J Anesth (2012) 26:892–899
DOI 10.1007/s00540-012-1426-2

REVIEW ARTICLE

The effects of estrogen on various organs: therapeutic approach for sepsis, trauma, and reperfusion injury. Part 2: liver, intestine, spleen, and kidney

Takashi Kawasaki · Irshad H. Chaudry

Received: 27 December 2011 / Accepted: 24 May 2012 / Published online: 23 June 2012

Abstract Several clinical studies show a gender dimorphism of immune and organ responsiveness in the susceptibility to and morbidity from shock, trauma, and sepsis. However, there are conflicting reports on the role of gender in outcomes. Animal studies of shock, trauma, and sepsis have confirmed that alterations in immune and organ functions are more markedly depressed in adult males and in ovariectomized and aged females. In this review, we discuss the effect of estrogen on liver, intestinal, splenic, and renal functions in an experimental model of sepsis, trauma, and reperfusion injury. To establish the role of gender in the outcome of these patients, more studies in clinical and experimental settings are required to determine whether gender-specific responses are global across the injuries or are observed in specific injury situations. Studies are also needed to delineate underlying mechanisms responsible for differences between males and females. The findings gained from the experimental studies will help in designing innovative therapeutic approaches for the treatment of sepsis, trauma, and reperfusion injury patients.

Keywords Shock · Trauma · Males · Females · Sepsis · Reperfusion · Estrogen

T. Kawasaki · I. H. Chaudry
Department of Surgery, University of Alabama at Birmingham, Birmingham, AL 35294, USA

T. Kawasaki (✉)
Department of Anesthesiology, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan
e-mail: takasi-k@med.uoeh-u.ac.jp

Introduction

It is well known that gender dimorphism exists in trauma, shock, and sepsis. In sepsis patients, the preponderance of morbidity and mortality was shown in males as compared to females [1]. As well as sepsis patients, there is a report that showed a significantly higher incidence of bacteremic infections in traumatized males than in females [2]. Another report also demonstrated a significantly higher incidence of pneumonia in males in severely injured patients [3]. Furthermore, a significantly higher survival rate was observed in women compared to men following the onset of sepsis [4]. Similar gender-dimorphic findings have been demonstrated in experimental studies following severe blood loss and the induction of sepsis [5, 6]. Immune response following trauma-hemorrhage (T-H) depends on the sex steroid environment. Gender-specific immune response may be caused by the different effects and roles of sex hormones. Several studies were conducted to elucidate the effect of sex steroids on cell-mediated immune responses following sepsis, trauma, and reperfusion injury. These studies showed that male sex hormones play an important role in mediating immunosuppressive effects. In contrast, female sex hormones are immunoprotective. In this article, we describe the role of estrogen in liver, intestinal, splenic, and renal pathogenesis in experimental animal settings.

Effect of estrogen on hepatic system

Sepsis

Studies have shown gender dimorphic response of the liver for endotoxemia. Erikoglu et al. [7] investigated the

differences between male and female rats and the effects of sex hormones on tissue changes in liver in a sepsis model. Female rats showed less liver tissue damage and less systemic endotoxemia than male rats. Estrogen treatment improved congestion, portal inflammation, and focal necrosis of the liver. Sener et al. [8] also showed estrogen protects liver function, which was assessed by serum aspartate aminotransferase and alanine aminotransferase levels, and oxidative liver injury by its antioxidant properties.

Trauma

Many studies have shown a beneficial effect of estradiol on liver function in trauma-hemorrhage shock models. Mizushima et al. [9] demonstrated that estradiol has salutary effects on depressed hepatocellular functions following trauma-hemorrhage in male animals. Administration of estradiol significantly improved hepatocellular function (i.e., maximal velocity and overall efficiency of in vivo indocyanine green clearance).

Kupffer cells (KC) have been reported as a major source of proinflammatory cytokines [i.e., interleukin (IL)-6, tumor necrosis factor (TNF)-α], which have been implicated in the pathogenesis of trauma-hemorrhage. Yokoyama et al. [10] investigated whether estradiol has a direct effect on KC cytokine production following trauma-hemorrhage. They found direct downregulation of KC IL-6 production by estradiol at a molecular level, which might explain in part the previously observed salutary effects of estradiol treatment following trauma-hemorrhage. Suzuki et al. [11] demonstrated that effects of estradiol on KC cytokine production (IL-6, TNF-α, IL-10) are mediated via estrogen receptor (ER)-α and via normalization of mitogen-activated protein kinase (MAPK) activation. Eckhoff et al. [12] also showed that KC-derived monocyte chemoattractant protein (MCP)-1 plays a major role in organ dysfunction after ischemia–reperfusion (I/R). They found that administration of estradiol following trauma-hemorrhage modulates MCP-1 release and reduces organ damage, and salutary effects of estradiol are mediated via ER-α [12]. In addition, Shimizu et al. [13] showed the salutary effects of estradiol against hepatic injury are mediated predominantly via ER-α, which directly modulates KC cytokine-induced neutrophil cytokine-induced neutrophil chemoattractant (CINC)-1 production and hepatic neutrophil accumulation following trauma-hemorrhage. Administration of estradiol following trauma-hemorrhage decreased KC TLR4 expression and also prevented the phosphorylation of p38 MAPK and NF-κB [14]; this was accompanied by normalization of KC IL-6, TNF-α, macrophage inflammatory protein (MIP)-1α, and MIP-2. TLR4 mediates mitochondrial DNA (mtDNA) damage and biogenic responses [15]. Mitochondrial transcription factor A (Tfam) is an essential regulator for mtDNA transcription and adenosine triphosphate (ATP) production. Increased ATP levels were associated with normalization of immune function following trauma-hemorrhage. Administration of estradiol following trauma-hemorrhage prevented the increase in KC TLR4, inducible nitric oxide synthase (iNOS), and cytokine production; this was accompanied by normalized ATP, Tfam, and mitochondrial cytochrome oxidase I (mtCOI) levels. Furthermore, the decreased KC ATP and mtCOI levels were not observed in TLR4 mutant mice following trauma-hemorrhage. Taken together, these findings suggest that downregulation of TLR4-dependent ATP production is critical to estradiol-mediated immunoprotection in KCs following trauma-hemorrhage. The KCs are macrophages in the liver whose major role is to clear circulating pathogens. Decreased phagocytic capacity of KCs may result in severe systemic infection. Hsieh et al. [16] found that the depressed KC phagocytic capacity following trauma-hemorrhage was enhanced by estrogen administration and that this occurs as a result of maintenance of Fc receptor expression and cellular ATP content via the activation of Akt. Trauma-hemorrhage suppressed KC phagocytosis by decreasing Fc receptor expression and Akt activation. Cellular ATP levels were also decreased following trauma-hemorrhage. Administration of estrogen following trauma-hemorrhage increased phospho-Akt levels and normalized KC phagocytosis.

With regard to the effects of estradiol on Akt activation, there have been some investigations whether estradiol prevents hepatic damage via Akt activation following trauma-hemorrhage. Hsu et al. [17] demonstrated that Akt/heme oxygenase (HO)-1 plays a role in estradiol-mediated attenuation of hepatic injury following trauma-hemorrhage. Trauma-hemorrhage increased hepatic injury marker (α-GST and MPO) activity, cytokines, intercellular adhesion molecule (ICAM)-1, and chemokine levels. These parameters were markedly improved in estradiol-treated animals following trauma-hemorrhage. Estradiol treatment also increased hepatic Akt activation and HO-1 expression. These results suggest that the salutary effects of estradiol in decreasing hepatic injury following trauma-hemorrhage are in part mediated via an ER-related, Akt-dependent upregulation of HO-1. Yang et al. [18] also demonstrated that Akt-dependent enhanced HO-1 modulates inflammatory responses and protects liver following trauma-hemorrhage in proestrus animals.

Although the protective effects of estradiol on cardiac functions are mediated via induction of heat shock proteins (HSPs), this hormone also prevents hepatic injury by attenuation of hepatic HSP32 mRNA/protein expression after trauma-hemorrhage [19]. In the liver, HSP32 and HSP70 were increased following trauma-hemorrhage.

Estradiol administration following trauma-hemorrhage and resuscitation increased liver HSP expression and ameliorated the impairment of liver function [20]. The ability of estradiol to induce HSP expression in the liver suggests that HSPs, in part, mediate the salutary effects of estradiol on liver function following trauma-hemorrhage.

Although the salutary effects of estradiol on liver functions are mediated via ER-α, the existence of another novel ER, G protein-coupled receptor (GPR)30, has been suggested as a candidate for triggering a broad range of estradiol-mediated signaling. GPR30 also acts independently of the ER to promote activation of the protein kinase A (PKA) pathway, which protects cells from apoptosis through Bcl-2. Hsieh et al. [21] examined whether the salutary effects of estradiol in attenuating hepatic injury after trauma-hemorrhage are mediated via GPR30- or ER-α-regulated activation of PKA-dependent signaling. At 2 h after trauma-hemorrhage, administration of estradiol conjugated to bovine serum albumin (E2-BSA, membrane impermeable) or estradiol induced the upregulation of ER-α and GPR30 and attenuated hepatic injury, which was accompanied by increases in PKA activity and Bcl-2 expression. Inhibition of PKA in E2-BSA-treated trauma-hemorrhage animals prevented the E2-BSA-induced attenuation of hepatic injury. In additional studies, isolated hepatocytes were transfected with small interfering RNA to suppress GPR30 or ER [21]. The results showed that suppression of GPR30 but not ER-α prevented E2-BSA- or estradiol-induced PKA activation and Bcl-2 expression. These results suggest that the nongenomic salutary effects of estradiol in reducing hepatic injury following trauma-hemorrhage are mediated through the PKA-dependent pathway via GPR30 but not ER-α.

Interestingly, administration of flutamide, an androgen receptor antagonist, following trauma-hemorrhage also decreased hepatic injury [22]. The salutary effects of flutamide appear to be mediated at least in part by increased estrogen levels and via an ER-related pathway. Another study [23] showed estradiol administration following trauma-hemorrhage in males appears to directly upregulate prolactin receptor (PRL-R) long-form gene expression in hepatocytes. Thus, it appears that higher levels of female sex steroids play an important role in maintaining liver function.

The fine balance between vasoconstrictors and vasodilators maintains portal circulation. Studies have shown that portal response to endothelin (ET)-1, a potent vasoconstrictor, is enhanced following hemorrhagic shock, which subsequently leads to impaired hepatic circulation and hepatic damage. Yokoyama et al. [24] investigated the effects of estradiol on portal response to ET-1 following trauma-hemorrhage. Peak portal pressure after the administration of ET-1 was significantly higher in trauma-hemorrhage animals compared to sham animals. This effect was significantly attenuated in the estradiol-treated animals. Furthermore, estradiol treatment restored bile production and prevented hepatic damage following trauma-hemorrhage. These results suggest the beneficial effects of estradiol following trauma-hemorrhage, at least in part, are caused by the attenuation of portal pressure response to increased ET-1.

Reperfusion injury

The salutary effects of estradiol are not restricted to trauma-hemorrhage, because estradiol also produces salutary effects following I/R to the liver. A previous study [25] demonstrated that pretreatment of animals with estrogen resulted in normalized KC function, amelioration of sinusoidal perfusion failure, and venular leukocyte–endothelial cell interaction following liver I/R. Other studies [12, 26] have also demonstrated that estradiol treatment significantly reduced liver necrosis, disintegration of hepatic cords, and neutrophil infiltration and overexpressed HSP70. The protective effects of estradiol against I/R injury to the liver are associated with selective modulation of MAPK kinases [27].

Effect of estrogen on the intestinal system

Sepsis

Using cecal ligation and puncture method in rats, Sener et al. [8] demonstrated that estrogen protects intestines against sepsis-induced injury. Malondialdehyde levels, myeloperoxidase activity, and collagen content were increased in the ileum in septic rats. Estrogen treatment improved this oxidative organ damage, suggesting that treatment with estrogen might be applicable in septic patients.

Trauma (perfusion failure)

The intestine is highly susceptible to hemorrhagic shock. Splanchnic ischemia is the initial event that releases injurious factors, leading to systemic disorders with high morbidity and mortality. Ba et al. [28] showed that ET-1 appears to play an important role in intestinal perfusion failure following trauma-hemorrhage. Estradiol administration following trauma-hemorrhage, however, modulated the vasoconstrictor effect of ET-1 and improved intestinal perfusion in male rats under those conditions. Another study [29] showed that estradiol administration following trauma-hemorrhage improves small intestinal blood flow. The authors found that angiotensin II (Ang II) plays a key

role in development of organ I/R injury. Estradiol administration following trauma-hemorrhage attenuated increased intestinal MPO activity, Ang II level, and Ang II subtype I receptor (AT1R) protein expression. The authors concluded that Ang II plays a role in producing small intestine inflammation following trauma-hemorrhage, and the salutary effects of estradiol on intestinal inflammation are mediated in part by Ang II and AT1R downregulation. Furthermore, Kuebler et al. [30] demonstrated estradiol improves systemic and intestinal perfusion following trauma-hemorrhage.

In addition to intestinal MPO activity, trauma-hemorrhage also led to an increase in intestinal TNF-α, IL-6, ICAM-1, CINC-1, CINC-3, and MIP-2 levels [31–33]. Hsu et al. [31] demonstrated that this increase was accompanied with a decrease in intestinal p38 MAPK activity. Administration of estradiol normalized all the foregoing parameters. These results suggest that the p38 MAPK pathway plays a critical role in mediating the salutary effects of estradiol on shock-induced intestinal injury. Another study showed that administration of flutamide following trauma-hemorrhage normalized all these parameters. The salutary effects of flutamide administration on attenuation of intestinal injury following trauma-hemorrhage appear to be mediated via upregulation of ER-β-dependent HO-1 expression [32]. Furthermore, these parameters were also improved significantly in estradiol-BSA-treated rats subjected to trauma-hemorrhage. The phosphoinositide 3-kinase (PI3K)/Akt pathway plays a critical role in mediating the nongenomic salutary effects of estradiol on attenuation of shock-induced intestinal tissue damage [33].

Reperfusion injury

The intestine is highly susceptible to ischemia–reperfusion (I/R) injury. Ozkan et al. [34] showed that resveratrol, an antioxidant with the property of an estrogen-receptor agonist, attenuates intestinal ischemia–reperfusion injury in rats.

Hypoxia and acidosis

Previous studies documented that proestrus female animals are more resistant to shock-induced acute gut mucosal injury than male animals. Homma et al. [35] investigated whether the female gut is more resistant to injury and produces a lesser inflammatory response than the male gut when exposed to conditions associated with shock states (hypoxia and acidosis). Administration of estradiol or the testosterone receptor antagonist flutamide in male rats abrogated the increase in gut mucosal injury and the increased IL-6 and MIP-2 response observed after hypoxia plus acidosis. These results suggest that gender differences in the ex vivo intestinal response to stresses such as hypoxia and acidosis exist and that the administration of estradiol or blockade of the testosterone receptor in male rats mitigates the gender dimorphic effects.

Effect of estrogen on splenic system

Sepsis

Several studies tried to evaluate the effect of estrogen on splenic macrophage/monocyte function in a two-hit model of trauma-hemorrhage and sepsis [36, 37]. These studies demonstrated that estrogen play a critical role in maintaining splenic macrophage responses after trauma-hemorrhage by suppressing proinflammatory cytokine production and prevent the increased lethality from subsequent sepsis.

Trauma

Trauma-hemorrhage induces marked dysregulation of immune response. Studies indicate that whereas immune functions in males are depressed, they are enhanced/maintained in females following trauma-hemorrhage [38]. Moreover, castration of male mice (i.e., androgen depletion) before trauma-hemorrhage prevented the depression of cell-mediated immunity following trauma-hemorrhage [39]. Angele et al. [40] demonstrated high testosterone or low estradiol levels appear to be responsible for depressing splenocyte immune functions such as splenocyte proliferation and IL-2 and IL-3 release in males after trauma-hemorrhage. Agents that block testosterone receptors or increase estradiol levels may therefore be helpful in improving depressed immune functions in male trauma patients. Knoferl et al. [36] also demonstrated that splenocyte proliferation and IL-2, IL-3, and interferon-γ release were maintained in proestrus sham-ovariectomized animals after trauma-hemorrhage, whereas they were suppressed in ovariectomized animals subjected to trauma-hemorrhage. They found that elevated circulating estradiol in proestrus females plays a direct role in the maintenance of immunocompetence after trauma-hemorrhage.

Estrogen also exhibits salutary effects on splenic macrophages [41, 42], splenic T lymphocytes [43], and splenic dendritic cells [44]. Suppression in the productive capacity of TNF-α and IL-6 following trauma-hemorrhage by splenic macrophages was prevented in estradiol- and ER-α agonist-treated mice [41]. Suzuki et al. [42] also demonstrated that ER-α agonist but not ER-β agonist administration following trauma-hemorrhage was as effective as estradiol in preventing the suppression in macrophage cytokine production. Thus, it appears that ER-α plays a

predominant role in mediating the salutary effects of estradiol on macrophage cytokine production following trauma-hemorrhage and that such effects are likely mediated via normalization of MAPK. Trauma-hemorrhage induces depressed release of IL-2 and IL-6 in T lymphocytes [43]. Increased synthesis of estradiol in proestrus females appears to be responsible for the maintenance of T lymphocyte cytokine release associated with the protection of immune functions after trauma-hemorrhage [43]. In addition to macrophages and T lymphocytes, the salutary effects of estradiol on splenic dendritic cell functions are mediated predominantly via ER-α. Our results [44, 45] showed apoptosis of splenic dendritic cells increased following trauma-hemorrhage; however, estradiol administration after trauma-hemorrhage normalized the rate of apoptosis. Moreover, splenic dendritic cell cytokine production, co-stimulating factors and MHC class II expression, and antigen presentation capacity were significantly decreased following trauma-hemorrhage; however, estradiol as well as ER-α agonist also prevented these depressions following trauma-hemorrhage.

Effect of estrogen on renal system

Reperfusion injury

Sexual dimorphism in response to renal injury has been reported. Males are much more susceptible to I/R-induced renal injury when compared with females. Previous study demonstrated that testosterone is responsible for this enhanced susceptibility of males [46]. Recently, Rusai et al. [47] suggested that testosterone upregulates serum and glucocorticoid-regulated kinase-1 (SGK-1) in the kidney during renal ischemia–reperfusion injury, contributing to sexual dimorphism. In contrast, estrogen attenuates renal ischemia–reperfusion injury through the PI3K/Akt/eNOS pathway via estrogen receptors [48].

Chronic renal failure

A recent study [49] demonstrated the impact of sexual dimorphism on chronic renal failure (CRF)-induced oxidative multiorgan damage. Kasimay et al. [49] investigated the effects of estradiol loss and estradiol supplementation on the progress of CRF. CRF-induced elevation in serum TNF-α in male animals was abolished when the animals were treated with estradiol whereas ovariectomy exaggerated TNF-α response. In ovariectomized females and in male animals with CRF, estradiol treatment reversed the malondialdehyde elevation in tissues (kidney, heart, lung, ileum, brain, liver, and gastrocnemius muscle), whereas depletion of glutathione in these tissues was prevented by estradiol treatment. Increased level of MPO activity was also reversed by estradiol treatment. In addition, the extent of tissue injury was relatively less in females, although ovariectomy exacerbated all the indices of oxidative injury. Furthermore, administration of estradiol improved CRF-induced systemic inflammatory outcomes in both male and female animals by depressing tissue neutrophil infiltration and modulating the release of inflammatory cytokines. These results suggest the salutary effects of estradiol on renal functions following adverse circulatory conditions.

Tissue-specific expression of ER

In this review, we describe the protective effects of estrogen on liver, intestine, spleen, and kidney (Table 1). Although estradiol administration improves organ and immune cell functions, ER subtypes have tissue compartment-specific roles in mediating the effects of estradiol on these functions (Table 2). Many studies [18, 50–52] investigated whether the salutary effects of estradiol are mediated via ER-α or ER-β. Yu et al. [53] explored whether the salutary effects of estradiol against trauma-hemorrhage-induced lung injury are mediated via ER-α or ER-β. They found the salutary effects of estradiol on attenuation of lung injury are mediated via ER-β, and ER-β-induced downregulation of iNOS likely plays a significant role in the ER-β-mediated lung protection following

Table 1 The effects of estrogen on various organs

Organ	Effect of estrogen	Reference
Liver	Congestion↓	[7]
	Portal inflammation↓	[7]
	Necrosis↓	[7]
	Kupffer cell	
	Cytokine production↓	[10, 11]
	MAPK activation↓	[11, 14]
	TLR4 expression↓	[14]
	Phagocytic capacity↑	[16]
	HO-1 expression↑	[17]
	Akt activation↑	[17]
	PKA activation↑	[21]
Intestine	MAPK(p38) activation↑	[31]
	HO-1 expression↑	[32]
	PI3K/Akt activation↑	[33]
Spleen	Splenocyte: proliferation↑	[36, 40]
	Macrophage: MAPK activation↑	[42]
	DC: antigen presentation capacity↑	[44]
Kidney	PI3K/Akt/eNOS pathway↑	[48]

MAPK mitogen-activated protein kinase, *PKA* protein kinase A, *DC* dendritic cell

Table 2 Tissue-specific role of estrogen in various organs

Organ	ER-α	ER-β
CNS	Unknown	Unknown
Lung	−	+
Heart	−	+
Liver	+	−
Spleen	+	−
Intestine	+	+
Kidney	−	+

CNS central nervous system, *ER* estrogen receptor

trauma-hemorrhage. There are conflicting data whether the protective effects of estrogen on cardiac function are mediated by ER-α or ER-β. Many studies demonstrated that the cardioprotective effects of estrogen are mediated via ER-β [50, 54–59]. However, other studies have shown that ER-α mediated the cardioprotective effects of estrogen [60–62]. Thus, it appears that both ER-α and ER-β play an important role in mediating the salutary effects of estrogen on the myocardium. ER-β plays an important role in cardiac performance and in the reduction of ET-1-induced vasoconstriction in the kidneys and lungs. In contrast, ER-α attenuated ET-1-induced vasoconstriction in the liver, whereas both ER-α and ER-β were equally effective in the small intestine [50]. ER-α agonist had the same effects as estradiol on cytokine production by KCs and splenic macrophages, and ER-β agonist had the same effects on alveolar macrophages and peripheral blood mononuclear cells [51]. In addition, administration of the ER-α agonist improved MPO activity and CINC-1, CINC-3, and ICAM-1 levels in the liver [18]. In contrast, ER-β agonist significantly improved these parameters in the lung. In the intestine, ER subtype specificity was not observed. ER-α mRNA expression was highest in the liver, whereas ER-β mRNA expression was greatest in the lung. Thus, the salutary effects of estradiol administration on organ function following trauma-hemorrhage are receptor subtype- and tissue specific.

Current limitations and future directions

The protective effects of estrogen in restoring organ function are through a genomic effect mediated through the intracellular receptors ER-α and ER-β, and also through a nongenomic effect mediated through cell-surface estrogen-binding receptors such as GPR30. Experimental studies clearly demonstrate that estrogen and ER agonists are useful therapeutic adjuncts in protecting organ function and improving outcome following trauma-hemorrhage. However, in the clinical setting, there are conflicting reports whether gender dimorphic responses are evident following injury. The reasons for the lack of uniform results appear to be that most studies do not take into consideration the hormonal status of the host at the time of injury. Thus, studies reporting protective effects of female gender following injury could be because the patients have high estrogen levels at the time of injury whereas those reporting a lack of protective effects in females could be the result of low estrogen levels in those specific patients. In view of this, it is important to carry out additional studies in which the hormonal status of the patient is measured as quickly as possible after injury and correlate sex steroid levels with the lack or prevalence of complications, circulating cytokine levels, incidence of organ dysfunction and failure, and length of hospital stay. Although a small number of investigators are examining some of these aspects [63, 64], more studies are needed to conclusively demonstrate in the clinical setting the merits of female versus male sex steroids in conferring protection following injury. Although many studies indicate beneficial effects of estrogen following trauma, more studies are also needed to fully understand the precise mechanism by which estrogen mediates its salutary effects under those conditions. In addition, animal studies have shown that estrogen increases the frequency of cancer (breast, cervix, vagina, kidney, and liver), and there is evidence that estrogen may increase the risk of various cancers in humans. Females who take estrogen after menopause are more likely to develop gallbladder diseases and blood clots. Also, males who take estrogen are more susceptible to prostate cancer, heart attack, blood clots in the lungs, and phlebitis. Therefore, it is important to avoid the prolonged continuous administration of estrogen. Confirming the current status of individual estrogen level and developing an estrogen therapy strategy depending on individual estrogen level are important for the best estrogen effects.

Acknowledgments This work is supported by NIH Grants RO1 GM37127 and RO1 GM39519.

References

1. Bone RC. Toward an epidemiology and natural history of SIRS (systemic inflammatory response syndrome). JAMA. 1992;268:3452–5.
2. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935–1972), with special reference to hospital-acquired cases. J Infect Dis. 1975;132:316–35.
3. Gannon CJ, Pasquale M, Tracy JK, McCarter RJ, Napolitano LM. Male gender is associated with increased risk for postinjury pneumonia. Shock. 2004;21:410–4.
4. Schroder J, Kahlke V, Staubach KH, Zabel P, Stuber F. Gender differences in human sepsis. Arch Surg. 1998;133:1200–5.

5. Zellweger R, Wichmann MW, Ayala A, Stein S, DeMaso CM, Chaudry IH. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. Crit Care Med. 1997;25:106–10.
6. Angele MK, Schwacha MG, Ayala A, Chaudry IH. Effect of gender and sex hormones on immune responses following shock. Shock. 2000;14:81–90.
7. Erikoglu M, Sahin M, Ozer S, Avunduk MC. Effects of gender on the severity of sepsis. Surg Today. 2005;35:467–72.
8. Sener G, Arbak S, Kurtaran P, Gedik N, Yegen BC. Estrogen protects the liver and intestines against sepsis-induced injury in rats. J Surg Res. 2005;128:70–8.
9. Mizushima Y, Wang P, Jarrar D, Cioffi WG, Bland KI, Chaudry IH. Estradiol administration after trauma-hemorrhage improves cardiovascular and hepatocellular functions in male animals. Ann Surg. 2000;232:673–9.
10. Yokoyama Y, Kuebler JF, Matsutani T, Schwacha MG, Bland KI, Chaudry IH. Mechanism of the salutary effects of 17beta-estradiol following trauma-hemorrhage: direct downregulation of Kupffer cell proinflammatory cytokine production. Cytokine. 2003;21:91–7.
11. Suzuki T, Shimizu T, Yu HP, Hsieh YC, Choudhry MA, Bland KI, Chaudry IH. 17 Beta-estradiol administration following trauma-hemorrhage prevents the increase in Kupffer cell cytokine production and MAPK activation predominately via estrogen receptor-alpha. Surgery (St. Louis). 2006;140:141–8.
12. Eckhoff DE, Bilbao G, Frenette L, Thompson JA, Contreras JL. 17-Beta-estradiol protects the liver against warm ischemia/reperfusion injury and is associated with increased serum nitric oxide and decreased tumor necrosis factor-alpha. Surgery (St. Louis). 2002;132:302–9.
13. Shimizu T, Suzuki T, Yu HP, Yokoyama Y, Choudhry MA, Bland KI, Chaudry IH. The role of estrogen receptor subtypes on hepatic neutrophil accumulation following trauma-hemorrhage: direct modulation of CINC-1 production by Kupffer cells. Cytokine. 2008;43:88–92.
14. Hsieh YC, Frink M, Thobe BM, Hsu JT, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. 17Beta-estradiol downregulates Kupffer cell TLR4-dependent p38 MAPK pathway and normalizes inflammatory cytokine production following trauma-hemorrhage. Mol Immunol. 2007;44:2165–72.
15. Hsieh YC, Frink M, Kawasaki T, Thobe BM, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Downregulation of TLR4-dependent ATP production is critical for estrogen-mediated immunoprotection in Kupffer cells following trauma-hemorrhage. J Cell Physiol. 2007;211:364–70.
16. Hsieh CH, Nickel EA, Chen J, Schwacha MG, Choudhry MA, Bland KI, Chaudry IH. Mechanism of the salutary effects of estrogen on kupffer cell phagocytic capacity following trauma-hemorrhage: pivotal role of Akt activation. J Immunol. 2009;182:4406–14.
17. Hsu JT, Kan WH, Hsieh CH, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Mechanism of estrogen-mediated attenuation of hepatic injury following trauma-hemorrhage: Akt-dependent HO-1 up-regulation. J Leukoc Biol. 2007;82:1019–26.
18. Yang S, Hu S, Chen J, Choudhry MA, Rue LW 3rd, Bland KI, Chaudry IH. Mechanism of hepatoprotection in proestrus female rats following trauma-hemorrhage: heme oxygenase-1-derived normalization of hepatic inflammatory responses. J Leukoc Biol. 2009;85:1015–26.
19. Shimizu T, Yu HP, Suzuki T, Szalay L, Hsieh YC, Choudhry MA, Bland KI, Chaudry IH. The role of estrogen receptor subtypes in ameliorating hepatic injury following trauma-hemorrhage. J Hepatol. 2007;46:1047–54.
20. Szalay L, Shimizu T, Suzuki T, Yu HP, Choudhry MA, Schwacha MG, Rue LW 3rd, Bland KI, Chaudry IH. Estradiol improves cardiac and hepatic function after trauma-hemorrhage: role of enhanced heat shock protein expression. Am J Physiol Regul Integr Comp Physiol. 2006;290:R812–8.
21. Hsieh YC, Yu HP, Frink M, Suzuki T, Choudhry MA, Schwacha MG, Chaudry IH. G protein-coupled receptor 30-dependent protein kinase A pathway is critical in nongenomic effects of estrogen in attenuating liver injury after trauma-hemorrhage. Am J Pathol. 2007;170:1210–8.
22. Shimizu T, Yu HP, Hsieh YC, Choudhry MA, Suzuki T, Bland KI, Chaudry IH. Flutamide attenuates pro-inflammatory cytokine production and hepatic injury following trauma-hemorrhage via estrogen receptor-related pathway. Ann Surg. 2007;245:297–304.
23. Yokoyama Y, Kitchens WC, Toth B, Schwacha MG, Bland KI, Chaudry IH. Upregulation of hepatic prolactin receptor gene expression by 17beta-estradiol following trauma-hemorrhage. J Appl Physiol. 2003;95:2530–6.
24. Yokoyama Y, Toth B, Kitchens WC, Schwacha MG, Rue LW 3rd, Bland KI, Chaudry IH. Estradiol's effect on portal response to endothelin-1 after trauma-hemorrhage. J Surg Res. 2004;121:25–30.
25. Burkhardt M, Slotta JE, Garcia P, Seekamp A, Menger MD, Pohlemann T. The effect of estrogen on hepatic microcirculation after ischemia/reperfusion. Int J Colorectal Dis. 2008;23:113–9.
26. Shen SQ, Zhang Y, Xiong CL. The protective effects of 17beta-estradiol on hepatic ischemia-reperfusion injury in rat model, associated with regulation of heat-shock protein expression. J Surg Res. 2007;140:67–76.
27. Vilatoba M, Eckstein C, Bilbao G, Frennete L, Eckhoff DE, Contreras JL. 17Beta-estradiol differentially activates mitogen-activated protein-kinases and improves survival following reperfusion injury of reduced-size liver in mice. Transplant Proc. 2005;37:399–403.
28. Ba ZF, Shimizu T, Szalay L, Bland KI, Chaudry IH. Gender differences in small intestinal perfusion following trauma hemorrhage: the role of endothelin-1. Am J Physiol Gastrointest Liver Physiol. 2005;288:G860–5.
29. Chen J, Yang S, Hu S, Choudhry MA, Bland KI, Chaudry IH. Estrogen prevents intestinal inflammation after trauma-hemorrhage via downregulation of angiotensin II and angiotensin II subtype I receptor. Am J Physiol Gastrointest Liver Physiol. 2008;295:G1131–7.
30. Kuebler JF, Jarrar D, Toth B, Bland KI, Rue L 3rd, Wang P, Chaudry IH. Estradiol administration improves splanchnic perfusion following trauma-hemorrhage and sepsis. Arch Surg. 2002;137:74–9.
31. Hsu JT, Kan WH, Hsieh CH, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Mechanism of estrogen-mediated intestinal protection following trauma-hemorrhage: p38 MAPK-dependent upregulation of HO-1. Am J Physiol Regul Integr Comp Physiol. 2008;294:R1825–31.
32. Yu HP, Choudhry MA, Shimizu T, Hsieh YC, Schwacha MG, Yang S, Chaudry IH. Mechanism of the salutary effects of flutamide on intestinal myeloperoxidase activity following trauma-hemorrhage: up-regulation of estrogen receptor-{beta}-dependent HO-1. J Leukoc Biol. 2006;79:277–84.
33. Yu HP, Hsieh YC, Suzuki T, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Mechanism of the nongenomic effects of estrogen on intestinal myeloperoxidase activity following trauma-hemorrhage: up-regulation of the PI-3K/Akt pathway. J Leukoc Biol. 2007;82:774–80.
34. Ozkan OV, Yuzbasioglu MF, Ciralik H, Kurutas EB, Yonden Z, Aydin M, Bulbuloglu E, Semerci E, Goksu M, Atli Y, Bakan V, Duran N. Resveratrol, a natural antioxidant, attenuates intestinal ischemia/reperfusion injury in rats. Tohoku J Exp Med. 2009;218:251–8.
35. Homma H, Hoy E, Xu DZ, Lu Q, Feinman R, Deitch EA. The female intestine is more resistant than the male intestine to gut

injury and inflammation when subjected to conditions associated with shock states. Am J Physiol Gastrointest Liver Physiol. 2005; 288:G466–72.
36. Knoferl MW, Angele MK, Schwacha MG, Bland KI, Chaudry IH. Preservation of splenic immune functions by female sex hormones after trauma-hemorrhage. Crit Care Med. 2002;30: 888–93.
37. Dienstknecht T, Schwacha MG, Kang SC, Rue LW, Bland KI, Chaudry IH. Sex steroid-mediated regulation of macrophage/ monocyte function in a two-hit model of trauma-hemorrhage and sepsis. Cytokine. 2004;25:110–8.
38. Choudhry MA, Bland KI, Chaudry IH. Gender and susceptibility to sepsis following trauma. Endocr Metab Immune Disord Drug Targets. 2006;6:127–35.
39. Mayr S, Walz CR, Angele P, Hernandez-Richter T, Chaudry IH, Loehe F, Jauch KW, Angele MK. Castration prevents suppression of MHC class II (Ia) expression on macrophages after trauma-hemorrhage. J Appl Physiol. 2006;101:448–53.
40. Angele MK, Ayala A, Cioffi WG, Bland KI, Chaudry IH. Testosterone: the culprit for producing splenocyte immune depression after trauma hemorrhage. Am J Physiol. 1998;274:C1530–6.
41. Hildebrand F, Hubbard WJ, Choudhry MA, Thobe BM, Pape HC, Chaudry IH. Are the protective effects of 17beta-estradiol on splenic macrophages and splenocytes after trauma-hemorrhage mediated via estrogen-receptor (ER)-alpha or ER-beta? J Leukoc Biol. 2006;79:1173–80.
42. Suzuki T, Shimizu T, Yu HP, Hsieh YC, Choudhry MA, Bland KI, Chaudry IH. Estrogen receptor-alpha predominantly mediates the salutary effects of 17beta-estradiol on splenic macrophages following trauma-hemorrhage. Am J Physiol Cell Physiol. 2007;293:C978–84.
43. Samy TS, Zheng R, Matsutani T, Rue LW 3rd, Bland KI, Chaudry IH. Mechanism for normal splenic T lymphocyte functions in proestrus females after trauma: enhanced local synthesis of 17beta-estradiol. Am J Physiol Cell Physiol. 2003;285: C139–49.
44. Kawasaki T, Choudhry MA, Suzuki T, Schwacha MG, Bland KI, Chaudry IH. 17Beta-estradiol's salutary effects on splenic dendritic cell functions following trauma-hemorrhage are mediated via estrogen receptor-alpha. Mol Immunol. 2008;45:376–85.
45. Kawasaki T, Fujimi S, Lederer JA, Hubbard WJ, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Trauma-hemorrhage induces depressed splenic dendritic cell functions in mice. J Immunol. 2006;177:4514–20.
46. Park KM, Kim JI, Ahn Y, Bonventre AJ, Bonventre JV. Testosterone is responsible for enhanced susceptibility of males to ischemic renal injury. J Biol Chem. 2004;279:52282–92.
47. Rusai K, Prokai A, Szebeni B, Meszaros K, Fekete A, Szalay B, Vannay A, Degrell P, Muller V, Tulassay T, Szabo AJ. Gender differences in serum and glucocorticoid regulated kinase-1 (SGK-1) expression during renal ischemia/reperfusion injury. Cell Physiol Biochem. 2011;27:727–38.
48. Satake A, Takaoka M, Nishikawa M, Yuba M, Shibata Y, Okumura K, Kitano K, Tsutsui H, Fujii K, Kobuchi S, Ohkita M, Matsumuro Y. Protective effect of 17beta-estradiol on ischemic acute renal failure through the PI3K/Akt/eNOS pathway. Kidney Int. 2008;73:308–17.
49. Kasimay O, Sener G, Cakir B, Yuksel M, Cetinel S, Contuk G, Yegen BC. Estrogen protects against oxidative multiorgan damage in rats with chronic renal failure. Ren Fail. 2009;31:711–25.
50. Ba ZF, Chaudry IH. Role of estrogen receptor subtypes in estrogen-induced organ-specific vasorelaxation after trauma-hemorrhage. Am J Physiol Heart Circ Physiol. 2008;295: H2061–7.
51. Suzuki T, Shimizu T, Yu HP, Hsieh YC, Choudhry MA, Schwacha MG, Chaudry IH. Tissue compartment-specific role of estrogen receptor subtypes in immune cell cytokine production following trauma-hemorrhage. J Appl Physiol. 2007;102:163–8.
52. Suzuki T, Yu HP, Hsieh YC, Choudhry MA, Bland KI, Chaudry IH. Estrogen-mediated activation of non-genomic pathway improves macrophages cytokine production following trauma-hemorrhage. J Cell Physiol. 2008;214:662–72.
53. Yu HP, Hsieh YC, Suzuki T, Shimizu T, Choudhry MA, Schwacha MG, Chaudry IH. Salutary effects of estrogen receptor-beta agonist on lung injury after trauma-hemorrhage. Am J Physiol Lung Cell Mol Physiol. 2006;290:L1004–9.
54. Ba ZF, Hsu JT, Chen J, Kan WH, Schwacha MG, Chaudry IH. Systematic analysis of the salutary effect of estrogen on cardiac performance after trauma-hemorrhage. Shock. 2008;30:585–9.
55. Hsieh YC, Choudhry MA, Yu HP, Shimizu T, Yang S, Suzuki T, Chen J, Bland KI, Chaudry IH. Inhibition of cardiac PGC-1alpha expression abolishes ERbeta agonist-mediated cardioprotection following trauma-hemorrhage. FASEB J. 2006;20:1109–17.
56. Hsieh YC, Yu HP, Suzuki T, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Upregulation of mitochondrial respiratory complex IV by estrogen receptor-beta is critical for inhibiting mitochondrial apoptotic signaling and restoring cardiac functions following trauma-hemorrhage. J Mol Cell Cardiol. 2006;41: 511–21.
57. Yu HP, Shimizu T, Choudhry MA, Hsieh YC, Suzuki T, Bland KI, Chaudry IH. Mechanism of cardioprotection following trauma-hemorrhagic shock by a selective estrogen receptor-beta agonist: up-regulation of cardiac heat shock factor-1 and heat shock proteins. J Mol Cell Cardiol. 2006;40:185–94.
58. Nikolic I, Liu D, Bell JA, Collins J, Steenbergen C, Murphy E. Treatment with an estrogen receptor-beta-selective agonist is cardioprotective. J Mol Cell Cardiol. 2007;42:769–80.
59. Gabel SA, Walker VR, London RE, Steenbergen C, Korach KS, Murphy E. Estrogen receptor beta mediates gender differences in ischemia/reperfusion injury. J Mol Cell Cardiol. 2005;38:289–97.
60. Liu CJ, Lo JF, Kuo CH, Chu CH, Chen LM, Tsai FJ, Tsai CH, Tzang BS, Kuo WW, Huang CY. Akt mediates 17beta-estradiol and/or estrogen receptor alpha inhibition of LPS-induced tumor necrosis factor-alpha expression and myocardial cell apoptosis by suppressing the JNK1/2-NFkappaB pathway. J Cell Mol Med. 2009;13:3655–67.
61. Wang M, Crisostomo P, Wairiuko GM, Meldrum DR. Estrogen receptor-alpha mediates acute myocardial protection in females. Am J Physiol Heart Circ Physiol. 2006;290:H2204–9.
62. Booth EA, Obeid NR, Lucchesi BR. Activation of estrogen receptor-alpha protects the in vivo rabbit heart from ischemia–reperfusion injury. Am J Physiol Heart Circ Physiol. 2005;289: H2039–47.
63. Gee AC, Sawai RS, Differding J, Muller P, Underwood S, Schreiber MA. The influence of sex hormones on coagulation and inflammation in the trauma patient. Shock. 2008;29:334–41.
64. Berry C, Ley EJ, Tillou A, Cryer G, Margulies DR, Salim A. The effect of gender on patients with moderate to severe head injuries. J Trauma. 2009;67:950–3.