to the fact that the mediators or

factors responsible for early cellular alterations are not fully understood and consequently not prevented, leading to a progressive deterioration of cell and organ function and even death.

A number of animal models such as bacteremia, endotoxemia, and endotoxic shock have been used to study the pathobiology of sepsis and such models have provided valuable information regarding the mechanisms responsible for cell and organ dysfunction under those conditions [17-23]. Other investigators have utilized the model of cecal ligation and puncture (CLP) to produce polymicrobial sepsis [18, 19, 24-32]. The model of CLP mimics many features of clinical sepsis-peritonitis. This model of sepsis is associated with an early, hyperdynamic phase (i.e., 2-10 h after CLP; characterized by increased cardiac output and tissue perfusion, decreased vascular resistance, hyperglycemia and hyperinsulinemia), which is followed by a late, hypodynamic phase (16 h after CLP and later; characterized by reduced cardiac output and tissue perfusion, increased vascular resistance, hypoglycemia and hypo-insulinemia) [30, 33-36]. By using the CLP model of sepsis in the rat, we have shown that hepatocellular dysfunction (as assessed by indocyanine green clearance) occurred early after sepsis despite hyperdynamic circulation including hepatic hyperperfusion [34, 37-40].

Kupffer cells (KCs) play an important role in producing pro-inflammatory cytokines such as TNF-α and IL-1β in sepsis [41, 42]. Administration of recombinant TNF-α in normal animals depressed hepatocellular function [43]. The exact mechanism of hepatocellular dysfunction during early sepsis is poorly understood. We and others have shown that cytochrome P450 (CYP) enzyme system, a superfamily of heme proteins responsible for the metabolism of a variety of endogenous and exogenous substances are significantly altered in sepsis [4-7].

Cytochrome P-450 (CYP) superfamily

The CYP enzyme system is a superfamily of heme proteins responsible for the metabolism of a vast array of endogenous and exogenous substances (xenobiotics) [44-47]. Seventeen mammalian CYP gene families have been identified, encoding approximately 60 distinct CYP isoforms [1]. CYP structure has been deduced and residues required for substrate binding, electron transfer, and heme binding have been identified [48, 49]. Within CYP families, CYP isoforms 1-4 play important roles in metabolizing a variety of xenobiotics [50] and endogenous compounds including steroids, bile acids, fatty acids, eicosanoids and retinoids [51-53]. Nearly all CYPs are designated with the root "CYP" followed by an Arabic numeral for the gene family (i.e. CYP2), a capital letter for subfamily (i.e. CYP2D) and another Arabic number for a certain gene (i.e. CYP2D6). The enzymes in the same family share almost 40% amino acid identity while the members of the subfamily shares almost 55% identity. CYP 1, 2, 3 families are the most important ones because CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 metabolize more than 90% of known drugs [2]. CYP3A4 is a major member of the P450 superfamily that metabolizes much more substrates than any other CYP enzymes including a number of clinically important drugs [54].

The highest concentrations of CYP isoforms are found in hepatocyte endoplasmic reticulum and microsomes, although CYP isoforms exist in varying amounts in most extra-hepatic tissues. The CYP3A family is most abundant in human liver [55] whereas, CYP1A2 is the predominant isoform in the rat liver [56]. CYP1A2 is involved in the metabolism of various exogenous agents such as theophylline, imipramine, and naproxen and can be inhibited by chemicals such as cimetidine and fluoroquinolones [56]. Moreover, CYP1A2 is a major determinant of lidocaine metabolism, a commonly used hepatic CYP function measure [57]. Another member of the CYP1A family is 1A1 and both CYP1A1 and 1A2 coexist in the rat liver.

Alterations of hepatic CYP450 in sepsis

Environmental factors which include medications (e.g., barbiturates, anticonvulsants, rifampin), foods (cruciferous vegetables), social habits (alcohol consumption, cigarette smoking), disease conditions (diabetes, inflammation, and infection) are all known to alter CYP isoforms [3]. Mediators involved in inflammation and sepsis can also alter hepatic CYP's drug metabolizing capabilities [58-60]. In animal models of endotoxemia and in cultured hepatocytes stimulated by endotoxin, CYP isoforms are dramatically decreased [58, 61-66]. The expression of CYP isoforms were

downregulated in cultured hepatocytes stimulated by pro-inflammatory cytokines, TNF-α, IL-1β, IFN-γ or IL-6 [67-73]. However, very little work has been performed with hepatic CYP in animal models of sepsis aside from measuring mixed function oxidase [74] and comparing CYP3A expression in sepsis with endotoxic shock [75].

In this regard, we examined whether the major CYP isoform in the rat liver, CYP1A2, is altered during the progression of sepsis and if so, whether reduction of this enzyme plays any role in the inflammatory response. Our results show that rat hepatic CYP1A2 mRNA was significantly downregulated at 10-20h and its proteins decreased at 20h after CLP [4]. Since hepatic perfusion is increased at the early stage of sepsis (e.g., 10h after CLP [30], the observed downregulation in CYP1A2 due to the decreased hepatic perfusion generally observed in severe sepsis and septic shock. Rather, the decreased CYP1A2 can be, in part, due to increase in pro-inflammatory cytokines such as TNF-α and IL-1β [76] which then directly suppress CYP1A2 mRNA [58, 66, 77].

In fact, it has been reported that pro-inflammatory cytokines released from KCs may directly downregulate hepatocyte CYP isoforms [78]. We have confirmed this finding using a KC and hepatocyte coculture system [6]. We have also shown that CYP inhibition by 1-aminobenzotriazole (ABT) in septic animals resulted in a significant increase in serum TNF-α, IL-1β, IL-6 and lactate, and more severe morphological changes in the liver [4]. This result is in agreement with the findings by Carcillo *et al.* who used ABT to inhibit CYP in the zymosan-induced inflammation which resulted in aggregation of neutrophils and significantly increased mortality [79]. Thus, the CYP enzyme system is essential in sepsis and its inhibition disposes the animal to exacerbated pro-inflammatory response and tissue injury.

Alterations of CYP in septic and severely injured patients

Very little has been known of the changes in CYP during sepsis or severe injury in humans. Shedlofsky et al. [65] reported that adult human volunteers given endotoxin showed decrease in metabolism of the CYP enzyme probe drugs which included antipyrine, hexobarbital and theophylline. The degree of inhibition of drug metabolism correlated with the circulating plasma levels of IL-6 in these endotoxin treated volunteers. Antipyrine metabolism is considered as a "gold standard" measure of mixed CYP450 mediated drug metabolism in humans. Carillo et al., [60] showed that children with sepsis had a two fold reduction in antipyrine clearance and those with multiple organ failure had a fourfold decrease in antipyrine clearance. Interestingly, this antipyrine clearance was inversely correlated with circulating levels of IL-6, nitrite plus nitrate levels and to number of organ failures.

Harbrecht et al., [80] further demonstrated that CYP activity is differentially altered in severely injured patients. In this study, twenty three multiply injured patients admitted to a trauma critical care unit were compared with healthy volunteers. CYP metabolizing activity was measured using the probe drugs mephenytoin (CYP-2C19), chlorzoxazone (CYP-2E1), dapsone (multiple CYP enzymes) and flurbiprofen (CYP-2C9). Mephenytoin metabolism was suppressed after injury and increased during post-injury recovery, whereas chlorozoxane was suppressed to a lesser degree. Measures of dapson and flurbiprofen metabolism were elevated throughout the study. Chlorzoxazone and mephenytoin metabolism correlated with multiple organ failure. Therefore, the metabolism of selected CYP isoforms may have potential for evaluating acute hepatic dysfunction in critically ill trauma patients.

In another study, 42 septic patients divided into survivors and non-survivors were evaluated for the *in vivo* activity of CYP using the aminopyrine breath test, a clinically well-established assay of hepatic CYP activity [81] prior to surgery and starting at sepsis onset on a daily basis. CYP activity was significantly decreased during the course of sepsis in both survivors and non-survivors group from the preoperative levels. Interestingly, CYP activity returned to normal levels in the survivor patients while they remained low in the non-survivors during the late phase. This study suggests that the aminopyrine breath test is a clinically useful tool for predicting outcome in the early stages of sepsis and helps when early surgical intervention is concerned.

Potential mechanism of CYP450 alterations

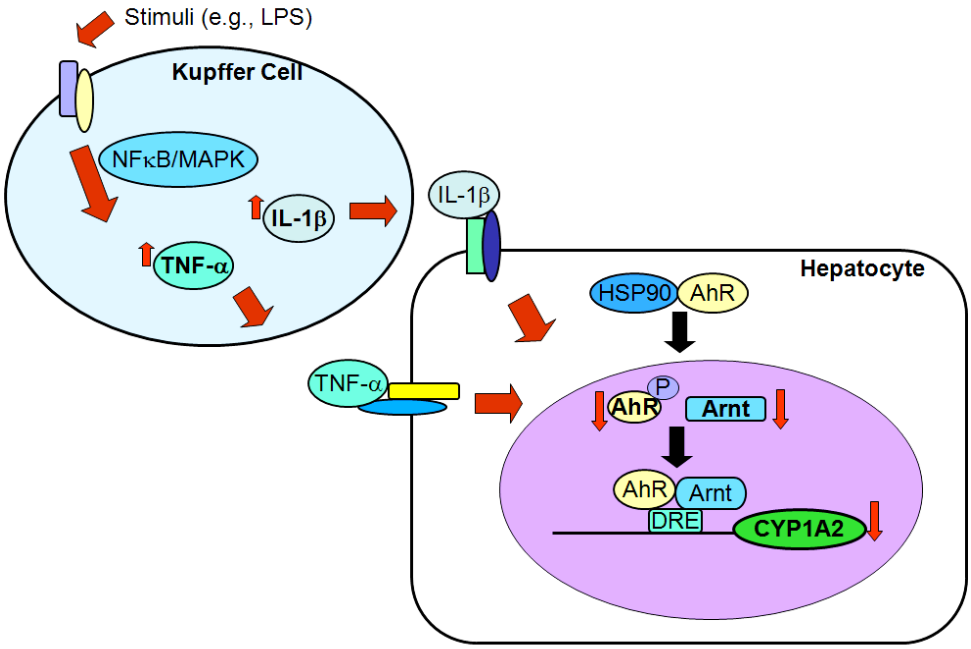

Figure 1. Schematic representation of the potential mechanism of CYP1A2 downregulation in sepsis: Transcriptional activation of CYPs involves the aryl hydrocarbon receptor (AhR), nuclear translocator (Arnt) and a chaperone protein, heat shock 90 (HSP90). In the absence of stimulation, AhR exists as a non-DNA binding heterometric complex with HSP90. Upon activation, AhR-HSP90 complex enters the nucleus and HSP90 dissociates, enabling AhR to be tyrosine phosphorylated and bind to Arnt. The AhR-Arnt complex then binds to dioxin responsive element (DRE) at the promoter region of CYP1A2 gene and initiates the transcription. During sepsis, extracellular stimuli (e.g., LPS) upregulate both TNF-α and IL-1β via NFκB and/or MAPK pathways and get released from Kupffer cells. The cytokines then bind to there respective receptors on hepatocytes and by mechanisms which are still unknown, downregulate both Arnt and AhR gene and protein thereby, decrease CYP1A2 mRNA expression.

Transcriptional activation of CYPs involves the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor as well as its nuclear translocator (Arnt) and a chaperone protein, heat shock 90 (HSP90) [82, 83]. Nuclear receptors such as AhR represent a superfamily of ligand modulated transcription factors. They mediate a variety of physiological responses to steroids, retinoids, thyroid hormones, and various xenobiotics [84]. These receptors play a key role in development, cell differentiation, and organ physiology [85]. Unlike water-soluble hormones, steroid hormones can enter the cell by simple or facilitated diffusion and transduce their signals to the genome via intracellular receptors [86]. After binding to its receptor, the hormone-receptor complex moves from the cytoplasm to nucleus, undergoing allosteric changes that enable the complex to bind to high affinity sites in the chromatin and modulate gene transcription [87]. More than 70 distinct members of the nuclear receptor superfamily have been identified [88].

Studies have shown that the transcription of CYP1A2 gene is mediated through the AhR signaling pathway [82, 83, 89]. This is further supported by the finding that the human hepatoma cell line SK-Hep-1 which expresses defective AhR, is associated with the lack of CYP1A2 expression [90]. In the absence of stimulation, AhR exists as a non-DNA-binding, ~300 kDa heteromeric complex, associated with the molecular chaperone HSP90 in a 1:2 ratio in the cytosol [91]. Upon stimulation, AhR-HSP90 complex enters the nucleus and subsequently dissociates, enabling AhR to be phosphorylated by tyrosine kinase. The activated AhR then forms a heterodimer

complex with its nuclear translocator Arnt [92]. Within the nucleus, the AhR-Arnt complex recognizes and binds to the specific regulatory sequences known as the dioxin responsive element (DRE) at the promoter region, and initiates the transcription of the CYP1A2 gene [93, 94]. HSP90 appears to be critical for folding of a ligand-binding conformation in AhR and for the ligand's inducibility [95, 96] (**Figure 1**).

We examined the expression of AhR and Arnt in both *in vitro* and *in vivo* conditions. For *in vitro* experiments, isolated Kupffer cells and hepatocytes together, Kupffer cells and hepatocytes separated by transwell membrane or hepatocytes alone were cultured in the presence of 100 ng/ml LPS for 24h. AhR and Arnt mRNA expressions were analyzed by reverse-transcription-polymerase chain reaction (RT-PCR) and protein levels were measured by Western blotting. Both AhR and Arnt mRNA and protein were significantly decreased in the LPS treated co-culture whereas; either hepatocytes alone or co-culture separated by membrane produced no changes in AhR or Arnt mRNA and protein. The observed downregulation of AhR and Arnt in the LPS treated co-culture were correlated with CYP1A2 and inversely associated with TNF-α and IL-1β [6]. Both AhR and CYP1A2 were decreased in hepatoma cells (H-4-II-E) treated with TNF-α or IL-1β for 48h [5]. For the *in vivo* studies, adult male rats were subjected to sepsis by cecal ligation and puncture; hepatic tissues were harvested at 5, 10, and 20h after CLP or sham operation. AhR and Arnt mRNA and protein were assessed. AhR mRNA decreased at 5h and remained downregulated at 10 and 20h after CLP. Hepatic CYP1A2 expression was also decreased at 10 and 20h after CLP [4]. That CYP1A2 and AhR were inversely correlated with TNF-α and IL-1β suggest increase in pro-inflammatory cytokines in sepsis play critical role in downregulating the CYP enzymes in sepsis and severe injury (**Figure 1**).

Cytokines induce inducible nitric oxide synthetase (iNOS) resulting in nitric oxide (NO) production in many cell types [97]. The iNOS mRNA level significantly increases 24 h after CLP [7, 98]. By the use of the NO inhibitor, it was shown that CLP caused decrease in CYP1A1, CYP1A2, and CYP2E1 and was reversed by the NO inhibitors. This suggests NO might contribute to the suppression of CYP in sepsis. It has also been postulated that since NO binds to the heme center of CYP directly and inhibits CYP activity [99], decreased CYP activity in sepsis could also be due to NO-mediated post-translational modification.

Future Studies and Perspectives

The CYP enzymes are crucial in the acquisition of metabolic activation and inactivation of clinically used drugs and toxins. We and others have shown that the CYP enzymes are significantly decreased in sepsis and severe injury. We further demonstrated that by using an experimental model of sepsis, this downregulation in sepsis is due to the decrease in AhR and Arnt, two critical transcription factors involved in the regulation of CYP1A2 mRNA. Our studies further showed that AhR and Arnt expressions were inversely correlated with pro-inflammatory cytokines in sepsis and that exposure to cells with such cytokines downregulated AhR and Arnt. These data collectively suggest that therapies directed towards decreasing pro-inflammatory cytokine release in sepsis, especially from the liver, can prevent the downregulation of the AhR signaling pathway and thereby protect CYP mRNA transcription. Further studies are warranted to examine the regulation of other CYP isoforms in sepsis and severe injury and delineate the role of post-translational modification such as nitrosylation in CYP activity.

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