The female reproductive cycle is an important variable in the response to trauma-hemorrhage

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Received 14 January 2000; accepted in final form 24 March 2000

Jarrar, Doraid, Ping Wang, William G. Cioffi, Kirby I. Bland, and Irshad H. Chaudry. The female reproductive cycle is an important variable in the response to trauma-hemorrhage. Am J Physiol Heart Circ Physiol 279: H1015–H1021, 2000.—Although immune functions in proestrus females are maintained after hemorrhage as opposed to decreased responses in males, it remains unknown whether such a sexual dimorphism also exists with regard to cardiovascular and hepatocellular functions under those conditions. To study this, male and female (estrus and proestrus) rats underwent a 5-cm midline laparotomy and were bled to and maintained at a mean blood pressure of 40 mmHg until 40% of the maximal bleed-out volume was returned in the form of Ringer lactate (RL). Rats were then resuscitated with four times the shed blood volume with RL. At 24 h thereafter, cardiac index; heart performance; hepatocellular function; and plasma estradiol, testosterone, and prolactin levels were measured. Cardiovascular and hepatocellular functions were depressed in males and estrus females (P < 0.05) but were not depressed in proestrus females after resuscitation. Plasma estradiol and prolactin levels were highest in proestrus females (P < 0.05), whereas males had high testosterone and the lowest estradiol levels (P < 0.05). Thus the female reproductive cycle is an important variable in the response to hemorrhage. Because low testosterone and high estradiol and prolactin levels appear to be beneficial for organ functions after trauma-hemorrhage, antagonism of testosterone receptors and/or increases in estradiol and prolactin levels in males and estrus females, respectively, may be novel approaches for improving organ functions under such conditions.

sex steroids; prolactin; cardiac output; liver function; circulating blood volume

CLINICAL AND EPIDEMIOLOGICAL studies have indicated gender differences in the response to various adverse circulatory conditions (19). In this regard, studies have shown that sex steroids have either deleterious or beneficial effects on cardiac and hepatic functions not only under normal conditions but also after circulatory stress. For example, testosterone-receptor blockade after trauma-hemorrhage has been shown to improve organ functions in males (22). Alternatively, castration 14 days before hemorrhagic shock prevented the depression in myocardial functions that is usually observed in males under those conditions (21).

It has been demonstrated that the proestrus state of the female rodent shows the highest plasma concentration of estradiol and prolactin (25). The plasma levels of both hormones are low on the morning of estrus and then gradually increase over diestrus to achieve their peak levels on the morning of proestrus (25). Studies by Slimmer and Blair (24) have shown that female rats in the proestrus stage of the reproductive cycle exhibit a more vigorous restitution response than either estrus females or males after simple hemorrhage. Furthermore, Wichmann et al. (31) have recently shown that female mice subjected to hemorrhage during the proestrus state have enhanced immune responses as opposed to decreased responses in males. In light of this, we hypothesized that the female reproductive cycle is an important variable not only with regard to immunological responses but also by influencing physiological responses (i.e., cardiac and hepatic functions) after trauma-hemorrhage and resuscitation (2). The proestrus and estrus phases of the reproductive cycle were selected because the endocrine status differs markedly between these two phases, with low estradiol and prolactin levels during estrus and maximal plasma concentrations during proestrus. The aim of the present study, therefore, was to determine whether high levels of estradiol and prolactin are associated with improved organ functions after soft-tissue trauma and severe hemorrhagic shock and crystalloid resuscitation.

MATERIALS AND METHODS

Experimental procedures. The previously described nonheparinized model of trauma-hemorrhage in the rat (4, 26) was used with minor modifications. Briefly, age-matched adult male and female Sprague-Dawley rats (males, 275–325 g; females, 200–250 g; Charles River Laboratories, Wilmington, MA) were fasted overnight before the experiment but were allowed water ad libitum. The stage of the female reproductive cycle was determined by regular examination of the

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vaginal smears by the same examiner. Proestrus was defined when both leukocytes and nucleated epithelial cells in approximately equal numbers were present on the vaginal smears. Estrus was characterized by large, squamous-type epithelial cells without nuclei. In female rats, experiments were performed only after at least one complete estrus cycle had been documented. The cycle phase was determined from the cytology of vaginal smears obtained daily at 0700–0830. The hemorrhage procedure began between 0900 and 1000. The rats were anesthetized by methoxyflurane (Mallinckrodt Veterinary, Mundelein, IL) inhalation, and catheters were placed in both femoral arteries and the right femoral vein [polyethylene (PE-50) tubing; Becton-Dickinson, Sparks, MD]. After catheterization of the first femoral artery, ~600 µl of blood were withdrawn as described below (see Plasma collection and storage). After this, a 5-cm midline laparotomy representing soft-tissue trauma was performed. The abdomen was then closed in layers, and the wounds were bathed with 1% lidocaine (Elkins-Sinn, Cherry Hill, NJ) throughout the surgical procedure to reduce postoperative pain. Rats were then bleed to and maintained at a mean arterial pressure (MAP) of 40 mmHg until the animals could not maintain a MAP of 40 mmHg unless extra fluid in the form of Ringer lactate was given. This time was defined as maximum bleed out, and the amount of withdrawn blood was noted. After this, the rats were maintained at a MAP of 40 mmHg until 40% of the maximum bleed-out volume was returned in the form of Ringer lactate. The animals were then resuscitated with four times the volume of the withdrawn blood over 60 min with Ringer lactate. The shed blood was not used for resuscitation. The catheters were then removed, the vessels were ligated, and the skin incisions were closed with sutures. Sham-operated animals underwent the same groin incision, which included the ligation of both femoral arteries and the right vein; however, neither hemorrhage nor resuscitation was carried out.

After the rats were returned to their cages, they were allowed food and water ad libitum. At 24 h after the completion of fluid resuscitation or sham operation, the animals were anesthetized with methoxyflurane and then catheterized via the right jugular vein. During the monitoring of MAP and heart rate, pentobarbital sodium (25–30 mg/kg body wt) administration was carefully carried out to keep animals in a state of depressed sensibility. After each bolus injection of pentobarbital, several minutes passed before heart rate and MAP reached steady-state levels. All animal experiments were performed in accordance with the guidelines of the Animal Welfare Act and the National Research Council’s Guide for the Care and Use of Laboratory Animals. This project was approved by the Institutional Animal Care and Use Committee of Rhode Island Hospital (Providence, RI).

Measurement of cardiac output. A 2.4-French fiberoptic catheter was placed into the right carotid artery, which was connected to an in vivo hemoflowmeter (Hospex Fiberoptics, Chestnut Hill, MA) as described previously (28). Indocyanine green (ICG; Cardio Green, Becton-Dickinson) solution was injected via the catheter in the jugular vein (1 mg/ml aqueous solution as a 50-µl bolus). Twenty ICG concentrations per second were recorded for ~30 s with the aid of a data-acquisition program (Asystent*; Asyst Software, Rochester, NY). The area under the ICG dilution curve was determined according to our previous publication (28) to calculate cardiac output (CO). CO was then divided by the body weight to determine cardiac index.

Measurement of hepatocellular function. Hepatocellular function was measured by the in vivo ICG clearance technique (29). ICG was administered by bolus injection (50 µl) of 1, 2, and 5 mg/ml ICG in aqueous solvent. The arterial concentration of ICG was recorded each second for 5 min. After this, the initial velocity of ICG clearance for each dose was calculated after performance of a nonlinear regression of the ICG clearance curves according to an e-raised second-order polynomial function (29). The initial velocities of ICG clearance were then plotted against the ICG doses according to the methods of Lineweaver-Burk (8). This results in a straight line, allowing for the determination of a maximum of ICG clearance (maximal velocity; \( V_{max} \)) and the Michaelis-Menten constant (\( K_m \)). In this active hepatocellular membrane transport system, \( V_{max} \) represents the functional hepatocyte ICG receptors, and \( K_m \) represents the efficiency of the active transport process (29).

Measurement of in vivo heart performance. After the determination of CO and hepatocellular function, the fiberoptic catheter in the right carotid artery was replaced with PE-50 tubing, which was manually stretched to reduce the outer diameter by ~60%. Under pressure control, this catheter was carefully advanced into the left ventricle. The position of the catheter was confirmed by recording of the characteristic left ventricle pressure curve. Data were analyzed from an in vivo heart performance analyzer (Micro-Med, Louisville, KY) as described in our previous publication (22a). Left ventricular performance parameters such as the maximal rate of pressure increase (+dP/dtmax) and decrease (−dP/dtmax) were documented with a data acquisition system (DMSI 200–8, Micro-Med).

Determination of circulating blood volume. Circulating blood volume (CBV) was determined by use of an in vivo ICG clearance technique as described previously (27). CBV in milliliters was calculated according to

\[
CBV = \frac{ICG\, dose\, (0.1\, mg/l)\times [ICG]_0}{[ICG]_0} \times 1.000
\]

where [ICG]o is the ICG concentration at baseline, and CBV in milliliters per 100 g body wt was then calculated.

Plasma collection and storage. At the start of the experiments, ~600 µl of heparinized whole blood for the determination of baseline hormone levels were withdrawn and replaced with ~2.4 ml of Ringer lactate. At the end of all measurements (i.e., 25 h after the end of trauma-hemorrhage and resuscitation), heparinized whole blood was obtained. Blood was placed in microcentrifuge tubes and then centrifuged at 16,000 rpm for 15 min at 4°C. Plasma and serum were separated, placed in pyrogen-free microcentrifuge tubes, immediately frozen, and stored (~70°C) until assay.

Determination of plasma sex steroids. Plasma testosterone was determined according to the use of a commercially available coated-tube RIA kit (Diagnostic Systems, Webster, TX) according to the manufacturer’s instructions. Cross-reactivity of the RIA was as follows: 100% for testosterone; 3.4% for 5α-dihydrotestosterone; 2.2% for 5α-androstane-3β,17β-diol; 2% for 11-oxotestosterone; and <1% for all other steroids. Plasma 17β-estradiol concentration was determined by use of a commercially available RIA kit specifically designed for rats and mice (ICN Biomedicals, Costa Mesa, CA). Cross-reactivity of the RIA was 100% for 17β-estradiol and 20% or 1.51% for estrone or estriol, respectively. For all other steroids, the cross-reactivity was <0.01%.

Determination of plasma prolactin levels. Prolactin levels were measured by use of an enzyme immunosorbent assay kit (SPI Bio, Massy Cedex, France) according to the manufacturer’s instructions. Cross-reactivity with rat luteinizing hormone, growth hormone, and thyroid-stimulating hormone is below 1%. The sensitivity of the assay is 0.5 ng/ml, and the mean interassay variation is 14%. The intra-assay coefficient
of variation is 9.4 and 8.6% in the lower and higher range, respectively.

Statistical analysis. Results are presented as means ± SE. One-way ANOVA and Student-Newman-Keuls test for multiple comparisons were used, and the differences were considered significant at P ≤ 0.05. There were 8, 6, and 6 animals in the sham-operated male, estrus, and proestrus groups, respectively, and 7, 8, and 8 animals in the male, estrus, and proestrus hemorrhaged groups, respectively.

RESULTS

Effects of trauma-hemorrhage on cardiac index. The results in Fig. 1 indicate that cardiac index was similar in the three groups of sham-operated animals (male, 39.5 ± 0.9; estrus, 40.9 ± 2.7; and proestrus, 39.2 ± 1.5 ml·min⁻¹·100 g⁻¹). In male and estrus female hemorrhaged animals, cardiac index decreased by 24.1 and 20.5% (30.0 ± 1.8 and 32.6 ± 1.7 ml·min⁻¹·100 g⁻¹; P < 0.05 compared with the corresponding shams), respectively. However, cardiac index in hemorrhaged proestrus female rats was similar to the respective sham group at 24 h after the completion of fluid resuscitation (38.3 ± 1.7 ml·min⁻¹·100 g⁻¹).

Effects of trauma-hemorrhage on heart performance. The +dP/dtmax (male, 10,858 ± 357; estrus, 11,224 ± 428; and proestrus, 11,713 ± 691 mmHg/s) and −dP/dtmax (male, 7,085 ± 429; estrus, 7,067 ± 511; and proestrus, 6,728 ± 380 mmHg/s) in the left ventricle were similar in the three groups of sham animals (Fig. 2, A and B). At 24 h after trauma-hemorrhage and crystalloid resuscitation, the +dP/dtmax in the left ventricle was decreased by 30.2 and 26.7% (7,585 ± 732 and 8,235 ± 1,131 mmHg/s; P < 0.05 compared with the corresponding shams) in male and female estrus rats, respectively (Fig. 2A). In contrast, the values for +dP/dtmax in posthemorrhaged female proestrus rats were similar to the respective sham animals (11,971 ± 812 mmHg/s) and were significantly higher than in hemorrhaged males and estrus females. In a similar fashion, the −dP/dtmax in the left ventricle was also diminished in male and female estrus rats after trauma-hemorrhage (4,915 ± 377 and 4,711 ± 492 mmHg/s, respectively; P < 0.05 compared with the corresponding shams). In female proestrus animals, however, −dP/dtmax was maintained at the level of sham-operated animals (6,852 ± 846 mmHg/s) and was significantly higher than in male and female estrus animals after trauma-hemorrhage.

Effects of trauma-hemorrhage on hepatocellular function. No significant difference in the Vmax of ICG clearance was evident between the sham animals (male, 1.1 ± 0.2; estrus, 1.2 ± 0.3; and proestrus, 1.0 ± 0.2 mg·kg⁻¹·min⁻¹; Fig. 3A). In male and estrus female rats subjected to trauma-hemorrhage and resuscitation, Vmax decreased by 80.1 and 83.2% (0.21 ± 0.03 and 0.19 ± 0.03 mg·kg⁻¹·min⁻¹), respectively, compared with the corresponding sham groups (P < 0.05). In contrast, proestrus female rats had significantly higher values for Vmax (0.83 ± 0.16 mg·kg⁻¹·min⁻¹) at 24 h after crystalloid resuscitation. As indicated in Fig. 3B, Km was similar in the three groups of sham-operated animals (male, 2.5 ± 0.5; estrus, 3.4 ± 0.7; and proestrus, 2.9 ± 0.7 mg/kg) and decreased by 64.9 and 79.8% (0.8 ± 0.2 and 0.7 ± 0.08 mg/kg) in male and estrus female rats, respectively, compared with the corresponding sham groups at 24 h after trauma-hemorrhage and resuscitation (P < 0.05). In contrast, Km was significantly higher in hemorrhaged proestrus female animals (3.0 ± 0.5 mg/kg) compared with male and estrus female rats (P < 0.05).

Effects of trauma-hemorrhage on CBV. CBV was found to be 6.51 ± 0.18, 6.56 ± 0.38, and 6.81 ± 0.29 ml/100 g in male and estrus and proestrus female animals, respectively (Fig. 4). At 24 h after trauma-
hemorrhage and crystalloid resuscitation, CBV was significantly decreased in all three groups (4.6 ± 0.19, 4.8 ± 0.29, and 4.9 ± 0.39 ml/100 g in male and estrus and proestrus female rats, respectively; P < 0.05) compared with the respective sham animals, with no significant difference between the hemorrhaged groups.

**Plasma estradiol levels.** Plasma levels of estradiol were found to be the highest in proestrus female animals (83 ± 5 pg/ml; Fig. 5A) and were significantly lower in male (32 ± 5 pg/ml) and estrus females (56 ± 8 pg/ml) rats at the start of the experiments (P < 0.05). At 24 h after trauma-hemorrhage and crystalloid resuscitation, plasma estradiol levels decreased by 31.2, 23.5, and 27.4% (21 ± 5, 43 ± 1.3, and 60 ± 6 pg/ml) in male and estrus and proestrus female animals, respectively, with a higher plasma concentration in proestrus females compared with the other two hemorrhaged groups (P < 0.05).

**Plasma testosterone levels.** Plasma levels of testosterone were found to be 2.7 ± 0.36 ng/ml in male rats at the start of the experiments and decreased by 89.5% (0.28 ± 0.06 ng/ml; P < 0.05) at 24 h after the completion of crystalloid resuscitation (Fig. 5B).

**Plasma prolactin levels.** Plasma levels of prolactin were found to be the highest in proestrus female rats (30.8 ± 9.0 ng/ml; Fig. 5C) and were lower in males (5.7 ± 1.4 ng/ml; P < 0.05) and estrus females (12.7 ± 3.85 ng/ml; P < 0.05) at the start of the experiment. There was no significant difference in plasma prolactin concentration at 24 h after trauma-hemorrhage and crystalloid resuscitation among the three groups.

**Effects of gender on body weight, total CBV, hematocrit, maximal bleed-out volume, and hemorrhage time.**
As shown in Table 1, age-matched male rats had a significantly higher body weight than female animals. Similarly, total CBV was higher in males ($P < 0.05$). Systemic hematocrit was $45.8 \pm 1.1\%$ in the male group and was lower in female estrus ($40.6 \pm 1.4\%$; $P < 0.05$) and proestrus animals ($43.5 \pm 1.1\%$). Maximal bleed-out volume (MBO) was also significantly higher in males compared with both female groups because of the higher body weight of male rats (Table 1). There was no significant difference in the time until 40% of the MBO volume was returned in the form of Ringer lactate in the three groups.

**DISCUSSION**

Accidental or intentional trauma is the leading cause of death in persons aged 1–38 yr in the United States (3, 10). In the past, most laboratory investigations into the pathophysiology of trauma and severe blood loss have used male animals. However, recent studies utilizing male and female rodents have shown that a sexual dimorphism exists with regard to the response to adverse circulatory conditions (24). The results of those experiments suggest that female sex steroids such as 17$\beta$-estradiol and prolactin are responsible for the more vigorous restitution response observed in proestrus females than in either estrus females or in males (24). The aim of the present study, therefore, was to determine whether the high levels of circulating estradiol and prolactin usually found during the proestrus phase of the reproductive cycle are associated with improved cardiovascular and hepatocellular functions after trauma-hemorrhage and crystalloid resuscitation. It should be mentioned that we used age-matched male and female rats in the present experiments instead of matching the groups by weight, because recent studies have indicated that not only gender but also age is an important variable in the response to trauma-hemorrhage (12).

Our results indicate that cardiac output, heart performance parameters, and hepatocellular function, as determined by ICG clearance technique, are significantly depressed in male and female estrus rats at 24 h after trauma and severe hemorrhagic shock. In female proestrus animals, however, organ functions were not significantly different compared with their respective sham group, i.e., female rats undergoing sham operation on the morning of the proestrus phase of the reproductive cycle. Moreover, our data indicate that the normalized cardiac and hepatic functions in proestrus female animals were associated with peak levels of estradiol and prolactin at the start of the experiment, whereas male and female estrus rodents had significantly lower plasma levels of estradiol and prolactin. Although plasma levels of prolactin were similar in all three groups at 24 h after crystalloid resuscitation, it appears that the high levels of prolactin found in proestrus females before the onset of trauma-hemorrhage have salutary effects on organ functions under those conditions. This is in line with our previous observation that even an only transient increase in endogenous prolactin secretion after metoclopramide administration was sufficient to improve organ functions under those conditions (11).

Together, our data demonstrate that ovarian and gonadal sex steroids as well as the anterior pituitary hormone prolactin are associated with the gender-dimorphic response to trauma and severe blood loss. Although 17$\beta$-estradiol levels were higher in female estrus animals than in males at the start of the experiment, it appears that this was not sufficient to protect organ functions after trauma-hemorrhage. It should be noted that for the determination of plasma hormone levels, each animal served as its own control, because we obtained blood samples at baseline, i.e., before the midline laparotomy and onset of blood loss, and at 24 h after trauma-hemorrhage and crystalloid resuscitation. Although testosterone was undetectable in the plasma of females in the present study, the biologically more active form, 5$\alpha$-dihydrotestosterone, has been found also in female rodents. However, because the measurement of 5$\alpha$-dihydrotestosterone requires larger volumes of blood samples and an extraction procedure because of cross-reactivity of the antibody with other steroids, measurement of 5$\alpha$-dihydrotestosterone was not performed in the present study.

Nevertheless, it appears that not only low levels of estrogens but also high levels of male sex steroids are responsible for the depression of organ functions after hemorrhagic shock. In this regard, we have previously shown that implantation of testosterone-releasing pellets in female mice caused a significant decrease in plasma levels of 17$\beta$-estradiol and a marked depression in immune functions as observed in male rodents, whereas vehicle-treated proestrus females maintained their immune responsiveness under those conditions (1). Nonetheless, it remains to be determined whether the high levels of estradiol alone or the combination of increased plasma concentration of estradiol and prolactin is responsible for the maintenance of organ functions after trauma and hemorrhage in proestrus females. Moreover, the exact mechanism by which ovarian and anterior pituitary hormones potentially improve organ functions after adverse circulatory conditions remains to be determined. Some of the biological effects of estrogens, for example, are well charac-

### Table 1. Comparison between male and female estrus and proestrus rats

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female Estrus</th>
<th>Female Proestrus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>$318 \pm 6.1^{+\dagger}$</td>
<td>$223 \pm 4.5$</td>
<td>$226 \pm 4.9$</td>
</tr>
<tr>
<td>Total CBV, ml</td>
<td>$18.3 \pm 0.5^{+\dagger}$</td>
<td>$14.2 \pm 0.7$</td>
<td>$15.4 \pm 0.5$</td>
</tr>
<tr>
<td>Hct, %</td>
<td>$45.8 \pm 1.1^{+\dagger}$</td>
<td>$40.6 \pm 1.4$</td>
<td>$43.5 \pm 1.1$</td>
</tr>
<tr>
<td>MBO, ml</td>
<td>$10.4 \pm 0.37^{+\dagger}$</td>
<td>$7.7 \pm 0.23$</td>
<td>$7.5 \pm 0.22$</td>
</tr>
<tr>
<td>Hemorrhage time, min</td>
<td>$90.5 \pm 1.8$</td>
<td>$91.1 \pm 0.5$</td>
<td>$90.8 \pm 0.6$</td>
</tr>
</tbody>
</table>

Data are means ± SE. Total CBV, total circulating blood volume from Fig. 4; Hct, systemic hematocrit; MBO, maximal bleed-out volume; hemorrhage time, total time in shock until start of resuscitation. For further details, see MATERIALS AND METHODS. Data were compared by 1-way ANOVA and Student-Newman-Keuls test. *$P < 0.05$ vs. female estrus and $\dagger P < 0.05$ vs. female proestrus.
terized and can be divided into rapid nongenomic and slower genomic effects (16). The immediate effects of estrogens are mediated via constitutive nitric oxide synthase (cNOS) (5, 13, 15). In this regard, several studies have indicated that activation of cNOS after severe shock is beneficial and results in an attenuated inflammatory response (7, 9). Another potential mechanism for the improved organ functions in the animals with the highest estradiol levels, i.e., female proestrus rats, could be the known ability of 17β-estradiol to diminish leukocyte adherence and migration (18). Several studies have shown that the microcirculatory perfusion failure observed after shock can be attributed to the enhanced leukocyte-endothelial interaction under those conditions (14). Moreover, experiments of Deshpande et al. (6) have shown that estradiol attenuates cytokine production by inhibition of the transcription factor (nuclear factor) NF-κB. Studies by Ramachandran et al. (20) have demonstrated that estradiol induces the expression of the 90-kDa heat shock protein (HSP)-90 in various tissues. Because the expression of HSPs is associated with protective effects after adverse circulatory conditions (17), it is possible that the normalized organ functions in proestrus females after trauma and severe hemorrhage could be due to induction of HSP-90. Despite the fact that one or more than one of the above mechanisms could be responsible for the protection of the proestrus females after trauma-hemorrhage, the precise mechanism of protection remains unknown.

In the present experiments we have included males for the following reasons. First, males, unlike females, have consistently low levels of estrogens with very little fluctuation over a period of time. Second, the surge in estradiol and prolactin in the morning of proestrus in female rats does explain only partially the sexual dimorphism in the response to trauma and severe blood loss. From previous data, it appears that in males, not only the lack of such an increase in estradiol and prolactin but also the high levels of testosterone are responsible for the depression in organ functions after trauma-hemorrhage (21, 22, 30).

In summary, our results indicate that female proestrus rats have normalized organ functions at 24 h after trauma-hemorrhage, whereas male and female estrus animals show a marked depression in cardiovascular and hepatocellular functions. The maintenance of cardiac and hepatic functions after severe blood loss is associated with high levels of 17β-estradiol and prolactin at the start of the experiment. However, it remains to be determined why teleologically females are better positioned to endure circulatory stress than males. In this regard, it could be speculated that the care for the offspring requires a more robust individual. This would explain why this advantage vanished in ovariectomized females, i.e., after menopause. Moreover, Offner et al. (19) have reported that males are at higher risk to develop infectious complications after major surgery than females. Although patients in this study were not stratified for their hormonal status, it could be speculated that higher estradiol levels in females might be responsible for the gender-dimorphic response. This notion is supported by the study of Schroder et al. (23), which showed that women had higher estradiol levels during sepsis and that these levels were associated with a significantly lower mortality and morbidity compared with males under those conditions. Thus a sexual dimorphism cannot only be observed in rodents but appears to also play a role in humans during critical illness. In conclusion, because low levels of testosterone and high estradiol and prolactin levels appear to be beneficial for cardiovascular and hepatocellular functions after trauma-hemorrhage, antagonism of testosterone receptors in males and increases in estradiol and prolactin plasma concentrations in estrus females may be novel approaches for improving organ functions under such conditions.

We thank Zheng F. Ba for superb technical assistance during the experiment and Deanna Oster for the measurement of plasma sex steroids.

This investigation was supported by National Institute of General Medical Sciences Award R21-GM-39518 (to I. H. Chaudry). P. Wang is the recipient of the National Institute of Allergy and Infectious Diseases Extramural Activities Independent Scientist Award KO2 AI-01461.

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