15-Deoxy-$\Delta^{12,14}$-prostaglandin J$_2$ prevents inflammatory response and endothelial cell damage in rats with acute obstructive cholangitis

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Watanabe K, Yokoyama Y, Kokuryo T, Kawai K, Kitagawa T, Seki T, Nakagawa A, Nagino M. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J$_2$ prevents inflammatory response and endothelial cell damage in rats with acute obstructive cholangitis. Am J Physiol Gastrointest Liver Physiol 298: G410–G418, 2010. First published January 7, 2010; doi:10.1152/ajpgi.00233.2009.—Acute obstructive cholangitis (AOC) due to infections in the bile duct is a common disease with a high mortality rate. Ligands for peroxisome proliferator-activated receptor-$\gamma$ (PPAR$\gamma$), such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J$_2$ (15D-PGJ$_2$), have been proposed as a new class of anti-inflammatory compounds. This study investigated the effect of 15D-PGJ$_2$ treatment on lipopolysaccharide (LPS)-induced acute obstructive cholangitis. The rats were randomly assigned to five groups: sham operation (Sham; simple laparotomy), sham operation with intraperitoneal saline infusion (Sham+Saline), sham operation with intraperitoneal LPS infusion (Sham+LPS), bile duct ligation (BDL) with saline infusion into the bile duct (BDL+Saline), and BDL with LPS infusion into the bile duct (BDL+LPS). Biochemical assays of blood samples, histology of the liver, portal venous pressure, hyaluronic acid clearance, and expression of inflammation-associated genes in the liver were evaluated. Furthermore, the Sham+LPS and the BDL+LPS group were divided into two groups (with and without 15D-PGJ$_2$ treatment), and their survival rates were compared. Biochemical assays of blood samples, portal venous pressure, hyaluronic acid clearance, and expression of inflammation-associated genes in the liver were all significantly higher in the BDL+LPS group compared with those in the BDL+Saline group, indicating the presence of increased liver damage in the first group. However, preoperative administration of 15D-PGJ$_2$ significantly improved these outcomes. Furthermore, the survival rate after establishment of cholangitis was significantly improved by the administration of 15D-PGJ$_2$ in the BDL+LPS group. These results clearly demonstrate that 15D-PGJ$_2$ inhibits the inflammatory response and endothelial cell damage seen in acute obstructive cholangitis and could contribute to improve the outcome of this pathology.

bile duct ligation; hyaluronic acid clearance; NF-\kappaB; portal venous pressure

ACUTE OBSTRUCTIVE CHOLANGITIS (AOC) due to infections in the biliary tract is a common occurrence in the clinical setting. Despite recent advances in the treatment of infectious diseases, AOC remains a significant cause of morbidity and mortality. One of the leading reasons for AOC-related death is acute liver failure, which can be triggered by an excessive inflammatory response in the liver. However, the precise mechanism of AOC-induced acute liver failure remains unclear.

A number of reports have focused on the role of proinflammatory cytokines, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and interleukin-6 (IL-6), in the pathophysiology of organ injury from AOC (14). Increases in the levels of these proinflammatory cytokines have been shown to correlate strongly with the severity of multiple organ failure and with the mortality from AOC (12). Exaggerated endogenous production of these proinflammatory cytokines is likely responsible for complications associated with sepsis, such as liver tissue injury (19, 36). Moreover, recent investigations have shown that the expression of several inflammatory cytokines is closely linked to the activation of transcriptional factors. For example, nuclear factor-$\kappa$B (NF-$\kappa$B) plays a critical role in sepsis, directing the transcription of many proinflammatory cytokine genes in animals of this pathology (38). It was also shown that NF-$\kappa$B expression is upregulated after AOC in both rats and humans (14, 41). In addition to an inflammatory response, injury to endothelial cells in the microvasculature is critical for the development of hepatic parenchymal cell injury in several liver-injury models, such as transplantation (4), ischemia-reperfusion (39), and sepsis model (43).

Peroxisome proliferator-activated receptor-$\gamma$ (PPAR$\gamma$) is a member of the nuclear receptor superfAMILY and a ligand-activated transcription factor with effects on inflammation, atherosclerosis, and cell proliferation. PPAR$\gamma$ forms a heterodimer with the retinoid X receptor, and upon activation by its ligands it binds to the PPAR response element in the promoter of genes allowing for transcription (49). Several experimental studies have shown that the natural PPAR$\gamma$ ligand, 15-deoxy-$\Delta^{12,14}$-prostaglandin J$_2$ (15D-PGJ$_2$), has potent anti-inflammatory properties (20). 15D-PGJ$_2$ is derived from arachidonic acid via the cyclooxygenase (COX) pathway through a series of dehydration steps. It has been shown that this natural PPAR$\gamma$ ligand inhibits the expression of several inflammatory response genes, including those encoding for the inducible nitric oxide synthase (iNOS), TNF-$\alpha$, gelatinase B, and COX-2. This inhibition is thought to be due to its antagonism of the activities of the activator protein-1 transcription factors and NF-$\kappa$B (33). On the basis of these findings, it can be postulated that 15D-PGJ$_2$ could prevent severe inflammatory responses induced by AOC, and it could have a beneficial effect on the outcome of AOC. However, this hypothesis has yet to be tested.

In this study, we characterized an animal model of AOC using a rat bile duct ligation (BDL) with lipopolysaccharide (LPS) infusion into the bile duct, which was previously described by Lee et al. (22). Thereafter, we investigated whether the PPAR$\gamma$ ligand 15D-PGJ$_2$ can decrease the inflammatory response and the subsequent liver damage and whether it can improve the survival rate in severe infectious conditions such as AOC.
ROLE OF 15D-PGJ2 IN ACUTE OBSTRUCTIVE CHOLANGITIS

MATERIALS AND METHODS

Materials. The natural PPARγ ligand 15D-PGJ2 was purchased from Biomol (Plymouth Meeting, PA). All other chemicals were purchased from Sigma Chemical (St. Louis, MO).

Animal and surgical procedure for ligation of the bile duct. Male Wistar rats (250–300 g) were purchased from SLC (Tokyo, Japan). The animals were kept in a temperature- and humidity-controlled environment in a 12-h light-dark cycle. Animals were allowed free access to water and food at all times. All experiments were approved by the University Committee on Animal Research, and all experimental animals received humane care in accordance with National Institutes of Health publication 86-23 “Guide for the Care and Use of Laboratory Animals.” The rats were randomly assigned to five groups: sham operation (Sham), sham operation with intraperitoneal saline infusion (Sham+Saline), sham operation with intraperitoneal LPS infusion (Sham+LPS), BDL with saline infusion into the bile duct (BDL+Saline), and BDL with LPS infusion into the bile duct (BDL+LPS). For intraperitoneal or intra-bile duct infusion, 0.2 ml of saline or LPS (1 mg/ml, purified from Escherichia coli O111:B4, Sigma, L2630-100MG) was used. All surgical procedures were performed under general anesthesia by inhalation of the diethyl ether. In the Sham group, the bile duct was isolated but not ligated. In the BDL group, the abdomen was opened by a median incision and a PE-10 polyethylene catheter (Imamura, Tokyo, Japan) was placed and tied with 5-0 silk on the bile duct. A microsyringe was connected to the catheter, and saline or LPS was slowly infused into the bile duct. The volume of fluid infused into the bile duct was based on a previous study showing that infusion of 0.20 ml of contrast material does not cause parenchymography (21). Thereafter, the bile duct was ligated at the proximal side of the PE-10 polyethylene catheter. Then, the PE-10 polyethylene catheter was removed and the distal side of the bile duct was ligated. The rats were euthanized 1, 3, 12, and 24 h after the surgery (n = 6–8 in each time point), and blood and liver tissue samples were harvested from the euthanized animals.

For another experiment, 15D-PGJ2, a ligand for PPARγ, was used to investigate the effects of PPARγ activation on LPS-induced acute liver injury. The rats were allocated into four experimental groups as follows: 1) Sham+LPS+15D-PGJ2; 2) Sham+LPS+Vehicle; 3) BDL+LPS+15D-PGJ2; and 4) BDL+LPS+Vehicle. Rats in the Sham+LPS and BDL+LPS groups received an injection of 15D-PGJ2 (0.5 mg/kg, bolus ip) 1 h prior to the surgical procedure. In contrast, 10% (vol/vol) dimethylsulfoxide (1 ml/kg, bolus ip) was used as vehicle agent. To assess the effect of 15D-PGJ2 on survival rates after severe cholangitis, 126 rats were divided into four experimental groups and monitored daily after the surgical treatment. In this experiment, two different concentrations of LPS (1 or 5 mg/ml) were used. In an additional experiment aimed to assess the effect of 15D-PGJ2 on survival rates after severe cholangitis, 64 rats in the four groups were euthanized 3 or 24 h after BDL to sample the plasma and liver tissue (n = 8 in each time point, LPS 1 mg/ml only).

Biochemical assay of blood sample. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), hyaluronic acid (HA), and total bilirubin (T-Bil) were measured by standard laboratory methods.

Histological changes after BDL. The liver tissue samples were immersed immediately in 10% buffered formalin and stored overnight. The samples were then dehydrated in a graded ethanol series and embedded in paraffin. Six-micrometer-thick sections were mounted on glass slides and stained with hematoxylin and eosin or Masson’s trichrome (for detection of fibrin).

Isolated liver perfusion study. The isolated liver perfusion was performed using a constant flow rate (30 ml/min), as described previously (6), with only minor modification. The rats were anesthetized with pentobarbital sodium (50 mg/kg ip). The liver was exposed through a wide transverse incision, and the portal vein was isolated and cannulated with a PE-200 catheter. The liver was perfused with

Fig. 1. Plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), hyaluronic acid (HA), and total bilirubin (T-Bil) levels at 1, 3, 12, and 24 h following bile duct ligation (BDL) or sham operation. Blood samples were obtained from the abdominal aorta. Data are means ± SE of 8 animals in each group. *P < 0.05 vs. Sham+LPS by ANOVA. **P < 0.05 vs. BDL+Saline by ANOVA.
warmed Krebs-Henseleit bicarbonate buffer (118 mmol/l NaCl, 4.7 mmol/l KCl, 1.2 mmol/l MgSO4, 1.2 mmol/l KH2PO4, 25 mmol/l NaHCO3, 0.1 mmol/l EDTA, and 2.5 mmol/l CaCl2; pH 7.4) for 10 min to wash out the blood. The perfusate was pumped from a reservoir into an overflow chamber and oxygenated using a disperser (95% O2-5% CO2). The temperature of perfusate was maintained at 37°C by warming the reservoir in a water bath. A pressure transducer was placed in line immediately before the portal inlet cannula to monitor the portal venous pressure (PVP).

**HA clearance and liver wet/dry weight ratio.** Clearance of HA was measured to determine sinusoidal endothelial cell damage. Livers in all three groups were perfused 24 h after the surgery. Each liver was perfused with Krebs-Henseleit bicarbonate buffer with a flow rate at 30 ml/min over the first 10-min period with a nonrecirculating system. Then the perfusion was changed to a recirculating system for the next 30 min. The total volume of the circulation buffer was maintained at 200 ml. Forty micrograms of HA (the final concentration, 200 ng/ml in the perfusate) was added to the Krebs-Henseleit bicarbonate buffer immediately after the recirculation started. During the reperfusion period and after 10 min allowed for stabilization, a small amount of perfusate was taken from the reservoir every 10 min for HA clearance assessment. HA levels were measured in perfusate samples by an enzyme-linked protein assay (Corgenix, Westminster, CO). After 30 min of reperfusion, the total liver was prepared for wet/dry weight ratio determination. The liver wet/dry weight ratio was determined to estimate the water content of the liver tissue, which is an indirect indicator of tissue edema and the endothelial cell injury.

**Determination of liver mRNA expression by real-time RT-PCR.** To measure changes in gene expression related to the inflammatory response, quantitative real-time RT-PCR analysis was performed with an Applied Biosystems Prism 7300 sequence detection system (Applied Biosystems, Foster City, CA). Total RNA was isolated from liver tissues by using a Qiagen RNeasy mini kit (Qiagen, Duesseldorf, Germany) according to the manufacturer’s protocol. cDNA was generated from the total RNA samples with use of a SuperScript III reverse transcriptase reagent (Invitrogen, Carlsbad, CA). Each reaction was performed in a 20-μl reaction mixture containing cDNA, each probe and primer set, and a 2× PCR Master Mix (Applied Biosystems). TaqMan gene expression assays (Applied Biosystems) for IL-6, TNF-α, NF-κB, iNOS, endothelial nitric oxide synthase (eNOS), PPARγ, and 18S rRNA (endogenous control) were purchased.

Fig. 2. Representative histological samples from Sham, BDL+Saline, and BDL+LPS livers at 3 h and 24 h after surgery. The micrographs are hematoxylin and eosin (H & E) and Masson trichrome staining of paraffin-embedded liver samples (×20 objective). Arrows indicate fibrin accumulation in the hepatic parenchyme.
HA clearance and wet/dry weight ratio using isolated liver/BDL group compared with the BDL, the baseline PVP was significantly higher in the BDL circulatory disturbance in our cholangitis model. At 24 h after damage. Therefore, we performed isolated liver perfusion to venous system, and it is associated with hepatic endothelial cell condition is mainly due to the increased resistance in the portal area, which was further confirmed by Masson's trichrome staining (Fig. 2, arrows). Previous studies have suggested that the BDL LPS group presented some fibrin accumulation in the portal area, which was further confirmed by Masson’s trichrome staining (Fig. 2, arrows). Previous studies have suggested that fibrin accumulation may be associated with the development of endothelial cell injury (10, 44). Therefore, the results indicated that the BDL+LPS group presented more severe hepatic endothelial damage than other groups.

**RESULTS**

*Plasma parameters for hepatic function.* The plasma AST and ALT levels were significantly higher after BDL compared with those after sham operation (Fig. 1). At 12 and 24 h after BDL, the levels of AST and ALT were further increased by an infusion of LPS into the bile duct (the BDL+LPS group). This indicated that, compared with BDL with saline infusion (the BDL+Saline group), BDL with LPS infusion induced more damage to the liver. In contrast, intraperitoneal LPS infusion (the Sham+LPS group) did not cause such liver damage. The plasma HA, a biomarker for sinusoidal endothelial cell injury (10, 29), and T-Bil levels, the other indicator for hepatic damage, also showed a similar trend, although HA was slightly higher in the Sham+LPS group (Fig. 1).

**Histological changes after BDL.** At 3 h after BDL, the BDL+LPS group had more inflammatory cell infiltration in the portal areas than the BDL+Saline group (Fig. 2). Furthermore, the portal area in the BDL+LPS group was more edematous than that in the BDL+Saline group. At 24 h after surgery, the BDL+LPS group presented some fibrin accumulation in the portal area, which was further confirmed by Masson’s trichrome staining (Fig. 2, arrows). Previous studies have suggested that fibrin accumulation may be associated with the development of endothelial cell injury (10, 44). Therefore, the results indicated that the BDL+LPS group presented more severe hepatic endothelial damage than other groups.

**Isolated liver perfusion study.** In many pathological liver conditions, the perfusion pressure in the portal venous system is increased owing to circulatory disturbance (45–48). This condition is mainly due to the increased resistance in the portal venous system, and it is associated with hepatic endothelial cell damage. Therefore, we performed isolated liver perfusion to measure the portal inflow pressure as an indicator of hepatic circulatory disturbance in our cholangitis model. At 24 h after BDL, the baseline PVP was significantly higher in the BDL+LPS group compared with the BDL+Saline group (Fig. 3A).

**HA clearance and wet/dry weight ratio.** We also examined HA clearance and wet/dry weight ratio using isolated liver perfusion study. A: portal venous pressure (PVP) measured by isolated liver perfusion. B: hepatic uptake of HA during a 20-min perfusion. C: liver wet/dry weight ratios after 30-min reperfusion. Data are means ± SE of 6 animals in each group. *P < 0.05 vs. BDL+Saline by ANOVA.
perfusion as an indicator of hepatic endothelial cell damage. At the point of 24 h after BDL, HA clearance in the BDL+LPS group was significantly lower than in the BDL+Saline or the Sham group (Fig. 3B). Furthermore, in the BDL+LPS group, the level of HA was found to be increased (therefore, negative clearance rate) even during the perfusion, probably because of an autonomous release of HA from the perfusing liver. In addition, wet/dry weight ratio of the liver in the BDL+LPS group was significantly higher than in the BDL+Saline or the Sham group (Fig. 3C). These results indicate severe damage in the hepatic endothelium in the BDL+LPS group compared with the BDL+Saline group.

**Real-time RT-PCR for inflammation-associated factors following BDL.** We next used real-time RT-PCR to examine the activation of representative inflammatory factors in the liver in three groups at the time points of 1, 3, 12, and 24 h after the surgery. The expression of inflammatory cytokine genes such as IL-6 and TNF-α mRNA in the BDL+LPS group was significantly increased 1 h after BDL (Fig. 4). In sharp contrast, the levels of these inflammatory cytokine genes did not show much change in the BDL+Saline group. It has been hypothesized that the inflammatory cytokines activate NF-κB and subsequently upregulate iNOS, resulting in increased production of nitric oxide (NO) (9). NO can react with oxygen radicals, leading to the generation of very reactive nitrogen species such as peroxynitrite (25), which can be a major cause of hepatocellular injury (31). Interestingly, our RT-PCR showed that NF-κB and iNOS mRNA levels in the BDL+LPS group peaked 3 h after the surgery, which is 2 h after the IL-6 and TNF-α peaks (Fig. 4). In contrast, 3 h after surgery, the expression of eNOS mRNA in the BDL+LPS group was significantly lower than in the Sham and BDL+Saline groups (Fig. 4). The expression of PPARγ mRNA in the liver gradually suppressed during the time course even in the Sham group, indicating that sham operation had similar effect on PPARγ expression to that found in the BDL group. However, the expression of PPARγ mRNA in the liver of the rats in the BDL+LPS group was significantly lower than in the BDL+Saline groups at 1, 3, and 12 h after surgery (Fig. 4). These results implied that in our cholangitis model the onset of inflammatory response in the liver occurred in an acute phase (1–3 h after the surgery). The sustained downregulation of PPARγ gene was also observed in the BDL+LPS group. Taking the results together with those of inflammation-related genes, we speculate that PPARγ system is...
substantially inactivated in the BDL+LPS group especially in the acute phase.

The effects of 15D-PGJ2 on LPS-induced acute liver injury. We next examined the effect of PPARγ activation in our acute cholangitis model using 15D-PGJ2, a ligand for PPARγ. In this experiment, two different concentrations of LPS (1 or 5 mg/ml) were used. Survival rates in the BDL+LPS+15D-PGJ2 group for both doses of LPS were significantly higher compared with the BDL+LPS+Vehicle group (Fig. 5). Furthermore, at 24 h after BDL, plasma HA and total bilirubin levels were significantly lower in the BDL+LPS+15D-PGJ2 group compared with those in the BDL+LPS+Vehicle group (Fig. 6). Moreover, at 3 h after BDL, mRNA levels in the liver for IL-6, TNF-α, NF-κB, and iNOS were all significantly lower in the BDL+LPS+15D-PGJ2 group compared with those in the BDL+LPS+Vehicle group (Fig. 7). These results implied that 15D-PGJ2 had a beneficial effect by inhibiting the inflammatory response and endothelial cell damage in the acute phase of obstructive cholangitis.

DISCUSSION

AOC is a common disease with high mortality rate (3, 37). It rapidly progresses to a severe form and leads to multiple organ dysfunctions that include liver failure. Despite recent advances in intensive care, treatment of AOC remains difficult. The primary treatment options, such as biliary tract drainage and administration of broad-spectrum antibiotics, can be insufficient once a systemic inflammatory response has been triggered. Therefore, to improve the outcome of AOC, it is necessary to elucidate its precise pathogenesis and to develop targeted and effective treatments.

An excessive inflammatory response (41) and sinusoidal endothelial damage (15) are the most important contributors to stress-induced liver dysfunction. Activation of NF-κB (32) and an increase in the release of inflammatory cytokines such as TNF-α and IL-6 may induce neutrophil overreaction that leads to organ failure. Augmented chemokine expression together with increased lipid peroxidation further aggravates liver injury in cholestatic rats (8). The interaction between neutrophils and sinusoidal endothelial cells can also lead to endothelial cell injury through the production of proteases and superoxides (13). In our cholangitis model, we found increased amounts of transaminases (AST and ALT) as well as HA levels in the BDL+LPS group compared with the BDL+Saline group. Moreover, the study of isolated liver perfusion showed much less HA clearance by the liver in the BDL+LPS group. These results indicate that the presence of LPS in the obstructed bile duct induces a severe inflammatory response as well as endothelial cell damage in the liver.

 Previous studies have also shown that sinusoidal endothelial cell injury induces the activation of the coagulation system and

![Fig. 5. Survival rate of rats in the Sham+LPS and the BDL+LPS models with or without 15D-PGJ2 treatment (0.5 mg/kg, bolus ip). Dimethylsulfoxide was used as vehicle. The difference among the groups was determined by Kaplan-Meier survival analysis. A: LPS 1 mg/ml. B: LPS 5 mg/ml. The number of rats used was 15–17 in each group.](http://ajpgi.physiology.org/)
leads to extensive fibrin deposition in the sinusoids (17, 40). Microcirculatory disturbances due to intrasinusoidal fibrin deposition may increase the total hepatic perfusion resistance, and they have been postulated to contribute to hepatocellular injury (5, 10). In our model, the BDL/H11001 LPS group presented histological evidence of fibrin deposition around the portal triad, as well as elevated portal inflow pressure, which was observed in the isolated liver perfusion study. These results further support the hypothesis that the presence of LPS in the obstructed bile duct induces severe sinusoidal endothelial damage in the liver.

It has been shown that PPARγ ligands exert anti-inflammatory effects in experimental sepsis models (16, 20). Recent studies confirmed that pretreatment with 15D-PGJ2 (a PPARγ ligand) ameliorates renal (7), hepatic (1, 26), and pancreatic (26) dysfunction in models of endotoxemia, hemorrhagic shock, and sepsis in vivo. However, the role of 15D-PGJ2 had not been examined in acute cholangitis. In the present study, we have demonstrated that in vivo treatment with 15D-PGJ2 in rats that have undergone BDL and LPS injection results in a significant suppression of LPS-induced inflammation-associated genes, indicating an anti-inflammatory effect of 15D-PGJ2 in this cholangitis model. The expression of the iNOS gene was also suppressed. Under pathological conditions, inflammatory cytokines activate NF-κB and induce the upregulation of iNOS (2). Subsequently, iNOS produces high levels of NO. Although NO exerts beneficial effects on our body by acting as an antibacterial (35), antiviral (27), or tumoricidal (30) agent, high levels of NO can react with oxygen radicals to form highly toxic compounds, such as peroxynitrite and hydroxyl radicals (9). Our in vivo study using different doses of LPS demonstrated an improved survival rate in the group with 15D-PGJ2 treatment compared with the vehicle group. We consider that the administration of 15D-PGJ2 induces beneficial effects in the liver through suppression of the expression of inflammation-associated factors and iNOS. This hypothesis was further confirmed by the lower expression of inflammation-associated factors and iNOS genes in the liver by RT-PCR. These results imply that PPARγ ligands such as 15D-PGJ2 have a beneficial effect in preventing liver failure induced by severe obstructive cholangitis.

The effects of 15D-PGJ2 have been shown not only in the liver, but also in the lung (11), kidney (23), and other organs. Therefore, with a peritoneal injection of 15D-PGJ2, it is uncertain whether this agent directly exerts beneficial effect on the liver or via a systemic effect. It may be difficult to prove in our model. Nonetheless, we still believe that 15D-PGJ2 directly exerts beneficial effects on the liver since we observed down-regulation of inflammation-related genes in the liver following intraperitoneal 15D-PGJ2 administration.

It could be argued that the infusion of LPS instead of bacteria into the bile duct might fail to fully reproduce clinical cholangitis. E. coli is the most frequent biliary pathogen isolated in patients with acute cholangitis in both western and eastern countries (18, 42). However, other species such as Klebsiella (another gram-negative rod) are also commonly isolated in patients with acute cholangitis (24). Therefore, we chose the use of LPS, a common pathogen found in both E. coli and Klebsiella, as a representative pathogen found in cholangitis. Furthermore, in many animal sepsis models, the LPS models show similar trends to models using E. coli (28, 34).

In summary, this study demonstrated the beneficial effects of 15D-PGJ2, a PPARγ agonist, in preventing liver injury and subsequent mortality in a model of acute obstructive cholangitis. The beneficial effects were mediated by the suppression...
of the inflammatory response and inhibition of hepatic endothelial cell damage. These results imply that in addition to 15D-PGJ2, a potential therapeutic target to improve the outcome of acute obstructive cholangitis.

REFERENCES


