Hormonal Influences on Cardiovascular Norepinephrine Transporter Responses in Healthy Women

Iryna Moldovanova, Christoph Schroeder, Giris Jacob, Christoph Hiemke, Andre Diedrich, Friedrich C. Luft, Jens Jordan

Abstract—Gender differences in human cardiovascular norepinephrine transporter function may be mediated through female sex hormones. We studied 16 healthy eumenorrheic women (25±1 years) during the early follicular phase (day 5±0) and midluteal phase (day 22±0) of the menstrual cycle. In a randomized, crossover, double-blind fashion, subjects ingested 8 mg of the selective norepinephrine transporter inhibitor reboxetine or placebo. We monitored heart rate, blood pressure, and thoracic bioimpedance at rest and during standard autonomic function tests, including head-up tilt. Venous estradiol and progesterone concentrations were higher in the luteal than in the follicular phase but did not differ between placebo and norepinephrine transporter inhibition testing days. On placebo, hemodynamics at rest and in response to different stressors were mostly identical between cycle phases. In the supine position, norepinephrine transporter inhibition increased blood pressure and stroke volume to a greater extent during the follicular than during the luteal phase. Conversely, the increase in heart rate and cardiac output with norepinephrine transporter inhibition was augmented in the luteal compared with the follicular phase. During head-up tilt with norepinephrine transporter inhibition, blood pressure and stroke volume decreased to a greater extent in the follicular than in the luteal phase. The tachycardic response to head-up tilt with norepinephrine transporter inhibition was augmented in the follicular phase. Our study suggests that sex hormones alter the hemodynamic response to norepinephrine transporter inhibition in women. The phenomenon may be explained by an effect of female sex hormones on norepinephrine transporter function, on compensatory cardiovascular responses, or both. (Hypertension. 2008;51:1203-1209.)

Key Words: menstrual cycle ■ female sex hormones ■ norepinephrine transporter ■ cardiovascular regulation ■ human

The neuronal norepinephrine transporter (NET) takes up synaptic norepinephrine in the brain and in peripheral tissues.1 Changes in NET function elicit profound cardiovascular and metabolic responses.2–4 NET inhibition in the brain reduces central sympathetic outflow through a “clonidine-like” activation of central α-2 adrenoreceptors. In contrast, peripheral NET inhibition increases norepinephrine availability.5,6 Genetic variability affects NET function.7 Familial postural tachycardia syndrome can be caused by a rare functional mutation in the NET gene.8 Remarkably, orthostatic symptoms in the family were more prominent in affected women than in men. In sporadic postural tachycardia syndrome, biochemical data might be consistent with impaired neuronal norepinephrine uptake.9,10 Yet, nongenetic factors regulating NET function in human subjects are poorly understood. Sex hormones are prime suspects in this regard. In animals, NET expression and function in different brain areas are modulated by testosterone,11 estradiol, and progesterone.12 Furthermore, postural tachycardia syndrome primarily affects women in their reproductive years.13 Finally, we observed a gender difference in the cardiovascular response to NET inhibition, suggesting that cardiac NET function may be reduced in women.14 We, therefore, hypothesized that female sex hormones reduce NET function in women. To address the issue, we tested cardiovascular responses to selective NET inhibition or placebo during the early follicular phase, when estradiol and progesterone concentrations are low, and again during the midluteal phase, when both hormones are elevated.

Methods

Subjects
We studied 16 young healthy women (25±1 years of age, body mass index: 21.8±0.5 kg/m²) with regular menstrual cycles. Women were
on no oral contraceptives or any other medications. Written informed consent was obtained before inclusion. The institutional review board of the Medical University Charité approved all of the procedures. The study was performed in adherence with the Declaration of Helsinki and all national regulations.

Protocol
We submitted women to identical cardiovascular autonomic tests on 4 separate days during 2 consecutive menstrual cycles. Testing was conducted during the early follicular phase (days 3 to 6) and during the midluteal phase (days 21 to 23) of both menstrual cycles. During 1 menstrual cycle, we conducted cardiovascular testing after subjects had ingested 8 mg of the selective NET inhibitor reboxetine (Edronax, Pharmacia Upjohn) 1 hour before testing. During the other menstrual cycle, subjects had ingested matching placebo in a similar fashion. Testing was conducted in a double-blind, randomized, and crossover fashion. Volunteers abstained from any substances that interfere with endogenous catecholamine production for ≥48 hours and fasted overnight before testing.

We placed antecubital intravenous lines in both arms, 1 for blood sampling and 1 for phenylephrine injection. An ECG recorded the heart rate continuously (Virdia CMS, Hewlett Packard). Brachial blood pressure was measured at regular intervals with an automated oscillometric device (Dinamap, Critikon). Beat-to-beat blood pressure was continuously monitored by a finger sphygmosmanometer (2300 Finapres, Ohmeda) that was kept at heart level throughout the experiments. Impedance cardiography (Cardioscreen, Medis) was used to measure changes in cardiac stroke volume. Special attention was paid to assure identical electrode positions between testing days.

After 30 minutes of supine rest, we obtained venous blood samples for measurements of sex hormones, plasma catecholamines, and reboxetine plasma concentrations. Then, subjects underwent a battery of standard cardiovascular autonomic function tests. Briefly, subjects performed a Valsalva maneuver by forced expiration into a tube connected to a manometer (15 seconds; 40 mm Hg), an isometric hand grip test at 30% of maximal voluntary contraction over 3 minutes, and a cold pressor test by placing the right hand in ice water (4°C) for 2 minutes. Then, incremental intravenous phenylephrine bolus doses were given to attain an increase in systolic blood pressure of 25 mm Hg, as described earlier. A sufficient resting period was allowed for blood pressure and heart rate to return to baseline values before bolus doses. Finally, subjects underwent a graded head-up tilt on a motorized tilt table. The tilt angle was increased by 15° every 3 minutes until 75° was reached. After 3 minutes at 75° head-up tilt, a second blood sample was drawn for measurements of catecholamines.

Data Acquisition and Analysis
ECG, finger blood pressure, and thoracic impedance signals were analog to digital converted at 500 Hz using the Windaq pro+ software (Dataq Instruments, Inc). Relative risk intervals (time between subsequent R waves in the ECG), blood pressure, and respiration were defined off-line using a program written by A.D. (Vanderbilt University) based on PV-wave software (Visual Numerics, Inc). Cardiac stroke volume was calculated according to Sramek’s formula. Cardiac output was calculated as stroke volume × heart rate. Systemic vascular resistance was calculated as mean arterial pressure divided by cardiac output. We report relative changes in stroke volume, cardiac output, and systemic vascular resistance.

Heart rate variability and systolic blood pressure variability were determined using spectral analysis in the high (0.15 to 0.4 Hz) and low frequency (0.04 to 0.15 Hz) band. The spontaneous baroreflex slope was calculated as the slope of the linear regression lines between the systolic blood pressure (SBP) and the subsequent R-R intervals (within the same or the next heart beat) values using the sequence technique. Sequences with ≥3 intervals, 0.5-mm Hg blood pressure changes, and 5-ms R-R interval changes were analyzed only if the correlation coefficients were >0.85.

Analytical Methods
Estradiol-17β and progesterone were determined by ELISA. Reboxetine plasma concentrations were measured with high-performance liquid chromatography. Plasma concentrations of catecholamines and their metabolites were determined by a modified high-pressure liquid-chromatographic method.

Statistics
All of the data are expressed as means±SEMs. We compared variances between the groups by using the F test. Intraindividual and interindividual differences in parametric data were compared by paired t tests, respectively. Nonparametric data were analyzed by Wilcoxon matched-pairs test. ANOVA testing for repeated measures with Bonferroni posthoc test was used for multiple comparisons. Relationships between parameters were assessed by linear regression analysis. A value for P<0.05 was considered significant.

Results
During the early follicular phase women underwent testing on day 5.0±0.3 with placebo and day 5.0±0.3 with reboxetine. During the midluteal phase, testing was conducted during days 22.0±0.2 and 22.0±0.2 with placebo and with reboxetine, respectively. Progesterone and estradiol plasma concentrations were low during the follicular phase (progesterone: 2.1±0.2 nmol/L; estradiol: 147±10 pmol/L) and elevated in the luteal phase (progesterone: 35.5±2.9 nmol/L; estradiol: 453±33 pmol/L; P<0.001 for both). Sex hormone concentrations were identical on placebo and on NET inhibition, both during early follicular and midluteal phases. Equally, reboxetine plasma concentrations were 190±12 ng/mL in the follicular phase and 180±14 ng/mL in the midluteal phase (P=0.25).

With placebo, supine blood pressure, heart rate, stroke volume, cardiac output, and total peripheral resistance were similar during both phases of the menstrual cycle. Compared with placebo, NET inhibition increased blood pressure 14±1/10±0 mm Hg in the follicular and 11±1/7±0 mm Hg in the luteal phase (P<0.01 for the difference between phases; Figure 1, top). NET inhibition increased supine heart rate 2±1 bpm in the follicular phase and 9±1 bpm in the luteal phase (P<0.001 between phases). The pressor response to NET inhibition was mediated through an increase in cardiac output (Figure 1, bottom). During the luteal phase, a decrease in systemic vascular resistance attenuated the pressor response.

Responses to isometric handgrip and cold pressor testing and the Valsalva maneuver are given in Table 1. With placebo, the pressor response to handgrip testing was slightly augmented in the follicular phase compared with the luteal phase. During NET inhibition, handgrip and cold pressor responses were profoundly reduced and did not differ between menstrual cycle phases. NET inhibition augmented the depressor response during phase II of the Valsalva maneuver, although heart rate was increased further.

During head-up tilt with placebo, blood pressure was well maintained. Blood pressure, heart rate, cardiac output, and systemic vascular resistance responses were similar in both cycle phases. During NET inhibition, blood pressure decreased during head-up tilt testing and more so in the follicular than in the luteal phase (Figure 2). NET inhibition
With placebo, supine venous plasma catechol concentrations were similar during both phases of the menstrual cycle (Table 2). Dihydroxyphenylglycol (DHPG) concentrations in the upright position tended to be increased in the luteal phase, whereas the DHPG:norepinephrine ratio was identical in both cycle phases. NET inhibition decreased supine and upright DHPG concentration and the DHPG:norepinephrine ratio. However, upright norepinephrine was increased, and DHPG:norepinephrine ratio was reduced in the luteal phase compared with the follicular phase.

With placebo, menstrual cycle phase had no influence on heart rate variability, blood pressure variability, or baroreflex sensitivity (Table 3). NET inhibition decreased heart rate variability in the time and in the frequency domain and low frequency systolic blood pressure oscillations to a similar degree during both cycle phases. Baroreflex sensitivity did not change with NET inhibition.

**Discussion**

We used a combination of pharmacological and physiological techniques to gain insight in the regulation of NET function through female sex hormones. Similar to previous investigators, we did not apply exogenous hormones. Instead, we studied women at defined time points during the regular menstrual cycle, namely, the early follicular and the midluteal phase.

Previous data from a vast number of studies on the influence of female sex hormones on blood pressure regulation is conflicting. Although some studies observed higher resting blood pressure during the follicular phase than during the luteal phase, others did not. In our study, we did not observe major differences in blood pressure regulation between cycle phases under placebo conditions. Conflicting findings may be explained by small sample sizes and different testing days throughout the menstrual cycle in the respective studies. In our view, however, the lack of consistent results speaks against a major direct effect of female sex hormones on blood pressure regulation. It seems more likely that hemodynamic effects of sex hormones are mediated indirectly by interaction with other cardiovascular regulators. Interaction of sex hormones and NET is suggested by colocalization of NET and sex hormone receptors in animal

### Table 1. Autonomic Function Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameter</th>
<th>Placebo</th>
<th>NET Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Follicular Phase</td>
<td>Luteal Phase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follicular Phase</td>
<td>Luteal Phase</td>
</tr>
<tr>
<td>Isometric hand grip</td>
<td>∆SBP, mm Hg</td>
<td>29±3</td>
<td>0.04*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23±2</td>
<td>20±2</td>
</tr>
<tr>
<td>Cold pressor</td>
<td>∆SBP, mm Hg</td>
<td>15±3</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4±2</td>
<td>4±2</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td>∆SBP IIA, mm Hg</td>
<td>−9±5</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0±5</td>
<td>5±5</td>
</tr>
<tr>
<td></td>
<td>∆SBP IIB, mm Hg</td>
<td>19±3</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>∆SBP IV, mm Hg</td>
<td>2.1±0.1</td>
<td>2.1±0.1</td>
</tr>
</tbody>
</table>

Changes in SBP (∆SBP) and heart rate (∆HR) in response to 3-minute isometric hand grip test, 2-minutes cold pressor test, and the Valsalva maneuver.

*P<0.05; †P<0.01; ‡P<0.001 NET inhibition vs placebo.
brains.\textsuperscript{25,26} In humans, NET density is highest in the locus coeruleus,\textsuperscript{27} a major noradrenergic nucleus in the brain that is implied in cardiovascular control. NET inhibition reduces the firing rate of locus coeruleus neurons in animals.\textsuperscript{28} Noradrenergic neurons in the human locus coeruleus express estradiol receptor mRNA.\textsuperscript{29} Furthermore, estradiol and progesterone have been shown to modulate NET expression and function in different brain areas in animals.\textsuperscript{12}

We manipulated NET function acutely through selective pharmacological blockade with reboxetine. Reboxetine is a highly selective NET inhibitor and does not bind to muscarinic cholinergic receptors or adrenoreceptors.\textsuperscript{30} These features make reboxetine a useful pharmacological tool to study NET physiology. Reboxetine plasma concentrations were identical during the follicular and luteal phases. Furthermore, hormone concentrations were not altered with NET inhibition.

**Figure 2.** Changes in systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP), heart rate (ΔHR), stroke volume (ΔSV), cardiac output (ΔCO), and total peripheral resistance (ΔTPR) during graded head-up tilt testing with NET inhibition (black symbols, drawn lines) compared with placebo (open symbols, dotted lines) in the follicular phase (diamonds) and in the luteal phase (squares). *P < 0.05, **P < 0.01 (ANOVA).

**Table 2. Catecholamines**

<table>
<thead>
<tr>
<th>Position</th>
<th>Parameter</th>
<th>Placebo</th>
<th>P</th>
<th>Luteal Phase</th>
<th>NET Inhibition</th>
<th>P</th>
<th>Luteal Phase</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>Epinephrine, pmol/mL</td>
<td>0.09 ± 0.03</td>
<td>0.89</td>
<td>0.08 ± 0.02</td>
<td>0.08 ± 0.01</td>
<td>0.19</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine, pmol/mL</td>
<td>1.0 ± 0.1</td>
<td>0.22</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.75</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>DHPG, pmol/mL</td>
<td>5.2 ± 0.2</td>
<td>0.31</td>
<td>5.8 ± 0.5</td>
<td>3.8 ± 0.3</td>
<td>0.97</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>DHPG/NE</td>
<td>5.9 ± 0.5</td>
<td>0.62</td>
<td>5.7 ± 0.5</td>
<td>4.2 ± 0.3</td>
<td>0.52</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>DOPA, pmol/mL</td>
<td>8.8 ± 0.5</td>
<td>0.49</td>
<td>8.5 ± 0.4</td>
<td>8.5 ± 0.6</td>
<td>0.01</td>
<td>7.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Dopamine, pmol/mL</td>
<td>0.22 ± 0.16</td>
<td>1.00</td>
<td>0.08 ± 0.03</td>
<td>0.12 ± 0.03</td>
<td>0.08</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>DOPAC, pmol/mL</td>
<td>9.5 ± 1.3</td>
<td>0.58</td>
<td>8.8 ± 0.6</td>
<td>11.1 ± 1.5</td>
<td>0.03</td>
<td>8.2 ± 1.3</td>
</tr>
<tr>
<td>Head-up tilt</td>
<td>Epinephrine, pmol/mL</td>
<td>0.25 ± 0.04</td>
<td>0.37</td>
<td>0.30 ± 0.06</td>
<td>0.16 ± 0.03</td>
<td>0.03</td>
<td>0.23 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine, pmol/mL</td>
<td>1.8 ± 0.1</td>
<td>0.6</td>
<td>1.9 ± 0.1</td>
<td>1.9 ± 0.2</td>
<td>0.003</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>DHPG, pmol/mL</td>
<td>6.4 ± 0.4</td>
<td>0.07</td>
<td>6.9 ± 0.4</td>
<td>4.0 ± 0.2</td>
<td>0.94</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>DHPG/NE</td>
<td>3.9 ± 0.4</td>
<td>0.71</td>
<td>4.1 ± 0.5</td>
<td>2.3 ± 0.2</td>
<td>0.005</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>DOPA, pmol/mL</td>
<td>8.1 ± 0.5</td>
<td>0.03</td>
<td>7.4 ± 0.3</td>
<td>8.4 ± 0.5</td>
<td>0.01</td>
<td>7.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Dopamine, pmol/mL</td>
<td>0.09 ± 0.05</td>
<td>0.25</td>
<td>0.10 ± 0.04</td>
<td>0.12 ± 0.04</td>
<td>0.09</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>DOPAC, pmol/mL</td>
<td>8.7 ± 1.0</td>
<td>0.39</td>
<td>8.0 ± 0.6</td>
<td>9.8 ± 1.4</td>
<td>0.35</td>
<td>8.0 ± 1.6</td>
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</tbody>
</table>

Venous plasma concentrations of catecholamines and their degradation products in the supine position and during head-up tilt. DHPG indicates dihydroxyphenylglycol; NE, norepinephrine; DOPA, dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid.

*P < 0.05, †P < 0.01, ‡P < 0.001 NET inhibition vs placebo, respectively.

§P < 0.05, ||P < 0.01, ‖P < 0.001 supine vs head-up tilt, respectively.
The observation suggests that differences in the response to reboxetine between cycle phases cannot be explained by hormonal influences on drug levels or vice versa. Sufficient NET inhibition during both cycle phases is suggested by a pronounced reduction in the DHPG/norepinephrine ratio. In our previous study, men showed a greater pressor response to NET inhibition than women. The pressor response was mediated through increased cardiac output. We did not observe a major gender difference in the effect of NET inhibition on the regulation of systemic vascular resistance. If all of these gender differences were explained by female sex hormones, they should be recapitulated during the menstrual cycle. During the early follicular phase when female sex hormone levels are low, NET responsiveness should be attenuated. In contrast, the typical “female” response to NET inhibition should be augmented during the midluteal phase. Indeed, NET inhibition increased blood pressure to a greater extent during the follicular phase than during the luteal phase. Unexpectedly, the increase in cardiac output was augmented in the luteal phase, albeit a smaller increase in stroke volume. The finding was explained by the profound increase in heart rate with NET inhibition that was 4-fold higher during the luteal phase than during the follicular phase.

Female sex hormones could affect NET function in the brain, in peripheral tissues, or in both sites combined. The DHPG:norepinephrine ratio did not change during the menstrual cycle and decreased similarly with selective NET inhibition. This observation excludes a profound systemic change in NET function during the menstrual cycle. However, NET function could be altered in specific tissues. Compared with other peripheral tissues, the heart is particularly dependent on NET function for the removal of norepinephrine from the synaptic cleft. Therefore, we expected that hormonal influences on NET inhibition should be particularly evident with respect to cardiac autonomic regulation. Indeed, changes in heart rate with NET inhibition were different between cycle phases, both at rest and during head-up tilt. However, heart rate variability and cardiac output responses during head-up tilt did not differ between cycle phases with NET inhibition. Moreover, the reduced pressor response to NET inhibition during the luteal phase was partly explained by a compensatory reduction in vascular resistance rather than by a difference in the cardiac output response.

Perusal of the physiological data may give indirect insight in central nervous NET responses. Animal studies showed that NET inhibition in the brain elicits a potent sympatholytic response through α-2 adrenoreceptor activation. In human subjects, systemic NET inhibition is associated with reductions in muscle sympathetic nerve activity, in low-frequency systolic blood pressure oscillations, and a decreased blood pressure response to cold pressor and handgrip testing, findings consistent with a central sympatholitic effect. In our study, NET inhibition reduced handgrip and cold pressor responses similarly during both phases of the menstrual cycle. This observation speaks against a major change in central sympathetic regulation through NET during the menstrual cycle.

Differences in the response to NET inhibition between cycle phases may possibly be explained by altered counter-regulatory responses to NET inhibition rather than major NET activity changes. NET interferes with normal vascular baroreflex regulation. The reduction in baroreflex blood pressure buffering with NET inhibition contributes to phenylephrine hyperresponsiveness in the present and in previous studies.
studies.\(^2,3,5\) When NET was inhibited during the luteal phase, hemodynamic stressor led to greater counterregulatory responses. For example, with head-up tilt, epinephrine, norepinephrine, and systemic vascular resistance increased more in the luteal than in the follicular phase on NET inhibition. Furthermore, low-frequency systolic blood pressure oscillations were better maintained when NET was inhibited in the luteal phase. We speculate that female sex hormones may rescue vascular baroreflex control during NET inhibition through a so-far-unknown mechanism.

Taken together, our study suggests that female sex hormones alter the cardiovascular response to systemic NET inhibition. However, our study does not provide evidence that female sex hormones elicit a major change in NET function. Thus, the gender difference in the response to NET inhibition may not be entirely explained by female sex hormones. The main limitation of our study is that we relied on endogenous fluctuations in sex hormone levels. We cannot exclude that some of the changes were unrelated to estradiol or progesterone. Moreover, we cannot distinguish between estradiol and progesterone responses, because both hormones differed markedly between cycle phases. Given the recent concerns regarding adverse effects, administration of exogenous sex hormones is difficult to justify in this setting. For practical reasons, it was impossible to study women on >4 occasions. We propose to study the individual effect of each hormone in future studies. Furthermore, assessing catecholamine spill-over from different vascular regions may further elucidate our findings.

**Perspectives**

We suggest that our study gives relevant insight into the interaction of female sex hormones and NET regulation in human subjects. Given the importance of NET for norepinephrine homeostasis, the paucity of data on the regulation of NET in humans is surprising. We propose that the effect of sex hormones on human NET expression and function should be further characterized.

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**Disclosures**

None.

**References**


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