Influence of Female Sex Hormones on Endothelium-Derived Vasoconstrictor Prostanoid Generation in Microvessels of Spontaneously Hypertensive Rats

Ana Paula V. Dantas, Regina Scivoletto, Zuleica B. Fortes, Dorothy Nigro, Maria Helena C. Carvalho

Abstract—Although female sex hormones may attenuate endothelial dysfunction in spontaneously hypertensive rats (SHR) by increasing endothelium-derived relaxing factors (EDRFs), the influence of ovarian hormones on the generation of endothelium-derived contracting factors (EDCFs) remains unknown. The aim of this study was to evaluate the effect of estrogen and progesterone on the generation of vasoconstrictor prostanoids and superoxide anion (O$_2^-$) by microvessels from SHR. Vascular reactivity to norepinephrine (NE), acetylcholine (ACh), and sodium nitroprusside (SNP) were evaluated in the mesenteric arteriolar bed from estrous (OE) and ovariectomized (OVX) SHR. OVX-SHR were treated for 24 hours or 15 days with estradiol and for 15 days with estradiol+progesterone. The vascular reactivity was evaluated in the absence or presence of indomethacin (INDO, 10 μmol/L) and sodium diclofenac (DIC, 10 μmol/L), ridogrel (RID, 50 μmol/L), dazoxiben (DAZ, 10 μmol/L), or superoxide dismutase (SOD, 100 U/mL). Prostanoid levels in the arteriolar perfusate of mesenteries with or without endothelium were measured by enzyme immunoassay. An increased reactivity to NE and reduced sensitivity to ACh were observed in microvessels from OVX-SHR compared with OE-SHR. There were no differences in the responses to SNP. Treatments with estradiol and estradiol+progesterone similarly restored these altered responses. INDO, DIC, RID, and SOD also restored the NE and ACh responses in OVX-SHR. DAZ had no effect on the vascular reactivities. The release of PGF$_2$α, but not of TXB$_2$ and 6-keto-PGF$_1α$, was greater in OVX-SHR than in OE-SHR microvessels with endothelium when stimulated by NE. This response was normalized by hormonal treatments. Neither NE nor ACh stimulated prostanoid production by microvessels without endothelium. These results suggest that estrogen may protect female SHR against severe hypertension partly by decreasing the synthesis of EDCFs such as PGH$_2$/PGF$_{2α}$ and O$_2^-$. (Hypertension. 1999;34[part 2]:914-919.)

Key Words: estrogen | progesterone | SHR | endothelium-derived contracting factors | prostanoids | superoxide

Women in the reproductive age are less prone to hypertension and hypertension-related diseases than men or postmenopausal women.¹ This observation suggests that ovarian hormones, especially estrogen, may confer premenopausal protection. Indeed, a reduction in estrogen levels after ovariectomy aggravates hypertension in spontaneously hypertensive rats (SHR).² In addition, although some authors have reported that estrogen exerts no influence on blood pressure,³ several studies have demonstrated that estrogen replacement can decrease blood pressure in this model of hypertension,⁴ as well as in postmenopausal women.⁵

One hypothesis to explain the beneficial effects of estrogen in the cardiovascular system is that estrogen can modulate the generation of endothelium-derived relaxing factors (EDRFs) such as nitric oxide. In vitro studies of certain isolated vessels have demonstrated a relationship between estrogen levels and nitric oxide generation.⁶⁻⁷ In contrast, the influence of estrogen on the biosynthesis of endothelium-derived constricting factors (EDCFs) in hypertension remains unknown.

Endothelial dysfunction in essential hypertension is characterized by a normal release of EDRFs and an enhanced release of EDCFs.⁸ This imbalance has been associated with impaired endothelium-dependent vasodilation in the blood vessels of adult SHR.⁹ The constricting factor released by the endothelium in hypertension is probably a vasoconstrictor prostanoid and/or superoxide anion, because the impairment of endothelium-dependent relaxation is restored by indomethacin, an inhibitor of cyclooxygenase, and by superoxide dismutase (SOD).¹⁰

Few studies have examined the influence of sex hormones on endothelial function in hypertension.¹⁴⁻¹⁵ Williams et al.¹⁶ reported that 17β-estradiol enhanced endothelium-dependent relaxation in the aorta of female SHR. Subsequently, Kauser and Rubanyi¹¹ demonstrated important gender differences in the endothelial dysfunction of SHR. In a previous study of microvessels from SHR, we demonstrated that estrogen may have a beneficial effect on endothelial dysfunction.²

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Although the influence of female sex hormones on endothelial dysfunction has been studied, the exact mechanism by which these hormones can interfere with the endothelial function in hypertension remains unknown. A few studies have shown that estrogen can modulate EDRF/nitric oxide (NO) generation in the endothelium, but nothing is known about the action of estrogen on the generation of EDCF in hypertension. In this work, we evaluated the influence of estrogen and progesterone on the generation of vasoconstrictor prostanoids (EDCFs) in microvessels from SHR.

**Methods**

The experiments were performed with 16- to 18-week-old female SHR obtained from the breeding stock at our own institute and housed according to institutional guidelines (constant room temperature, 12-hour light/dark cycle, 60% humidity, standard rat chow and water ad libitum). The rats were divided into physiologically estrous (OE) and ovariectomized (OVX) groups. At the age of 16 to 18 weeks, physiological estrus was determined by microscopic evaluation of vaginal smears. Ovariectomy was performed at 12 weeks of age under chloral hydrate anesthesia (450 mg/kg). After an abdominal incision, the ovaries were clamped and removed, and the skin was then sutured before the animals were returned to their cages. The rats were used 30 days after surgery. Thirty days after ovariectomy, OVX rats were treated for 24 hours with estradiol 140 μg/kg SC (OVX+E(24 hours)) or for 15 days with subcutaneously implanted 21-day release pellets containing estradiol 0.05 mg [OVX+E(15 days)] or estradiol 0.05 mg progesterone 50 mg [OVX+E+P(15 days)].

To measure plasma hormone levels, the blood samples were collected from the abdominal aorta of anesthetized SHR and then centrifuged to separate the serum. Serum estrogen and progesterone levels were determined by enzyme immunoassay (Cayman Chemical Co), and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were measured by radioimmunoassay (Amersham Life Science) with 125I-labeled LH/FSH.

**Measurement of Arterial Blood Pressure**

Mean arterial pressure was determined in conscious, freely moving rats. One day before the arterial pressure was recorded, the rats were anesthetized with chloral hydrate (450 mg/kg), and a Tygon catheter was inserted into the iliac artery via the femoral artery. The catheter was tunneled subcutaneously, exteriorized at the back of the neck, and connected to a pressure transducer (Narco Bio-System). The mean arterial pressure was recorded over a 30-minute period with a chart recorder (Narco Bio-System).

**Vascular Reactivity in the Perfused Arteriolar Bed**

The perfused mesenteric arteriolar bed was prepared as previously described. Concentration-effect curves (CECs) to norepinephrine (NE, 0.1 to 30 μmol/L), acetylcholine (ACh, 1 nmol/L to 30 μmol/L), and sodium nitroprusside (0.01 nmol/L to 1 nmol/L) were obtained. All curves were performed in the presence of desipramine (inhibitor of NE uptake) (10 nmol/L). The vascular responses were evaluated as changes in the perfusion pressure measured with a pressure transducer (RP-1500B) and recorded on a chart recorder (Narco Bio-System). The vasodilator responses to ACh and sodium nitroprusside were calculated as percentages of the contractions induced by NE (5 μmol/L) to determine the influence of vasoconstrictor prostanoids on the vascular reactivity of SHR. CECs were obtained in the presence and absence of preparations treated with indomethacin (10 μmol/L) or sodium diclofenac (10 μmol/L) (cyclooxygenase inhibitors), ridogrel (a thromboxane [TX] A2/prostaglandin [PG] H2 receptor antagonist, 50 μmol/L), or dazoxiben (a TXA2 synthetase inhibitor, 10 μmol/L). To evaluate the influence of superoxide anion (O2-•) on the vascular reactivity of SHR, the preparations were treated with SOD (100 U/mL). Each drug was added separately to the perfusing Krebs-Henseleit solution 30 minutes before the CEC was obtained and was maintained throughout the experiment. Another series of experiments evaluated the generation of O2-• after the addition of arachidonic acid. The response to arachidonic acid (0.01 to 500 μmol/L) was examined in OE-SHR and OVX-SHR after preconstriction with NE (5 μmol/L) in the presence or absence of SOD (100 U/mL).

**Measurement of Prostanoids**

The ability of isolated perfused mesenteric vascular beds from OE-, OVX-, and hormone-treated OVX-SHR to release PGF2α, TXA2, and PGI2 (measured as TXB2 and 6-keto-PGF1α) was assessed by quantifying the levels of these prostanoids in 1-mL samples of perfusate collected immediately before and after stimulation with ACh (0.001 μmol/L) or NE (30 μmol/L). These concentrations were chosen because of the hyposensitivity to ACh (EC50) and hyperreactivity to NE (maximal responses) in OVX-SHR compared with OE-SHR. The levels of PGF2α, TXB2, and 6-keto-PGF1α in perfusate from preparations with or without endothelium were determined with enzyme immunoassay kits (Cayman Chemical Co). The inactivation of the endothelium from mesenteric arteriolar bed was performed by superfusing the preparation with sodium deoxycholate 0.3% as described by Cusma-Pelogia et al.

**Drugs**

The following drugs were used: norepinephrine bitartrate, acetylcholine chloride, desipramine, sodium nitroprusside, arachidonic acid, indomethacin, sodium diclofenac, sodium deoxycholate, and 17β-estradiol bitartrate from Sigma Chemical Co. Janssen, Cilag (Brazil) and Pfizer Co (Brazil) kindly supplied ridogrel and dazoxiben, respectively. Twenty-one-day release pellets containing 17β-estradiol or 17β-estradiol+progesterone were purchased from Innovative Research of America. All drugs used in the CECs were diluted in Krebs-Henseleit solution.

**Statistical Analysis**

The results are shown as mean±SEM for maximal responses or mean and 95% confidence intervals (95% CI) for EC50. Statistical analysis was performed with 1-way ANOVA followed by the Tukey test for multiple comparisons. Values were considered statistically significant when P<0.05.

**Results**

The mean arterial pressure of freely moving rats was higher in OVX-SHR than in OE-SHR. Acute and chronic treatments with estradiol reduced the elevated blood pressure in OVX-SHR to levels similar to those observed in OE-SHR. The association of estradiol+progesterone did not change the responses observed with estradiol (Table). The Table also shows the changes in uterine weight relative to changes in estrogen/progesterone concentrations. The decrease in estrogen and progesterone levels after ovariectomy increased levels of LH but not FSH and decreased uterus weight. Acute treatment of OVX-SHR with estradiol increased estrogen levels and uterus weight. Chronic treatment with estradiol increased the concentration of serum estradiol and uterus weight to levels similar to those observed in OE-SHR. Estradiol+progesterone treatment increased the serum concentrations of estrogen and progesterone and enhanced uterus weight in OVX-SHR. The elevated LH levels in OVX-SHR decreased after hormonal treatments. These data demonstrate the effectiveness of the hormone doses used in OVX-SHR.

**Vascular Reactivity**

In all experiments using a constant flow rate on a perfused mesenteric arteriolar bed, we did not observe a change in basal perfusion pressure (mm Hg) among the groups (data not shown). Compared with microvessels from OE-SHR, the
Effect of Hormonal Treatments on Blood Pressure, Serum Estradiol, Progesterone, LH and FSH Levels, Uterus Weight, and Body Weight in Ovariectomized Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OE</th>
<th>O VX</th>
<th>O VX + E (24h)</th>
<th>O VX + E (15d)</th>
<th>O VX + E + P (15d)</th>
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<tbody>
<tr>
<td>Blood pressure, mm Hg</td>
<td>157.9±1.9 (10)</td>
<td>174.9±4.6 (10)*</td>
<td>154.0±4.3 (8)§</td>
<td>148.9±3.2 (8)§</td>
<td>146.1±5.8 (8)§</td>
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<tr>
<td>Body weight, g</td>
<td>195.4±4.2 (30)</td>
<td>202.9±1.9 (30)</td>
<td>200.5±2.7 (24)</td>
<td>203.2±1.5 (24)</td>
<td>201.2±1.6 (24)</td>
</tr>
<tr>
<td>Uterus weight, mg/100 g body wt</td>
<td>45.4±5.1 (30)</td>
<td>19.4±1.2 (30)†</td>
<td>68.7±6.7 (24)*§</td>
<td>59.9±1.8 (24)*§</td>
<td>54.3±4.4 (24)*§</td>
</tr>
<tr>
<td>Serum estradiol, pg/mL</td>
<td>203.2±13.1 (10)</td>
<td>67.3±11.5 (10)†</td>
<td>384.9±16.1 (8)§</td>
<td>184.5±10.8 (8)§</td>
<td>190.4±17.3 (10)§</td>
</tr>
<tr>
<td>Serum progesterone, pg/mL</td>
<td>901.3±5.0 (10)</td>
<td>736.6±9.9 (10)†</td>
<td>786.0±2.8 (8)†∥</td>
<td>779.5±5.8 (8)∥</td>
<td>914.8±1.7 (8)∥</td>
</tr>
<tr>
<td>Serum LH, pg/mL</td>
<td>0.29±0.02 (10)</td>
<td>1.11±0.15 (10)†</td>
<td>0.41±0.05 (8)§</td>
<td>0.48±0.05 (8)§</td>
<td>0.48±0.12 (8)§</td>
</tr>
<tr>
<td>Serum FSH, pg/mL</td>
<td>2.60±0.17 (10)</td>
<td>3.56±0.03 (10)*</td>
<td>3.21±0.10 (8)</td>
<td>2.79±0.22 (8)</td>
<td>2.93±0.42 (8)</td>
</tr>
</tbody>
</table>

OE indicates physiological estrus; O VX, ovariectomized; O VX + E (24h), ovariectomized treated acutely (24 hours) with estradiol; O VX + E (15d), ovariectomized treated chronically (15 days) with estradiol; O VX + E + P (15 d), ovariectomized treated chronically (15 days) with estradiol + progesterone. Values are expressed as the mean±SEM of the number of animals indicated in parentheses.

*P<0.05 vs OE; †P<0.05 vs O VX; ‡P<0.05 vs OVX.

Preparations from O VX-SHR were more responsive to NE. This difference was abolished by treatment with hormones (Figure 1A). Diclofenac corrected the impaired response to NE in O VX-SHR but did not alter the corresponding responses in preparations from O E-SHR (Figure 1B). Indomethacin, another cyclooxygenase inhibitor, also corrected and even depressed the hyperreactivity of O VXR-SHR to NE compared with O E-SHR (Figure 1B). Ridogrel, but not dazoxiben, decreased the hyperreactivity to NE of vessels from O VX-SHR (Figure 1C). SOD treatment reduced the reactivity in microvessels from O VX-SHR to levels similar to those observed in O E-SHR (Figure 1D). Ovariectomy also impaired ACh-induced, endothelium-mediated relaxation. The sensitivity, but not the maximum relaxation, to ACh was impaired ACh-induced, endothelium-mediated relaxation. Those observed in O E-SHR (Figure 1D). Ovariectomy also increased the hyperreactivity to NE of vessels from O VX-SHR (Figure 1C). SOD treatment reduced the maximal responses to NE in O VX-SHR but did not alter the corresponding responses in preparations from O E-SHR. Dazoxiben (Figure 1C) had no effect on the sensitivity to ACh. SOD (Figure 1D) was also effective in restoring the endothelium-dependent relaxation in O VX-SHR. There were no differences in the endothelium-independent relaxations induced by sodium nitroprusside in preparations from O E (EC50, 0.12 μmol/L; 95% CI, 0.04 to 0.44) and O VX-SHR (EC50, 0.10 μmol/L; 95% CI, 0.04 to 0.31). Treatment with female sex hormones or indomethacin did not affect the sensitivity to sodium nitroprusside (data not shown).

Microvessels from O VX-SHR rats exhibited vasoconstriction in response to exogenous arachidonic acid, whereas microvessels isolated from O E-SHR exhibited vasodilation (Figure 3). Pretreatment with SOD (100 U/mL) decreased the vasoconstriction in O VX-SHR microvessels but did not change the relaxation in O VX-SHR vessels (Figure 3).

**Figure 1.** Maximal responses to NE in mesenteric arteriolar beds isolated from female O E-SHR, O VX-SHR, O VX-SHR treated for 24 hours with estradiol (140 μg/kg SQ) [O VX + E (24h)], O VX-SHR treated for 15 days with estradiol (0.05 mg/pellet) [O VX + E (15d)], and O VX-SHR treated for 15 days with estradiol (0.05 mg/pellet) + progesterone (50 mg/pellet) [O VX + E + P (15d)] (A). The reactivity to NE in O E-SHR and O VX-SHR was evaluated in the presence and absence of indomethacin (INDO, 10 μmol/L) and sodium diclofenac (DIC, 10 μmol/L) (B), ridogrel (RID, 50 μmol/L) or dazoxiben (DAZ, 10 μmol/L) (C), and SOD (100 U/mL) (D). Data represent the mean±SEM. *P<0.05 vs OE; †P<0.05, ††P<0.001 vs O VX.
with or without endothelium, the release of TXA₂ and PGI₂ was not affected by ovariectomy or exogenously administered hormones. However, NE, but not ACh, markedly enhanced the release of PGF₂α by mesenteric preparations with endothelium from OVX rats compared with OE rats. The increased release of PGF₂α observed in preparations from OVX rats was corrected by hormonal treatments.

Discussion

The present study demonstrates that the long-term depletion of ovarian hormones increases the mean arterial pressure in conscious OVX-SHR and aggravates the already existing hypertension. The treatment of OVX-SHR with estradiol (24 hours or 15 days) corrected the increase in blood pressure induced by ovariectomy. Concomitant treatment with progesterone did not modify the response to estrogen. These observations suggest that estrogen may be important in the cardiovascular regulation of certain physiopathological situations. In fact, a decrease in blood pressure of menopausal women and of gonadectomized animals treated with estrogen has been described.

The effects of estrogen are multiple, but the mechanism by which this hormone can interfere with the cardiovascular system in hypertension is still unclear. Although some studies have shown that estrogen may have a modulatory role on endothelial function in hypertensive animals and humans, a few reports have evaluated arterioles, the most important vascular territory that controls peripheral resistance. Earlier studies have suggested that the regulation of peripheral vascular resistance in females and males may not be the same and have proposed that female sex hormones may have an important role in the modulation of the peripheral resistance.

In this study, we examined whether ovarian hormones can regulate arteriolar tone by modulating endothelial function and thus contribute to the less pronounced hypertension observed in OE-SHR. Our results suggest that estrogen, but not progesterone, modulates the endothelial function of mesenteric arterioles isolated from female SHR. Conversely, these results may also be secondary to the differences in blood pressure. Similar findings in women have recently been reported. Postmenopausal women undergoing coronary angiography were found to have reversal of ACh-induced vasospasm when treated with infusions of estradiol.

Several studies have investigated the role of endothelium-derived NO in mediating the effects of estrogen on vasomotor tone. Estrogen stimulates the synthesis of NO in numerous tissues from normotensive animals and humans. Likewise, in hypertensive rats, estrogen affects the release and/or action of endothelium-derived NO. We have demonstrated recently that estrogen increases the activity of NO synthase in mesenteric microvessels from ovariectomized SHR, suggesting that this hormone modulates endothelial dysfunction in arterioles by preserving NO synthesis.

However, endothelium-dependent contractions caused by ACh are smaller in aortic rings from female SHR than male SHR. Because endothelium-dependent contractions to ACh can be explained by the increased production of EDCFs, the stimulatory role of female hormones on EDRF/NO production is not sufficient in itself to account for...
the modulation of endothelial function in hypertensive rats. This observation suggests that ovarian hormones can modulate endothelial function in SHR by a concomitant increase of EDRF/NO and a decrease in the generation of EDCFs, such as prostaglandins. Indeed, Kähönen et al.16 have demonstrated that the treatment of mesenteric arteries with diclofenac abolished the differences in the responses to ACh between female and male SHR previously described by Kauser and Rubanyi.11

Our study demonstrated an accentuated dose-dependent vasoconstriction to arachidonic acid in microvessels from OVX-SHR and a slight vasodilation in arterioles from OE-SHR. In addition, the results obtained after the treatment of mesenteric arterioles from OVX-SHR with cyclooxygenase inhibitors suggest that the removal of ovarian steroid hormones increases the generation of cyclooxygenase-derived vasoconstrictors. In agreement with our data, a recent study of mesenteric arteries from ovariectomized normotensive rats demonstrated that estrogen suppresses a cyclooxygenase-dependent vasoconstriction.20 Thus, the beneficial effect of estrogen in vascular function may be attributed, in part, to a direct action on cyclooxygenase-mediated responses. The decrease in the vasoconstrictor response to NE was more marked with indomethacin than with diclofenac. These results suggest that indomethacin may have activities other than cyclooxygenase inhibition. Indeed, it has been shown that indomethacin may inhibit calcium influx into stimulated smooth muscle cells.21

To identify the vasoconstrictor prostanoids involved in the altered reactivity in OVX-SHR, the possibility of TXA2 or PGH2 involvement was evaluated first. The effects of ridogrel on the vascular reactivity to NE and ACh were similar to those seen with cyclooxygenase inhibitors. Dazoxiben did not modify the vascular responses, suggesting that PGH2, but not TXA2, was the most likely EDCF involved in the altered reactivity after ovariectomy.

To confirm these results, the levels of various PGH2 metabolites (PGF2α, PGI2, and TXA2) were determined after stimulation with NE or ACh. In microvessels with intact endothelium from OVX-SHR, NE, but not ACh, increased the production of PGF2α compared with that observed in OE-SHR. In contrast, ovariectomy did not alter the release of PGI2 and TXA2 stimulated by NE or ACh. The increased release of PGF2α in microvessels from OVX-SHR was normalized by estradiol. Progesterone did not modify this effect of estrogen. Neither NE nor ACh increased the release of these prostanoids by microvessels without endothelium. Together, these results indicate that endothelium-derived PGH2 and/or PGF2α may be involved in the more pronounced endothelial dysfunction in SHR in the absence of estrogen. Compared with our data from OVX rats, some reports have proposed the involvement of endothelium-derived PGH2 in endothelial dysfunction.20 Conversely, whether and to what extent the increase of PGF2α generation would account for the enhanced endothelial dysfunction in OVX-SHR remains an open question. Although very large, nonphysiological concentrations of PGF2α (>10−7 mol/L) are necessary to cause constriction of microvessels,22 some studies have shown that physiological amounts of PGF2α, associated with low-estrogen conditions, cause an intense endometrial vasoconstriction leading to the menstrual discharge.23

Therefore, these EDCFs do not necessarily have to be prostanoids, because O2− can also be classified as a cyclooxygenase-derived EDCF.24 Cyclooxygenase-derived EDCFs at least partially impair endothelium-dependent vasodilation by inactivating NO2, indicating that these factors may include oxygen free radicals, such as superoxide (O2−).25 It has been proposed that PGH2 may modulate the generation of O2− in the endothelium. In addition, oxygen free radicals produce contractions of the rat aorta that are augmented in SHR and are reduced in the presence of a cyclooxygenase inhibitor.27

Because the inactivation of endothelium-derived NO by O2− participates in endothelial dysfunction in hypertension,10 we also examined the influence of female sex hormones on cyclooxygenase-derived O2−. Many reports have related the protective effect of estrogen on endothelial function to its
antioxidant property. The antioxidant effect of estrogen may be attributed to its phenolic structure, which scavenges oxygen free radicals. Estrogen may also exert its antioxidant action by regulating the action of antioxidant enzymes, such as SOD. Our data from the OVX-SHR in the presence of SOD suggest a role for O2 in the impaired endothelial function after ovariectomy. In addition, SOD decreased the vasoconstrictor response to exogenous arachidonic acid in OVX-SHR. Thus, the less pronounced endothelial dysfunction observed in estrous female SHR may reflect a decreased generation of cyclooxygenase-derived vasoconstrictor prostaglandins and O2-. Although we are tempted to associate O2- generation with the formation of endothelium-derived cyclooxygenase products in microvessels of OVX-SHR, we cannot discard the influence of estrogen on other sources of O2-, such as NADH/NADPH oxidases and xanthine oxidases in endothelial and smooth muscle cells. Further studies are necessary to elucidate the precise relationship between estrogen and O2- generation.

In conclusion, our results suggest that estrogen may exert a beneficial effect on the generation of EDCFs, such as PGH2, PGF2α, and/or O2-, in microvessels of female SHR. Because O2- has been proposed to directly inactivate NO, the decreased release of cyclooxygenase-derived vasoconstrictor products by microvessels from OE-SHR may favor the diminished endothelial dysfunction not only by decreasing vasoconstriction but also by preserving the beneficial effects of endothelium-derived NO. Because endothelial dysfunction plays an important role in cardiovascular diseases, it is possible that these effects could contribute to the lower incidence and slower progression of hypertension in women.

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