BPA disrupts 17-estradiol-mediated hepatic protection against ischemia/reperfusion injury in rat liver by upregulating the Ang II/AT1R signaling pathway

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Abstract. Bisphenol A (BPA), a xenoestrogen commonly used in plastics, may act as an endocrine disruptor, which indicates that BPA might be a public health risk. The present study aimed to investigate the effect of BPA on 17β-estradiol (E2)-mediated protection against liver ischemia/reperfusion (I/R) injury, and to identify the underlying mechanisms using a rat model. A total of 56 male Sprague Dawley rats were randomly divided into the following seven groups: i) Sham; ii) I/R; iii) Sham + BPA; iv) I/R + BPA; v) I/R + E2; vi) I/R + E2 + BPA; and vii) I/R + E2 + BPA + losartan [LOS; an angiotensin II (Ang II) type I receptor (ATIR) antagonist]. A rat model of hepatic I/R injury was established by inducing hepatic ischemia for 60 min followed by reperfusion for 24 h. When ischemia was induced, rats were treated with vehicle, E2, BPA or LOS. After 24 h of reperfusion, blood samples and hepatic tissues were collected for histopathological and biochemical examinations. The results suggested that 4 mg/kg BPA did not significantly alter the liver function, or Ang II and AT1R expression levels in the Sham and I/R groups. However, 4 mg/kg BPA inhibited E2-mediated hepatic protection by enhancing hepatic necrosis, and increasing the release of alanine transaminase, alkaline phosphatase and total bilirubin ($P<0.05$). Moreover, BPA increased serum and hepatic Ang II levels, as well as AT1R protein expression levels in the E2-treated rat model of liver I/R injury ($P<0.05$). LOS treatment reversed the negative effects of BPA on hepatic necrosis and liver serum marker levels, although it did not reverse BPA-mediated upregulation of serum and hepatic Ang II levels, or hepatic AT1R expression. Therefore, the present study suggested that BPA disrupted E2-mediated hepatic protection following I/R injury, but did not significantly affect healthy or I/R-injured livers; therefore, the mechanism underlying the effects of BPA may be associated with upregulation of the Ang II/AT1R signaling pathway.

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Introduction

Bisphenol A (BPA) is a xenoestrogen (XE) that is extensively produced for the manufacture of polycarbonate plastic (1). Ubiquitous exposure to BPA is associated with a series of health problems, including obesity, diabetes and disorders of the reproductive system (2-4). Previous studies have reported that BPA may also affect liver function, and high levels of urinary BPA are associated with non-alcoholic fatty liver disease in adults in the United States (5-8). Another study reported that serum aspartate transaminase and alanine transaminase (ALT) levels were not altered following exposure to low level BPA (5 mg/kg), but were significantly increased following exposure to high level BPA (50 mg/kg) in rats (9).

Liver ischemia/reperfusion (I/R) injury occurs during a number of clinical events, including liver transplantation, partial hepatectomy and hemorrhagic shock (10). The pathophysiological processes of liver I/R injury are multifactorial and characterized by various clinical manifestations ranging in severity from asymptomatic elevation of serum transaminases to hepatic failure (11). Despite improvements in perioperative management and surgical techniques, liver I/R injury continues to be an important clinical issue. Previous studies have demonstrated that 17-estradiol (E2) protects the liver against I/R injury by reducing microvascular dysfunction and inflammatory responses (12), increasing vasodilator nitric oxide (NO) production (13) and preventing impaired Kupffer cell activity (14). Furthermore, a previous study reported that E2 provides hepatoprotection against I/R injury by downregulating the angiotensin II (Ang II)/Ang II type I receptor (AT1R) signaling pathway (15). However, the role of BPA during liver I/R injury has not been previously reported.

Previous studies have demonstrated that BPA can attenuate the physiological function of estrogen and inhibit the production of testosterone (16,17). Moreover, BPA can reduce the activity of multiple hepatoprotective enzymes, including catalase, total glutathione S-transferase, total glutathione peroxidase and total superoxide dismutase (18). Therefore, the present study aimed to investigate whether BPA disrupted E2-mediated hepatic protection against I/R injury, and to identify the possible underlying mechanisms using a rat model.

Materials and methods

Animals. Male Sprague-Dawley rats (weight, 190-210 g; age, 9-10 weeks old) were purchased from the Animal Center of Xi'an Jiaotong University. Animals were kept in standard housing conditions at 22±2˚C with 12-h light/dark cycles, 45-60% humidity, and free access to food and water. Animal experiments were conducted according to the National Institutes of Health Guidelines on the Use of Laboratory Animals (12). The present study was approved by the Xi'an Jiaotong University Health Science Center Ethics Committee.

Model of total hepatic I/R. Previous studies have demonstrated that short periods (60 min) of global liver ischemia result in reversible cell injury, in which liver oxygen consumption returns to control levels when the oxygen supply is reestablished following ischemia (19). However, reperfusion following prolonged warm ischemia (>120 min) results in irreversible cell damage (19). Therefore, the present study established a 60 min global liver ischemia model, which simulated the clinical situation of warm ischemia after the Pringle maneuver (20) in hepatic surgery. Rats were fasted for 16-18 h prior to the operation. Rats were anesthetized using 64% N_2O, 32% O_2 and 4% isoflurane and anesthesia was maintained using 65% N_2O, 32% O_2 and 3% isoflurane. Rats were ventilated endotracheally during the operation. A median incision was made in the upper abdomen and the hepatic pedicle was clamped using a non-invasive microvascular clip to induce total liver I/R. After 60 min, the clamp was removed to allow reperfusion. Sham controls received the laparotomy procedure without hepatic pedicle clamping. After closing the abdominal cavity, rats were allowed to recover with free access to food and water. At 24 h post-reperfusion, rats were euthanized by overdose with intravenous sodium pentobarbital (100 mg/kg) followed by exsanguination. Subsequently, the liver tissues and 5 ml venous blood drawn from the inferior vena cava were harvested for subsequent experiments.

Experimental design. A total of 56 rats were randomly divided into the following seven experimental groups (n=8/group): i) Sham; ii) I/R; iii) Sham + BPA; iv) I/R + BPA; v) I/R + E2; vi) I/R + E2 + BPA; and vii) I/R + E2 + BPA + Losartan (LOS). BPA (Tokyo Chemical Industry Co., Ltd.) and E2 (Sigma-Aldrich; Merck KGaA) were dissolved in DMSO, and diluted in saline. The final concentration of DMSO was <0.1%. BPA (4 mg/kg) or E2 (4 mg/kg) were administered intravenously when the laparotomy procedure began. LOS (30 mg/kg; Wuhan Boster Biological Technology, Ltd.) was administered intraperitoneally when the laparotomy procedure began. The Sham and I/R groups received only dilution vehicle (saline).

Histological assessment of I/R injury. Formalin-fixed (10%, 24 h, room temperature) paraffin-embedded liver tissues were cut into 5 μm-thick sections, and stained with hematoxylin (15 min) and eosin (5 min) at room temperature to estimate the severity of I/R injury. Sections were examined for the following signs: Nuclear pyknosis, loss of hepatocellular borders or areas of necrosis. Stained sections were observed in at least 10 randomly selected fields with a light microscope (magnification, x400) and examined for the following signs: Nuclear pyknosis, loss of hepatocellular borders or areas of necrosis. Sections were scored using according to a previously described formula: Necrotic area/total area of the field (21), and analyzed using Image-Pro Plus software (version 6.0; Media Cybernetics, Inc.).

Measurement of serum hepatic damage markers. At 24 h post-reperfusion, harvested blood samples were centrifuged at 3,000 x g for 5 min at 4˚C for serum separation and serum concentrations of ALT, alkaline phosphate (ALP) and total bilirubin (TBIL) were detected using the AU400 automated chemistry analyzer according to the manufacturer's protocol (Olympus Corporation).

Measurement of Ang II. Rat liver tissue was homogenized and total protein was extracted using T-PER™ tissue protein extraction buffer (Pierce; Thermo Fisher Scientific, Inc.) containing protease inhibitors. Protein concentration was determined using the Coomassie brilliant blue method. Serum and hepatic Ang II levels were measured using an Ang II ELISA kit (cat. no. ABIN416068; Uscn Life Science Inc.), according to the manufacturer's protocol.

Western blotting. The hepatic tissue expression levels of AT1R were detected using the western blotting. Total protein was extracted using T-PER™ tissue protein extraction buffer (Pierce; Thermo Fisher Scientific, Inc.) containing protease inhibitors. Protein concentration was determined using the Coomassie brilliant blue method. The mass of the proteins loaded in per lane was 50 μg. Protein was separated by 10% SDS-PAGE and transferred onto nitrocellulose membranes (GE Healthcare Life Sciences). The membranes were blocked with 5% bovine serum albumin (cat. no. CSB-NP009501B; CUSA Bio.) at 37˚C for 1 h, and washed three times with ice-cold PBS. Subsequently, the membranes were incubated at 37˚C for 2 h with the following primary antibodies: Anti-AT1R (cat. no. sc-31181; 1:1,000; Santa Cruz Biotechnology, Inc.) and anti-β-actin (cat. no. sc-130656; 1,000; Santa Cruz Biotechnology, Inc.). Following primary incubation, the membranes were incubated with a horseradish peroxidase-conjugated donkey anti-rabbit IgG secondary antibody (cat. no. NA934; 1:1,000; GE Healthcare Life Sciences) for 1 h at 37˚C. Protein bands were visualized using an enhanced chemiluminescence detection system (GE Healthcare Life Sciences) and the UVP BioSpectrum500 imaging system (UVP, LLC). Protein expression was quantified using Quantity One software (version 4.6.9; Bio-Rad Laboratories, Inc.) with β-actin as the loading control.

Statistical analysis. Data are presented as the mean ± SD. Statistical analyses were performed using SPSS software

(version 24.0; IBM Corp.). Comparisons among groups were analyzed using one-way ANOVA followed by Tukey's post hoc test. P<0.05 was considered to indicate a statistically significant difference.

Results

Histological changes. At 24 h post-reperfusion, liver tissues were harvested. No significant morphological changes were observed between the Sham and Sham + BPA groups. However, severe necrosis, extensive nuclear pyknosis and loss of intercellular borders were detected in the I/R and I/R + BPA groups. Compared with the I/R and I/R + BPA groups, the I/R + E2 group displayed a significantly reduced percentage of hepatic necrosis (52±6 vs. 22±3.2% and 50±5.5 vs. 22±3.2%, respectively; P<0.05; Fig. 1); however, BPA treatment decreased E2-mediated hepatoprotective effects (45±5.6%; P<0.05 vs. I/R + E2 group). Furthermore, it was demonstrated that LOS treatment significantly reversed the negative effect of BPA on E2-mediated hepatoprotection (25±3%; P<0.05 vs. I/R + E2+BPA group; Fig. 1).

Liver function. Serum concentrations of ALT, ALP and TBIL in the Sham + BPA group were not significantly different at 24 h post-reperfusion compared with the Sham group (all P>0.05). However, the I/R and I/R + BPA groups displayed significantly higher serum concentrations levels of ALT, ALP and TBIL compared with the Sham and Sham + BPA groups (P<0.05). Moreover, compared with the I/R and I/R + BPA groups, the I/R + E2 group displayed significantly reduced levels of the serum markers (all P<0.05); however, BPA treatment significantly inhibited the hepatoprotective activity of E2 against I/R injury (all P<0.05 vs. I/R + E2 group). In addition, the results suggested that LOS treatment reversed the negative effect of BPA on E2 in the rat model of liver I/R injury (Fig. 2).

Serum and hepatic Ang II levels. At 24 h post-reperfusion, there were no significant differences in serum and hepatic Ang II levels between the Sham and Sham + BPA groups (all P>0.05). By contrast, the levels of serum and hepatic Ang II in the I/R and I/R + BPA groups were significantly higher compared with the Sham and Sham + BPA groups (P<0.05). Furthermore, E2 treatment significantly reduced the levels of serum and hepatic Ang II compared with the I/R and I/R + BPA groups (all P<0.05), and BPA treatment inhibited the hepatoprotective activity of E2 against liver I/R injury (all P<0.05 vs. I/R + E2 group). However, LOS treatment did not significantly alter serum and hepatic Ang II levels in the I/R + E2 + BPA group (all P>0.05 vs. I/R+E2+BPA+LOS group) (Fig. 3).

Expression of hepatic AT1R. The hepatic tissue expression level of AT1R was determined by western blotting. At 24 h post-reperfusion, there were no significant differences in the expression of AT1R protein between the Sham and Sham + BPA groups (P>0.05). However, hepatic AT1R expression levels in the I/R and I/R + BPA groups were significantly higher compared with the Sham and Sham + BPA groups (P<0.05). The results indicated that E2 treatment significantly decreased hepatic AT1R expression levels compared with the I/R and I/R + BPA groups (all P<0.05); however, BPA treatment also inhibited E2-mediated effects on AT1R expression (P<0.05 vs. I/R+E2 group). Additionally, LOS treatment did not alter hepatic AT1R expression in I/R + E2 + BPA rats (P>0.05 vs. I/R+E2+BPA group) (Fig. 4).

Discussion

BPA is an endocrine disrupting chemical (EDC) widely used in various industries, including dentistry (1). BPA has attracted attention due to its threat to human health, as it can alter the expression of neural genes including oxytocin and vasopressin, leading to abnormal social behaviors (22).

Ang II receptors are present in two forms: AT1R and AT2R (23). The physiological function of Ang II and AT1R, as well as their role in the pathogenesis of certain diseases are not completely understood. However, compared with AT1R, it is difficult to investigate the functions of AT2R, at least in part due to the relatively low expression levels in cells (23). Previous studies investigating Ang II and its receptors have primarily focused on the Ang II/AT1R axis (24-27); therefore, the present study investigated the effects of BPA on hepatic damage and the Ang II/AT1R signaling pathway in a rat model of liver I/R injury. A previous study reported that 0.4 mg/kg/day BPA in rats is close to the current reference daily limit for human exposure by the U.S. Environmental Protection Agency (28). In another study assessing the effects of BPA on the cognitive function of rats, it was indicated that 0.4 mg/kg/day BPA caused a significant decline in spatial memory; however, anxiety-like behavior was only observed in the high-dose BPA group (4 mg/kg/day) (28). A previous study investigating the effects of perinatal maternal exposure to BPA on the behavior of rat offspring, it was reported that male offspring in the 4 mg/kg group displayed significantly lower responses compared with control rats (29); therefore, 4 mg/kg BPA was used in the present study.

It has been reported that 25 mg/kg/day BPA leads to increased serum levels of liver enzymes and defects in the morphology of the liver in rats (30). Moreover, Kazemi *et al* (31) indicated that 5 μg/kg BPA induced reactive oxygen species production and increased antioxidant gene expression in rats; however, the morphological and functional responses of the liver were not investigated. In the present study, 4 mg/kg BPA did not affect the liver microstructure and enzymes in the Sham or I/R groups. Furthermore, it was demonstrated that there were no significant differences in serum Ang II levels, hepatic Ang II levels and AT1R protein levels between rats treated with or without BPA alone. Therefore, the results suggested that 4 mg/kg BPA may not affect liver function or the Ang II/AT1R signaling pathway in healthy or I/R-injured livers.

The hepatoprotective effect of E2 against I/R injury has been previously reported in rodent models (32-34). The possible mechanisms underlying the actions of E2 include: Apoptosis inhibition (21); increasing serum NO levels and decreasing serum tumor necrosis factor-α levels (35); regulating the expression of heat shock protein (36); modulating the activities of mitogen-activated protein kinase (37); and downregulating the Ang II/AT1R signaling pathway (16). Moreover, previous clinical studies have demonstrated that

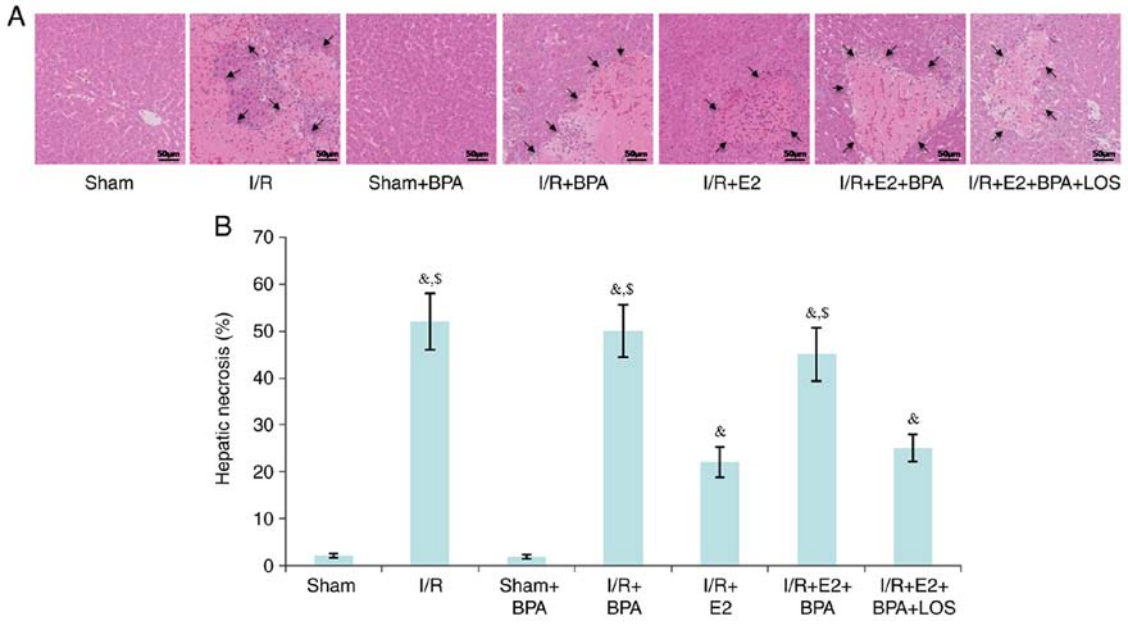

Figure 1. Hepatic histopathology. (A) Representative images of hematoxylin-eosin stained hepatic tissue sections displaying typical necrosis around the venous areas (indicated by black arrows; magnification, x400). (B) Quantification of hepatic necrosis. $^{\&}$P<0.05 vs. Sham or Sham + BPA; $^{\$}$P<0.05 vs. I/R + E2 or I/R + E2 + BPA + LOS. BPA, bisphenol A; I/R, ischemia/reperfusion; E2, 17β-estradiol; LOS, losartan.

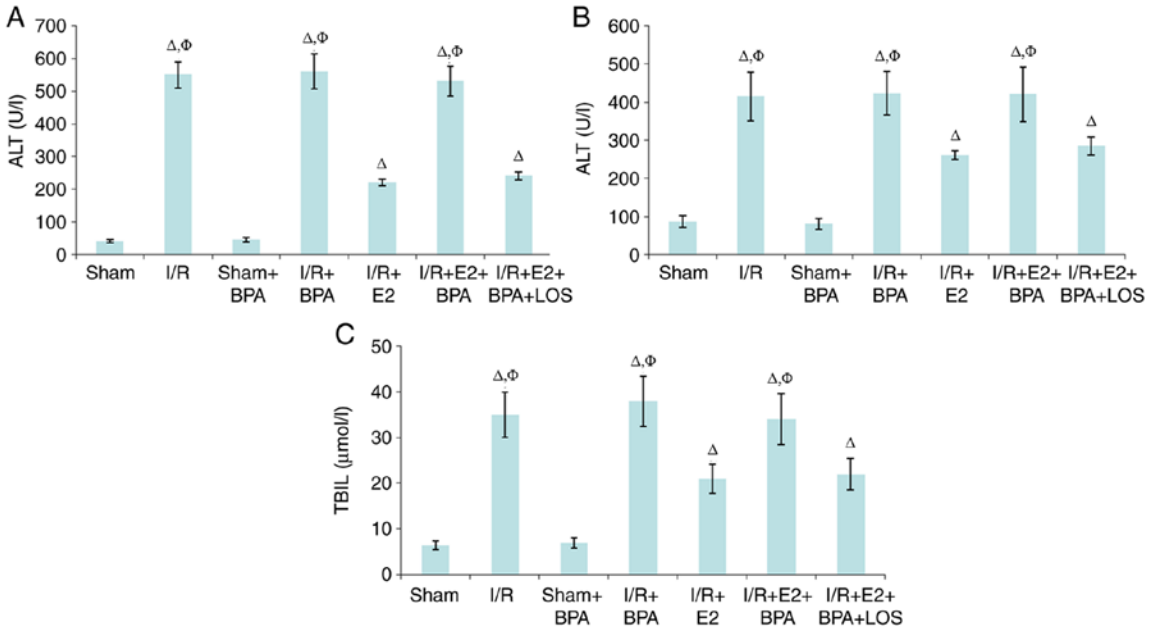

Figure 2. Effects of BPA, E2 and LOS on serum marker levels. Serum levels of (A) ALT, (B) ALP and (C) TBIL at 24 h post-reperfusion. $^{\Delta}$P<0.05 vs. Sham or Sham + BPA; $^{\Phi}$P<0.05 vs. I/R + E2 or I/R + E2 + BPA + LOS. BPA, bisphenol A; E2, 17β-estradiol; LOS, losartan; ALT, alanine transaminase; ALP, alkaline phosphatase; TBIL, total bilirubin; I/R, ischemia/reperfusion.

female livers are more tolerant to I/R injury compared with male livers, which may be explained by E2 (38,39). BPA, a well-characterized XE, interacts with estrogen receptors to act as an agonist or antagonist via estrogen receptor-dependent signaling pathways; therefore, BPA plays a role in the pathogenesis of several endocrine disorders, including female and male infertility, precocious puberty and hormone dependent tumors (40). It has been hypothesized that BPA may have a negative effect on the protective effect of E2 against hepatic I/R injury. The present study examined whether BPA disrupted E2-mediated hepatic protection against I/R injury, and the possible underlying mechanisms. The results suggested that E2 protected the liver against I/R injury by attenuating hepatic necrosis, and lowering serum levels of ALT, ALP and TBIL. Furthermore, BPA, as an EDC, abolished certain hepatoprotective activities of E2 by aggravating hepatic necrosis, and increasing the release of ALT, ALP and TBIL, as demonstrated by biochemical and histological analyses.

Ang II is the major effector or peptide of the renin-angiotensin system (41). Previous studies have revealed that Ang II

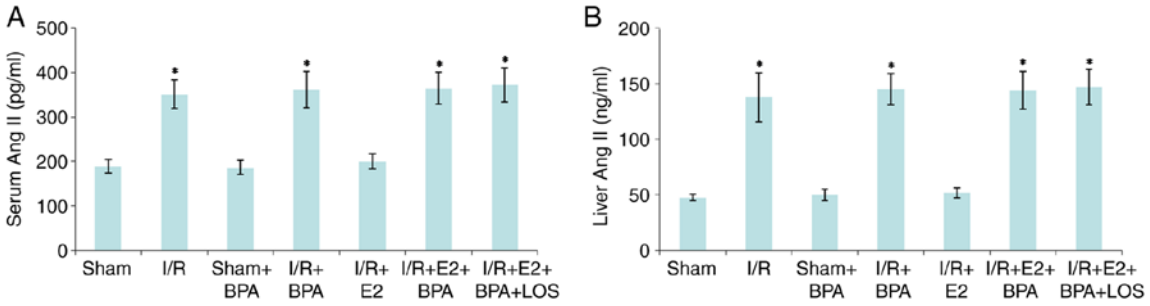

Figure 3. Effects of BPA, E2 and LOS on Ang II expression. (A) Serum and (B) hepatic Ang II expression levels at 24 h post-reperfusion. *P<0.05 vs. Sham, Sham + BPA or I/R + E2. BPA, bisphenol A; E2, 17β-estradiol; LOS, losartan; Ang II, angiotensin II; I/R, ischemia/reperfusion.

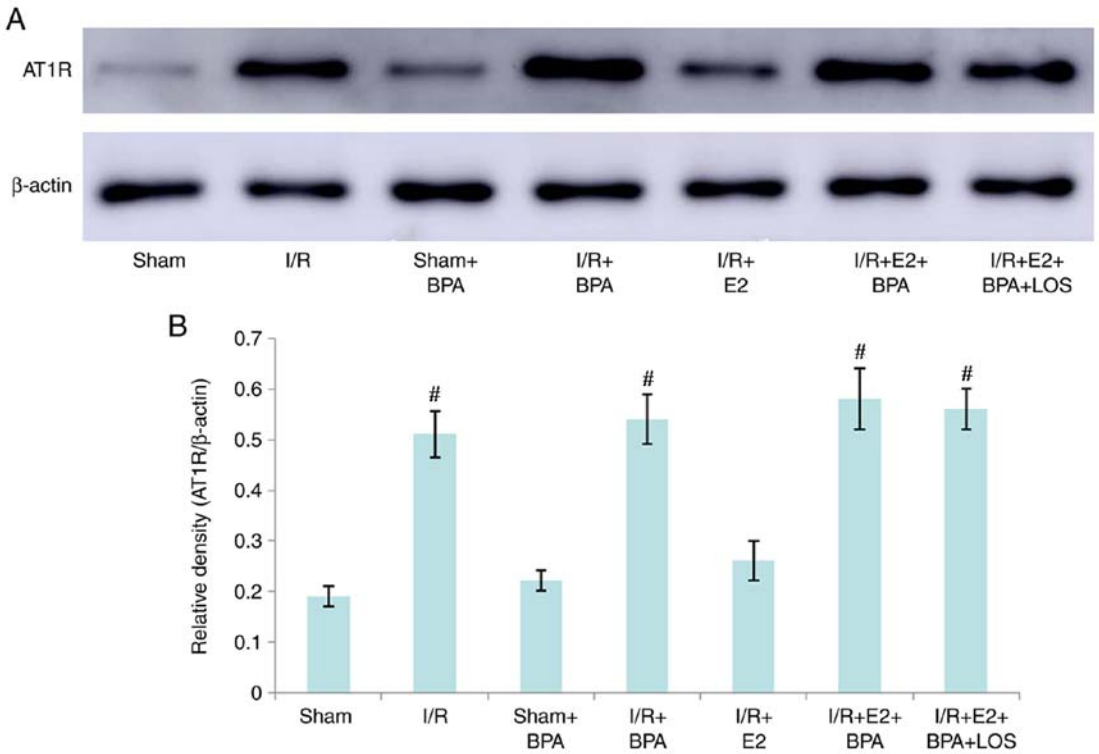

Figure 4. Expression of hepatic AT1R at 24 h post-reperfusion. Hepatic AT1R protein expression levels were (A) determined by western blotting and (B) quantified. #P<0.05 vs. Sham, Sham + BPA or I/R + E2. AT1R, angiotensin II type I receptor; I/R, ischemia/reperfusion; BPA, bisphenol A; E2, 17β-estradiol; LOS, losartan.

can induce a series of proinflammatory responses by increasing adhesion molecule expression (42), leukocyte-endothelial interaction (43), activator protein 1 and NF-κB activation (44), reactive oxygen species production (45) and proinflammatory cytokine accumulation (46). Moreover, the role of Ang II and its primary receptor, AT1R, in the process of liver I/R injury has been previously reported. Alfany-Fernandez *et al* (47) reported that Ang II receptor antagonists protect non-steatotic liver grafts against I/R damage. Furthermore, Sabry *et al* (48) revealed that the hepatoprotective effect of Apelin-13 against I/R injury was related to suppression of the Ang II/AT1R signaling pathway. The results of the aforementioned studies were consistent with the results of the present study. In addition, our previous study indicated that E2 hepatoprotection against I/R injury occurs via downregulation of the Ang II/AT1R signaling pathway (15). However, whether BPA disrupts the hepatoprotective activity of E2 against I/R injury by modulating the Ang II/AT1R signaling pathway is not completely understood. A previous studies has demonstrated that oral administration of BPA induces high blood pressure in mice by upregulating Ang II (49). Another *in vitro* study reported that following BPA treatment, Ang II expression is upregulated in vascular smooth muscle cells, and the Ang II receptor antagonist LOS attenuates BPA-induced cell proliferation (50). The results of the present study suggested that although BPA did not significantly affect the Ang II/AT1R signaling pathway in the rat model of hepatic I/R injury without E2 treatment, BPA treatment significantly increased the levels of serum and hepatic Ang II, as well as the expression of AT1R protein in the liver in the ER-treated rat model of hepatic I/R injury.

Previous studies have indicated that chronic use of LOS can decrease the expression of AT1R. Abbasloo *et al* (51) reported that treatment with LOS (10 mg/kg; intraperitoneally) for 5 days reduces the expression of AT1R in cardiac tissue in a rat model of I/R injury. Furthermore, Panico *et al* (52) demonstrated that renal I/R-induced cardiac levels of AT1R

were decreased following LOS treatment (10 mg/kg in drinking water) for 7 days. However, the results of the present study suggested that LOS treatment did not significantly alter serum and liver Ang II levels, or liver AT1R protein expression following hepatic I/R injury; however, LOS reversed the negative effect of BPA on certain E2-mediated hepatoprotective activities. A potential explanation for the discrepancies between the results of the present study and the results of previous studies could be the different doses and courses of treatments used. In the present study, LOS was administered once (30 mg/kg; intraperitoneally) at 24 h before tissue harvesting, which may alter AT1R function, but not AT1R expression. Therefore, further studies are required to identify the mechanisms underlying LOS-mediated regulation of the Ang II/AT1R axis.

In conclusion, to the best of our knowledge, the present study was the first to suggest that upregulation of the Ang II/AT1R signaling pathway may play an important role in BPA-mediated disruption of the hepatoprotective activities of E2 against I/R injury. Moreover, the Ang II/AT1R axis may serve as a promising target for the development of hepatoprotective strategies to prevent BPA-induced liver damage.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LY, YZ and YS analyzed and interpreted the experimental animal data. ZL and LS performed the histological examination of the liver. MZ performed the PCR and western blotting. LY was a major contributor in writing the manuscript. SW designed the experiments and reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Xi'an Jiaotong University Health Science Center Ethics Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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