Estradiol improves cardiac and hepatic function after trauma-hemorrhage: role of enhanced heat shock protein expression

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heme oxygenase-1; organ dysfunction; tumor necrosis factor-α; estrogen; injury

THE DELETEROUS EFFECTS OF hemorrhagic shock and septic shock on organ functions are well established (12, 34, 41). Nonetheless, studies have also shown that upregulation of heat shock protein (HSP) under the same conditions has protective effects (18, 19, 35, 38). HSPs, sometimes termed molecular chaperones, are highly conserved intracellular proteins that play an important role in the folding of the newly synthesized proteins and prevent the aggregation of denatured proteins (9). In addition, a particular HSP, HSP32, also known as heme oxygenase-1, appears to act as a potent vasodilator and antioxidant-producing agent in many organs against insults, such as ischemia and oxidative stress (22). HSP upregulation was first observed with hyperthermia, but other stresses, such as ischemia, free radicals, or proinflammatory cytokines can also induce their expression (24). Furthermore, HSP induction appears to play a critical role in the protection against the pathophysiological effects of low-flow states, since its induction results in protection, whereas their inhibition lead to exacerbation of the injury (14, 26).

Previous studies have suggested an association between gender and mortality after traumatic injury (7). Furthermore, findings from both clinical and experimental conditions suggest that females are more tolerant to injury than males (6, 7). In this regard, estrogen has been shown to be protective under ischemic conditions (34). Interestingly, estrogen can modulate HSP induction (29) and recent findings from our laboratory suggest that the attenuated liver injury in proestrus females after trauma-hemorrhage is, in part, due to the upregulation of HSP32 by estradiol (36). Whereas Lu et al. (17) reported the estrogen-induced HSP production after ischemia, other investigators have observed a similar effect of estrogen under physiologic conditions (29). Moreover, the production of the different HSPs showed not only gender but also organ dependence (37). Nonetheless, it remains unknown whether or not estrogen administration after trauma-hemorrhage can modulate HSP expression and attenuate organ injury. Although recent findings from our laboratory have suggested that the attenuated liver injury in proestrus females after trauma-hemorrhage is due, in part, to the enhanced HSP32 expression (36), it remained unclear whether other members of the HSP family (i.e., HSP60, HSP70) are also involved in the salutary effect of estrogens under such conditions. The aim of the present study was to determine the relationship between HSP and cardiac/liver dysfunction and whether estrogen mediates its salutary effects on heart/liver functions via modulation of HSP levels after trauma-hemorrhage.

MATERIALS AND METHODS

Animals. Adult male (275–325 g) Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were used in this study. Rats were allowed to acclimatize in the animal facility for 1 wk before the experiments. All experiments were performed in accordance with the National Institutes of Health guidelines for the use of experimental animals.

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animals and approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham.

**Experimental procedures.** Rats were fasted overnight before the experiment but allowed water ad libitum. Trauma-hemorrhage was induced as described previously in detail (11). Briefly, the rats were anesthetized by isoflurane (Athane; Minrad, Bethlehem, PA) inhalation before the induction of soft-tissue trauma (i.e., 5-cm midline laparotomy). The abdomen was then closed in layers and catheters were placed in both femoral arteries and the right femoral vein [polyethylene (PE-50) tubing; Becton-Dickinson, Franklin Lakes, NJ]. The wounds were bathed with 1% lidocaine (Elkins-Sinn, Cherry Hill, NJ) throughout the surgical procedure to minimize postoperative pain. The rats were then allowed to awaken, after which they were rapidly bled to a mean arterial pressure (MAP) of 35–40 mmHg within 10 min. The time at which the animals could no longer maintain a MAP of 35–40 mmHg without fluid infusion was defined as maximum bleed-out volume. The rats were maintained at this MAP until 40% of the shed blood was returned in the form of Ringer lactate.

The animals were then resuscitated with four times the volume of shed blood with Ringer lactate over 60 min. After resuscitation, the catheters were removed, the vessels were ligated, and skin incisions were closed with sutures. Sham-operated animals underwent the same groin dissection, which included ligation of the femoral artery, and catheters were placed in the femoral vein to administer agents; however, neither trauma-hemorrhage nor resuscitation was carried out. The animals were returned to their cages and allowed food and water ad libitum until death, 5 h after the end of resuscitation. In the treatment group, 1 mg/kg of body wt iv 17β-estradiol (Sigma, St. Louis, MO) was administered at the end of the resuscitation (34). Although we have not measured serum levels after administration of 17β-estradiol in this study, our previous studies (11) have shown that administration of this dose of estradiol after trauma-hemorrhage increased plasma estradiol levels to ~200 pg/ml. Furthermore, our previous studies have shown that treatment of animals with 1 mg/kg body wt estradiol after trauma-hemorrhage restored cardiac and liver functions similar to those observed in proestrous females after trauma-hemorrhage (11, 36, 42).

**Determination of cardiac performance.** At 5 h after hemorrhage or sham operation, the animals were anesthetized with pentobarbital sodium. A tip-reduced PE-50 catheter was placed into the right carotid artery to measure MAP. The catheter was then advanced into the left ventricle. Left ventricular contractility parameters, such as the maximal rate of left ventricular pressure increase [+dp/dt(max)] and decrease [−dp/dt(max)] were determined (11). Cardiac output was determined by using an indocyanine green (ICG) dilution technique (11). Briefly, the right jugular vein was isolated and cannulated by using PE-50 tubing under isoflurane anesthesia. A 2.4-Fr fiberoptic catheter (Hospex Fiberoptics, Chestnut Hill, MA) was inserted into the right carotid artery and placed at the level of the aortic arch for continuous measurement of ICG concentration with an in vivo hemoreflectometer (Schwarzer-Picker International, Munich, Germany). The area under the curve was determined, and cardiac output was calculated according to the principle of dye dilution.

**Determination of liver function and injury.** At 5 h after the end of resuscitation or sham operation, a laparotomy was performed, and the intestines were covered with wet gauze to minimize the evaporative fluid loss (36). The portal vein was identified and exposed. The common bile duct was cannulated with a PE-10 catheter, and the bile flow was measured in preweighed tubes. For the determination of in vivo bile production, bile was collected for 10 min; throughout liver flow was measured in preweighed tubes. For the determination of in vitro bile production, bile was collected for 10 min; throughout liver flow was measured in preweighed tubes. For the determination of in vivo bile production, bile was collected for 10 min; throughout liver flow was measured in preweighed tubes. For the determination of in vitro bile production, bile was collected for 10 min; throughout liver flow was measured in preweighed tubes.

The isolated liver perfusion model was performed as described previously with minor modification (43). The liver was exposed through a wide transverse incision, and the portal vein was isolated. After cannulation of the portal vein with a PE-240 catheter, the liver was perfused with Krebs-Henseleit bicarbonate buffer (in mM: 118 NaCl, 4.7 KCl, 1.2 MgSO4, 1.2 KH2PO4, 25 NaHCO3, 0.1 EDTA, and 2.5 CaCl2, pH 7.4) for 10 min to wash out the blood. The isolated liver perfusion was performed using a constant flow rate (100 ml·min⁻¹·kg body wt⁻¹). The warmed perfusate was pumped from a reservoir into an overflow chamber and oxygenated via an elastic tubing oxygenator (95% O2-5% CO2). The temperature of the perfusate was maintained at 36–37°C by warming the reservoir in a water bath. The liver was perfused for 60 min with a recirculating system. The total volume of perfusate during recirculating perfusion was 150 ml. Before the determination of in vitro ICG clearance (a measure of hepatocellular function), the isolated liver was perfused with Krebs-Henseleit buffer for 30 min without recirculation and then perfused with an additional 400 ml of perfusate containing 8 mg ICG with recirculation. Samples of effluent were collected for 30 min after ICG administration. The ICG concentration in the effluent was determined using a spectrophotometer at a wavelength of 800 nm (40). Before the start of recirculation and during recirculation, the perfusate was also sampled for the measurement of lactic dehydrogenase (LDH) level. Additionally, similar to the in vivo measurement, bile was collected into preweighed tubes throughout the experiment.

Blood and liver perfuse samples were collected in microcentrifuge tubes at 5 h after the end of resuscitation or sham operation. After centrifugation, samples were separated, immediately frozen, and stored at ~80°C until assayed. As a marker of liver injury, serum alanine aminotransferase (ALT) and the LDH content of the perfusates were determined by using a colorimetric reaction kit according to the manufacturer’s instructions (Sigma).

**Measurement of plasma cytokine content.** Plasma levels of TNF-α, IL-6, and IL-10 were determined using ELISA kits (Pharmingen, San Diego, CA) according to the manufacturer’s instructions.

**Determination of tissue HSP expression by quantitative real-time PCR.** The mRNA levels of HSP32, HSP60, and HSP70 in heart and liver were determined by real-time PCR as described previously (42). Total RNA was isolated from liver and heart tissues using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer’s protocol. cDNA was generated from the total RNA samples by using a transcription kit (TaqMan reverse transcription reagents; Applied Biosystems, Foster City, CA). Each real-time PCR reaction was performed in a mix of 10 μl reaction mixture containing 20 ng of cDNA, 2× PCR Master Mix (Applied Biosystems), and each probe and primer set. TaqMan gene expression assays (Applied Biosystems) for HSP32, HSP60, and HSP70 were purchased as a probe and primer set. The reaction mixture was denatured for one cycle of 2 min at 50°C, 10 min at 95°C, and incubated for 40 cycles (denaturing for 15 s at 95°C and annealing and extending for 1 min at 60°C) using ABI Prism 7900HHT (Applied Biosystems). All samples were tested in triplicate, and average values were used for quantification. 18S rRNA was used as an endogenous control. Analysis was performed using SDS v2.2 software (Applied Biosystems) according to the manufacturer’s instructions. The comparative cycle threshold (CT) method (∆∆CT) was used for quantification of gene expression. The average of the sham group was set as onefold induction, and other data were adjusted to that baseline.

**Statistical analysis.** Data are presented as means ± SE. Statistical differences among groups were determined by one-way ANOVA followed by Tukey’s test. The differences were considered significant if P < 0.05.

**RESULTS**

**Cardiac performance.** Cardiac output decreased significantly in nontreated rats after trauma-hemorrhage. Administration of estradiol after trauma-hemorrhage increased cardiac output to values similar to those of sham-operated animals (Fig. 1A). Furthermore, positive and negative dp/dt(max) was significantly depressed at 5 h after trauma-hemorrhage. Although treatment of rats with estradiol after trauma-hemorrh-
rhage increased both positive and negative dp/dt, the levels of positive and negative dp/dt remained significantly lower compared with those observed in sham-operated rats (Fig. 1, B and C).

Hepatic function and injury. Trauma-hemorrhage significantly decreased bile production (Fig. 2, A and B) and ICG uptake (Fig. 2C) in the nontreated rats. Administration of 17β-estradiol after trauma-hemorrhage restored bile production to sham levels and significantly prevented the decrease in ICG uptake compared with untreated trauma-hemorrhage rats. However, the levels of ICG remained significantly lower compared with sham animals.

Serum ALT and liver perfusate LDH levels were used as markers of hepatic injury. Trauma-hemorrhage induced a significant increase in serum ALT (Fig. 3A) and perfusate LDH (Fig. 3B) levels. 17β-estradiol administration significantly attenuated the trauma-hemorrhage-induced release of ALT and LDH.

Plasma cytokine levels. Plasma TNF-α, IL-6, and IL-10 levels were significantly increased at 5 h after resuscitation in trauma-hemorrhage animals compared with sham animals (Fig. 4). Estradiol treatment prevented the trauma-hemorrhage-induced elevation in plasma TNF-α and IL-6 levels (Fig. 4, A and B). Plasma IL-10 levels were unaffected by estradiol treatment (Fig. 4C).

Tissue HSP mRNA expression. Five hours after trauma-hemorrhage, elevated HSP32 but decreased HSP60 mRNA levels were observed in the heart (Fig. 5A and B). In contrast, the cardiac HSP70 mRNA level was not significantly affected by trauma-hemorrhage at 5 h after resuscitation (Fig. 5C). After 17β-estradiol administration, HSP32, HSP60, and HSP70 mRNA expression were increased significantly compared with the nontreated trauma-hemorrhage group. The levels of HSP32 and HSP70 mRNAs in estradiol-treated trauma-

Fig. 1. Effects of estradiol (E2; 1 mg/kg body wt) treatment on cardiac output (A) and maximal rate of left ventricular pressure [dp/dtmax] changes (B and C) at 5 h after trauma-hemorrhage (T-H) and resuscitation. Estradiol was administered in a 1 mg/kg body wt dose. Data are presented as means ± SE of 6 animals in each group. *P < 0.05 vs. sham and T-H+E2; #P < 0.05 vs. sham.

Fig. 2. Effects of estradiol treatment (1 mg/kg body wt) on changes in bile production in vivo (A) and liver perfusion ex vivo (B) after T-H and resuscitation. C: liver indocyanine-green (ICG) uptake during liver perfusion. Parameters were measured at 5 h after T-H. Data are presented as means ± SE (n = 6 animals/group). *P < 0.05 vs. sham and T-H+E2; #P < 0.05 vs. sham.

Fig. 3. Effects of estradiol (1 mg/kg body wt) treatment on serum alanine aminotransferase (ALT; A) and lactic dehydrogenase (LDH) content of the liver perfusate (B) at 5 h after T-H and resuscitation. Data are presented as means ± SE (n = 6 animals/group). *P < 0.05 vs. sham and T-H+E2; #P < 0.05 vs. sham.
hemorrhage rats were also significantly more compared with the sham group. The increase in HSP60 mRNA after estradiol administration was not significantly different from that of sham animals.

In the liver, HSP32 and HSP70 mRNA expression were elevated at 5 h after trauma-hemorrhage (Fig. 6, A and C). Conversely, HSP60 mRNA level did not change after trauma-hemorrhage (Fig. 6B). Estradiol administration after trauma-hemorrhage significantly increased HSP32, HSP60, and HSP70 expression in the liver. The enhanced levels of HSP mRNA expression after 17β-estradiol administration were significantly different from both the sham and nontreated trauma-hemorrhage group.

DISCUSSION

There is a growing body of evidence that indicates that HSP upregulation plays a central role in the preservation of organ function after ischemic and low-flow conditions (16, 31). Previous studies from our laboratory have shown salutary effects of estrogen in restoring organ functions after trauma-hemorrhage (11). Furthermore, studies have also shown that estrogen can induce the expression of HSPs (17, 29, 34). Moreover, trauma-hemorrhage-induced HSP32 in the liver of female proestrus rats (with elevated plasma estradiol) exceeded that of their male counterparts (36). This gender dimorphism in HSP32 expression correlated with decreased organ damage and improved hepatic function. In the present study, estradiol induced HSP32, HSP60, and HSP70 in the heart and liver, and these increases in mRNA expression were associated with attenuation of organ damage and restoration of cardiac and hepatic functions. Although we did not measure HSPs expression in this study, our recent findings suggest that both HSPs mRNA and protein expression follow a similar trend at 24 h after trauma-hemorrhage (44). However, it remains unknown whether similar changes occur in HSPs protein expression in the heart and liver at 5 h after trauma-hemorrhage and resuscitation.

HSPs are a disparate group of proteins that mediate their protective effects via diverse mechanisms. For instance, HSP60 and HSP70 serve as molecular chaperones by assisting the folding of peptides, and this feature helps to maintain protein structures under stress conditions. HSP60 is localized in the mitochondria and is reported to be helpful in maintaining electron chain integrity. In the event of the disruption of mitochondrial electron transport chain, mitochondria generate H2O2, cytochrome c release and apoptosis. In this regard, HSP60 upregulation is also shown to be protective for cardiomyocytes against ischemia-reperfusion (10). Furthermore, it has been reported that HSP60 acts as an endogenous ligand of Toll-like receptor-4 (TLR4) receptors (28). TLR4 receptors are a key element in LPS signaling (2). Previous studies have shown that HSP60 has a dual effect on TLR4-mediated signaling. On the one hand, the exogenously administered HSP60

Fig. 4. Cytokine levels in the plasma at 5 h after T-H and resuscitation with or without estradiol (1 mg/kg body wt) treatment. TNF-α (A), IL-6 (B), and IL-10 (C) productions. Data are presented as means ± SE (n = 5–6 animals/group). *P < 0.05 vs. sham and T-H+E2; #P < 0.05 vs. sham.

Fig. 5. Effects of estradiol (1 mg/kg body wt) treatment on heat shock protein (HSP)32, HSP60, and HSP70 mRNA expressions in the heart at 5 h after T-H and resuscitation. HSP32 (A), HSP60 (B), and HSP70 (C) mRNA expressions were determined by the real-time PCR method. The endogenous control was 18S rRNA. Alterations of HSP expressions are considered relative to the sham. The average expression level of the sham group was set to 1.0. Data are presented as means ± SE (n = 6 animals/group). *P < 0.05 vs. sham; #P < 0.05 vs. sham and T-H; @P < 0.05 vs. T-H.
Heat and hypoxia activate HSF-1, which is present in the cytoplasm in an inactive, monomeric form. Upon activation, HSF-1 has been shown to regulate the expression of HSP in the lung under various stimuli, such as LPS or gram-negative bacteria. HSP70 is the most widely investigated member of the HSP family; however, its role in organ protection is obscure. It is well established that HSP70 is upregulated after ischemic insult, and it can prevent both cardiac and hepatic injuries (3, 20). Studies have suggested that HSP70, similar to HSP60, assists the transfer of newly synthesized proteins into the mitochondria, thus maintaining overall mitochondrial integrity (25, 30). Beyond the protein stabilizing effect, HSP70 can reduce cytokine responses. Nonetheless, while the underlying mechanisms have not been fully elucidated, there is a growing body of evidence that HSP70 can block proinflammatory cascade via the suppression of NF-κB activation (19).

HSP32 differs from the previous HSPs, since its enzymatic activity presents its protective effect. HSP32, known as heme oxygenase-1, the inducible member of the heme oxygenase enzyme family, is responsible for heme elimination. The accumulation of free heme under hypoxic conditions entails the development of its toxic effects; therefore elimination from the cellular milieu is essential. Carbon monoxide, the by-product of heme degradation, can activate soluble guanylate cyclase and induce vasodilatation via cGMP (23). An additional mechanism of the HSP32-mediated tissue protection may be the CO-mediated activation of the Ca^{2+}-dependent potassium (K_{Ca}) channels. Because the activation of K_{Ca} channels leads to hyperpolarization of the smooth muscle cells, their stimulation results in decreased vascular contractility (40). Furthermore, it has also been reported that HSP32 upregulation inhibits the expression of adhesion molecules and may, therefore, prevent subsequent leukocyte-endothelial cell interactions (33). The other product of HSP32 enzyme activity, bilirubin, also has potent antioxidant activity. Although the HSP32-mediated bilirubin production is limited, the oxidized bilirubin (biliverdin) can be regenerated by biliverdin reductase, forming a potent redox cycle (1). In this regard, it has been reported that the HSP32 upregulation also protects mitochondrial function and prevents ATP-depletion after oxidative stress (4).

It could be argued that the present study used measurement at a single time point, i.e., at 5 h after treatment, and thus it remains unclear whether the salutary effects of estradiol are sustained for longer periods of time, i.e., 24 h after treatment (5, 6). In this regard, our previous studies have shown that if the improvement in organ functions by any pharmacological agent is evident early after treatment, those salutary effects are sustained for prolonged intervals and they also improve the survival of animals (6). Thus although a time point other than 5 h was not examined in this study, on the basis of our previous studies, it would appear that the salutary effects of estradiol on HSP and organ functions would be evident, even if one measured those effects at another time point after trauma-hemorrhage and resuscitation (5). Furthermore, although we examined the expression of HSP in the heart and liver, we have not examined whether HSP expression is also altered in other organs, such as the lungs, and if so, whether estradiol has any salutary effects on the expression of HSP in the lung under those conditions. It can also be argued that we should have included a sham group treated with estradiol in this study to determine whether estradiol per se has any effect on cardiac and hepatic function and the expression of HSPs in shams. In this regard, studies of Hamilton et al. (8) have shown that although female rats have higher HSP than males, administration of estradiol in females resulted in further increase in HSP72 and protected female cardiomyocytes after hypoxia and reoxygenation (8, 37). Furthermore, our previous studies have shown that administration of estradiol alone did not produce any change on cardiac and hepatic functions in sham-operated animals, but its administration improved cardiac and hepatic functions after trauma-hemorrhage (21). Since estradiol administration in itself did not influence cardiac and hepatic function in sham-operated animals (21), we did not examine the effects of estradiol on HSPs in sham operated animals in this study.

Although the mechanism by which estradiol upregulates HSP after trauma-hemorrhage remains to be established, previous studies have suggested that HSP synthesis is controlled by a family of transcription factors, the heat shock factors (HSF). In this respect, four HSFs have been identified, but only HSF-1 has been shown to regulate the expression of HSP in response to ischemia, hypoxia, heat, stretch, or injury (27). Heat and hypoxia activate HSF-1, which is present in the cytoplasm in an inactive, monomeric form. Upon activation,
HSF-1 migrates to the nucleus where it binds to the heat shock element, which is present in the promoter of the stress response gene and initiates HSP transcription and synthesis. HSF-1 has been reported to be expressed in hearts (15), and it protects cardiomyocytes from ischemia-reperfusion injury in the transgenic mouse model (27). In addition, a role of NF-κB in estradiol upregulation of HSP has also been suggested in recent studies. In this regard, studies have suggested that in female rats’ cardiomyocytes, estrogen pretreatment decreased lactate dehydrogenase release with hypoaxia (8). This protective effect persisted despite blockade of HSF-1 by decoys. However, an NF-κB decoy prevented the increase in HSP72 and abolished the estrogen-associated protection during hypoaxia. Thus these findings suggest that activation of NF-κB is also critical for estrogen-associated protection. It therefore appears that multiple pathways exist by which estrogen may mediate its salutary effects, and thus studies are needed to delineate the role of HSF-1 and NF-κB in estrogen-mediated salutary effects on liver and heart function after trauma-hemorrhage.

In summary, HSP upregulation has multiple potentials for protecting tissue integrity and preventing organ dysfunction and thus may play a significant role in the salutary effects of estradiol treatment after trauma-hemorrhage. Our results suggest that the induction of HSPs is an important mechanism by which estradiol improves cardiac and hepatic functions after trauma-hemorrhage. Although this study could not present evidence for a direct link between the salutary effects of estradiol and the upregulation of the observed HSPs, our study has shown that estradiol induced HSP expression after trauma-hemorrhage. Nonetheless, since estradiol can mediate its effects in multiple ways, it is not suggested that HSP upregulation is the exclusive effect of estradiol action under such conditions. Further studies delineating the relationship between estrogen and HSP family may enable us to develop new therapeutic modalities for hemorrhagic shock.

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