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REVIEW ARTICLE

The effects of estrogen on various organs: therapeutic approach for sepsis, trauma, and reperfusion injury. Part 1: central nervous system, lung, and heart

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Abstract Although several clinical studies show a gender dimorphism of immune and organ responsiveness in the susceptibility to and morbidity from shock, trauma, and sepsis, there are conflicting reports on the role of gender in outcomes. In contrast, results obtained from experimental studies clearly support the suggestion that gender plays a significant role in post-injury pathogenesis. Studies performed in a rodent model of trauma-hemorrhage have confirmed that alterations in immune and organ functions after trauma-hemorrhage are more markedly depressed in adult males and in ovariectomized and aged females; however, both are maintained in castrated males and in proestrus females. Moreover, the survival rate of proestrus females subjected to sepsis after trauma-hemorrhage is significantly higher than in age-matched males or ovariectomized females. In this respect, organ functions and immune responses are depressed in males with sepsis or trauma, whereas they are unchanged or are enhanced in females. This article reviews studies delineating the mechanism by which estrogen regulates cerebral nervous, lung, and heart systems in an experimental model of sepsis, trauma, or reperfusion injury.

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Introduction

Studies indicate that traumatic injury induces immune dysfunction, which is associated with an increased susceptibility to sepsis, organ failure, and mortality [1–5]. Increased susceptibility to infection and a higher risk of complications are secondary to the inhibitory effect of trauma-hemorrhage on cell-mediated immune responses and microbicidal activity by cells of the innate immune system. Despite the progress made in patient management over the last decade, sepsis and subsequent multiple organ failure continue to be the major cause of morbidity and mortality in injured patients. Many factors are involved in the post-injury pathogenesis, but male gender and age are reported to be the major risk factors for the development of sepsis and multiple organ failure following trauma [6–11]. Several investigators are exploring the influence of gender on the individual response to trauma, shock, and sepsis. The significantly higher incidence of bacteremic infections in traumatized males than in females was first reported in 1975 [8]. In 1992, increased morbidity and mortality from sepsis in males compared to females was also reported in a retrospective study [7]. In addition, clinical studies observed that male gender was associated with increased mortality in geriatric blunt trauma patients [12] and that there was a significantly higher survival rate in women (74 %) compared to men (31 %) following the onset of sepsis [13]. Furthermore, male gender was identified as an independent risk factor for the development of severe infection in surgical patients [14]. A retrospective study incorporating 30,286 trauma victims with an injury severity

score (ISS) of >15 demonstrated a significantly higher incidence of pneumonia in males [15]. Trauma patients with an ISS of <15 displayed no differences in the incidence of pneumonia. In contrast, there is a report that female gender does not protect blunt trauma patients from the development of adult respiratory distress syndrome, pneumonia, or sepsis [16]. Other investigators [17–19] have demonstrated equivalent survival rates in males and females after traumatic injury. Moreover, some reports [20–22] have demonstrated that female gender is a risk factor for mortality and complication in patients with trauma. Recent studies also showed gender dimorphism in susceptibility to infections [23, 24] and in prognosis of cancer [25]. These differences may be due to many factors, including the sample size, patient triage, and variation in patient care protocol. Patient age also plays a crucial role in analyzing outcomes. However, studies which have investigated the effect of age and its association with gender dimorphism following injury have also produced conflicting results [11, 20, 26, 27]. Therefore, it is necessary to perform these studies in a better controlled setting. This is not possible in clinical studies because it is difficult to control all of the factors that are known to influence outcome in trauma patients. However, such controlled settings are possible in experimental animal studies. In this regard, experimental studies allow the well-controlled use of laboratory animals and administration of drugs to determine the role of sex hormones in post-injury pathogenesis. In this article, we discuss the effect of estrogen on cerebral and cardiopulmonary systems, as part of a set of papers on the role of estrogen in sepsis, trauma, or reperfusion injury pathogenesis in experimental animal settings.

Genomic and nongenomic effects of estrogen

A number of studies have demonstrated that estrogen exerts beneficial effects in trauma, shock, and sepsis [28–32]. Both endogenous and exogenous estrogens are beneficial in those settings. Estrogen acts through the estrogen receptors (ER) ER-α and ER-β. Furthermore, the effects of estrogen are mediated by two different mechanisms: genomic and nongenomic (membrane-initiated steroid signaling, MISS; Fig. 1). The genomic effects of estrogen require estrogen to passively diffuse into the cell and, after binding to its receptor, estrogen acts as a transcription factor by binding to specific DNA response elements. Alternatively, the estrogen–receptor complex regulates the production of a specific protein in a more indirect manner through transcription factor. On the other hand, MISS effects may be mediated by classic-type ERs residing in the cell membrane, such as ER-α and ER-β, or by more non-classic-type receptor proteins, such as the G protein-coupled receptor (GPR) 30. This results in the modification of intracellular signaling pathways and kinases.

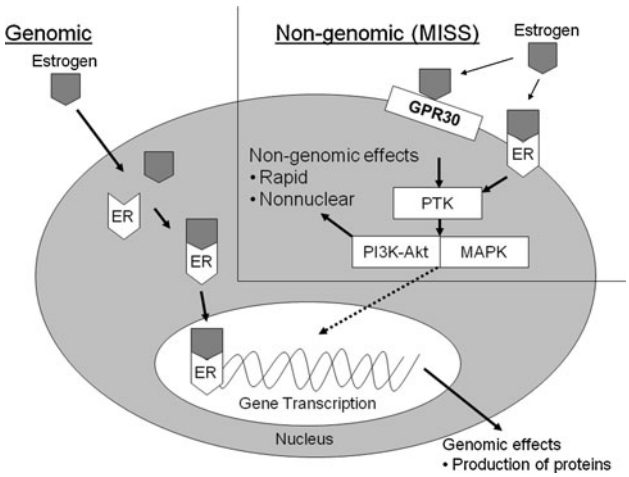

Fig. 1 Genomic and nongenomic effects of estrogen. *ER* estrogen receptor, *PTK* protein tyrosine kinases, *PI3K* phosphatidylinositol 3-kinase, *MAPK* mitogen-activated protein kinase

Effect of estrogen on the central nervous system (CNS)

Previous studies have shown that many inflammatory mediators, such as inflammatory cytokines, nitric oxide (NO), and reactive oxygen species, are involved in CNS dysfunction in sepsis, trauma, and reperfusion injury. Studies involving animal models of acute CNS stroke, trauma, hemorrhage, and ischemia strongly indicate that sex and/or hormonal status are important determinants of outcome after these conditions.

Sepsis

Tissue homeostasis results from a balance between cell proliferation and cell death by apoptosis. Its dysregulation also leads to organ dysfunction. Estradiol affects proliferation as well as apoptosis in hormone-dependent tissues. Pisera et al. [33] investigated the apoptotic response of the anterior pituitary gland to lipopolysaccharide (LPS) in cycling female animals, and also investigated the influence of estradiol on this response in ovariectomized animals. Their results indicate that estradiol induces apoptosis and enables the proapoptotic action of LPS in the anterior pituitary gland. They also suggested that estrogens may be involved in anterior pituitary cell renewal during the estrus cycle, sensitizing lactotropes to proapoptotic stimuli.

Sexual dimorphism also exists in the response of the hypothalamic–pituitary–adrenal (HPA) axis to inflammatory stress. Using an animal model of endotoxemia, Chisari et al. [34] demonstrated that there is sexual dimorphism in

the activity of the HPA axis. They found that, whereas estradiol plays a stimulatory role on adrenal function, testosterone inhibits adrenal glucocorticoid production. This study further indicates a clear sexual dimorphism in middle-aged animals with endotoxemia. These results may be relevant to the treatment of Gram-negative sepsis in aged patients.

Trauma-hemorrhage

Akabori et al. [35] have recently demonstrated that microglial cells, resident central macrophages, play a central role in exacerbating cell-mediated inflammation in CNS following trauma-hemorrhage. Following trauma-hemorrhage, plasma and hypothalamic tumor necrosis factor (TNF)-α levels increased, along with the activation of microglial cells. Furthermore, trauma-hemorrhage increased the microglial TNF-α productive capacity in vitro. Administration of estradiol following trauma-hemorrhage prevented these inflammatory responses. In rats pretreated with the microglial inhibitor minocycline, decreased microglial TNF-α production and hypothalamic TNF-α levels were observed, but plasma TNF-α levels were not altered following trauma-hemorrhage. Thus, trauma-hemorrhage induces inflammatory responses even in the hypothalamus, and estradiol appears to be a useful adjunct for downregulating microglial cell-mediated inflammatory response following trauma-hemorrhage.

Reperfusion injury

Hall et al. [36] demonstrated sex differences in postischemic neuronal necrosis in gerbils. They produced severe incomplete hemispheric ischemia by unilateral carotid occlusion. The males displayed significantly greater neuronal necrosis compared to the females. Disruption of the blood–brain barrier (BBB) is a critical event during cerebral ischemia. Liu et al. [37] found that estradiol attenuates BBB disruption induced by cerebral ischemia–reperfusion injury in rats. These results suggest an important role for estrogen as the therapeutic strategy against ischemic stroke of the CNS.

CNS injury

Previous studies have suggested that NO is produced in the CNS following injury-induced expression of inducible nitric oxide synthase (iNOS), and that NO from the CNS has a harmful effect on the CNS. Estradiol as well as progesterone administration decreased the level of iNOS expression in vitro and improved neurological outcome. Coughlan et al. [38] investigated the effects of progesterone on stroke-induced expression of iNOS in mice, as well as cytokine-induced expression of iNOS and its transcriptional activators in cells relevant to injury. They observed a significant reduction in stroke-induced iNOS transcript in progesterone-treated mice and in cultured macrophages. Another study demonstrated that estradiol and progesterone decreased the level of iNOS expression in vitro and improved neurological outcome. These observations suggest the involvement of iNOS in the neuroprotective effects of estradiol as well as progesterone.

Regarding the acute CNS injuries associated with oxidative and excitotoxic stress, Regan et al. [39] showed the protective effect of estrogen on CNS function. In that study, they assessed the effect of estrogen in three injury paradigms that may be relevant to CNS hemorrhage, trauma, and ischemia. Their results suggest that estrogen may be beneficial in acute CNS injuries associated with oxidative and excitotoxic stress.

Lebesgue et al. [40] examined the ability of estradiol to protect hippocampal neurons from lateral fluid percussion brain injury. They used ovariectomized female rats and assessed the effects of estradiol on hippocampal neurons. In their results, estradiol did not significantly alter cell apoptosis and the number of hippocampal neurons. In addition, estradiol at physiological levels did not significantly alter injury-induced loss of memory. These data indicate that estradiol at physiological levels does not ameliorate trauma-induced hippocampal injury or cognitive deficits in ovariectomized female rats, and thus higher doses of estrogen should be used under these conditions in order for it to be effective.

Effect of estrogen on the respiratory system

Sepsis

Recent research has recognized that estrogen plays a critical role in improved outcomes of sepsis. Erikoglu et al. [41] showed that estrogen administration improves congestion, edema, and emphysematous and inflammatory changes in the lung in the sepsis model of rats. Christaki et al. [42] also demonstrated that ER-β agonist administration provides a survival advantage in the pneumococcal pneumonia model of sepsis.

Trauma

Severe trauma and hemorrhagic shock can lead to acute lung injury. Caruso et al. [43] demonstrated that protection against trauma-hemorrhage-induced lung injury was greatest during the estrus and proestrus stages of the menstrual cycle, and decreased with progression to diestrus. During the diestrus stage of the menstrual cycle (when

gonadal hormones levels are lowest), rats were more sensitive to the trauma-hemorrhage-induced lung injury, indicating that gonadal hormones modulate trauma-hemorrhage-induced lung injury.

Neutrophil infiltration is a key step in the development of organ dysfunction following trauma-hemorrhage. Frink et al. [44] showed that estradiol administration following trauma-hemorrhage prevented neutrophil infiltration via the modulation of keratinocyte-derived chemokines (KDC). In addition, treatment with estradiol decreased KDC gene expression and protein in the lung. This was accompanied by a decrease in neutrophil infiltration and edema formation in the lung. These results suggest that estradiol prevents lung neutrophil infiltration and organ damage in part by decreasing KDC during the post-traumatic immune response.

Hsieh et al. [45] also demonstrated that protective effects of estradiol on lung injury following trauma-hemorrhage are mediated via the downregulation of lung migration inhibitory factor (MIF) and TLR4-induced cytokine/chemokine production. Administration of recombinant MIF protein with estradiol abolished the estradiol-mediated decrease in lung TLR4, lung IL-6, TNF-α, monocyte chemoattractant protein-1, and KDC levels. Administration of recombinant MIF protein also prevented the estradiol-mediated reduction in neutrophil influx and tissue damage in the lungs following trauma-hemorrhage.

Hsu et al. [46] found that extracellular signal-regulated protein kinase (ERK) plays a role in the estradiol-mediated attenuation of lung injury and proinflammatory mediators after trauma-hemorrhage. Trauma-hemorrhage led to a significant increase in lung ERK phosphorylation, which was associated with increased lung myeloperoxidase activity, wet-to-dry weight ratio, IL-6, TNF-α, intercellular adhesion molecule (ICAM)-1, cytokine-induced neutrophil chemoattractant (CINC)-1, and macrophage inflammatory protein-2 levels. Administration of estradiol or ERK inhibitor after trauma-hemorrhage attenuated the trauma-hemorrhage-induced increase in lung injury markers, ERK phosphorylation and cytokines/chemokines, and ICAM-1 production. These results collectively suggest that the salutary effects of estradiol on the lung after trauma-hemorrhage are mediated via an ERK pathway and subsequent downregulation of proinflammatory mediator production.

Kan et al. [47] also found that estradiol administration after trauma-hemorrhage reduces lung injury through a mechanism involving ER-dependent activation of the endothelial NO synthase (eNOS)/protein kinase G (PKG)/vasodilator-stimulated phosphoprotein (VASP) pathway. Estradiol treatment after trauma-hemorrhage resulted in an increase in eNOS expression/phosphorylation, PKG-I activation, and VASP/p-VASP expression, which paralleled a decrease in lung injury. Inhibition of NOS abolished the estradiol-induced increase in PKG-I activity, VASP/p-VASP expression. Blockade of eNOS, PKG-I, and ER exacerbated lung inflammation and injury. These results thus suggest that activation of the eNOS-PKG/VASP pathway by estradiol protects against trauma-hemorrhage-induced lung injury.

Effect on pulmonary vasculature

Recent studies have demonstrated the effects of estrogen on the pulmonary vasculature [48]. Estrogen plays a critical role in improving outcomes in the settings of trauma, shock, sepsis, myocardial ischemia/reperfusion, and acute lung injury. In the pulmonary vasculature, estrogen causes vasodilation and attenuates the vasoconstrictor response to various stimuli, including hypoxia. This is mediated by increased levels of prostacyclin and NO as well as decreased levels of endothelin-1. In addition, effects on intracellular signaling pathways and several kinases as well as anti-inflammatory mechanisms may also contribute to the protective effects of estrogen. Estrogen exerts a variety of nongenomic actions, which may also be useful for future therapeutic interventions in pulmonary vascular disease.

Estrogen also has an effect on pulmonary vascular permeability. A previous study [49] showed that ioxaglate, an ionic contrast medium, dose-dependently increased pulmonary vascular permeability in sham-operated and ovariectomized animals. Ovariectomized animals showed a 2.6-fold increase in aggravation of vascular permeability by ioxaglate compared to sham-operated animals. Estradiol valerate dose-dependently blocked ioxaglate-increased vascular permeability in ovariectomized animals. These findings suggest that climacterium is included, at least in part, in the risk factors for contrast-induced adverse pulmonary reactions, and that this risk is lowered by estrogen treatment.

Effect of estrogen on the cardiovascular system

Sepsis

Regarding the effects of estradiol on cardiac function during endotoxemia, some reports [50, 51] have shown the salutary effects of this hormone on hemodynamic changes following endotoxic shock. Zhu et al. [50] investigated the role of Rac1 and estrogen on sex differences in cardiac TNF-α expression during endotoxemia. Treatment of male mice with estradiol attenuated myocardial dysfunction during endotoxemia. LPS induces Rac1 activation, which contributes to NADPH oxidase activity and phosphorylation of ERK1/2/p38 MAPK, leading to TNF-α expression in the heart. The sex difference in TNF-α expression is

estrogen dependent and mediated via Rac1-dependent NADPH oxidase/ERK1/2 and the p38 MAPK pathway in LPS-stimulated hearts. Palacios et al. [51] investigated the effects of post-treatment with a synthetic estrogen, ethinyl estradiol, on the hemodynamics of animals challenged with LPS. Post-treatment with ethinyl estradiol attenuated hemodynamic changes in endotoxic shock.

Trauma-hemorrhage

Gender differences also exist in the cardiovascular system. Following trauma-hemorrhage, cardiac output, stroke volume, and cardiac contractility ($+dP/dt$) decreased significantly. Trauma-hemorrhage also leads to diminished cardiac performance in male animals [52, 53]. Treatment of male animals with the androgen receptor antagonist flutamide improved cardiovascular functions following trauma-hemorrhage [54]. Alternatively, castration of male animals two weeks prior to trauma-hemorrhage also prevented depression of myocardial function following trauma-hemorrhage [55]. Furthermore, Kuebler et al. [56] demonstrated differences in the regulation of plasma and tissue volumes between males and proestrus females following trauma-hemorrhage. They found that circulating blood volume increased in proestrus females during and after trauma-hemorrhage compared to males, which might contribute to the improved organ functions in proestrus females under those conditions.

Mizushima et al. [57] demonstrated that female sex steroids have salutary effects on depressed cardiovascular functions following trauma-hemorrhage in male animals. Left ventricular performance, cardiac output, and hepatocellular function decreased significantly at 24 h after trauma-hemorrhage and resuscitation in male rats. They also showed that administration of estradiol in males following trauma-hemorrhage significantly improved cardiac performance and cardiac output. Since then, many studies have examined the effects of estradiol on cardiomyocyte inflammatory mediator expression following trauma-hemorrhage. Nickel et al. [58] demonstrated that estrogen decreased the elevated HIF-1α, NF-κB, and IL-6 levels after trauma-hemorrhage in cardiomyocytes. Yang et al. [59] also demonstrated that there is an inverse correlation between cardiomyocyte IL-6 levels and cardiac function after trauma-hemorrhage. Estradiol administration following trauma-hemorrhage attenuated cardiomyocyte IL-6 gene expression. The salutary effects of estradiol on cardiac function after trauma-hemorrhage may be due in part to decreased HIF-1α expression and IL-6 synthesis in cardiomyocytes.

Additional studies have shown that estradiol influences the expression of heat shock protein (HSP) after trauma-hemorrhage. Szalay et al. [60] found that estradiol administration following trauma-hemorrhage and resuscitation increased heart HSP expression and improved cardiac function. Other investigators also demonstrated that the salutary effects of estradiol on cardiac function were mediated via upregulation of HSP expression [61, 62]. Szalay et al. [63] also demonstrated that estradiol treatment induced increased heme oxygenase (HO)-1 mRNA expression, HO-1 protein levels, and HO enzyme activity in cardiac tissue. Thus, the salutary effects of estradiol administration on cardiac function after trauma-hemorrhage are also mediated in part via upregulation of HO-1 expression and activity.

A large number of studies have investigated the effect of estradiol on intracellular signaling pathways in cardiomyocytes following trauma-hemorrhage. p38 mitogen-activated protein kinase (MAPK) activates a number of HSPs, including HSP27 and αβ-crystallin, in response to stress. Activation of HSP27 or αβ-crystallin is known to protect organs/cells by increasing the stability of actin microfilaments. Hsu et al. [61] showed that cardiac functions were depressed after trauma-hemorrhage, but those functions were normalized by estradiol administration. Phosphorylation of cardiac p38 MAPK, HSP27, and αβ-crystallin was also increased by estradiol administration. These results suggest that the salutary effects of estradiol on cardiac function after trauma-hemorrhage are mediated in part via upregulation of p38 MAPK and subsequent phosphorylation of HSP27 and αβ-crystallin. Kan et al. [64] further showed that the salutary effects of estradiol on cardiac functions following trauma-hemorrhage are mediated through the activation of p38 MAPK and subsequent eNOS expression and phosphorylation. They also showed that the administration of estradiol following trauma-hemorrhage restored cardiac Akt phosphorylation [65, 66] and further increased HO-1 expression [65]. These results suggest that the estradiol-meditated improvement in cardiac function following trauma-hemorrhage occurs via Akt-dependent HO-1 upregulation. In addition, Liu et al. [67] demonstrated that estradiol has cardioprotective effects through Akt phosphorylation. In cardiomyocytes, estradiol inhibits their apoptosis and TNF-α production via activation of Akt. Yu et al. [68] also showed that the PI3K/Akt pathway plays a critical role in mediating the salutary effects of estradiol on cardiac function and cardiomyocyte apoptosis following trauma-hemorrhage. Regarding the effect of estradiol on apoptosis, Strehlow et al. [69] showed estradiol's anti-apoptotic effect on bone marrow-derived endothelial progenitor cells.

Estradiol treatment following trauma-hemorrhage attenuates the depression in cardiac mitochondrial functions. PGC-1α [peroxisome proliferator-activated receptor (PPARγ) coactivator-1α], a key regulator of cardiac mitochondrial ATP production, activates PPARγ and mitochondrial transcription

factor A (Tfam), which regulate proteins, fatty acid and ATP metabolism [i.e., FAT/CD36, MCAD, and cytochrome-c oxidase subunit (COX) I]. PGC-1 also induces mitochondrial genes by activating transcription factors such as nuclear respiratory factor 2 (NRF-2), which regulates mitochondrial proteins (i.e., Tfam, COX IV, and β-ATP synthase). Hsieh et al. [70, 71] demonstrated that estradiol treatments attenuated the decrease in cardiac mitochondrial ATP, abrogated the trauma-hemorrhage-induced lipid accumulation, and normalized PGC-1α, PPARγ, FAT/CD36, MCAD, Tfam, NRF-2, and COX I and IV after trauma-hemorrhage. Estradiol mediates its effects via ER-mediated upregulation of PGC-1. Estradiol is known to regulate mitochondrial DNA (mtDNA)-encoded genes, including mitochondrial respiratory complex (MRC) proteins. Depressed MRC activity has been reported to promote the release of cytochrome c from mitochondria and induce apoptosis. Estradiol treatment after trauma-hemorrhage normalizes MRC-IV gene expression and inhibits mitochondrial apoptotic signaling pathways [72].

Reperfusion injury

Ischemia/reperfusion (I/R) also lead to cardiac dysfunction [73]. It is recognized that myocardial inflammation plays a crucial role in I/R-induced myocardial dysfunction. There are many important reports on this topic from Daniel Meldrum's group [10, 73–78]. Inflammatory mediators such as TNF-α, IL-1β, and IL-6 are produced by cardiomyocytes and contribute to myocardial functional depression and apoptosis. The inflammatory response, including the p38 MAPK signaling cascade and the expression of proinflammatory cytokines such as TNF-α and IL-1β, may precipitate cardiomyocyte apoptosis following I/R injury. Apoptosis may be an essential component of the pathogenesis of heart failure, and there is evidence that myocyte apoptosis in the failing human heart is markedly lower in women than in men [73]. Sex hormones are important modifiers of the acute inflammatory response to injury, and female sex steroids such as estradiol have a protective effect on I/R injury [10, 73–78]. Kuhar et al. [79] demonstrated that estradiol improved coronary flow and decreased arrhythmias after I/R. Furthermore, Chandrasekar et al. [80] showed that locally delivered estradiol significantly enhanced re-endothelialization and endothelial function after percutaneous transluminal coronary angioplasty (PTCA), possibly by improving the expression of eNOS. Since endothelial dysfunction can promote both restenosis and coronary spasm, they concluded that local estradiol administration may be a promising new approach for improving long-term results after PTCA.

Table 1 The effects of estrogen on various organs

Organ	Effect of estrogen	References
CNS	Hypothalamus inflammatory response ↓	[35]
	Microglial cell inflammatory response ↓	[35]
	Blood–brain barrier (BBB) disruption ↓	[37]
	NO production ↓	[38]
Lung	Congestion ↓	[41]
	Edema ↓	[41]
	Emphysematous change↓	[41]
	Keratinocyte-derived chemokines (KDC) ↓	[44]
	Migration inhibitory factor (MIF) ↓	[45]
	MAPK(ERK) activation ↓	[46]
	Endothelial eNOS/PKG/VASP pathway ↑	[47]
	Vascular permeability ↓	[49]
Heart	Cardiac output ↑	[57]
	HIF-1α ↓	[59]
	HSP ↑	[60–62]
	HO-1 ↑	[63, 65]
	MAPK activation ↑	[61]
	eNOS ↑	[64, 80]
	Akt activation ↑	[65–68]
	Cardiac mitochondrial function ↑	[70, 71]
	Cardiomyocyte apoptosis ↓	[73]

Conclusions

A major consequence of sepsis, trauma, and reperfusion injury is the suppression of organ and immune cell functions. The findings reviewed in this article suggest that the tissue response to these stresses is gender dimorphic, and that sex steroids play a decisive role in the depression or maintenance of organ functions following injury. High circulating estrogen levels due to endogenous or exogenous administration have protective effects. In this review, we describe the protective effects of estrogen on CNS, lung, and heart (Table 1). The protective effects of estrogen in restoring organ function occur via a genomic effect mediated through intracellular receptors, ER-α and ER-β. Experimental studies clearly demonstrate that estrogen and ER agonists are useful therapeutic adjuncts for protecting organ functions and improving outcome following sepsis, trauma, and reperfusion injury.

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