Sympathetic Nerve Activity in Monozygotic Twins
Identical at Rest but Not During Arousal

Linda C. Lundblad, John J. Eskelin, Tomas Karlsson, B. Gunnar Wallin, Mikael Elam

Abstract—Microneurographic recordings of human muscle sympathetic nerve activity responses to sudden sensory stimuli (ie, arousal) have revealed 2 intraindividually reproducible response profiles in healthy young males that predict different neural and blood pressure responses to more sustained stress. Approximately 50% of subjects inhibit muscle sympathetic nerve activity during arousal, whereas the remaining 50% do not, and the latter group displays a markedly greater blood pressure increase in response to arousal, as well as during and after 3 minutes of mental arithmetic. Studying a group of monozygotic twins (10 pairs, 2 excluded from analysis), the aim of the present study was to evaluate the degree of genetic determination of these sympathetic response profiles. Muscle sympathetic burst incidence at rest was similar in twins, with a within-pair burst incidence ratio of 0.87±0.02 (SEM) compared with 0.73±0.07 found in unrelated pairs (P=0.002), confirming a previous study from our laboratory. In contrast, the sympathetic responses to arousal showed large twin within-pair variance (arousal inhibition ratio 0.56±0.11), which did not significantly differ (P=0.939) from the variance in pairs of unrelated subjects (0.46±0.11). The finding that human muscle sympathetic nerve responses to arousal are less determined by genotype than the resting level of corresponding sympathetic nerve activity suggests that the arousal response pattern is more prone to be altered by environmental factors. This raises the possibility that these intraindividually reproducible sympathetic neural response profiles can be modified in a positive direction from a cardiovascular risk perspective. **(*Hypertension*. 2017;69:964-969. DOI: 10.1161/HYPERTENSIONAHA.117.09079.)**

Key Words: blood pressure ■ genetics ■ human ■ monozygotic twins ■ muscle sympathetic nerve activity

Hypertension constitutes a major risk factor for cardiovascular disease[1] and for the total disease burden in the world today.[2] Traditionally, focus has been on the resting blood pressure level,[3] but blood pressure variability has received increasing attention, and several studies have found that increased 24-hour blood pressure variability is associated with increased target-organ damage.[4–7] Although genetic factors are known to account for 50% of the variance of the resting blood pressure level in the population,[8,9] a recent, large twin study suggested that the corresponding figure for blood pressure variability is only 25%.[10] In other words, blood pressure variability seems to be less genetically controlled than blood pressure level.

Mental stress initiates a well-documented transitory fight-or-flight like neurocirculatory reaction entailing blood pressure increase, tachycardia, and vasoconstriction of splanchnic/renal and cutaneous, but not skeletal muscle, vascular beds,[11] leading to a redistribution of blood flow toward muscle. Direct recordings of sympathetic nerve traffic to human muscles (muscle sympathetic nerve activity, MSNA) have shown that the activity consists of irregularly occurring bursts of vasoconstrictor impulses under potent baroreflex control.[12] In healthy subjects at rest, MSNA burst incidence (BI) is remarkably stable over many years,[13,14] whereas the interindividual variability is large.[15] Monozygotic twins, however, display similar MSNA BIs,[16] indicating strong genetic or common environment influences on resting sympathetic activity.

In response to arousal, ≈50% of healthy subjects display a brief inhibition of MSNA (thus, favoring muscle vasodilation and limited blood pressure increase), whereas 50% show an unchanged or increased MSNA (favoring muscle vasoconstriction and more marked blood pressure increase).[17,18] Furthermore, in a recent study, an individual's MSNA response to arousal was found to predict how that individual's MSNA and blood pressure responded during more prolonged stress.[19]

Against this background, the aim of the present study was to test the hypothesis that genetic control of resting MSNA is stronger than that of MSNA responses evoked by arousal. To this end, we have compared both resting MSNA BIs and MSNA responses to arousal stimuli between the individuals in pairs of monozygotic twins. Our results reveal a striking difference between these 2 comparisons.

Method

Ten pairs of healthy male monozygotic twins, aged 29 to 45 (average 40) years were recruited via the Swedish Twin Registry (for zygocity determination and validity; cf Magnusson et al[20]). Recordings of MSNA were obtained from all subjects, but in 1 pair, both twins felt

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discomfort during the recording despite adjustments of the recording site, preventing the arousal protocol, and this pair was excluded from analysis. Another pair was also excluded because of 1 twin receiving carbamazepine 2×400 mg/d orally as antiepileptic medication. Each pair of the reported twins had grown up together in the same environment and did not differ significantly in body mass index (25±2.1 SD for the group; difference range within pairs 0.5–1.9 U). Supine resting arterial blood pressure level for the twin pairs was 115/70±7.0/6.8 SD. The reported 16 subjects received no regular medication. Tobacco, caffeine, alcohol, and physical exercise were not allowed for 12 hours before the examination.

All subjects gave written informed consent, and the study was approved by the Human Ethics Committee of Gothenburg University, Gothenburg, Sweden, in accordance with the Declaration of Helsinki.

The twins were also used as a control group. For this purpose, all twin pairs were split, and each individual twin was matched with an unrelated twin, as close as possible in age (mean age difference 2.6 years, range 1–6 years), to form a control pair.

Measurements

Subjects were resting in a semi-upright sitting position (upper body ≈125° and lower legs ≈30° from the horizontal plane). Multiunit MSNA was recorded with an insulated tungsten microelectrode (impedance 1 or 5 MΩ; FHC, Maine), with a tip diameter of a few micrometers, inserted into the common peroneal nerve at the left fibular head. A reference electrode was inserted subcutaneously a few centimeters away, and a surface Ag/AgCl electrode on the leg served as a ground electrode. The nerve signal was amplified (gain 40 000, filtered (band pass) 0.7–2 kHz) using a low noise, electrically isolated, amplifier (Neuro Amp EX front-end and head stage; ADInstruments, Australia). A muscle nerve fascicle was localized by electric stimuli delivered through the microelectrode, and small electrode adjustments were made until a site was found in which sympathetic impulses with good signal-to-noise ratio could be recorded. The filtered and integrated nerve signals were sampled (200 Hz) and stored together with other signals on a personal computer, using a DT9804 AD converter (Data Translation Inc, MA) with locally produced software.

ECG was monitored with Ag/AgCl electrodes on the chest and respiratory movements using a strain gauge belt, strapped around the lower part of the chest. Mean arterial blood pressure (MAP) was monitored continuously with a cuff around the middle phalanx of the third finger on the left hand using the volume clamp method (Finometer model 1, cuff size medium; Finapres Medical System, Arnhem, The Netherlands).

During microneurography, the subjects underwent a period of passive rest of 15 minutes followed by an arousal test lasting 60 minutes. The arousal test consisted of electric stimuli delivered in an irregular fashion. The electric stimulus was a constant voltage square wave pulse (0.2–0.8 ms duration, 40–150 V) triggered by the R-wave of the ECG with a 200 ms delay, delivered to the index finger of the left hand. The intervals between the electric stimuli varied between 30 and 180 s. The strength of the electric stimulus was individually set for each subject and adjusted to be as high as possible without causing any movement of the subject. The strength was set before the microneurography started and remained the same throughout the whole arousal test. Resting arterial blood pressure was measured after the termination of the experimental protocol. The subject was resting in a supine position, and 3 consecutive measurements were performed with an automatic sphygmomanometer (Omega 1400, cuff size Adult 11; Invivo Research Inc, FL) on the left upper arm, and a mean value of the 3 readings was calculated.

Data Analysis

At the end of a 15-minutes resting period, a 5-minutes interval free of artifacts was chosen as baseline period in which the number of MSNA bursts were manually identified, counted automatically by the software, and expressed as burst frequency (bursts per minute) and BI (bursts per 100 heart beats).

During the 60-minute arousal protocol, the electric stimulation periods (burst number −9 to 1; Figure 1) were visually checked and rejected if containing artifacts. The effects elicited by the remaining electric stimuli (30 stimuli given, on average 29 analyzed) were analyzed as follows:

The electric stimulus was delivered in a cardiac cycle, for example, between R waves 0 and 1 in Figure 1. During this cardiac cycle, a sympathetic burst can be generated in the nervous system, denoted as burst 1, and will arrive at the recording electrode after a delay corresponding to the baroreflex latency. In the quantitative analysis, to calculate the degree of MSNA inhibition, the amplitudes of prestimulus bursts −9 to −2 were averaged to generate a control amplitude, against which the lowest averaged burst amplitude of burst number 0 or 1 was used to calculate the degree of inhibition (Figure 1). Absent bursts were included and given the value of zero.[21]

To decide whether the stimulation caused a significant inhibition in a subject, we defined an inhibitory threshold in the following way: In 2 previous studies on healthy subjects in which the present stimulation protocol had been used, we quantified the effects of dummy stimuli (a dummy stimulus being a trigger pulse not followed by an electric stimulus, ie, the subject was unaware of a dummy stimulus). The result showed that in 95% of a group of 21 control subjects (independent subjects to this study), the amplitude reduction of bursts 0 or 1 was <30%, or expressed differently, the random variability of burst amplitude after a dummy stimulus was <30%. Hence, we define that a subject inhibits if the MSNA amplitude was reduced by ≥30% after an electric stimulus.

Statistics

Results are presented as mean±SEM. Difference in variability between the twins and the control group was tested with the 2-sample F test for equal variances. Differences within twin pairs and controls were tested with the paired *t* test. A value of $P<0.05$ was considered significant.

Results

Rest

Successful MSNA recordings of resting and arousal protocols were obtained from all 8 included twin pairs (16 subjects). When comparison for BI was made within pairs, the intrapair MSNA differences were 8.3±1.03 for twins and 19.7±5.8 for controls. Corresponding values for burst frequency for twins were 4.5±1.1 and 12.7±2.9 for controls. The MSNA differences were smaller among the twins than in the control group, with a significant difference for both BI ($P<0.001$) and burst frequency ($P=0.002$). The within-pair BI ratio at rest was 0.87±0.02 for twins compared with 0.73±0.07 found in unrelated pairs, with a significant difference of $P=0.002$, illustrated in Figure 2. MAP at rest monitored during nerve recording was 85±3.2 mm Hg, not significantly different from the resting blood pressure measured after termination of the experiment (systolic 115±1.8 mm Hg, mean 84±1.6 mm Hg, diastolic 69±1.8 mm Hg; $P=0.57$). Mean heart rate monitored during nerve recording was 55.7±1.3 bpm during rest before the arousal test and 55.9±1.2 bpm monitored with an automatic sphygmomanometer after completion of the test and did not differ significantly ($P=0.89$).

Arousal Test

Out of the 16 subjects, 12 showed varying degrees of MSNA inhibition after electric stimulation, whereas the remaining 4 showed no inhibition. Among the 8 twin pairs, an inhibition was found in both subjects of 4 pairs, whereas inhibition in 1 but not the other twin occurred in 4 pairs. No pair displayed a lack of inhibition in both subjects. Individual data for the

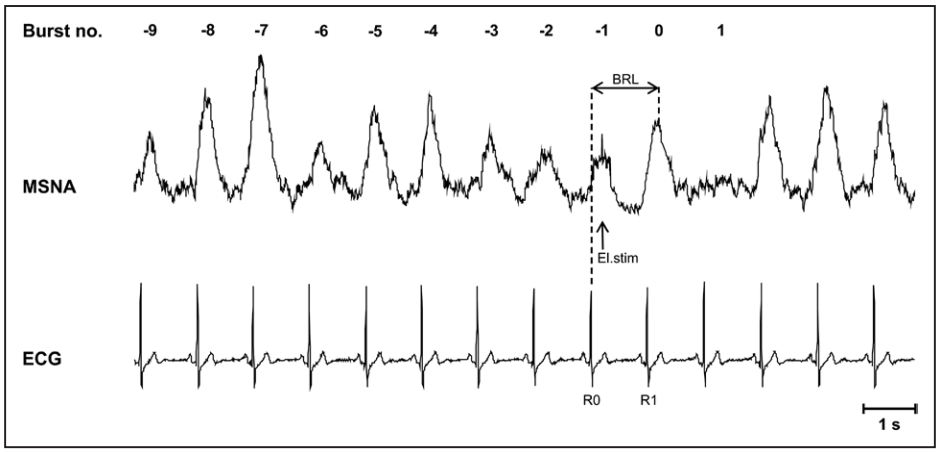

Figure 1. The timing of arousal stimuli in relation the ECG and the mean voltage neurogram. An electric stimulus was delivered with a 200 ms delay after R wave R0 (note stimulus artifact in neurogram). Baroreflex latency, indicated as BRL, is defined as time from R wave 0 of the ECG (R0) to the peak of burst 0 in the mean voltage neurogram (shown with the dotted lines). To calculate the degree of MSNA (muscle sympathetic nerve activity) inhibition, the amplitudes of bursts number −9 to −2 were averaged to generate a control amplitude, against which the lowest burst amplitude of bursts number 0 or 1 was compared with (ie, burst no 1 in this example). Note that for this schematic figure, a sequence with a burst in each cardiac cycle was deliberately chosen to illustrate which bursts were included in the analysis of arousal responses. Such sequences were rare in our subjects, with resting burst incidence ranging from 27% to 88%.

degree of the arousal-induced MSNA inhibition for all twin pairs are shown in Figure 3. The within-pair variance in MSNA response during arousal was 0.56±0.11 for twins compared with 0.46±0.11 in unrelated pairs, which showed no difference between monozygotic twins and unrelated controls (P=0.939), illustrated in the right panel of Figure 2. Examples of averaged responses in a twin pair with similar and a pair with discordant inhibition are shown in Figure 4. MAP was 86±3.3 mm Hg, and mean heart rate was 55.9±1.3 bpm monitored during arousal, none of them differing significantly from the values monitored during rest (P=0.18 for MAP, and P=0.71 for heart rate).

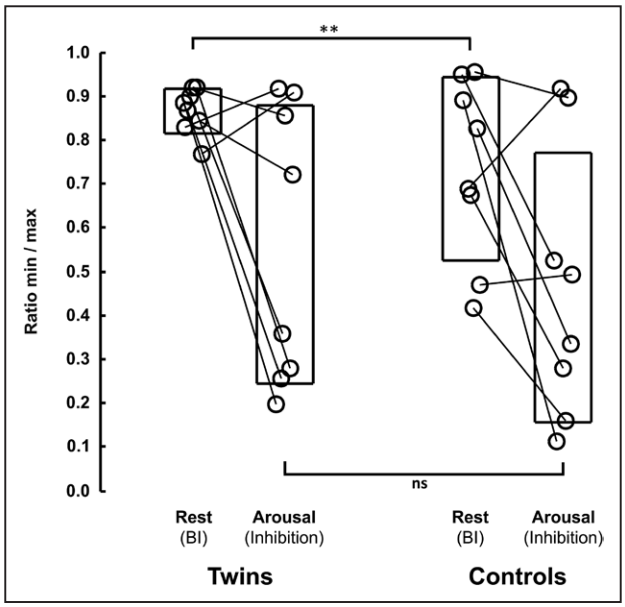

Figure 2. Comparison of within-pair ratios of muscle sympathetic nerve activity (MSNA) burst incidence (BI) at rest and arousal-induced MSNA inhibition between twin pairs (**left**) and unrelated control pairs (**right**). Ratios are ≤1 because the highest value was placed in the denominator. The results show that MSNA BI at rest differs less in twin pairs compared with that in control pairs (P=0.002). The within-pair variance in MSNA during arousal did not differ between monozygotic twins and unrelated controls (P=0.939). The lines connect the ratio values of resting MSNA BI and arousal inhibition for each pair.

Discussion

The quest of this study was to test the hypothesis that human muscle vasoconstrictor neuron responses to arousal are less genetically controlled than their resting activities. While our results confirmed that both subjects in pairs of monozygotic twins have similar resting BIs,[16] we found that responses to arousal were similar in both subjects of only 4 of the 8 pairs of twins. In fact, for all twin pairs, the within-pair variance did not differ from the variance found in nonrelated pairs. Hence, our findings support our primary hypothesis.

As mentioned in the introduction, our group has previously demonstrated that the immediate MSNA response to

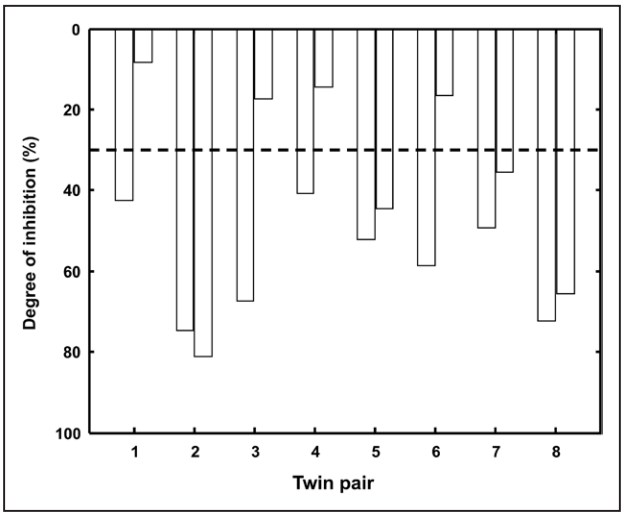

Figure 3. Degree of arousal-induced muscle sympathetic nerve activity (MSNA) inhibition in 8 monozygotic twin pairs. The dashed line indicates the 30% inhibition level used to define inhibition. Note that in 4 pairs, 1 twin displays inhibition while the other twin does not.

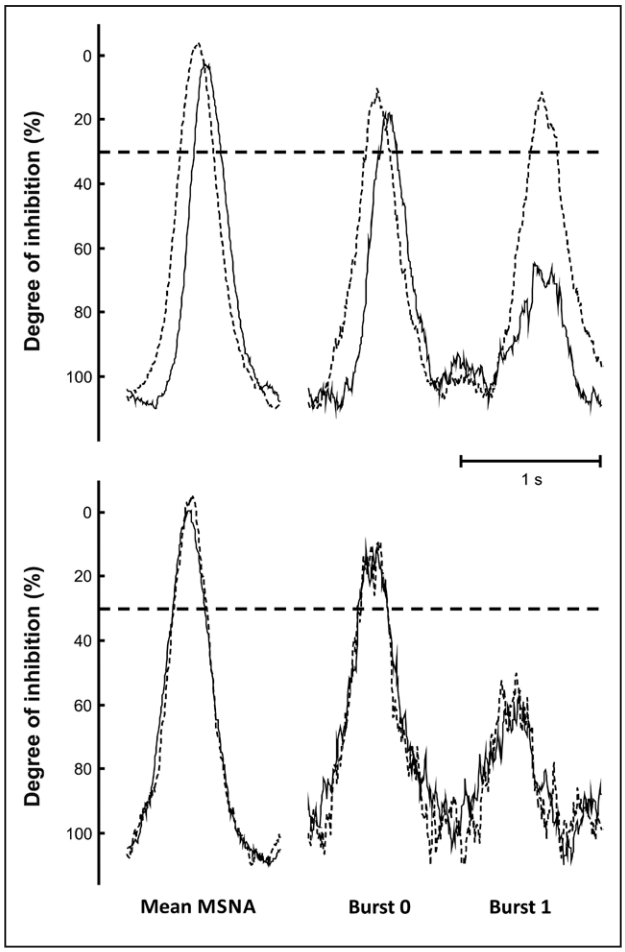

Figure 4. The calculated degree of inhibition of muscle sympathetic nerve activity (MSNA) during arousal in 1 twin pair with discordant (**upper**, twin pair no 3 in Figure 3) and 1 with similar reactions (**lower**, twin pair no 8 in Figure 3). The left burst in each panel is the average of bursts −9 to −2 for all stimuli, against which bursts 0 and 1 are compared.

different forms (visual, auditory, and touch) of surprising sensory stimuli (ie, evoking arousal) shows marked interindividual variability: ≈50% of investigated healthy subjects show an inhibition of 1 or 2 sympathetic bursts, whereas the remaining 50% display no such inhibition.[17,18,22] These MSNA arousal responses also show intraindividual reproducibility in repeated investigations over at least 6 months.[18]

In addition, an individual's arousal response has been found to predict his MSNA and blood pressure responses during a 3-minute mental stress test (paced arithmetic's): subjects who displayed MSNA inhibition during arousal also showed a reduction of MSNA and a lesser blood pressure increase during mental stress, compared with subjects without arousal-induced MSNA inhibition.[19] These previous findings illustrate that there are interindividual differences in sympathetic responses to acute stress. In view of the present results, these differences are less genetically determined than the interindividual differences in resting sympathetic activity. In this respect, our present findings agree with the blood pressure variability results of Xu et al[10] (cf Introduction).

It is worth noting that for the whole twin study group, MAP and heart rate monitored at rest and during the arousal protocol did not differ significantly, nor did they differ from values measured after termination of the recording. Hence, our arousal protocol may be considered as mild. It did not elicit a sustained increase in heart rate or blood pressure, but revealed interindividual differences in MSNA arousal responses that can herald blood pressure responses to stress.[19] It should be underlined that the focus of the present study is on heritability of different neural arousal responses, the long-term hemodynamic and clinical implications of which need to be studied.

Using functional magnetic resonance imaging, Godinez et al[23] recently reported that monozygotic twins with generally shared environmental influences (prenatal, schooling, and socioeconomic factors), but discordant in exposure to severe stress during development (before age 18 years), differed in brain activation pattern during an emotional word-face Stroop task. Twins exposed to severe stress showed greater activation of the basal ganglia, the limbic system, and the ventral and medial regions of the prefrontal cortex, including the anterior cingulate cortex, compared with their twin sibling.[23] Interestingly, several neuroimaging studies of autonomic control have observed a relationship between the anterior cingulate cortex and sympathetic responses in the periphery.[24–27] In our present study, all twin pairs reported remarkably shared environmental conditions, including shared schools and occupations, as well as recreational activities (including choice of sports), and they specifically denied differences in major life events. Thus, the present findings suggest that sympathetic responses to arousal may be modulated by more subtle environmental aspects. Whether this environmental influence is mediated via epigenetic mechanisms or other factors remains to be elucidated.

Limitations

We are presently studying MSNA arousal responses in females, but to date, all published studies on these response characteristics have been based on male subjects. Hence, the present study of heritability regarding sympathetic arousal responses was limited to male twins. Like many studies using intraneural recording techniques, our study group size is limited, as was the availability of monozygotic twins. However, our present study closely replicated the finding reported by Wallin et al,[16] of little within-pair variance in resting MSNA, in a new group of twins. In contrast, the within-pair variance in MSNA arousal responses was large, equaling that of unrelated pairs. Investigation of more twin pairs could affect the degree of variance but hardly change our conclusion that MSNA arousal responses are more prone to environmental modulation, compared with resting MSNA.

Finally, a third limitation of this study is that 12 subjects in the group of reported twins exhibited MSNA inhibition during arousal, leaving only 4 subjects without significant MSNA response. With such unbalanced neural response profiles, statistical analysis of differences in stimulus-induced blood pressure or heart rate responses was deemed inappropriate. Consequently, while our present twin data illustrate that MSNA during arousal is less governed by our genetic code than MSNA at rest, the hemodynamic consequences of different MSNA response profiles discussed earlier[18,19]

cannot be properly illustrated in this study group. Whether these differences in arousal responses will lead to different long-term circulatory consequences can, at present, only be hypothesized.

Perspectives

Our principal finding that human MSNA responses during arousal are less determined by genotype than the resting level of MSNA suggests that the arousal response pattern may be altered by environmental factors, possibly mediated by epigenetic modifications. Whether different sympathetic arousal response profiles have always existed or there has been a slow successive adaptation to a society that has become less prone to physical confrontation or reflects acculturation in general[28,29] is an intriguing question. This is especially so because it may come at a high cardiovascular price in a modern society, often characterized by sensory overload. If short-lasting arousal reactions lacking inhibition of vasoconstrictor activity to the muscle vascular bed herald a risk for hypertension and related disease, as indicated by our previous studies on larger groups of healthy subjects with versus without MSNA inhibition during arousal,[18,19] future studies should address long-term clinical implications of this response pattern and whether it can be modified in a positive direction from a cardiovascular risk perspective. Although effects of cognitive therapy on cardiovascular morbidity/mortality remain to be established, the positive effects of physical activity are broadly recognized. In fact, within-pair comparisons of monozygotic twins have shown that a more active twin has a 32% reduced risk of cardiovascular disease mortality compared with a less active twin,[30] supporting a causal link between physical activity and cardiovascular morbidity. Whether alterations of sympathetic arousal responses contribute to this link remains to be evaluated.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The only previous microneurographic study of monozygotic twins found evidence of marked genetic determination of human muscle sympathetic nerve activity at rest. The present study confirms this finding but, in addition, reveals contrasting findings during stimulus-induced arousal: no sign of genetic determination of the arousal response.

What Is Relevant?

- In healthy subjects, sympathetic responses to arousal show reproducible interindividual differences that have been found to predict neural and blood pressure responses to mental stress and may, thus, indicate risk for development of hypertension. The present finding suggests that environmental factors rather than genotype mainly determine this risk factor.

Summary

Human muscle sympathetic nerve activity during arousal is less determined by genotype than the resting level of sympathetic activity.

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