Cytochrome P450 Dysregulations in Thioacetamide-Induced Liver Cirrhosis in Rats and the Counteracting Effects of Hepatoprotective Agents

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ABSTRACT:
Dysregulations of cytochromes P450 (P450s) under liver injury have been extensively studied. However, little is known about the possible reversing effects of hepatoprotective agents, the understanding of which is of great importance in guiding clinical dosage adjustment for patients with liver injury. This study aims to investigate the dysregulation patterns of major P450s in thioacetamide (TAA)-induced liver cirrhosis in rats and the potential counteracting effects of hepatoprotective agents schisandra lignans extract (SLE) and dimethyl diphenyl bicarboxylate (DDB). TAA intoxications for 6 weeks induced apparent liver injury and dramatically reduced the hepatic protein expressions of CYP1A2, CYP2C6, CYP2E1, and CYP3A2 to 18, 71, 30, and 21% of that in the normal control, respectively. Both SLE and DDB treatments could significantly reverse the TAA-induced loss of P450 protein levels, which may be ascribed to their hepatoprotective effects and direct P450-inducing effects that have been confirmed in healthy rats. However, the recovery of enzyme activities of most P450s by SLE and DDB treatment was less evident than that for the protein expression levels. TAA exhibited NADPH+, time-, and concentration-dependent inactivating effects on all of the four major P450 isoforms; both DDB and GSH showed little effects on counteracting such an inactivation efficacy. These findings provided a good explanation on the disproportional effects of hepatoprotective agents in recovering the protein levels and enzyme activities of TAA-induced dysregulated P450s.

Introduction
Thioacetamide (TAA), a potent selective hepatotoxin, is well known to induce both acute and chronic hepatic failure (Steib et al., 2010; Zaldívar et al., 2010; Ishikawa et al., 2011). Prolonged exposure to TAA always results in bile duct proliferation and liver cirrhosis histologically similar to that in human viral hepatitis infection (Hunter et al., 1977; Ledda-Columbano et al., 1991; Yeh et al., 2004). Because of this virtue, TAA has been widely applied to develop animal models of liver fibrosis and/or cirrhosis mimicking human nonbiliary liver diseases. From these animal models, many important pathological processes and involved mechanisms of liver fibrosis/cirrhosis had been disclosed, contributing to the development of novel diagnostic and therapeutic approaches and hepatoprotective drugs.

Human liver diseases caused by various factors usually lead to the dysregulations of most drug-metabolizing enzymes (DMEs), especially cytochromes P450 (P450s), which necessitates the dosage adjustment of therapeutic drugs in patients with severe liver diseases. Because TAA-induced liver fibrosis/cirrhosis models have been widely applied to mimic human liver diseases, it is definitely important to understand TAA-induced dysregulation patterns of DMEs. Unfortunately, the present understanding of this critical issue is extremely limited. Increased expression of CYP2E1 and CYP2A5 was observed in TAA-induced liver injury models (Camus-Randon et al., 1996; Avni et al., 2003); a previous report showed that nicotine metabolism was significantly decreased in the TAA-induced fibrotic rat livers, associated with the down-regulated protein levels of most P450s (Nakajima et al., 1998). However, TAA-induced potential regulation of enzyme activity of P450s remains unclear. TAA is a thiono-sulfur-containing compound and is readily bioactivated by CYP2E1 and flavin-containing monooxygenase to produce acetamide and thioacetamide-S-dioxide. These reactive metabolites may covalently bind to various proteins, which is indeed the major mechanism of TAA on causing liver toxicity. On the basis of these characteristics,

ABBR EVIATIONS: TAA, thioacetamide; DME, drug-metabolizing enzyme; P450, cytochrome P450; SLE, schisandra lignans extract; DDB, dimethyl diphenyl bicarboxylate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, y-glutamyl transferase; ALP, alkaline phosphatase; Tbil, total bilirubin; RLM, rat liver microsomes; PVDF, polyvinylidene fluoride; UGT, UDP-glucuronosyltransferase.
we hypothesized that TAA intoxication may lead to both the transla-
tional dysregulations and the direct enzyme inactivation of P450s. To
test this hypothesis, both protein levels and enzyme activities of major
P450s were determined in the chronic TAA-treated rat livers. Poten-
tial inactivating effects of TAA on P450s were performed in the in
vitro liver microsomal incubation systems.

In addition, it should be noted that the patients with liver diseases
are usually inclined to consume hepatoprotective agents. Therefore, it
is important to understand whether such hepatoprotective agents can
influence the dysregulated P450s in injured livers, which is of critical
concern for adjusting the dosage regimen of coadministered drugs.
Current understanding of such an important issue is extremely limited.
We have found that the hepatoprotective agent schisandra ligan-
s extract (SLE) was effective at protecting the liver from CCl4-induced
damage and restoring the pharmacokinetic characteristics of its ligan-
s components, indicating the recovery of some P450s (Xie et al., 2010).
Based on a TAA-induced liver cirrhosis rat model that better mimics human liver cirrhosis, the present study was further designed to
determine whether SLE treatment would be effective at recovering
TAA-induced dysregulations of major P450s.

Materials and Methods

Chemicals and Reagents. TAA was obtained from Jiahui Medicine Chem-
ical Company LLC (Anhui, China). Dimethyl diphenyl dicarboxylate (DDB)
was purchased from Hangzhou Dengyun Pharm and Tech Co., Ltd Pharmacy
(Zhejiang, China). The ethanol extract of Schisandra chinensis Baill (SLE)
was purchased from Nanjing Qingze Pharmaceuticals Company (Jiangsu,
China). Midazolam, chlorozoxazone, diclofenac, phenacetin, and acetamina-
phen were obtained from the National Institute for the Control of Pharmaeutical
and Biological Products (Beijing, China). 4′-Hydroxydiclofenac, 4′-hy-
droxymidazolam, 6-hydroxychlorozoxone, glucose 6-phosphate, NADP+,
and glucose-6-phosphate dehydrogenase were purchased from Sigma-Aldrich
(S. Louis, MO). High-performance liquid chromatography-grade acetonitrile,
methanol, and ethyl acetate were obtained from Merck (Darmstadt, Germany).
Deionized water was purified using a Milli-Q system (Millipore Corpora-
tion, Billerica, MA). Radio immunoprecipitation assay analysis buffer, phenylmeth-
anesulfonyl fluoride, and SDS-polyacrylamide gel electrophoresis sample-
loading buffer were purchased from Beyotime Institute of Biotechnology
(Jiangsu, China). Polyvinylidene difluoride (PVDF) membranes were obtained
from Millipore (Shanghai, China). Rabbit anti-rat CYP3A2 polyclonal anti-
body, rabbit anti-rat CYP2E1 polyclonal antibody, and mouse anti-rat
CYP1A2 polyclonal antibody were from Millipore Bioscience Research Re-
agents (Temecula, CA). Mouse anti-rat CYP2C6 polyclonal antibody was from
Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Mouse anti-rat β-actin
polyclonal antibody and horseradish peroxidase-conjugated goat anti-rabbit
IgG and goat anti-mouse IgG were purchased from Boster Biological Tech-
nology, Ltd. (Wuhan, China). An enhanced chemiluminescence kit was pur-
chased from Thermo Fisher Scientific (Waltham, MA).

Animals and Experimental Design. Male Sprague-Dawley rats (180–220

Fig. 1. Representative photomicrographs of histopathological studies of livers
stained with hematoxylin and eosin. Rats were treated with TAA (200 mg/kg)
intraperitoneally twice a week for 6 weeks; SLE and DDB were administered to rats
intragastrically for 2 weeks once a day at the beginning of 5th week. Left, A–E,
magnification, 100×. Right, a–e, magnification, 200×. A, a, normal. B, b, TAA-
treated rats. C, c, rats treated with SLE 100 mg/kg + TAA. D, d, rats treated with
SLE 400 mg/kg + TAA. E, e, rats treated with DDB 200 mg/kg + TAA.
Clint of liver microsomal P450s in normal, TAA-induced hepatic injury rats treated with or without SLE and DDB.

**Results**

TAA-Induced Liver Cirrhosis and Hepatoprotective Effects of SLE and DDB. We have reported previously that TAA intoxication for 8 weeks caused severe liver damage in rats (Hao et al., 2011). The present study showed that TAA intoxication for 6 weeks could also induce apparent hepatic injury, as evidenced by the significantly enhanced levels of serum ALT, AST, ALP, and Tbil (p < 0.01). SLE and DDB treatment for 2 weeks could partially reverse TAA-induced alternations of serum ALT, AST, and Tbil levels, supporting the hepatoprotective effects of both SLE and DDB (Supplemental Fig. 1). TAA induced extensive changes in liver morphology including steatosis, inflammation, fibrosis, centrilobular necrosis, and scattered cetes. The intrinsic clearance (Clint) values were determined by nonlinear regression analysis of the enzyme activity-substrate concentration data using the Michaelis-Menten model.

Mechanism-based inactivations of TAA on microsomal P450s were assessed using a two-step procedure. Primary incubations were performed in a media containing 0.5 mM NADPH, 5 mM ml RLM, and various concentrations of TAA in 100 mM phosphate buffer (pH 7.4) in a final volume of 200 μl. At various time points (0, 5, 10, 15, and 30 min), 20 μl of the primary reaction media was removed and added into a secondary reaction media containing specific P450 substrate, NADPH-regenerating system, and buffer as usual. All experimental procedures of the secondary incubations were the same as those described above for the enzyme activity assay of P450s. All incubations were performed in triplicates.

**Western Blot Analyses.** Protein levels of the major rat P450 isoforms were determined by a Western blot analysis. Liver protein samples (10 μg protein/ lane) were separated by SDS-polyacrylamide gel electrophoresis with an 8% polyacrylamide gel and were transferred to a PVDF membrane by electroblotting. The PVDF sheets were blocked in 5% nonfat dry milk in Tris-buffered saline/0.05% Tween 20 (TBST) at 37°C for 1 h. The blots were incubated with primary antibodies diluted in 5% nonfat dry milk in TBST overnight at 4°C followed by incubation with goat anti-rabbit (CYP2E1 and CYP3A2) or goat anti-mouse (CYP1A2 and CYP2C6) secondary antibodies for 1 h. The primary antibodies against CYP1A2, CYP3A2, CYP2C6, and CYP2E1 were diluted 1:1500, 1:1500, 1:1000, and 1:1000, respectively. For reference, β-actin was detected using a polyclonal antibody (1:200) for 1 h and then was incubated with secondary antibody horseradish peroxidase-conjugated goat anti-rabbit IgG (1:1500) for 1 h at 37°C. The immunoblots were developed with enhanced chemiluminescence detection method with reagents from BioWorld Technology, Inc. (Minneapolis, MN). Proteins were detected by enhanced chemiluminescence kit. Quantification of relative P450 levels was performed by laser densitometry of the X-ray films. The density of the immunoreactive bands was analyzed using ImageJ software (National Institutes of Health, Bethesda, MD).

**Statistical Analysis.** The values of the experimental data were expressed as mean ± S.D. Statistical significances were evaluated using one-way analysis of variance, followed by the post hoc least significant difference method for multiple comparisons. The difference was considered significant when p < 0.05.
lymphomononuclear infiltration in hepatic parenchyma. Treatment with SLE exhibited dose-dependent reversal effects on TAA-induced liver fibrosis, characterized with decreased necrotic zones and hepatocellular degeneration (Fig. 1).

**Expression of Hepatic P450s in TAA-Induced Cirrhotic Livers.** Hepatic P450 protein levels were determined by Western blot analyses. TAA intoxication significantly decreased CYP1A2, CYP2C6, CYP2E1, and CYP3A2 protein levels to 18, 71, 30, and 21% of that of the normal control, respectively. SLE and DDB treatment markedly attenuated TAA intoxication, causing down-regulation of the protein levels of all these P450s, especially for CYP3A2 and CYP2E1 (Fig. 2). It was noted that the protein levels of some P450s in SLE- and DDB-treated rats were even higher than those in the normal control group; CYP3A2 protein levels in SLE (100 and 400 mg/kg)- and DDB (200 mg/kg)-treated rats were 1.09-fold, 1.37-fold, and 1.56-fold of that in the normal control; CYP2E1 protein level in DDB-treated rats was 2.26-fold of that in the normal control (Fig. 2).

**Activity of Hepatic P450s in TAA-Induced Cirrhotic Livers.** Liver microsomes were prepared from each group of rats to test the enzyme activities of P450s using the typical probe substrate approach. Results are shown in Table 1. As evidenced from Clint values, TAA intoxication markedly decreased the activity of CYP1A2, CYP2E1, CYP3A2, and CYP2E1 to 49, 33, 69, and 43% of that in the normal control, respectively. SLE and DDB treatment partially reversed TAA-induced loss of CYP1A2, CYP2E1, and CYP3A4 activity. In contrast, CYP2C6 activity was less affected by SLE and DDB treatment. Correlation analysis showed that the activity and protein expression were consistent for CYP1A2 and CYP3A2, but not for CYP2E1 and CYP2C6 (Fig. 3).

**Activity and Expression of Hepatic P450s in Healthy Rats Treated with SLE/DDB.** To clarify the effects of SLE and DDB on regulating normal rat liver P450s, rats were treated with SLE and DDB for 2 weeks, and the activity and expression of CYP1A2, CYP2C6, CYP3A2, and CYP2E1 were determined. As shown in Table 2, SLE and DDB showed inhibitory effects on CYP1A2, whereas both SLE and DDB largely enhanced the activity of CYP2C6, CYP3A2, and CYP2E1. Consistently, the results of Western blot analysis showed the decrease of CYP1A2 but the increase of CYP2C6, CYP3A2, and CYP2E1 protein levels in the livers of SLE- and DDB-treated healthy rats (Fig. 4).

**Mechanism-Based Inhibitory Effects of TAA on P450s.** In view of the bioactivation characteristics of TAA, we further investigated the potential mechanism-based inhibitory effect of TAA on P450s. TAA (0, 5, 50, 200, and 400 μM) was incubated with normal RLMs by adding the NADPH-regenerating system; the remaining enzyme activity at indicated time points was determined by a typical dilution approach (Brady et al., 1987; Li et al., 2009). Appropriate controls, lacking TAA, were included to ensure that the loss of activity was not due to TAA irrelevant inactivation. Without the addition of NADPH, TAA has little effect on inactivating P450s (data not shown). TAA inhibited CYP1A2, CYP2C6, CYP3A2, and CYP2E1 activity in a concentration- and time-dependent manner when NADPH was included in the incubations (Fig. 5). The observed first-order rate constants (k_{inact}) for the inactivation of P450s by individual concentrations of TAA were obtained from the slope of individual lines. These slopes were fit to a Kitz-Wilson plot, which is shown in the inset of Fig. 5. The calculated K_{I} and k_{inact} values are shown in Table 3. As evidenced from the k_{inact}/K_{I} values, it seems that

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**Table 2**

Clint of liver microsomal P450s in healthy rats treated with SLE and DDB

<table>
<thead>
<tr>
<th>Group</th>
<th>CYP1A2</th>
<th>CYP2C6</th>
<th>CYP3A2</th>
<th>CYP2E1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clint</td>
<td>Clint</td>
<td>Clint</td>
<td>Clint</td>
</tr>
<tr>
<td></td>
<td>μL/min·mg</td>
<td>1.00</td>
<td>μL/min·mg</td>
<td>1.00</td>
</tr>
<tr>
<td>Control</td>
<td>0.3741</td>
<td>0.0079</td>
<td>0.0412</td>
<td>0.0095</td>
</tr>
<tr>
<td>SLE (100 mg/kg)</td>
<td>0.2728</td>
<td>0.0142</td>
<td>0.0759</td>
<td>0.0101</td>
</tr>
<tr>
<td>SLE (400 mg/kg)</td>
<td>0.2027</td>
<td>0.0252</td>
<td>0.0985</td>
<td>0.0192</td>
</tr>
<tr>
<td>DDB (200 mg/kg)</td>
<td>0.3502</td>
<td>0.0216</td>
<td>0.0895</td>
<td>0.0240</td>
</tr>
</tbody>
</table>
CYP3A2 and CYP2C6 were more susceptible than CYP1A2 and CYP2E1 to the TAA-induced mechanism-based enzyme inactivation’s. The addition of DDB and reduced GSH to the primary incubation systems had little effect on protecting against TAA-induced enzyme inactivations of P450s (Fig. 6).

**Discussion**

Intensive understanding of P450s dysregulation patterns in liver injury is of critical concern because of its significance in guiding clinical dosage regimen adjustment in patients with liver diseases. Considering that patients with liver diseases are inclined to consume hepatoprotective agents, it is important to understand the mixed effects of pathological factors and hepatoprotective agents on regulating P450s. The present study contributes to confirm that the protein levels and enzyme activities of P450s were decreased in TAA-induced rat cirrhotic livers. Upon NADPH-dependent bioactivation, TAA was able to inactivate enzyme activities of P450s in a time- and concentration-dependent manner. Treatment with hepatoprotective agents SLE and DDB could partially restore TAA-induced protein loss of P450s but had little direct effect on antagonizing enzyme-inactivating effects of TAA.

Dosage regimen adjustment for many therapeutic drugs is necessary for patients with severe liver diseases, because of the dysregulations of various DMEs in damaged livers. However, it remains a difficult issue for designing an ideal dosage adjustment regimen because various DMEs are not altered in a uniform extent in the damaged livers. The case may be further complicated by the concomitant ingestion of hepatoprotective agents that may directly or indirectly regulate the protein expression and/or enzyme activities of DMEs. Taking SLE and DDB as examples, the present study highlighted the importance of studying the regulation of DMEs by hepatoprotective agents in damaged livers. In accordance with a previous report (Nakajima et al., 1998), we confirmed that the protein levels of all the four major P450 isozymes were significantly reduced by chronic TAA intoxication, albeit to a varying extent for different isozymes. Results revealed that the hepatoprotective agents SLE and DDB largely attenuated TAA-induced protein loss of most P450 isozymes. The protein levels of CYP2E1 and CYP3A2 in TAA-intoxicated rats with SLE and DDB treatment were even higher than those in the normal control rats. These results suggest that SLE and DDB may have direct inducing effects on P450s. For this consideration, both protein levels and enzyme activities of major P450s were determined in the healthy rats treated with SLE and DDB for 2 weeks.

![FIG. 4. Western blot analyses of P450s in the liver samples of healthy rats treated with SLE and DDB. Rats were intragastrically treated with SLE and DDB once a day for 2 weeks. Protein expression levels of CYP1A2, CYP2C6, CYP3A2, and CYP2E1 were determined via Western blot analysis; β-actin was used as an internal standard to normalize all samples.](https://example.com/fig4)

![FIG. 5. Time- and concentration-dependent inactivation of P450s by TAA. TAA (0, 5, 50, 200, and 400 μM) was incubated with normal RLMs by adding the NADPH-regenerating system; the remaining enzyme activity was then determined by a typical dilution method. The $k_{obs}$ was obtained from the slope of the individual lines, and these slopes were fit to a Kitz-Wilson plot (inset). A, CYP2C6; B, CYP1A2; C, CYP3A2; D, CYP2E1.](https://example.com/fig5)
Results showed that SLE and DDB treatment could significantly enhance the protein expressions and enzyme activities of most P450 isozymes except CYP1A2, for which an inhibitory effect was observed instead. Previously, we had also confirmed that after long-term consumption, SLE could induce the protein expression of CYP3A2 in both the rat intestine and the rate liver (Lai et al., 2009). Schisandra had been proven to be a strong inducer of CYP3A4 and CYP2C9 through pregnane X receptor in normal hepatocyte cultures (Mu et al., 2006). Together, these results indicate that SLE and DDB have direct inducing effects on P450s, which provides a good explanation about why the protein expression levels of CYP3A2 and CYP2E1 in TAA-intoxicated and SLE/DDB-treated rats are up-regulated to a level higher than that in the normal control. Although SLE and DDB show inhibitory effects in CYP1A2, the loss of CYP1A2 in TAA-damaged livers could be largely restored by treatment with hepatoprotective agents, suggesting a differential regulating effect in between healthy and damaged livers by hepatoprotective agents. These results in combination suggest that the restoration of P450s in damaged livers by hepatoprotective agents may be ascribed to both the direct enzyme-inducing effects and the hepatoprotective-driving consequent effects.

Using the typical probe substrate approach, we found that the enzyme activities of all the major P450s were significantly decreased in TAA-induced cirrhotic livers. We were surprised to find that the enzyme activities of most P450s were not restored in proportion to the protein levels by treatment of hepatoprotective agents. In view that TAA can be bioactivated by CYP2E1 to produce highly reactive metabolite di-S-oxide (Kang et al., 2008), we hypothesized that TAA upon bioactivation may inactivate P450s. Our results showed that TAA exhibited both time- and concentration-dependent inhibitory effect on all the four P450 isozymes when NADPH was added to initiate bioactivations. In contrast, TAA had little effect on inhibiting P450s when NADPH was omitted from the incubation systems. In accordance, we have recently found that TAA could also inactivate UDP-glucuronosyltransferases (UGTs) (Hao et al., 2011). In addition, DDB and GSH could not counteract such an inactivation; this result may suggest that the oxidative stress produced from the procedure of TAA bioactivation has little effect on inactivating P450s. It is thus understandable why the recovery effects of hepatoprotective agents in these enzyme activities are less evident than that in the protein levels of P450s in TAA-intoxicated rats. We have shown that both SLE and DDB had little effect on inhibiting TAA metabolism. Furthermore, the results from the present study suggest that SLE and DDB cannot inhibit CYP2E1, which was identified as the major enzyme responsible for TAA bioactivation and hepatotoxicity. Together, our results suggest that the hepatoprotective effects of SLE and DDB are not likely resourced from the direct influence on the metabolic bioactivation of TAA. In combination with our previous report (Hao et al., 2011), our results provide novel evidence supporting the previous assumption that TAA hepatotoxicity is mainly caused by TAA’s reactive metabolites on covalently modifying macromolecules (Chieli and Malvaldi, 1984). However, it is important to note that the TAA chronic intoxication leads to a differential regulating mode between P450s and

![Fig. 6](https://dmd.aspetjournals.org/)

**Fig. 6.** The effects of DDB and GSH on TAA-induced inactivation of P450s. TAA (50 μM) was incubated with normal RLMs containing a NADPH-regenerating system with or without the addition of DDB (2, 10, and 50 μM) or GSH (0.2, 1, 5 mM); the remaining enzyme activity of CYP2C6, CYP1A2, CYP3A2, and CYP2E1 was then determined by a typical dilution method. *p ≤ 0.05 versus control.

<table>
<thead>
<tr>
<th>P450 Isozymes</th>
<th>$K_I$ (μM)</th>
<th>$k_{inact}$ (min⁻¹)</th>
<th>$k_{inact}/K_I$ (min⁻¹/μM⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>10.558</td>
<td>0.018</td>
<td>0.0017</td>
</tr>
<tr>
<td>CYP2C6</td>
<td>22.812</td>
<td>0.074</td>
<td>0.0033</td>
</tr>
<tr>
<td>CYP3A2</td>
<td>58.914</td>
<td>0.056</td>
<td>0.0010</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>6.700</td>
<td>0.026</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

**TABLE 3**

Mechanism-based inactivation effects of TAA in P450s in vitro

TAA (0, 5, 50, 200, and 400 μM) was incubated with normal rat liver microsomes containing a NADPH regenerating system; the remaining enzyme activity was then determined by a typical dilution method. $K_I$ and $k_{inact}$ values were calculated from the Kitz-Wilson plot; $k_{inact}/K_I$ values were calculated to indicate the inactivation rate.
UGTs, although both can be inactivated by TAA bioactivation. In addition, the effects of hepatoprotective agents on regulating P450s and UGTs are also different. It may deserve further research to delineate the direct effects and underlying mechanisms of TAA’s reactive metabolites on inactivating various DMEs, thus providing strong scientific evidence on explaining the diverse regulating patterns of DMEs in TAA-induced cirrhotic livers.

On the basis of the TAA-induced liver fibrosis/cirrhosis model and the study of SLE and DDB, the present study highlights the importance of investigating the mixed effects of hepatic pathological factors and treatment by hepatoprotective agents on regulating P450s. Our results show that TAA intoxication causes a tremendous loss of P450s, whereas the treatments with the hepatoprotective agents SLE and DDB attenuate the protein loss of P450s. SLE and DDB have a direct inducing effect on most of the P450 isozymes except CYP1A2 in healthy rats. TAA exhibits a NADPH-, time-, and concentration-dependent inactivating effect on all of the four P450 isozymes, and both DDB and GSH have little effect on countering such an inactivation effect, providing a good explanation about the disproportionate recovery of protein levels and enzyme activities of P450s by treatment with hepatoprotective agents. Hopefully, our results will stimulate wide interest in investigating the effects of various hepatoprotective agents on regulating DMEs in injured livers, the understanding of which is pivotal in guiding the design of a dosage adjustment regimen for patients with severe liver diseases.

Authorship Contributions

Participated in research design: Y. Xie, G. Wang, and Hao.

Conducted experiments: Y. Xie, H. Wang, Jiang, Yao, Kang, Zhou, T. Xie, and Hao.

Performed data analysis: Y. Xie and Hao.

Wrote or contributed to the writing of the manuscript: Y. Xie and Hao.

References


Cytochrome P450 dysregulations in thioacetamide induced liver cirrhosis in rats and the counteracting effects of hepatoprotective agents

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Drug Metabolism and Disposition

Supplemental Fig.1. Serum biochemical parameters of liver function after 6 weeks of TAA intoxication. Rats were treated with TAA for 4 weeks and then co-treated with or without SLE/DDB for another 2 weeks. Data are expressed as percentage (%) of control values (mean ± S.D., n=6). * p≤0.05, ** p≤0.01, vs. normal control; † p≤0.05, †† p≤0.01, vs. TAA control.