Possible Genetic Influence on the Strength of Human Muscle Nerve Sympathetic Activity at Rest

B. Gunnar Wallin, M. Masanari Kunimoto, Johan Sellgren

Large reproducible interindividual differences in the strength of human muscle nerve sympathetic activity have been demonstrated previously without satisfactory explanation. We undertook the present study to investigate whether a genetic influence may be a factor of importance. Microneurographic recordings of sympathetic impulse traffic were made in the peroneal nerve in nine pairs of monozygotic male twins and eight pairs of age-matched male subjects without family relationship. The strength of the sympathetic activity was quantitated as number of sympathetic bursts per 100 heart beats and bursts per minute. Group mean values of muscle sympathetic activity, heart rate, and blood pressure were similar in the two groups. Intrapair differences (mean±SEM) of sympathetic activity were 5.4±1.7 bursts per 100 heart beats (1.7±0.5 bursts per minute) for the twins and 19.4±3.2 bursts per 100 heart beats (11.8±2.5 bursts per minute) for the control subjects (P<.01 for both). The degree of reproducibility between twins is similar to that reported previously between repeated recordings in the same subject. The finding may indicate that the strength of sympathetic outflow to muscle is controlled genetically. If so, we speculate that this may contribute to the heritability of blood pressure in both normotensive and hypertensive subjects.

(Hypertension. 1993;22:282-284.)

Key Words • genetics • twins • sympathetic nerve activity • microneurography • peroneal nerve

Human muscle sympathetic nerve activity (MSA) consists of bursts of vasoconstrictor impulses occurring in the cardiac rhythm. Subjects resting in the recumbent posture display large interindividual differences in the incidence of such bursts, and these differences are reproducible over many months. The reason for the interindividual differences is unclear. MSA increases with age and shows a weak, negative relation to resting heart rate; recently, a weak, positive relation to blood pressure was found. However, these factors explain only a small part of the variability, because at all ages, heart rates, and blood pressures, there are still large interindividual differences in MSA. Blood pressure is known to be influenced by genetic factors both in normotensive subjects and in patients with arterial hypertension. As illustrated by different animal models of hypertension, the inherited factors may vary. In spontaneously hypertensive rats, an increased sympathetic nervous activity may be a primary factor, whereas in the Dahl strain, renal handling of sodium is also important. In humans, evidence of genetic influence on components of the renin-angiotensin-aldosterone system and on plasma norepinephrine has been published. Because both renin and plasma norepinephrine may be influenced by sympathetic nerve activity, this may be the common denominator for the findings.

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found with an acceptable signal-to-noise ratio for sympathetic impulses. To reduce noise, we passed the original nerve signal through a bandpass filter (700 to 2000 Hz) and a discriminator and then monitored it continuously on an oscilloscope and loudspeaker. The original nerve signal was also rectified and fed through a resistance-capacitance circuit (time constant, 0.1 second) to obtain a mean voltage (integrated) display of the neurogram. Original and mean voltage neurograms were stored (together with electrocardiogram [ECG] and respiratory movements) on analog tape. Details of the technique and evidence for the sympathetic nature of the recorded signals have been given previously.3 For analysis, the mean voltage neurogram and ECG were displayed on a chart using an ink-jet recorder (Mingograph 600, Siemens Elema, Solna, Sweden) with a paper speed of 3 to 5 mm/s. Nerve activity was quantitated visually from the chart and expressed as number of nerve impulses. To reduce noise, we passed the original nerve signal through a bandpass filter (700 to 2000 Hz) and a discriminator and then monitored it continuously on an oscilloscope and loudspeaker.

**Table 1. Group Data of Muscle Sympathetic Nerve Activity, Heart Rate, Blood Pressure, and Respiratory Rate**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 16)</th>
<th>Twins (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>34.6 ± 1.4</td>
<td>35.7 ± 1.5</td>
</tr>
<tr>
<td>Bursts per 100 heart beats</td>
<td>43.6 ± 3.4</td>
<td>50.6 ± 3.3</td>
</tr>
<tr>
<td>Bursts per minute</td>
<td>26.9 ± 2.0</td>
<td>31.5 ± 2.2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>62.5 ± 1.5</td>
<td>63.2 ± 2.1</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>90.1 ± 2.2</td>
<td>90.3 ± 1.9</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>13.1 ± 0.7</td>
<td>14.1 ± 0.9</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

**Table 2. Differences Between Subjects in a Pair**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (eight pairs)</th>
<th>Twins (nine pairs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursts per 100 heart beats</td>
<td>19.4 ± 3.2</td>
<td>5.4 ± 1.7*</td>
</tr>
<tr>
<td>Bursts per minute</td>
<td>11.8 ± 2.5</td>
<td>1.7 ± 0.5*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>8.0 ± 2.0</td>
<td>6.1 ± 1.8</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>9.1 ± 1.9</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>2.6 ± 1.0</td>
<td>2.4 ± 0.3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *P < .01 vs control subjects.

mm Hg for control subjects (nonsignificant difference, P = .13), but for MSA the differences were much smaller among the twins than in the control group. When expressed as bursts per 100 heart beats, the intrapair MSA difference was 5.4 ± 1.7 for the twins and 19.4 ± 3.2 for the control subjects (P < .01). When expressed as bursts per minute, corresponding values were 1.7 ± 0.5 and 11.8 ± 2.5, respectively (P < .01). In the Figure, the difference between groups is illustrated by a plot of the ratio of the MSA values in each pair (all ratios < 1.0 because the biggest value in each pair was put in the denominator). When expressed as bursts per minute, the ratios were 0.94 ± 0.01 and 0.65 ± 0.07 for control subjects; when expressed as bursts per minute, corresponding values were 0.94 ± 0.01 and 0.66 ± 0.07, respectively (significant differences, P < .01 for both). In agreement with previous observations,6 MSA increased with age (r = .55 for bursts per 100 heart beats and r = .60 for bursts per minute, P < .01 for both), but the differences in MSA between the two subjects in a pair were not related to age.

**Discussion**

The present data show that monozygotic twins have very similar strength of MSA at rest. The mean intrapair differences, 5.4 bursts per 100 heart beats and 1.7 bursts per minute, are similar to the differences re-
ported previously from repeated recordings in the same subject. For example, when MSA was recorded two or three times in seven subjects (interval between recordings, 3 weeks to 21 months), the mean difference was 4.8 bursts per 100 heart beats, and in three recordings in nine subjects, the mean difference was 1 burst per minute between recording one and two (recording interval, 3 days) and 2 bursts per minute between recording two and three (recording interval, 3 to 5 months). This similarity, together with the facts that twins and control subjects were age matched and had similar group mean values of MSA, heart rate, and blood pressure, suggests that the strength of MSA is controlled genetically. However, a contributory influence from environmental factors cannot be excluded, because the twins had been brought up together, and this was not the case for the control subjects. This point may be resolved by studies of monzygotic twins brought up in different environments and/or unrelated subjects raised in the same family.

Because sympathetic outflow is differentiated, the finding cannot automatically be extended to other sympathetic nerves. It may, however, be valid also for cardiac sympathetic activity, because there is recent evidence that resting interindividual differences in MSA and cardiac norepinephrine spillover are proportional to each other. Arterial blood pressure is a product of total peripheral resistance and cardiac output. Because the vascular bed of skeletal muscle accounts for close to 20% of total peripheral vascular resistance, a genetic influence on MSA may provide part of the explanation of why there is a heritable influence on blood pressure in normotensive subjects. That our intrapair difference in blood pressure in the twins (5.0 mm Hg) was not significantly smaller than in the control subjects (P<.13) does not exclude this possibility; blood pressure is a variable influenced also by several nonneural factors, and in addition the number of subjects in our study was small compared with that of Feinleib et al and Rose et al. How a link between the genetic material and the strength of sympathetic nerve traffic is established is unclear. Several genes coding for proteins involved in blood pressure regulation, such as renin, atrial natriuretic factor, mineralocorticoids, and adrenergic receptors, have been identified, but whether these and/or other still unidentified genes are involved remains to be established.

In patients with essential hypertension, there is evidence of increased sympathetic activity to the heart and kidney; for MSA, an increase has been found in some studies. In view of this, we speculate that a genetic influence on sympathetic nerve traffic to muscle (and perhaps also to the heart, see above) may contribute to the heritability of essential hypertension.

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References

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