Inhibition of Matrix Metalloproteinases Minimizes Hepatic Microvascular Injury in Response to Acetaminophen in Mice

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The acetaminophen (APAP)-induced hepatic centrilobular necrosis is preceded by hepatic microcirculatory dysfunction including the infiltration of erythrocytes into the space of Disse. The purpose of this study was to examine the involvement of matrix metalloproteinases (MMPs) in the hepatic microvascular injury elicited by APAP. Male C57Bl/6 mice were pretreated with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, an MMP-2/MMP-9 inhibitor (5 mg/kg, ip) 30 min before oral gavage with 600 mg/kg of APAP. The hepatic microvasculature in anesthetized mice was observed using established in vivo microscopic methods 2 and 6 h after APAP. The levels of mRNAs and activities of MMP-2 and MMP-9 in the liver were increased from 1 h through 6 h after APAP gavage. APAP increased alanine transferase (ALT) levels (41.1-fold) and resulted in centrilobular hemorrhagic necrosis at 6 h. Pretreatment with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid attenuated ALT values by 71% as well as the necrosis. APAP decreased the numbers of perfused sinusoids in centrilobular regions by 30% and increased the area occupied by infiltrated erythrocytes into Disse space. 2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid restored the sinusoidal perfusion to 90% of control levels and minimized extrasinusoidal area occupied by erythrocytes. The present study showed that increased MMPs during APAP intoxication are associated with hepatocellular damage and with hepatic microcirculatory dysfunction including impaired sinusoidal perfusion and infiltration of erythrocytes in Disse space. 2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid attenuated APAP-induced parenchymal and microvascular injury. These results suggest that MMPs participate in APAP hepatotoxicity mediated by sinusoidal endothelial cell injury, which results in impairment of microcirculation.

Key Words: microcirculation; sinusoidal endothelial cell; hemorrhage; hepatotoxicity.

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(Deleve et al., 2003b; Hanumegowda et al., 2003) as well as in cold preservation injury of the liver in humans and in rats (Upadhya et al., 1997). The similar pattern of SEC injury to monocrotaline and cold preservation suggests that MMPs are responsible for hepatic microvascular injury in response to toxic doses of APAP, and that inhibition of MMPs might attenuate APAP-induced liver injury. As a result, the present study was conducted to examine the effect of an MMP inhibitor on hepatic microcirculation after APAP administration using in vivo microscopic methods (McCuskey, 1986).

MATERIALS AND METHODS

Experimental animals. Male C57Bl/6 mice (7–8 weeks of age), weighing 23–25 g, were purchased from Charles River Laboratories (Charles River, ME), and were used for these experiments. All animals were allowed free access to food and water and were fasted 24 h before the experiments. The present study was performed in adherence to the National Institutes of Health guideline for the use of experimental animals and followed protocol approved by the Animal Care and Use Committee of the University of Arizona. Acetaminophen (600 mg/kg liquid Tylenol; McNeil-PPC, Ft. Washington, PA) was given to mice by oral gavage. At 30 min before APAP gavage, the MMP-2/MMP-9 inhibitor 2-{[(4-biphenylsulfonyl) amino]-3-phenyl-propanic acid (Calbiochem, La Jolla, CA) 0.5 and 5 mg/kg, ip) was administered. The mean inhibitory concentrations (IC50) for MMP-2 and MMP-9 are 0.31 and 0.24 μmol/l, respectively, in in vitro enzymatic assay using synthetic substrates (Tamura et al., 1998). Animals receiving the same amount of vehicle (1% DMSO) served as controls.

In vivo microscopy. Animals were anesthetized with urethane (2 mg/g b.w., subcutaneously). The hepatic microvascular responses were examined using established high resolution in vivo microscopic methods (McCuskey, 1986). Briefly, a compound binocular microscope (Leitz, Wetzlar, Germany) adapted for in vivo microscopy was equipped to provide either transillumination or epifluorescence, as well as video microscopy using a charge-coupled device (CCD) camera (MTI, Michigan City, IN). The liver was exteriorized through a left subcostal incision and positioned over a window of optical grade mica in a specially designed tray mounted on a microscopic stage. The tray provided for the drainage of irrigating fluids, and the window overlaid a long working distance condenser. The liver was covered by a piece of Saran Wrap (Dow Chemical, Midland, MI), which held it in position and limited movement. Homeostasis was insured by a constant suffusion of the organ with Ringer’s solution maintained at body temperature. With the ×80/0.1 numerical aperture water immersion objective (Leitz 80×/1.00, Wetzlar, Germany) employed for these studies, the methods permitted visualization of the cells comprising the sinusoidal lining, the formed elements of the blood, the nuclei, nucleoli, mitochondria, and fat droplets in hepatic cells, and bile canaliculi. Under optimal conditions, the resolution was 0.3–0.5 μm. Microvascular events were observed and recorded for at least 30 s for subsequent off-line analysis using a Sony Betacam video tape recorder (Sony Medical Electronics, Park Ridge, NJ).

Kupffer cell function was assessed by measuring the phagocytosis of fluorescent 1.0-μm latex particles (Fluoresbrite-fluorescent monodispersed polystyrene microspheres; Polysciences, Warrington, PA) by individual cells. The latex was diluted 1:10 with sterile saline and injected in 0.1 ml volume through a mesenteric vein using a 30-gauge lymaphangiography needle (Becton Dickinson and Co., Franklin Lakes, NJ). The distribution and relative number of phagocytic Kupffer cells was measured by counting the number of cells that phagocytosed latex particles in a standardized microscopic field 15 min after each mice had received the injection of latex. To assess regional distribution, the number of phagocytic Kupffer cells per microscopic field was counted in ten perportal and ten centrilobular regions in each animal. The relative adequacy of blood perfusion through the sinusoids was evaluated by counting the number of perfused sinusoids in the same ten microscopic fields in which the numbers of phagocytic sinusoids were determined. Because reduced perfusion of individual sinusoids can limit the delivery of the latex particles to Kupffer cells in these vessels, the ratio of Kupffer cells that phagocytosed latex particles to perfused sinusoids was used as an overall index of Kupffer cell phagocytic activity.

To examine the interaction of leukocytes with the sinusoidal wall, quantification of leukocytes adhering to the endothelial lining of sinusoids was calculated by counting the number of leukocytes per unit length of sinusoid (adherent leukocytes/100 μm) in the same microscopic fields. A leukocyte was defined as adhering to the sinusoidal wall if it remained stationary for at least 30 s. The results were averaged, and the data were represented as the average number in each animal.

To quantify the extent of hemorrhage elicited by APAP gavage, the area occupied by extrasinusoidal red blood cell (RBC)s was measured in the same microscopic fields using a computer-assisted digital imaging processor (Scion Image, Scion Corp., Frederick, MD). The results were expressed as extrasinusoidal area occupied by RBCs (μm²/10 centrilobular regions).

Sampling and ALT assay. In a separate set of experimental animals, blood was collected from the inferior vena cava, and the samples were separated by centrifugation at 13,000 × g for 5 min at 4°C. The samples were stored at −70°C until assays were performed. The serum activities of alanine aminotransferase (ALT) were measured by enzymatic procedures using a diagnostic kit (Sigma Chemical Co., St. Louis, MO).

Histology. The hepatic tissues were immediately fixed with 10% formalin. After fixation, the tissues were dehydrated with a graded series of ethanol solutions and embedded in paraffin. The sections (5 μm) from the paraffin-embedded tissues were stained with hematoxylin and eosin (H&E).

MMPs activity assay. The liver was perfused with phosphate buffered saline (PBS) and was removed from the animal. Then the left lobe of the liver was sectioned into 0.5 cm blocks, snap frozen in liquid nitrogen, and stored at −70°C until assays were performed. The levels of MMP-2 and MMP-9 were measured by a commercially available ELISA kit (Amersham Biosciences, Piscataway, NJ). Briefly, 25 mg of the liver tissue was homogenized in 50 mM Tris-HCL containing 1 mM monothioglycerol. The homogenized samples were centrifuged at 13,000 × g for 10 min. Following the manufacturer’s instructions, 100 μl of either standard or experimental sample(s) was added to the designated wells and incubated overnight at 4°C. After incubation, the plate was washed four times and blotted dry. Aminophenylmercuric acetate (AMPA) was added to all wells, and the plate was incubated at 37°C. Then the plate was read at a wavelength of 405 nm using an ELISA plate reader. Total MMP-2 and MMP-9 activity was calculated using the standard curve for this assay. The results were expressed as ng/g liver tissue.

Semiquantitative analysis of MMP-2 and -9 mRNA. The liver was perfused with PBS and was removed from the animal. Part of the left lobe of the liver was cut into 0.1-cm blocks and placed into a cryovial containing 1.5 ml of RNALater (Qiagen Valencia, CA) and equilibrated at 4°C overnight then stored at −70°C until assays were performed. Total RNA was extracted from the tissue using a commercially available kit (Promega, Madison, WI). Total RNA was quantitated using a spectrophotometer 260/280 program and stored at −70°C. Semiquantitative RT-PCR was performed using a PCR kit (USB, Cleveland, Ohio). To standardize the reactions, the primers for murine β-actin (Chemicon, Temecula, CA), MMP-2, and MMP-9 (BioMol, Plymouth Meeting, PA) were added to each reaction tube and all three cDNAs were amplified. From preliminary experiments, we determined 28 cycles to be optimal. Briefly, 10 μl of PCR product and standards were added to designated wells. Denaturing solution was added to all wells and incubated for 10 min. After incubation, hybridization buffer was added to each well and incubated for 30 min at 37°C. The plate was then washed three times and blotted dry. The Strep-HPR conjugate was added to all wells, and the plate was incubated for 30 min. The Strep-HPR conjugate was aspirated off, and the plate was washed three times. Finally 100 μl of substrate was added, and the plate was incubated for 10 min at 37°C. After incubation 100 μl of stop solution was added to each well. The plate was
immediately read on an ELISA plate reader at 450 nm. MMP-2 and -9 levels were calculated from the standard curve generated in this assay.

**Measurement of hepatic total glutathione.** Hepatic total glutathione (GSH) was determined colorimetrically using a commercially available kit (Oxford Biomedical Research, Oxford, MI) as described previously (Ito et al., 2004).

**Statistical analysis.** All data were expressed as means ± SE. Multiple comparisons were performed using one-way analysis of variance (ANOVA) with a post-hoc Fisher’s test. Differences were considered to be significant for $p$ values less than 0.05.

**RESULTS**

Figure 1A shows time course of changes in the levels of MMP-2 and MMP-9 total activities in the liver after oral gavage with 600 mg/kg APAP. The levels of total MMP-2 activity were significantly increased from 2 h (3.2-fold) through 6 h (4.4-fold) after APAP gavage. The levels of total MMP-9 activity did not change significantly up to 4 h, but were increased (3.6-fold) by 6 h. Total MMP-9 activity was lower than total MMP-2 activity at each time point. We also tried to detect active forms of MMP-2 and MMP-9; however, all of these levels were below the detection levels (data not shown). This low availability of active forms of MMP-2 and MMP-9 may be attributed to the removal of extracellular active forms of the enzymes during the procedure of washing the liver with PBS to clear out the blood elements.

Figure 1B illustrates changes in the mRNA expression of MMP-2 and MMP-9 in the liver treated with APAP. The levels of MMP-2 mRNA expression were progressively increased from 1 (2.7-fold) to 6 h (6.7-fold) after APAP gavage, when compared with those in untreated liver (time = 0). Also, hepatic expression of MMP-9 mRNA was increased from 1 (2.3-fold) to 6 h (3.4-fold). These findings suggest that APAP induced *de novo* synthesis of pro forms of MMPs.

To determine whether inhibition of MMPs attenuates liver injury elicited by APAP, 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, an MMP-2/MMP-9 inhibitor (0.5 and 5 mg/kg) or vehicle (1% DMSO in PBS) was given. Figure 2A shows the effect of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid on ALT levels 6 h after APAP administration. Oral gavage with APAP caused a significant increase in ALT levels (41.1-fold) when compared with water-gavaged mice. Pretreatment with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid decreased ALT levels by 71.3% in a dose-dependent manner. Oral gavage with APAP exhibited centrilobular necrosis associated with hemorrhage and congestion (Fig. 2B). 2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid reduced hemorrhagic centrilobular necrosis; however, it failed to eliminate the necrosis completely (Fig. 2C). Based on these results, we selected a dose of 5 mg/kg 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid for remaining studies.

Table 1 summarizes the effects of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid on liver microcirculation at 2 h after APAP gavage. Although 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid did not change the sinusoidal perfusion and Kupffer cell phagocytic activity in mice treated with APAP, it significantly reduced the infiltration of RBCs in the space of Disse. As shown in Figure 3, the numbers of perfused sinusoids in periportal and centrilobular regions 6 h after APAP gavage were significantly decreased by 13.1% and 30.0%, respectively, when compared with water-gavaged animals (Fig. 3A). Pretreatment with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid restored the sinusoidal perfusion to 90% of control levels. APAP increased the area occupied by infiltrated RBCs in Disse space, and 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid significantly reduced the infiltration of RBCs (Fig. 3B). Although the administration of APAP increased Kupffer cell phagocytic activity in periportal and centrilobular regions by 1.2-fold and 1.7-fold, respectively, 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid did not change the phagocytic activity in mice receiving APAP (Fig. 3C). APAP failed to induce any changes in the numbers of leukocytes adhering to the sinusoids (data not shown).

2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid reduced total activity of MMP-2 (25.6%) and MMP-9...
FIG. 2. Effect of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, an MMP-2/MMP-9 inhibitor on liver injury 6 h after APAP administration. Mice were pretreated with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid (0.5 or 5 mg/kg, ip) 30 min before APAP gavage. (A) 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid reduced ALT levels in mice treated with APAP. Veh, vehicle; MMPI, matrix metalloproteinase-2 and -9 inhibitor, 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid. Data are the means ± SE from five to seven mice per group. *p < 0.05 versus water-gavaged mice pretreated with vehicle. †p < 0.05 versus APAP-gavaged mice pretreated vehicle. (B) There was significant centrilobular necrosis together with hemorrhage and congestion. (C) 2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid reduced necrosis and hemorrhage. Arrow heads indicate infiltration of erythrocytes. CV, central vein. Original magnification, ×400.

TABLE 1
Effects of Pretreatment of Mice with 2-[(4-Biphenylsulfonyl) Amino]-3-Phenyl-propionic Acid on Liver Microcirculation 2 Hours After APAP Gavage

<table>
<thead>
<tr>
<th>APAP gavage</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>MMPI</td>
</tr>
<tr>
<td>No. of perfused sinusoids (/field)</td>
<td>4.9 ± 0.1</td>
<td>4.9 ± 0.1</td>
</tr>
<tr>
<td>Periportal</td>
<td>4.0 ± 0.1</td>
<td>4.2 ± 0.1</td>
</tr>
<tr>
<td>Centrilobular</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.0</td>
</tr>
<tr>
<td>Kupffer cell phagocytic activity</td>
<td>0.6 ± 0.1</td>
<td>0.4 ± 0.0</td>
</tr>
<tr>
<td>Periportal</td>
<td>161.1 ± 70.3</td>
<td>0.0 ± 0.0*</td>
</tr>
<tr>
<td>Centrilobular</td>
<td>161.1 ± 70.3</td>
<td>0.0 ± 0.0*</td>
</tr>
<tr>
<td>Area occupied by infiltrated RBCs in Disse space (μm²/10 centrilobular regions)</td>
<td>161.1 ± 70.3</td>
<td>0.0 ± 0.0*</td>
</tr>
</tbody>
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Data are shown as means ± SE. Mice were pretreated with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, an MMP-2/MMP-9 inhibitor (MMPI) (5 mg/kg, ip) or vehicle (1% DMSO) 30 min before oral gavage with APAP (600 mg/kg). There were 6 animals in each group.

*p < 0.05 vs. vehicle-treated mice.

(29.8%) in the liver from mice treated with APAP, although this inhibitor did not significantly change the levels of MMP-2 and MMP-9 mRNAs in the liver (Table 2).

The bioactivation of APAP during the initiation phase of the liver injury causes a significant decrease in hepatic GSH levels, which correlates with APAP hepatotoxicity (Mitchell et al., 1973b). To address the question whether 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid may affect APAP bioactivation, we measured hepatic GSH levels. As shown in Table 3, total hepatic GSH levels 1 h after APAP gavage were decreased by 69.7% in comparison with those at time 0. In animals pretreated with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, GSH contents 1 h after APAP also were reduced to the similar levels to animals pretreated with vehicle.

DISCUSSION

The results of the present study show that MMP-2 and MMP-9 mRNA expression and activity in the liver are increased following a toxic dose of APAP gavage. Increased MMP activity is associated with hepatocellular damage as indicated by increased ALT levels and centrilobular necrosis and with hepatic microcirculatory disturbances including reduced sinusoidal perfusion and infiltration of RBCs in Disse space. The MMP-2/MMP-9 inhibitor, 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid attenuates APAP-induced increased ALT levels and liver microcirculatory dysfunction. These observations suggest that MMPs participate in APAP hepatotoxicity mediated by early SEC injury, which results in impairment of microcirculation.

Oral gavage with APAP induced hepatic mRNA expression of MMP-2 and MMP-9 as early as 1 h after APAP. At the same time, MMP-2 in the liver was activated 2 h after APAP, and MMP-9
activation was shown at 6 h after APAP. The reasons for the disconcordance between mRNA levels and enzyme activity for MMP-9 within 6 h after APAP gavage remain unclear; however, the induced levels of MMP-9 mRNA from 1 to 4 h after APAP gavage were not sufficient for MMP-9 activation. The levels of mRNA expression of MMP-2 and MMP-9 following APAP gavage were the same, though the activity of MMP-2 was significantly higher than that of MMP-9. These results indicate that increased hepatic expression and activity of MMP-2 and, to a lesser degree, of MMP-9 correlated with liver injury elicited by APAP. Recently, Gardner et al. (2002) have reported that MMP-9 mRNA expression is increased 18 h after an intraperitoneal administration of 300 mg/kg APAP to mice, but not at 6 h after. The different results between others and us may be due to different doses and routes of APAP administration. Late induction of MMP-9 may be related to regression of hepatic necrotic tissue following acute injury.

It is known that Kupffer cells and hepatic stellate cells have the capacity to secrete MMPs (Arthur et al., 1989; Knittel et al., 1999; Theret et al., 1999; Winwood et al., 1995). Recently, isolated SECs from rat liver are suggested to be another source of MMPs (Deleve et al., 2003; Upadhya and Strasberg, 1999). In addition, increased activity of MMPs including MMP-2 and MMP-9 is demonstrated in isolated SECs from the rat liver exposed to cold preservation (Upadhya et al., 1997) and to...
monocrotaline (Deleve et al., 2003b). However, major sources of MMPs in APAP hepatotoxicity remained to be elucidated.

Induction of MMP-2 and MMP-9 during APAP hepatotoxicity indicates that MMPs play a role in the injury. As a result, mice were treated with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid, an MMP-2/MMP-9 inhibitor, prior to APAP gavage. The pretreatment with 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid reduced ALT levels, an indicator of liver injury, by inhibiting activities of MMP-2 and MMP-9. However, its inhibitory effect on ALT levels was partial, as evidenced by sustained relatively high values of ALT, which was consistent with histological findings of remaining necrosis in centrilobular hepatocytes. Early induction of MMP-2 and MMP-9 also was associated with occurrence of the infiltration of RBCs in Disse space at 2 h after APAP gavage, when the levels of transaminase remain unchanged (Ito et al., 2003). 2-[(4-Biphenylsulfonyl) amino]-3-phenyl-propionic acid eliminated the infiltration of RBCs during the early phase of APAP toxicity. In addition, the administration of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid attenuated APAP-induced hepatic microcirculatory dysfunction, including impaired sinusoidal perfusion and infiltration of RBCs in Disse space at 6 h after APAP treatment. Histological studies also revealed that MMP inhibitor eliminated hemorrhage. These findings suggest that inhibition of MMPs attenuated SEC injury to APAP, as indicated by elimination of infiltrated RBCs in Disse space, and restored sinusoidal blood flow. Alternatively, induction of MMPs may be involved in gap formation in SECs of the liver treated with toxic doses of APAP, leading to penetration of RBCs in the space of Disse and to dehiscence of SEC from the space of Disse. Although the inhibitory effects of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid on enzyme activities for MMP-2 and MMP-9 are partial (approximately 30% decrease), prevention of accumulation of RBCs from the early stage of APAP toxicity would minimize ischemic parenchymal cell injury following a toxic dose of APAP gavage and thereby suppress raised ALT values after APAP gavage.

It has been suggested that cold preservation of SECs and treatment of SECs with monocrotaline cause disassembly of filamentous (F)-actin, which in turn mediates the secretion of MMPs from SECs (Deleve et al., 2003b; Upadhya and Strasberg, 1999). The initial morphological changes in SECs during cold preservation injury and monocrotaline-induced sinusoidal obstruction syndrome (hepatic veno-occlusive disease) include rounding up and an appearance of gap formation in SECs (Deleve et al., 1999, 2003a; Momii and Koga, 1990). The actin cytoskeleton play a role in maintaining cell shape, and depolymerization of F-actin results in the structural changes in cellular cytoskeleton characterized by rounding up of SECs and gap formation in SECs. Release of MMPs as a result of F-actin disassembly also contribute to digestion of component of tissue matrix such as fibronectin and type IV collagen in the space of Disse, leading to the Disse space enlargement (Walker et al., 1983), and to detachment of SECs from the Disse space. However, the mechanisms by which APAP injures SECs are unknown.

The bioactivation of APAP, resulting in the formation of the reactive metabolite, presumably NAPQI, depletes intracellular sources of GSH (Mitchell et al., 1973b). To determine whether the protective effect of MMP-2/MMP-9 inhibitor was through inhibition of metabolic activation of APAP, hepatic GSH was measured in APAP-gavaged mice receiving the inhibitor. The results showed that MMP inhibitor did not suppressed the initial dropped hepatic total GSH levels following APAP gavage, suggesting that inhibitory effect of 2-[(4-biphenylsulfonyl) amino]-3-phenyl-propionic acid on liver injury is not mediated through a decrease in bioactivation of APAP.

In summary, increased MMPs during APAP intoxication are associated with hepatocellular damage and with hepatic microcirculatory dysfunction including impaired sinusoidal perfusion and infiltration of RBCs in the Disse space. Inhibition of MMPs attenuates APAP-induced liver injury and may provide a useful therapy for the prevention of APAP hepatotoxicity.

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REFERENCES


