

REVIEW

GENDER AND SEX HORMONES INFLUENCE THE RESPONSE TO TRAUMA AND SEPSIS – POTENTIAL THERAPEUTIC APPROACHES

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Several clinical and experimental studies have demonstrated gender dimorphism in immune and organ responsiveness and in the susceptibility to and morbidity from shock, trauma, and sepsis. In this respect, cell-mediated immune responses have been shown to be depressed in males following trauma-hemorrhage, whereas they were maintained/enhanced in proestrus females. Furthermore, sex hormones have been shown to be responsible for this gender-specific immune response following adverse circulatory conditions. More specifically, studies indicate that androgens produce immunodepression following trauma-hemorrhage in males. In contrast, female sex steroids appear to exhibit immunoprotective properties following trauma and severe blood loss. With regard to the underlying mechanisms, receptors for sex hormones have been identified on various immune cells suggesting direct effects of these hormones on the immune cells. Alternatively, indirect effects of sex hormones, ie, modulation of cardiovascular responses or androgen- and estrogen-synthesizing enzymes, might contribute to gender-specific immune responses. Recent studies indicate that sex hormones, eg, dehydroepiandrosterone (DHEA), also modulate the function of peripheral blood mononuclear cells in surgical patients. Thus, the immunomodulatory properties of sex hormones/receptor antagonists/sex steroid synthesizing enzymes following trauma-hemorrhage suggests novel therapeutic strategies for the treatment of immunodepression in surgical patients.

KEYWORDS: Gender. Sex steroids. Hemorrhagic shock. Immune depression. Immunomodulation.

INTRODUCTION

Several clinical and experimental studies suggest that gender affects humoral and cell-mediated immune responses. In this regard, a remarkable female preponderance of autoimmune diseases, ie, systemic lupus erythematosus (SLE) (female to male ratio of 9:1), Hashimoto's thyroiditis, rheumatoid arthritis, and primary biliary cirrhosis, has been observed in both humans and experimental studies.¹⁻⁴ In addition, higher levels of circulating plasma antibody titers have been found in females compared to males.⁵

While it is plausible that some sex-linked genes may contribute to the genetic predisposition for the disease, other likely culprits for this gender bias are male and female sex hormones.^{2,6} In this respect, the onset and course of autoimmune lupus in the F1 NZB/NZW mouse model varies depending on the sex steroid environment. In contrast to males, female mice of this strain are known to develop lupus erythematosus. Pre-pubertal administration of 5 α -dihydrotestosterone, however, prevents the onset of the disease.^{7,8} Similarly, change of sex steroid environment by castrating male mice leads to development of lupus erythematosus in normally unaffected males.^{8,9} Moreover, administration of estradiol to female mice increased the levels of anti-dsDNA antibodies.¹⁰ Thus, in contrast to male sex steroids, female sex steroids appear to exhibit immunoenhancing effects on B-cell function. Further support for the notion that male and female sex steroids differently affect autoimmune disease processes comes from

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studies that demonstrate lower androgen and increased estrogen metabolite levels in women with SLE compared to age-matched healthy female controls.¹¹⁻¹³ Moreover, increased estrogenic activity has been reported in patients with lupus erythematosus.¹³

Sexual dimorphism also seems to play a role in cell-mediated immune responses. In this respect, Calzolari demonstrated as early as 1898 an enlargement of the rabbit's thymus when castrated before sexual maturity, thereby indicating a connection between sexual environment and immunology.¹⁴ In more recent studies, skin allograft rejection time has been reported to be shorter in males compared to females.¹⁵ Castration of male mice, however, has been found to balance those gender differences by increasing time for skin rejection.¹⁵

The above mentioned studies collectively suggest that gender as well as male and female sex steroids exhibit immunomodulatory properties on humoral and cell-mediated immune functions under normal conditions and following disease processes. In this review article, gender-specific immune responses as well as the effects of sex steroids on cell-mediated immunity following shock will be discussed. This article will focus on macrophages and T-cells, since those immune cells are known to be a first line of defense in host resistance and play a central role in the regulation of the immune system.¹⁶ The aim of this review is to emphasize the importance of gender and the state of the estrus cycle in females on the immune response following trauma and severe blood loss. Furthermore, the potential for modulating sex hormone effects as novel strategies for the treatment of immunodepression will be discussed.

Gender dimorphism in trauma, shock and sepsis

Several investigators are attempting to elucidate the influence of gender on the individual response to trauma, shock, and sepsis. In this respect, male gender and age are reported to be risk factors for development of sepsis and multiple organ failure following trauma.¹⁷⁻²³ These epidemiological studies report that the majority of injured victims are young males.^{20,21} Gender differences, however, exist not only in the prevalence of trauma, but also in the increased susceptibility to septic complications after trauma and blood loss as well as after major surgery. In this respect, Offener et al identified male gender as an independent risk factor for the development of severe infection in surgical patients.²⁴ In a retrospective study incorporating 4 major sepsis studies, Bone reported a preponderance of morbidity and mortality from sepsis in males as compared to females.¹⁷ McGowan et al also reported a significantly higher incidence of bacteremic infections in traumatized

males than in females.¹⁹ Furthermore, a retrospective study incorporating 30,286 trauma victims with an injury severity score (ISS) > 15 demonstrated a significantly higher incidence of pneumonia in males.²⁵ Trauma patients with an ISS < 15 displayed no differences in the incidence of pneumonia.²⁵ Moreover, Schroder et al have shown a significantly higher survival rate in women (74%) compared to men (31%) following the onset of sepsis.²⁶

In addition to differences in the incidence of gender-dimorphic septic complications, gender-specific cytokine patterns have been observed in surgical patients. Oberholzner et al found significantly elevated IL-6 and procalcitonin levels in male trauma patients compared to females.²⁷ Wichmann et al²⁸ indicated that despite comparable preoperative cell counts, significant postoperative gender differences regarding B-lymphocyte, T-lymphocyte, T-helper cell counts, and NK cell counts were evident. While only a short, insignificant depression of these immune competent cells was detected in women, men suffered long-lasting (5 days) depression of these cells. Furthermore, women showed a more pronounced immediate (day 1) proinflammatory response (circulating IL-6) after abdominal surgery.²⁸ Conversely, Majetschak et al²⁹ did not find gender-specific cytokine responses in trauma patients with an ISS > 16. In male trauma victims with septic complications, however, increased IL-6 and TNF- α levels were evident. This increase was not observed in female trauma victims with septic complications.²⁹

Similar gender-dimorphic findings have been demonstrated in experimental studies following severe blood loss and the induction of sepsis or sepsis-like states (Fig. 1).³⁰⁻³² Female Wistar rats have been reported to be more resistant to lethal circulatory stress induced by trauma or intestinal ischemia.³² In addition, female mice in the proestrus state of their estrus cycle tolerate sepsis better than male mice as demonstrated by increased survival rates of females following polymicrobial septic challenge (female survival rate 60% compared to 25% in male animals).³¹ This improved survival was associated with maintained splenocyte

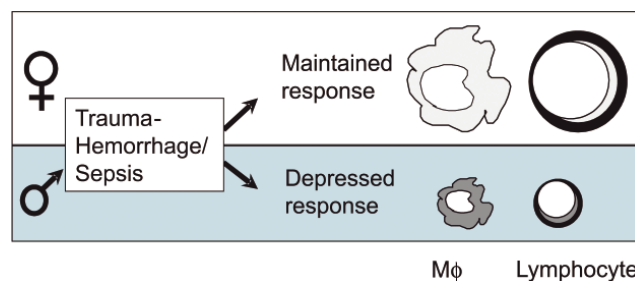


Figure 1 - Schematic illustration of the effect of gender on cell-mediated immune responses following trauma and severe blood loss.

functions in females compared to depressed immune responses in male mice under those conditions.³¹ Moreover, female mice in the proestrus state of the estrus cycle have been found to exhibit normal/enhanced splenic and peritoneal macrophage cytokine release as opposed to depressed immune responses in males following trauma-hemorrhage.³⁰ Furthermore, proestrus female mice show enhanced release of splenocyte Th1 lymphokines, ie, IL-2, IFN- γ , compared to depressed Th1 lymphokine release capacities in male mice following trauma-hemorrhage.³⁰ Four hours following LPS injection, 4-fold greater plasma IL-1 levels have been found in female mice than in male animals.³³ Thus, higher levels of proinflammatory cytokines early following the induction of sepsis in female mice might contribute to the better maintained immune responses in females under those conditions. In contrast to Th1 lymphokines, the release of the anti-inflammatory Th2 lymphokine IL-10 has been found to be increased in males and decreased in females following trauma-hemorrhage.³⁴ In addition, studies by Altura et al indicate that female rats maintain reticuloendothelial system phagocytic activity following circulatory stress which might further protect immune response under those conditions.³²

In addition to peripheral immune cells, gender-specific immune responses have also been demonstrated in the thymus, the primary site of T-cell lymphopoiesis.^{35,36} Thymocytes and lymphocytes from normal female mice have been reported to respond more vigorously to exogenous and allergenic antigens than do cells from male mice.³⁶ Moreover, an increased thymocyte apoptosis rate was evident in males but not in proestrus females following trauma-hemorrhage.³⁵ The increased apoptotic frequency in male animals was associated with a depressed IL-3 release capacity of thymocytes and a significant reduction in thymocyte count.³⁵ Since thymocyte apoptosis was determined at 3 days following trauma-hemorrhage, it remains unknown whether an increased rate of thymic apoptosis in females was evident at an earlier or later time point than used in this study.³⁵ It also remains to be determined whether the presence of enhanced apoptosis in the T-cell lymphopoietic tissue (eg, the thymus in male mice) contributes directly and/or indirectly to the development of host immunosuppression following trauma-hemorrhage in males through the loss of maturing T-cells. Alternatively, the increased apoptotic rate in males following trauma-hemorrhage might be an attempt by the immune system to eliminate potential autoreactive T cells that might be induced in an increased number following trauma-hemorrhage in males.³⁷ Further studies are required to address the question of whether the increased thymocyte apoptotic rate is detrimental to the immune system or

whether the increased thymic apoptosis in males prevents additional deleterious effects on the host by eliminating potentially harmful cells. Further support for the importance of the thymus in mediating the effects of sex steroids on the immune system comes from studies using castrated NZB/NZW mice, which develop systemic lupus erythematosus.³⁸ In those experiments, thymectomy has been found to abrogate the protective effects of administered androgens on the induction of systemic lupus erythematosus.³⁸

Studies have also suggested that the estrus cycle influences the immune responses following hemorrhage. In this regard, studies by Wichmann et al and Krzych et al suggest that the proestrus state of the estrus cycle is characterized by a more vigorous immune response compared to the diestrus state.^{30,39,40} Similarly, the highest levels of IL-1 secretion observed in mononuclear cells, have been encountered during the follicular phase of the menstrual cycle in women.⁴¹⁻⁴³ These peaks of responsiveness appear to correspond with elevated levels of estrogen and pregnenolone during the proestrus state.⁴⁰ Thus, differences in the estrogenic state might explain why some clinical studies have failed to demonstrate gender differences in the immune response following trauma and adverse circulatory conditions.

Immune response following shock depends on sex steroid environment

Several studies were conducted in order to elucidate the effect of sex steroids on cell-mediated immune responses following trauma-hemorrhage. In this respect, the responsible hormones in gender-specific immune response originate primarily from the gonads and secondarily from the thymus and the hypothalamus-pituitary gland (Fig. 2).⁴⁴⁻⁵⁰ Male gender seems to play an important role in mediating

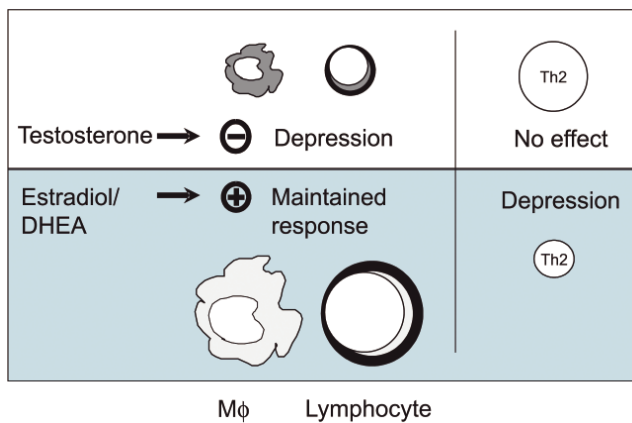


Figure 2 - Schematic illustration of the effect of male and female sex hormones on cell-mediated immune responses, ie, macrophage function and Th1 and Th2 lymphocyte responses following trauma and severe blood loss.

immunosuppressive effects. Experimental studies indicated that depletion of male sex steroids by castration 2 weeks prior to the onset of trauma-hemorrhage prevented the depression of splenic and peritoneal macrophage cytokine release, as well as splenocyte immune responses following trauma-hemorrhage.^{47,49-51} Moreover, depression of MHC II expression in splenic and peritoneal macrophages was prevented by depletion of testosterone prior to trauma-hemorrhage.⁵² In addition, castration of male mice^{47,49} normalized the increased proinflammatory cytokine release by Kupffer cells normally observed in intact males following trauma-hemorrhage.⁵³

To identify whether testosterone itself is responsible for the depression of cell-mediated immune responses following hemorrhage in males, studies were conducted in which female mice were pretreated with 5 α -dihydrotestosterone (DHT) for 2 weeks prior to trauma-hemorrhage.^{45,46} The results demonstrated that female mice that had artificially elevated plasma testosterone levels (ie, comparable to males), displayed similar immune responses to hemorrhage as males, namely depression of splenic and peritoneal macrophage function.⁴⁵ Furthermore, pretreatment of female mice with DHT depressed the release of Th1 lymphokines, ie, IL-2, IFN- γ , by splenocytes following trauma-hemorrhage to levels comparable to normal male animals.⁴⁶ A similar change of sex steroid environment by depletion of female steroids by ovariectomy prior to trauma-hemorrhage depressed cell-mediated immune responses following trauma-hemorrhage, thereby increasing the lethality from subsequent sepsis.⁵⁴ In this respect, female sex steroids seem to exhibit enhancing effects on cell-mediated immune responses⁵⁴⁻⁵⁶. Recent investigations indicate that castrated male animals treated with DHT exhibit depressed cell-mediated immune responses comparable to normal male animals, whereas additional administration of estradiol prevented the depression of immune responses.^{47,50} Moreover, elevated circulating 17 β -estradiol levels in proestrus females have been shown to play a direct role in the maintenance of immunocompetence after trauma-hemorrhage.⁵⁴ In addition, a single dose of estradiol following trauma-hemorrhage and resuscitation restored diminished splenocyte and splenic macrophage immune functions.^{57,58} This improvement in the immune responses was associated with a significantly increased survival rate following the induction of subsequent sepsis.⁵⁸ These findings therefore indicate that the depressed splenic and peritoneal immune responses after trauma-hemorrhage can be normalized by estradiol administration. Similarly, Asai et al demonstrated stimulatory effects of estradiol on the responsiveness of human PBMCs to LPS *in vitro*.⁵⁹

Thus, estrogen appears to be the causative factor in the

maintenance of immunocompetence in females after trauma-hemorrhage, and its administration in ovariectomized or postmenopausal females following trauma-hemorrhage should be helpful in preventing immune depression under such conditions. The judicious use of female sex steroids or the antagonists of androgens represent potentially novel approaches for the treatment of immune depression following trauma and severe hemorrhagic shock.

Sex steroids differently affect the cardiovascular system

Recent studies indicate that gender also affects cardiovascular responses.⁶⁰ Castration of male rats 2 weeks prior to the onset of trauma-hemorrhage prevented the depression of myocardial function as evidenced by significantly higher values of heart performance *in vivo*.⁶¹ Similarly, treatment of male rats with the androgen receptor antagonist, flutamide, has also been found to prevent the depression of cardiovascular responses following trauma and severe blood loss.⁶² Moreover, trauma-hemorrhage lead to diminished cardiac performance and lower organ blood flow in male animals.^{63,64} Recently, differences in the regulation of plasma and tissue volumes between males and proestrus females during and after trauma-hemorrhage have been found.⁶⁵ In this respect, proestrus females showed an increased circulating blood volume during and after trauma-hemorrhage which might contribute to the improved immune and organ functions in females.⁶⁵ Moreover, cardiovascular and hepatocellular functions were maintained in proestrus females after resuscitation, whereas they showed depression in males and estrus females.⁶⁰

Estradiol has been found to exhibit protective effects on cardiovascular responses following adverse circulatory conditions.^{32,66} Administration of 17 β -estradiol significantly improved cardiac performance, cardiac output, and hepatocellular function, and attenuated the increase in plasma IL-6 levels.⁶⁶ These studies therefore indicate that female and male sex steroids exhibit divergent effects on cardiovascular responses under normal conditions and following shock. However, the exact relationship between cardiovascular and immune responses contributing to the gender dimorphism following trauma and severe blood loss remains to be elucidated.

Influence of age on gender-specific immune responses

The influence of gender was investigated not only in young (6-8 weeks old) but also in middle-aged (1 year old) and aged (2 years old) mice. Interestingly, in the population of aged mice with decreased levels of sex steroids, a

reversed gender-related immune response following trauma-hemorrhage has been identified.^{34,67,68} As opposed to young mice, aged male mice exhibit enhanced release capacities for proinflammatory cytokines by splenic macrophages and Th1 cytokines by splenic lymphocytes compared to depressed release in aged females following trauma-hemorrhage.^{34,67,68} Changes in the levels of male and female sex steroids with age appear to contribute to the loss of the immunoprotective properties present in younger females. Further studies are required to elucidate whether the advantage in the morbidity and mortality from sepsis might be lost in older females or become comparable to that of aged male mice.

The results described above are in accordance with clinical findings demonstrating a higher mortality rate in septic post-menopausal women compared to male patients.⁶⁹ McLauchlan et al⁶⁹ reviewed a group of 125 patients with a mean age of 66 years who were admitted to the intensive care unit with abdominal sepsis. The hospital mortality rate was 63% and the factors associated with mortality included age and female sex. In addition, Watanakunakorn's⁷⁰ review of the medical records of patients who fulfilled the criteria for the diagnosis of *Staphylococcus aureus* endocarditis indicated that, at age 60 or older, female gender was associated with higher mortality. The above studies collectively suggest that age, gender, as well as the state of the estrus cycle in females should be taken into consideration in designing not only experimental, but also clinical studies examining immune responses following trauma-hemorrhage.

Potential mechanisms

Several studies indicate that sex steroids might exhibit direct immunomodulatory effects on immune cells. In this respect, the presence of estrogen receptors on various immune cells, ie, thymocytes, macrophages, and leukocytes, has been demonstrated.^{2,71} Moreover, the testosterone receptor antagonist, flutamide, restored macrophage and splenocyte as well as cardiovascular function following trauma-hemorrhage in vivo.^{72,73} Thus, sex steroids may modulate immune responses directly via specific receptor mediated processes. Further in vitro studies have demonstrated immunomodulatory properties of sex steroids on immune cells in vitro. In this regard, addition of DHT to the culture medium decreased the release of IL-3 and increased the apoptotic frequency of thymocytes harvested from sham and hemorrhaged animals.³⁵ Studies by Chao et al have shown that peritoneal macrophage TNF production can be increased if they are cultured in the presence of estradiol.⁷⁴ Furthermore, the cytotoxic T lymphocyte ac-

tivity has been found to be increased after addition of estrogen to the culture media in vitro.²

Trauma itself seems to play a role in different immunomodulatory properties of sex steroids. In this respect, under physiological plasma testosterone levels, trauma-hemorrhage is associated with depressed cell-mediated immune responses, whereas sham-operated animals do not show such a depression.^{45-47, 50} Furthermore, recent studies indicate that the synthesis of sex steroids is altered following trauma-hemorrhage.^{75,76} An increased dihydrotestosterone synthesis and a decreased catabolism of this steroid hormone have been demonstrated in male T lymphocytes following trauma-hemorrhage whereas the reverse occurs in proestrus females, ie, increased synthesis and decreased catabolism of estradiol take place in the T lymphocytes.^{75,76}

These studies demonstrate several potential mechanisms by which sex steroids might modulate immune responses following adverse circulatory conditions. Nonetheless, we are in the early stages of elucidating the complex interactions of sex hormones and the immune system. Further studies will be required to determine the exact underlying pathways that are influenced by sex steroids under normal as well as following trauma-hemorrhage.

Potential therapeutic strategies

Androgen receptor antagonists

Several animal studies have shown beneficial effects of castration by depleting plasma testosterone levels prior to trauma and hemorrhage. In order to transfer those effects into clinical usage, studies mimicking castration by the use of the androgen receptor antagonist, flutamide, were conducted. Administration of flutamide at a dosage of 25 mg/kg body weight following trauma-hemorrhage and resuscitation normalized the depressed splenic and peritoneal macrophage cytokine release.⁷³ In addition, flutamide administration on 3 consecutive days following trauma-hemorrhage not only restored the depressed splenocyte and splenic macrophage cytokine release even after the induction of subsequent sepsis but also significantly decreased the mortality of post-hemorrhaged animals subjected to a subsequent septic challenge.⁷² Since flutamide is used in patients with testicular cancer for periods longer than 3 days without major adverse effects, the short-term use of this androgen receptor antagonist in male trauma patients would appear to be a safe and useful adjunct for the treatment of immune and cardiovascular depression under those conditions.

The steroid hormone dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is the major circulating steroid hormone in humans. As an intermediate in the

sex steroid synthesis it can be metabolized to both testosterone and estrogen. In view of the immunoenhancing effects of estrogen administration following trauma-hemorrhage, DHEA has been reported to exhibit predominantly estrogenic effects in a male hormonal environment.⁷⁷ In additional studies, DHEA administered at a dose of 100 mg per animal prevented the depression of cell-mediated immune responses following trauma-hemorrhage and resuscitation as evidenced by maintained splenic and peritoneal macrophage cytokine release and normalized splenocyte lymphokine release.^{78,79} In addition, administration of DHEA following trauma-hemorrhage significantly improved the survival rate of animals subjected to subsequent sepsis compared to vehicle-treated animals.⁷⁸ Similar to the experimental results, DHEA normalized the depressed proinflammatory cytokine release capacities of human peripheral blood mononuclear cells (PBMCs) following major abdominal surgery in vitro.⁸⁰ The effect of DHEA on PBMC function followed a dose-dependent manner. Thus, DHEA might also exhibit beneficial effects in male trauma patients by preventing the depression of cell-mediated immune responses under those conditions. In the United States, DHEA is widely used as an over-the-counter drug without any serious side effects. In female trauma victims, administration of estrogen appears to be a useful adjunct for decreasing mortality under those conditions.

SUMMARY

Despite the fact that gender differences in the morbidity and mortality from trauma, shock, and sepsis have been

observed in several clinical studies, alterations in the immune functions following shock have been investigated primarily using young male laboratory animals. Recently numerous studies have been initiated investigating the effect of gender, age, and sex hormones on immune responses following shock and trauma. The findings of our studies suggest that low testosterone and/or high estradiol appears to be protective for the host following trauma and severe blood loss. Although the exact underlying mechanism(s) for the immunomodulatory properties of sex hormones on cell-mediated immune and cardiovascular responses following trauma-hemorrhage remain unknown, there is evidence that both direct and indirect effects of sex steroids act synergistically in modulating the immune and cardiovascular responses. In this respect, sex hormone receptors have been identified on various immune cells suggesting receptor mediated processes. Other studies suggest the release of secondary mediators that alter immune responses following adverse circulatory conditions. In view of these findings, clinically relevant therapeutic strategies have been developed using the androgen receptor antagonist, flutamide, and/or estrogen or agents with estrogenic effects, eg, DHEA, which might yield safe and useful therapeutic adjunct approaches for the treatment of immune and cardiovascular depression in trauma victims. Moreover, gender should be taken into account when studying the immune or cardiovascular responses following trauma and shock. This notion is supported by the observation that immunomodulatory strategies using IL-10 improved survival in males but not in females following trauma-hemorrhage and subsequent sepsis.⁸¹

RESUMO

Angele MK, Frantz MC, Chaudry IH. Hormônios sexuais influenciam a resposta ao trauma e à sepsis – possíveis soluções terapêuticas. CLINICS. 2006;61(5):479-88.

Uma série de estudos clínicos e experimentais demonstram a existência de dimorfismo sexual das respostas imunológicas e orgânicas, bem como da suscetibilidade e morbidade em relação ao choque, ao trauma e à sepse. Respostas imunes celularmente mediadas apresentam-se deprimidas em machos em resposta ao binômio trauma-hemorragia, mas conservados/enaltecidos em fêmeas em proestro. Adicionalmente demonstra-se que os hormônios sexuais são responsáveis por esta dicotomia de resposta sexualmente específica, em condições cardiovasculares adversas. Estudos específicos indicam que os andrógenos produzem

imunodepressão pós-trauma hemorragia em machos. Em contraste, esteróides sexuais femininos parecem exibir propriedades imunoprotetoras após episódios de trauma com ou sem perda importante de sangue. No terreno dos mecanismos subjacentes, foram identificados receptores para hormônios sexuais em várias células do sistema imunológico, sugerindo a existência de efeitos diretos destes hormônios sobre tais células. Alternativamente, observam efeitos indiretos de hormônios sexuais tais como modulação das respostas cardiovasculares das enzimas sintetizadores de andrógeno e estrógeno, que podem contribuir para as estas respostas sexualmente diferenciadas. Estudos recentes indicam que os hormônios sexuais, como por exemplo a dehidroepiandrosterona também modulam a função de células mononucleares da série branca em pacien-

tes cirúrgicos. Assim, as propriedades imunomodulatórias de hormônios sexuais/antagonistas de receptores/enzimas sintetizadores de esteróides após a ocorrência de trauma ou de hemorragia sugerem o caminho para novas estratégias terapêuticas para o tratamento de imunodepressão em

pacientes cirúrgicos.

UNITERMOS: Dimorfismo sexual. Esteroides sexuais. Choque hemorrágico. Depressão immune. Imunomodulação.

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