Alterations in Hepatic Gene Expressions of CYP2C11, CYP2C6V, and CYP2D3 Enzymes in Endotoxemic Rats

Endotoksemik Sıçanlarda CYP2C11, CYP2C6V ve CYP2D3 Enzimlerinin Karaciğer Gen Ekspresyonlarındaki Değişimi

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Abstract

Objective: Human cytochrome P450 2C9 (CYP2C9), CYP2C19, and CYP2D6 (corresponding to rat CYP2C11, CYP2C6V, and CYP2D3, respectively) are the major enzymes responsible for the metabolism of a wide range of drugs and chemicals. Changes in CYP efficiency are associated with disease susceptibility that can lead to drug toxicity or ineffective therapy. We aimed to examine the effects of lipopolysaccharide (LPS)-induced endotoxemia on gene expressions of hepatic microsomal CYP enzymes in rats.

Material and Methods: Male Wistar albino rats were allocated into two subgroups of control and LPS. Saline or LPS (10 mg/kg) of same volume (1 mL/kg) was intraperitoneally (i.p.) injected into rats. After 4 hours, liver tissues were removed. Hepatic mRNA expressions of the CYP enzymes were quantitatively analyzed using real-time polymerase chain reaction (PCR).

Results: Hepatic gene expressions of CYP2C11 and CYP2C6V decreased (3.35 and 2.25 fold, respectively) in the endotoxemic rats; however, CYP2D3 expression did not change.

Conclusion: Our results revealed that endotoxemia changes CYP2C11- and CYP2C6V-mediated drug metabolism. Therefore, drug dosage must be cautiously adjusted in the patients with endotoxemia and sepsis.

Keywords: Endotoxemia, liver, gene expressions, cytochrome P450 enzymes

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Öz

Amaç: İnsan sitokrom P450 2C9 (CYP2C9), CYP2C19 ve CYP2D6 (sıçanlardaki karşılıkları sırasıyla; CYP2C11, CYP2C6V ve CYP2D3) enzimleri, çok sayıdaki ilacın ve kimyasalın metabolizmasından sorumlu olan ana enzimlerdir. CYP enzim etkinliğindeki değişimler, ilaç toksisitesine veya tedavi yetersizliğine neden olarak hastalığa karşı duyarlılığı etkileyebilir. Bu bilgiler ışığında, sıçanlarda lipopolisakkarit (LPS) ile indüklenen endotoksemi modeli oluşturarak hepatik mikrozomal CYP enzim ekspresyonlarındaki değişimini araştırmayı amaçladık.

Gereç ve Yöntemler: Wistar albino cinsi erkek sıçanlar kontrol ve LPS olmak üzere iki alt gruba ayrılmıştır. Aynı hacimdeki (1 mL/kg) salin solüsyonu veya LPS maddesi (10 mg/kg) intraperitoneal yolla sıçanlara enjekte edilmiştir. Bu uygulamadan dört saat sonra karaciğer dokuları çıkarılmıştır. CYP enzimlerinin karaciğer mRNA gen ekspresyonları, eş zamanlı polimeraz zincir reaksiyonu (PZR) ile nicel olarak analiz edilmiştir.

Bulgular: CYP2C11 ve CYP2C6V'nin karaciğer gen ekspresyonu endotoksemik sıçanlarda 3,35 ve 2,25 kat azalmıştır, ancak CYP2D3 ekspresyonu değişmemiştir.

Sonuç: Bulgularımız endotokseminin CYP2C11 ve CYP2C6V aracılı ilaç metabolizmasını değiştirdiğini ortaya koymuştur. Bu nedenle endotoksemi ve sepsis bulgusu olan hastalarda bu enzimlerle metabolize edilen ilcaları kullanırken doz ayarlamasına dikkat edilmelidir.

Anahtar kelimeler: Endotoksemi, karaciğer, gen ekspresyonu, sitokrom P450 enzimleri

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Introduction

The enzyme family of cytochrome P450 (CYP) is responsible for majority of the drug metabolism reactions. CYP enzymes also help in the metabolism of steroids, fatty acids, carcinogens, prostaglandins, xenobiotics, and several natural compounds (1). To date, many clinically important gene families, such as CYP2C9, CYP2C19, and CYP2D6, have been identified. CYP enzymes are mainly located in the liver, which is the major site of drug metabolism (2). The CYP2C9 (corresponding to rat CYP2C11) enzyme metabolizes about 40 drugs, including phenytoin; oral anticoagulant drugs, such as warfarin and acenocoumarol; selective angiotensin-II receptor blockers, such as valsartan and losartan; oral antidiabetic drugs, such as tolbutamide, glyburide, and glibenclamide; and many nonsteroidal anti-inflammatory drugs (3). The CYP2C19 (corresponding to rat CYP2C6V) enzyme facilitates the metabolism of several drugs, including antiepileptics, barbiturates, benzodiazepines, proguanil, nelfinavir, voriconazole, and proton pump inhibitors (4). Furthermore, the CYP2D6 (corresponding to rat CYP2D3) enzyme promotes metabolism of about 25% of clinically used drugs, such as β blockers, opiates, neuroleptics, antiarrhythmics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and some toxic plant substances (5). Drugs are usually converted to the less active or inactive metabolites by CYP enzymes. However, some drug metabolites are more active. Therefore, alterations in the activity and amount of the liver CYP enzymes can lead to toxicity or ineffective therapy (6, 7).

With the increase of microorganisms in the body, inflammatory cells, particularly macrophages, try to eliminate the microorganisms by releasing the cytokines and mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), along with free radicals. However, excessive amount of microbes as observed in endotoxemia and sepsis lead to massive and uncontrolled release of these free radicals and inflammatory cytokines. Oxidative stress and hyperinflammation are responsible for multiple organ failure and even death in endotoxemia and sepsis (8, 9).

Some environmental factors especially using drugs, such as barbiturates and rifampin; consumed foods; and underlying diseases are the factors that may affect the activity of CYP enzymes. Goktas et al. showed that CYP2C9 and CYP2C19 enzyme activities were reduced in Behçet's disease, an autoimmune disease, compared to healthy volunteers. In their opinion, the reason for this reduction may be associated with inflammatory mediators and cytokines, such as TNF-α, that increase in autoimmune diseases (10, 11). In a cell culture study, lipopolysaccharide (LPS), interferon gamma (IFN-γ), TNF-α, IL-1β, and IL-6 were shown to reduce the expression of some CYP enzyme isoforms, including CYP3A4 and 2C8 (12).

In the light of the above information, it was aimed to examine the changes in the human CYP2C9, CYP2C19, and CYP2D6 (corresponding to rat CYP2C11, CYP2C6V, and CYP2D3, respectively) expressions in endotoxemic rats.

Material and Methods

Sixteen adult Wistar albino male rats weighing 250–300 g were accommodated in an air controlled room at 21±2°C, 50±10% humidity, 12-h light/12-h dark cycle with access ad libitum to fresh water and commercial standard laboratory rodent pellet diet. The present study was approved by the local ethics committee before the commencement of any interventions (Approval No: 2015/99) and managed according to the guidelines of European Community and the Helsinki and Tokyo Declarations.

Endotoxemia Model, Tissue Acquisition, and Storage

Animals were randomly categorized into two subgroups of control (saline treated) and LPS (endotoxin treated). LPS derived from *Escherichia coli* (O111:B4; Sigma-Aldrich, Inc., USA; 10 mg/kg) or 0.9% non-pyrogenic sterile saline at the same volume (1 mL/kg) was intraperitoneally (i.p.) injected to rats. Four hours after the injections, animals were injected with chloral hydrate (Sigma-Aldrich, Inc., USA; 400 mg/kg/i.p.) to induce general anesthesia and subsequently liver tissues were removed (13, 14). The liver tissues were immediately submerged in RNA*later*® RNA Stabilization Reagent (Qiagen, Hilden, Germany) solution and incubated at 2°C-8°C overnight. After the incubation, tissue samples were stored at -20°C until RNA extraction.

Tissue Homogenization and Total RNA Isolation

The stabilized tissues were disrupted and homogenized using the TissueRuptor homogenizer (Qiagen, Hilden, Germany). The total RNA was extracted using RNeasy Plus Universal Mini Kit (Qiagen, Hilden, Germany) as described in the manufacturer's protocol and quantified by absorption measurements at 260 nanometer (A260 nm). Additionally, the purity of RNA was determined by measuring the ratio A260 nm/A280 nm using a Nanodrop 2000 spectrophotometer (Thermo Scientific, Wilmington, Delaware, USA). The ratios of absorbance >1.8 at 260 and 230 nm (A260:A230) and of absorbance >2.0 at 260 and 280 nm (A260:A280) were considered acceptable indicators of RNA purity.

The Complementary DNA (cDNA) Synthesis and Quantitative Real-Time Polymerase Chain Reaction (RT-PCR) Analysis

Firstly, total RNA (approximately 25 ng) from each sample was taken and converted to the first strand cDNA by using the RT² First Strand kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. The obtained cDNA samples were labeled with QuantiTect SYBR Green polymerase chain reaction (PCR) Master Mix (Qiagen, Hilden, Germany) and then gene expressions were quantitatively analyzed using specific primers (Table 1) for CYP enzymes (CYP2C11, CYP2C6V1, and CYP2D3) and β-actin, which is a housekeeping gene. The RT-PCR procedures were performed using *Rotor-Gene Q* (Qiagen, Hilden, Germany).

Analysis of Gene Expression via $2^{-\Delta\Delta CT}$ Method

The RT² profiler PCR array online software version 3.5 was used for the analysis of data (http://www.sabiosciences.com/pcrarraydataanalysis.php). An excel sheet was used to determine a fold change and two normalized average cycle threshold (CT) values for each PCR reaction. The quantification of PCR array was based on the calculation of the CT value. When the CT value was >32, the gene was considered not detectable. When the signal was under detectable limits, CT was defined as 35 for the calculation of ΔCT. The average CT value was measured for both target genes and β-actin, and the ΔCT was calculated using the formula ΔCT=CT of target gene–CT of β-actin. The ΔΔCT was also measured using the formula ΔΔCT=ΔCT of target gene–ΔCT of βactin. N-fold differences of the target gene expression relative to normal sample counterpart were represented as $2^{-\Delta\Delta CT}$. Decreased mRNA expression or downregulated gene was described as an n-fold change ≤0.5 or n-fold regulation ≤–2; normal mRNA expression was described as an n-fold change ranging from 0.501 to 1.999 or n-fold regulation ranging from –1.999 to 1.999. Increased mRNA expression or upregulated gene was described as an n-fold change or regulation ≥2.0 (15).

Table 1. Primers for target genes of CYP enzymes and β-actin

Gene Symbol	Primers
Human CYP2C9 (corresponding to rat CYP2C11)	Forward: 5'-CACCAGCTATCAGTGGATTTGG-3', Reverse: 5'-GTCTGCCCTTTGCACAGGA-3'
Human CYP2C19 (corresponding to rat CYP2C6V1)	Forward: 5′-ATGGATCCTTTTGTGGTCCTT-3′, Reverse: 5′-TGCTTCTTCAGACAGGAATG-3′
Human CYP2D6 (corresponding to rat CYP2D3)	Forward: 5'-TAACTCTTCCCTGGATGCCTTCAA-3' Reverse: 5'GTCCCGGATGTGGCCCTTCTCAAA-3'
β-actin	Forward: 5'-CCAGATCATGTTTGAGACCTTCAA-3', Reverse: 5'-GTGGTACGACCAGAGGCATAC-3'

CYP2C9: Cytochrome P450 Family 2 Subfamily C Member 9; CYP2C11: Cytochrome P450 Family 2 Subfamily C Member 11; CYP2C19: Cytochrome P450 Family 2 Subfamily C Member 19; CYP2C6V1: Cytochrome P450 Family 2 Subfamily C Polypeptide 6 Variant 1; CYP2D6: Cytochrome P450 Family 2 Subfamily D Member 6; CYP2D3: Cytochrome P450 Family 2 Subfamily D Member 3

Table 2. Comparison the levels of CYP2C11, CYP2C6V, CYP2D3 mRNA expression between two groups

	$2^{-\Delta\Delta CT}$		Fold change		Fold up- or downregulation
Gene Symbol	LPS	Control	LPS/control	95% confidence interval	LPS/control
CYP2C11	0.020246	0.067803	0.30	(0.20, 0.40)	-3.35
CYP2C6V	1.111494	2.496661	0.45	(0.32, 0.58)	-2.25
CYP2D3	0.155098	0.305395	0.51	(0.40, 0.62)	-1.97

LPS: lipopolysaccharide; CT: cycle threshold

Results

The hepatic mRNA gene expression of CYP2C11 was found to be downregulated by 3.35-fold (0.067803–0.020246) in the endotoxemic rats. Additionally, LPS injection led to a 2.25-fold downregulation (2.496661–1.111494) in the hepatic mRNA gene expression of CYP2C6V. However, there was no significant change in hepatic CYP2D3 expression in the endotoxemic rats (Table 2).

Discussion

The disturbance of drug metabolism can lead to drug toxicity or reduce efficacy depending on the active, inactive, less active, or toxic metabolite formation. Changes of enzyme gene expression and activity are of great importance for the drugs with narrow therapeutic index, such as warfarin, phenytoin, and flecainide, which are metabolized by CYP2C9, CYP2C19, and CYP2D6, respectively.

Several immune-based (inflammatory) pre-clinical and clinical studies have shown that activities and expressions of CYP subfamily enzymes changed in a state of inflammation. This disruption occurs primarily due to reductions of gene expression and activation of CYP enzymes by inflammatory cytokines and oxidative stress products (12, 16-18). It has been shown that CYP2C9 and CYP2C19 activities decreased in Behçet's disease, which an autoimmune disease. Therefore, warfarin and phenytoin dosages must be carefully adjusted in Behçet's disease, otherwise serious adverse reactions or toxicity may occur (10, 11). The activities of CYP2D6 and CYP3A4 were found to be lower in patients with chronic hepatitis C (19). IL-6 administration suppresses the CYP2C8, CYP3A4, CYP2C9, and CYP2C19 mRNA expressions in a human hepatocyte culture (20). Hepatic expressions of CYP3A1, CYP3A2, CYP3B1, and CYP3B2 decreased after the induction of arthritis by a *Mycobacterium tuberculosis* adjuvant (18). Several reports from animal studies have indicated that some CYP enzymes are unaffected by inflammation and that some are even induced by it (12, 16, 21). Expressions of hepatic CYP3A2 and CYP2C11 and renal CYP2E1 were found to be lower in the recombinant adenovirus-injected rats, but CYP4A expression was induced (22, 23).

Previous studies have shown that LPS-induced systemic infection is associated with changed drug metabolism. LPS did not affect the CYP2C9 and CYP2C19 expressions, but reduced the CYP2C8 and CYP3A4 expressions in human hepatocytes (12). Intracerebroventricular injection of LPS in rats decreased the CYP2C11 expression and activity, but i.p. injection at the same concentration (0.1 µg) did not affect these parameters. The dose and route of LPS administration directly affect the enzyme expression levels (24).

In the present study, we found that i.p. injection of LPS at a dose of 10 mg/kg in rats decreased the hepatic gene expressions of CYP2C11 and CYP2C6V (70% and 55%, respectively). Furthermore, endotoxemia did not affect the hepatic CYP2D3 gene expression. Therefore, dosages of the drugs that are metabolized by CYP2C9 and CYP2C19 must be carefully adjusted in the endotoxemic and septic patients.

In conclusion, our results provide novel evidences that endotoxemia seems to affect the drug metabolism and can lead to drug toxicity or ineffective therapy. Particularly, drugs with narrow therapeutic index must be carefully given to the patients with endotoxemia and sepsis. In addition, hepatic expressions of these enzymes should be investigated in a cecal ligation and puncture-induced hyperdynamic and hypodynamic septic shock model.

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