Selective Norepinephrine Reuptake Inhibition as a Human Model of Orthostatic Intolerance

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Background—Observations in patients with functional mutations of the norepinephrine transporter (NET) gene suggest that impaired norepinephrine uptake may contribute to idiopathic orthostatic intolerance.

Methods and Results—We studied the effect of the selective NET blocker reboxetine and placebo in a randomized, double-blind, crossover fashion on cardiovascular responses to cold pressor testing, handgrip testing, and a graded head-up tilt test (HUT) in 18 healthy subjects. In a subset, we determined isoproterenol and phenylephrine sensitivities. Subjects ingested 8 mg reboxetine or placebo 12 hours and 1 hour before testing. In the supine position, heart rate was 65 ±2 bpm with placebo and 71 ±3 bpm with reboxetine. At 75° HUT, heart rate was 84 ±3 and 119 ±4 bpm with placebo and with reboxetine (P <0.0001). Mean arterial pressure was 85 ±2 with placebo and 91 ±2 mm Hg with reboxetine while supine (P <0.01) and 88 ±2 mm Hg and 90 ±3 mm Hg at 75° HUT. Blood pressure responses to cold pressor and handgrip testing were attenuated with reboxetine. Reboxetine increased the sensitivity to the chronotropic effect of isoproterenol and the pressor effect of phenylephrine. Vasovagal reactions occurred in 9 subjects on placebo and in 1 subject on reboxetine.

Conclusions—Selective NET blockade creates a phenotype that resembles idiopathic orthostatic intolerance. This observation supports the hypothesis that disordered norepinephrine uptake mechanisms can contribute to human cardiovascular disease. Our study also suggests that NET inhibition might be useful in preventing vasovagal reactions.

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Key Words: autonomic □ baroreflex □ adrenoreceptors □ catecholamines □ syncope

idiopathic orthostatic intolerance, which is also referred to as postural orthostatic tachycardia syndrome, has been estimated to affect 500 000 Americans. The syndrome is characterized by orthostatic adrenergic symptoms in the absence of orthostatic hypotension but accompanied by at least a 30-bpm orthostatic increase in heart rate. Increased muscle sympathetic nerve activity while supine and elevated plasma norepinephrine concentrations in the supine position and with standing might suggest that idiopathic orthostatic intolerance results from excessive sympathetic nerve traffic and norepinephrine release. However, at least in a subgroup of patients, the increase in plasma norepinephrine concentration can be explained by decreased norepinephrine clearance rather than increased norepinephrine spillover. Thus, released norepinephrine could have an augmented and prolonged effect. Observations in a family with a genetic form of orthostatic intolerance suggest that the impairment in norepinephrine transporter dysfunction. In this family, raised orthostatic heart rate and increased plasma norepinephrine concentrations segregated with a functional mutation of the norepinephrine transporter (NET) gene. NET dysfunction may be a common feature in a larger number of patients with idiopathic orthostatic intolerance. This hypothesis is suggested by the hyposensitivity to the norepinephrine-releasing effect of tyramine observed in patients with idiopathic orthostatic intolerance. Whether or not NET is sufficient to cause the idiopathic orthostatic intolerance phenotype is unknown. To address this issue, we conducted extensive physiological and pharmacological studies in healthy subjects in the presence or absence of selective NET blockade.

Methods

Subjects

We studied 18 healthy control subjects (8 men, 10 women, aged 30.3±2 years, body-mass index (BMI) 22.5±0.6 kg/m²). Written informed consent was obtained before study entry. All studies were approved by the institutional review board.
Protocol
Forty-eight hours prior to study, volunteers received a diet free of substances that could interfere with catecholamine measurements. We conducted 2 separate studies. In the first study, we determined the effect of NET blockade on cardiovascular reflexes and the response to head-up tilt testing. In the second study, in 8 healthy subjects (4 men, 4 women, aged 30±2 years, BMI 22±1 kg/m²), we assessed the effect of systemic application of adrenoreceptor agonists in the presence or absence of NET blockade. In both studies, subjects ingested 8 mg reboxetine (Edronax, Pharmacia Upjohn) or matching placebo 12 hours and 1 hour before the study. Studies with placebo and with reboxetine were conducted on separate days in a double-blind crossover fashion after an overnight fast.

Instrumentation
Respiration, transthoracic bioimpedance, and ECG were measured continuously (Cardioscreen, Medis GmbH). Cardiac stroke volume was calculated according to Sramek’s formula.9 Beat-by-beat blood pressure (Finapres, Ohmeda) and brachial arterial blood pressure (Dinamap, Critikon) were determined. During tilt testing, the left middle cerebral artery (MCA) was insonated through the temporal window using a 2-MHz probe (Pioneer, EMD) that was at a constant position by a headset. Cerebrovascular resistance index was calculated as mean blood pressure divided by the corresponding mean flow velocity.10

Autonomic Reflexes and Head-Up Tilt Testing
The sinus arrhythmia ratio (SA ratio) was calculated as the ratio of the longest to the shortest RR interval during 90 seconds controlled breathing (5-second inhalation and 5-second exhalation). Patients performed a Valsalva maneuver (40 mm Hg pressure for 15 seconds). Responses to isometric handgrip (30% maximum contraction for 3 minutes) and cold pressor testing were determined. Then, the subjects were gradually tilted upright by 15° every 3 minutes until 75° head-up tilt (HUT) was reached. The subjects remained at 75° HUT for additional 30 minutes or until presyncopal symptoms occurred.

Responsiveness to Systemic Adrenoreceptor Agonism
Responses to incremental intravenous bolus doses of phenylephrine were evaluated as described previously.11 In a subgroup, we determined the effect of incremental bolus doses of nitropropressin. Thereafter, we infused incremental doses of the nonselective β-adrenoreceptor agonist isoproterenol. The infusion was started at a rate of 0.25 μg/min and increased in 5-minute intervals until a heart rate increase of at least 25 bpm was reached. The doses of each drug that would change blood pressure by 12.5 mm Hg or heart rate by 25 bpm were determined. Moreover, we calculated the cumulative increase in systolic blood pressure in the 120-second interval after onset of the phenylephrine effect (systolic blood pressure change · 120 seconds). We determined the dose that would lead to a cumulative increase in systolic blood pressure of 500 mm Hg · second by extrapolation from individual dose-response curves.

Spectral Analysis and Baroreflex Sensitivity
The spontaneous baroreflex sensitivity was assessed using the sequence technique.12 Heart rate and blood pressure variability were determined as described elsewhere.13,14

Statistics
All data are expressed as mean±SEM. Intraindividual differences were compared by the paired t test or the Wilcoxon test. ANOVA testing for repeated measures was used for multiple comparisons. If necessary, data were log transformed before analysis. Relationship between parameters was assessed by linear regression analysis. A value of P<0.05 was considered significant.

Results
Clinical Characteristics
Most subjects experienced side effects after NET blockade with reboxetine. Nine subjects complained about sleeplessness. Six subjects noticed increased sweating, shivering, and piloerection. Palpitations were noticed by 4 and fatigue, vertigo, and limb weakness by 2 subjects. One subject each complained about dryness of the mouth, headache, urinary urgency, restlessness, visual changes, or nausea. On placebo, 2 subjects noticed sleeplessness. One subject each experienced fatigue, vertigo, or nonspecific symptoms.

Head-Up Tilt Testing
Supine heart rate was 65±2 bpm with placebo and 71±3 bpm with reboxetine (P=0.01, Figure 1 top). After 3 minutes of 75° head-up tilt, the heart rate was 84±3 bpm with placebo and 119±4 bpm with reboxetine (P<0.0001, Figure 1 top). Supine brachial blood pressure was 117±2/70±2 and
125±3/74±2 mm Hg with placebo and with reboxetine, respectively (P<0.01 for systolic and diastolic blood pressure, Figure 1 middle and bottom). After 3 minutes of 75° head-up tilt, blood pressure was 112±3/73±2 mm Hg with placebo and 119±3/77±3 with reboxetine (NS). The increase in thoracic impedance with head-up tilt was similar with placebo and with reboxetine (Figure 2). Immediately prior to tilting down, heart rate was 80±3 bpm with placebo and 124±3 bpm with reboxetine (P<0.0001, Figure 3 top). On placebo, typical vasovagal reactions with a drop in heart rate and blood pressure occurred in 9 cases. With reboxetine, only 1 vasovagal reaction occurred (P<0.01, Figure 3 bottom).

With head-up tilt, the decrease in stroke volume was more pronounced with reboxetine (Figure 4 top). Cardiac output was higher with reboxetine, particularly in the upright position (Figure 4 middle). In the supine position, total peripheral resistance was similar with placebo and with reboxetine. The increase in peripheral resistance during head-up tilt was blunted with reboxetine (Figure 4 bottom).

In the supine position with placebo, peak and mean MCA velocities were 89±4 cm/s and 63±3 cm/s, respectively. With reboxetine, peak MCA velocity was 85±4 cm/s, mean MCA velocity was 61±3 cm/s, and regional cerebrovascular resistance was 1.6±0.1 while supine. The decrease in peak and mean MCA velocity with head-up tilt was more pronounced with reboxetine (Figure 5). Reboxetine treatment was associated with an increase in regional cerebrovascular resistance (Figure 5).

**Autonomic Reflex Testing**

The respiratory sinus arrhythmia tended to be slightly decreased with reboxetine (Table 1). Reboxetine treatment led to a more pronounced depressor response during phase II of the Valsalva maneuver. The blood pressure overshoot in phase IV was similar with placebo and with reboxetine. The Valsalva ratio was increased with reboxetine mainly due to an augmented heart rate response during phase II. Reboxetine attenuated the pressor response to handgrip testing. With placebo, cold pressor testing increased blood pressure 27±2/20±1 mm Hg. Reboxetine blunted the cold pressor response in every subject (6±2/7±1 mm Hg, P<0.0001 compared with placebo) (Figure 6).
Heart Rate and Blood Pressure Variability and Baroreflex Sensitivity

In the supine position heart rate variability tended to be lower with reboxetine than with placebo (Table 2). With head-up tilt, heart rate variability was suppressed with reboxetine, mainly due to a decrease in the high frequency component of the RR interval. In the supine position, the low-frequency component of systolic blood pressure was lower with reboxetine (Figure 7). With head-up tilt, the blood pressure variability became more pronounced, but there was no difference between placebo and reboxetine. Supine spontaneous baroreflex variability was similar with placebo and with reboxetine. With head-up tilt, reboxetine suppressed baroreflex sensitivity more than placebo.

Pharmacological Testing

The phenylephrine dose that increased systolic blood pressure 12.5 mm Hg was 58±2 (range 14 to 207) μg with placebo and 20±4 (range 4 to 35) μg with reboxetine (P<0.05). Reboxetine increased the cumulative effect of phenylephrine on systolic blood pressure in all subjects. The phenylephrine dose that elicited a cumulative pressor effect of 500 mm Hg · second was 36±6 (range 16 to 68) μg with placebo and 6±2 (range 3 to 16) μg with reboxetine (P<0.01). Phenylephrine 25 μg decreased heart rate 10±1 bpm with placebo and 11±2 bpm with reboxetine. Nitroprusside sensitivity increased in all 4 subjects tested. The dose that decreased systolic blood pressure 12.5 mm Hg was 0.5±0.1 (range 0.2 to 0.7) μg/kg with placebo and 0.2±0.1 (range 0.2 to 0.4) μg/kg with reboxetine (P<0.05). Nitroprusside 0.4 μg/min increased heart rate 8±2 bpm with placebo and 21±2 bpm with reboxetine (P<0.05). The isoproterenol dose that increased heart rate 25 bpm was 1.2±0.2 (range 0.8 to 2.0) μg/min with placebo and 0.6±0.1 (range 0.4 to 1.2) μg/min with reboxetine (P<0.05). With placebo, incremental infusion of isoproterenol did not elicit a major change in blood pressure. In contrast, on reboxetine, isoproterenol elicited a dose-dependent depressor response. With the maximal dose of isoproterenol that was given during both interventions (0.9±0.1 μg/min), systolic blood pressure changed 1±3 (range −7 to +16) mm Hg during placebo and −16±3 mm Hg (range −4 to 28) during reboxetine (P<0.001).

Figure 6. Individual changes in systolic blood pressure after 1-minute cold pressor testing on placebo and on reboxetine. The closed circle indicates the mean value. Reboxetine blunted the cold pressor response (P<0.0001).

Table 1. Autonomic Reflex Testing

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Reboxetine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus arrhythmia ratio</td>
<td>1.5±0.1</td>
<td>1.4±0.1</td>
<td>0.05</td>
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<tr>
<td>Valsalva phase II</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ΔSBP, mm Hg</td>
<td>−8±2.9</td>
<td>−28±5.9</td>
<td>&lt;0.01</td>
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<tr>
<td>HR, bpm</td>
<td>92±3.2</td>
<td>103±3.7</td>
<td>&lt;0.01</td>
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<tr>
<td>Valsalva phase IV</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mm Hg</td>
<td>18±2.1</td>
<td>17±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>56±2.1</td>
<td>55±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.6±0.1</td>
<td>1.9±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Handgrip testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP, mm Hg</td>
<td>22±3.5</td>
<td>11±3.9</td>
<td>0.06</td>
</tr>
<tr>
<td>ΔDBP, mm Hg</td>
<td>16±2.0</td>
<td>6±1.4</td>
<td>&lt;0.01</td>
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<tr>
<td>Cold pressure testing</td>
<td></td>
<td></td>
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<tr>
<td>ΔSBP, mm Hg</td>
<td>27±1.8</td>
<td>6±2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔDBP, mm Hg</td>
<td>20±1.3</td>
<td>7±1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ΔSBP indicates change in systolic blood pressure; ΔDBP, change in diastolic blood pressure; and HR, heart rate.
TABLE 2. Heart Rate and Blood Pressure Variability and Baroreflex Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Supine Placebo</th>
<th>Reboxetine</th>
<th>P</th>
<th>Upright Placebo</th>
<th>Reboxetine</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>RMSSD, ms</td>
<td>80±13</td>
<td>57±9</td>
<td>0.08</td>
<td>30±3</td>
<td>8±1</td>
<td>&lt;0.0001</td>
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<tr>
<td>pnn50, %</td>
<td>25±5</td>
<td>18±5</td>
<td>0.11</td>
<td>5±2</td>
<td>0±0</td>
<td>&lt;0.05</td>
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<tr>
<td>HF_RRI, ms²</td>
<td>674±141</td>
<td>471±118</td>
<td>&lt;0.05</td>
<td>131±28</td>
<td>22±8</td>
<td>&lt;0.01</td>
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<tr>
<td>LF_RRI, ms²</td>
<td>1259±379</td>
<td>1302±350</td>
<td>0.91</td>
<td>822±230</td>
<td>208±128</td>
<td>0.07</td>
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<tr>
<td>LF/HF_RRI</td>
<td>2.4±0.5</td>
<td>3.0±0.4</td>
<td>0.38</td>
<td>7.5±1.2</td>
<td>12.3±4.1</td>
<td>0.28</td>
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<tr>
<td>HF_SBP, mm Hg²</td>
<td>2±0</td>
<td>3±1</td>
<td>0.54</td>
<td>6±1</td>
<td>8±2</td>
<td>0.83</td>
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<td>LF_SBP, mm Hg²</td>
<td>9±2</td>
<td>1±0</td>
<td>&lt;0.05</td>
<td>20±5</td>
<td>16±7</td>
<td>0.98</td>
</tr>
<tr>
<td>BRS+, ms/mm Hg</td>
<td>18±2</td>
<td>22±2</td>
<td>0.18</td>
<td>6±1</td>
<td>2±0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BRS−, ms/mm Hg</td>
<td>19±3</td>
<td>20±2</td>
<td>0.55</td>
<td>6±1</td>
<td>3±0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Upright indicates 75° head-up tilt; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; pnn50, proportion of successive normal-to-normal interval differences greater than 50 ms; HF_RRI, RR variability in the high-frequency range; LF_RRI, RR variability in the low-frequency range; LF/HF_RRI, ratio between RR variability in the low-frequency range and RR variability in the high-frequency range; LF_SBP, systolic blood pressure variability in the low-frequency range; BRS+, baroreflex slope (upsloping segments); and BRS−, baroreflex slope (downsloping segments).

Discussion

We tested the hypothesis that selective pharmacological blockade of the norepinephrine transporter leads to hemodynamic changes that resemble idiopathic orthostatic intolerance. Idiopathic orthostatic intolerance features orthostatic tachycardia of at least 30 bpm in heart rate with standing without significant orthostatic hypotension. In our subjects, the selective norepinephrine uptake blocker reboxetine caused a slight increase in supine heart rate and a dramatic increase in upright heart rate, whereas upright blood pressure was well maintained. A large number of subjects experienced hyperadrenergic symptoms on reboxetine. The effects resemble the syndrome produced by a genetic defect in the norepinephrine transporter.

Reboxetine is a highly selective norepinephrine uptake inhibitor and does not bind to muscarinic cholinergic receptors or adrenergic receptors. In previous studies, the tricyclic antidepressant desipramine was used to characterize the effect of NET blockade on catecholamine turnover. One disadvantage of using desipramine is that the drug does not selectively target the NET and also inhibits serotonin uptake. Furthermore, desipramine binds to numerous receptors that are involved in cardiovascular regulation, such as muscarinic cholinergic receptors and α-adrenergic receptors.

Selective NET blockade induced major changes in the regulation of vascular tone in our subjects. Throughout the experiment, blood pressure was slightly higher with reboxetine compared with placebo. Interestingly, in some studies patients with orthostatic intolerance exhibited greater supine blood pressure values than age- and sex-matched control subjects. The hemodynamic adjustment mechanisms to upright posture were markedly different with placebo and with NET blockade. With both interventions, central blood volume, as indicated by thoracic impedance, was similar in the supine position and decreased to a similar degree with head-up tilt. With placebo, the decrease in central blood volume was mainly compensated by a robust increase in systemic vascular resistance. With NET blockade, blood pressure was maintained mainly through an increase in heart rate. Furthermore, NET blockade strongly attenuated the response to cold pressor and handgrip testing. The depressor response during phase II of the Valsalva maneuver was profoundly increased.

The increase in basal blood pressure and the orthostatic tachycardia with NET blockade may be related in part to increased synaptic norepinephrine concentrations acting on postsynaptic adrenergic receptors. Earlier observations have shown that the heart is particularly dependent on NET function. This dependence may explain the disproportionate increase in heart rate with NET inhibition. Imbalance between sympathetic activation of the heart and the vasculature has also been described in patients with idiopathic orthostatic intolerance. Increased sensitivity to the chronotropic effect of β-adrenergoreceptor agonists is an alternative explanation for the orthostatic tachycardia that occurs in the idiopathic orthostatic intolerance syndrome. We observed an increase in the sensitivity to the chronotropic effect of isoproterenol infusion during NET blockade. The mechanism of isoproterenol-induced tachycardia is complex and may involve direct stimulation of cardiac β-1 adrenergoreceptors and β-2 adrenergic receptor-mediated norepinephrine release from postganglionic adrenergic neurons. The latter effect is likely to be enhanced during NET blockade. Moreover, a
significant part of isoproterenol-induced tachycardia is baroreflex-mediated as a consequence of β-2 adrenoceptor-mediated vasodilation.\textsuperscript{1,2,3,4,5}

The paradoxical changes in vascular regulation are consistent with an inhibitory effect of reboxetine on sympathetic nervous system responses. Our finding that sensitivities to the blood pressure changing effect of phenylephrine, nitroprusside, and isoproterenol were markedly increased support the notion that autonomic control of vascular tone is impaired. Acute nonselective NET inhibition decreases sympathetic nerve traffic and systemic norepinephrine spillover.\textsuperscript{6} In our study, selective NET blockade decreased the low-frequency component of blood pressure variability (Mayer-waves), which is related to sympathetic modulation of vascular tone.\textsuperscript{7,8} The decrease in sympathetic traffic and in sympathetic modulation of vascular tone may be a compensatory baroreflex-mediated response to the slight increase in basal blood pressure. An alternative explanation is that changes in central nervous norepinephrine turnover directly influence sympathetic outflow. Moreover, in the periphery, excessive synaptic norepinephrine may lead to feedback inhibition of norepinephrine release through activation of presynaptic α-adrenergic receptors.\textsuperscript{9} The fact that isoproterenol and phenylephrine effects were increased during reboxetine is evidence against a major decrease in end-organ responsiveness due to downregulation of postsynaptic α- and β-adrenoceptors. Thus, central and peripheral effects of NET inhibition induce a unique physiological state that is characterized by a rigid sympathetic regulation of vascular tone.

A subgroup of patients with orthostatic intolerance exhibits a paradoxical decrease in cerebral blood flow with standing, despite sustained systemic blood pressure.\textsuperscript{10,11,12,13,14} The decrease in cerebral blood flow is one possible explanation for orthostatic symptoms in the idiopathic orthostatic intolerance syndrome. In our study, cerebral blood flow velocity decreased moderately with upright posture. This effect was enhanced with NET blockade. Our findings suggest that NET dysfunction may contribute to cerebral vasocostriction with upright posture.

With placebo treatment, we observed a large number of typical vasovagal reactions with head-up tilt testing. NET blockade not only caused orthostatic tachycardia but also decreased the risk for vasovagal reactions. None of the subjects had a history of spontaneous vasovagal syncope. Nevertheless, our findings may have important implications as to the pathogenesis and treatment of vasovagal syncope. In our study, subjects underwent head-up tilt testing with reboxetine and placebo in a randomized crossover fashion. Therefore, tilt table training\textsuperscript{15} does not contribute to the effect of reboxetine on the occurrence of vasovagal reactions. Instead, NET inhibition seems to specifically interact with the physiological mechanisms involved in vasovagal reactions. We suggest that raising synaptic norepinephrine concentrations may prevent vasovagal reactions. This hypothesis is supported by elegant studies on the effect of sympathetic stimulation with yohimbine and sympathetic deactivation with clonidine in patients with recurrent vasovagal syncope.\textsuperscript{16} Yohimbine prevented vasovagal reactions. In contrast, clonidine worsened the propensity to vasovagal reactions. These findings and our observations challenge the concept that excessive sympathetic drive to the heart causes vasovagal reactions through activation of ventricular stretch-sensitive receptors (“ventricular hypothesis”).

We conclude that selective NET blockade creates a phenotype that resembles idiopathic orthostatic intolerance. NET blockade causes a slight increase in basal blood pressure; however, the blood pressure response to sympathetic stimuli is profoundly decreased. Thus, interindividual variability in NET function might have opposing effects on resting blood pressure and on blood pressure responses to sympathetic stimuli. Our observation supports the hypothesis that disordered norepinephrine uptake mechanisms may contribute to human cardiovascular disease. Moreover, our findings provide a rationale for studying the genetic and nongenetic influences on NET function. Finally, our study suggests that NET inhibition might be useful in preventing vasovagal reactions.

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References


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