Hypertension

Muscle Sympathetic Nerve Activity Averaged Over 1 Minute Parallels Renal and Cardiac Sympathetic Nerve Activity in Response to a Forced Baroreceptor Pressure Change

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Background—Despite the accumulated knowledge of human muscle sympathetic nerve activity (SNA) as measured by microneurography, whether muscle SNA parallels renal and cardiac SNAs remains unknown.

Method and Results—In experiment 1, muscle (microneurography, tibial nerve), renal, and cardiac SNAs were recorded in anesthetized rabbits (n=6) while arterial pressure was changed by intravenous bolus injections of nitroprusside (3 μg/kg) followed by phenylephrine (3 μg/kg). In experiment 2, the carotid sinus region was vascularity isolated in anesthetized, vagotomized, and aorta-denervated rabbits (n=10). The 3 SNAs were recorded while intracarotid sinus pressure was increased stepwise from 40 to 160 mm Hg in 20-mm Hg increments maintained for 60 seconds each. Muscle SNA averaged over 1 minute was well correlated with renal (r=0.96±0.01, mean±SE) and cardiac (r=0.97±0.01) SNAs in experiment 1 (baroreflex open-loop condition). In experiment 2, muscle (microneurography), tibial nerve, renal, and cardiac SNAs were recorded while intracarotid sinus pressure was increased stepwise from 40 to 160 mm Hg in 20-mm Hg increments maintained for 60 seconds each. Muscle SNA averaged over 1 minute was well correlated with renal (r=0.96±0.01, mean±SE) and cardiac (r=0.97±0.01) SNAs in experiment 2 (baroreflex closed-loop condition).

Conclusions—Muscle SNA averaged over 1 minute parallels renal and cardiac SNAs in response to a forced baroreceptor pressure change. (Circulation. 2005;112:384-386.)

Key Words: catecholamines • muscles • nervous system, autonomic • nervous system, sympathetic

Sympathetic nerve activity (SNA) plays a crucial role in controlling circulation both in healthy humans and in patients with cardiovascular diseases. Activation of SNA increases heart rate, cardiac contractility, peripheral vascular resistance, and arterial pressure. Pathologically elevated SNA worsens survival in chronic heart failure and can induce lethal arrhythmias. Therefore, SNA has been an important target in the study of cardiovascular physiology and pathophysiology. In humans, activities of sympathetic nerves innervating blood vessels in skeletal muscles (muscle SNA) have been measured directly by microneurographic techniques and considered a proxy of systemic SNA. Those studies have contributed greatly to the understanding of the significance of SNA in circulatory physiology (including exercise, aging, and baroreflex) and pathophysiology (including hypertension, heart failure, myocardial infarction, and neurally mediated syncope).

Despite the accumulated knowledge about muscle SNA, whether muscle SNA parallels other SNAs innervating visceral organs, including the kidney and heart, remains unknown. The reason is that the human microneurographic technique is limited to measurements in the upper and lower extremities, face, and mouth. Because the kidney and heart are important organs for circulatory control, the relation between muscle SNA and renal or cardiac SNA is very important. Accordingly, by recording calf muscle SNA by microneurography simultaneously with renal and cardiac SNAs in anesthetized rabbits, we sought to determine whether muscle SNA averaged over 1 minute truly parallels renal and cardiac SNAs in response to baroreflex forcing.

Methods

Animals were cared for in accordance with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Science approved by the Japanese Physiological Society. Sixteen Japanese white rabbits (2.4 to 3.3 kg) were anesthetized by intravenous injection (2 mL/kg) of a mixture of urethane and α-chloralose and were mechanically ventilated with O2-enriched room air. Body temperature was maintained at 38°C with a heating pad. Arterial pressure (AP) was measured with a high-fidelity pressure transducer (Millar Instruments) inserted retrogradely from the right femoral artery.

After a retroperitoneal incision was made and a middle thoracotomy performed, left renal and left cardiac SNAs were recorded by stainless steel wire electrodes (Bioflex wire AS633, Cooner Wire). After the flexors in the dorsal middle region of the right thigh were incised, a tungsten microelectrode (model 26-05-1, Federick Haer) was inserted retrogradely from the right femoral artery.

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Co) was inserted into the left tibial nerve to record muscle SNA, based on human\textsuperscript{2-15} and animal\textsuperscript{16} microneurography. We identified muscle SNA by the following discharge characteristics: (1) afferent activity induced by tapping of the calf muscles but not by gently touching the skin and (2) excitatory and inhibitory responses to a decrease and an increase in baroreceptor pressure, respectively. The nerve fibers peripheral to the electrodes were ligated securely to eliminate afferent signals. The preamplified signals of SNAs were bandpass filtered at 150 to 1000 Hz except those of muscle SNA in experiment 2 (480 to 5000 Hz). These signals were full-wave rectified and lowpass filtered (cutoff frequency, 30 Hz) to quantify nerve activity.

Experiment 1: Baroreflex Closed-Loop Condition

The rabbits were maintained in a supine position \((n=6)\). All baroreceptor afferents and vagal nerves were intact. Three SNAs and AP were recorded at a 200-Hz sampling rate with a 12-bit analog-to-digital converter. After 2 minutes of baseline recording, nitroprusside (3 \(\mu g/\text{kg}\)) and, after a 2-minute delay, phenylephrine (3 \(\mu g/\text{kg}\)), was injected as a bolus via the right femoral vein. The data were stored on the hard disk of a dedicated laboratory computer system for later analysis.

Experiment 2: Baroreflex Open-Loop Condition

To strictly control baroreceptor pressure \((n=10 \text{ rabbits})\), a baroreflex loop was opened by vascular isolation of the carotid sinuses.\textsuperscript{14} Bilateral intracarotid sinus pressure (CSP) was controlled by a servo-controlled piston pump.\textsuperscript{14} Bilateral vagal and aortic depressor nerves were sectioned at the middle of the neck to eliminate reflexes from the cardiopulmonary region and the aortic arch. After surgical preparation, CSP was increased stepwise from 40 to 160 mm Hg in increments of 20 mm Hg. Each pressure step was maintained for 60 seconds. The 3 SNAs were recorded and stored as in protocol 1.

Data and Statistical Analysis

We averaged SNAs over 1 minute and generated scatterplots for muscle SNA against renal or cardiac SNA. For each type of SNA, and AP gradually decreased, muscle SNA was again increased. Subsequent phenylephrine injection increased AP by 16±3 mm Hg while muscle SNA was increased. Subsequent phenylephrine injection increased AP by 41±9 mm Hg while muscle SNA was decreased. Thereafter, as AP gradually decreased, muscle SNA was again increased. These responses of muscle SNA were similar to those of renal and cardiac SNAs (Figure 1A). When presented as SNA vs muscle SNA were similar to those in renal or cardiac SNA:

Results

In experiment 1 (baroreflex closed-loop condition), nitroprusside injection decreased AP by 16±3 mm Hg while muscle SNA was increased. Subsequent phenylephrine injection increased AP by 41±9 mm Hg while muscle SNA was decreased. Thereafter, as AP gradually decreased, muscle SNA was again increased. These responses of muscle SNA were similar to those of renal and cardiac SNAs (Figure 1A). When presented as SNA vs renal or cardiac SNA were both close to the line of identity (Figure 1B). All animals showed strong correlations between 1-minute muscle and renal SNAs \((r=0.97±0.01; \text{ range, 0.96 to 0.99})\) and between 1-minute muscle and cardiac SNAs \((r=0.97±0.01; \text{ range, 0.95 to 0.99})\). The baroreflex relation of muscle SNA against CSP was almost superimposable on that of renal or cardiac SNA in individual animals. The parameters in a reverse-sigmoid logistic function fitted in muscle SNA were similar to those in renal or cardiac SNA:

increases in CSP, similar to renal and cardiac SNAs (Figure 2A). All animals showed strong correlations between 1-minute muscle and renal SNAs \((r=0.97±0.01; \text{ range, 0.96 to 0.99})\) and between 1-minute muscle and cardiac SNAs \((r=0.97±0.01; \text{ range, 0.95 to 0.99})\). The baroreflex relation of muscle SNA against CSP was almost superimposable on that of renal or cardiac SNA in individual animals. The parameters in a reverse-sigmoid logistic function fitted in muscle SNA were similar to those in renal or cardiac SNA:
$P_1 = 99 \pm 1, 97 \pm 1,$ and $96 \pm 1 \text{ AU}; P_2 = 0.11 \pm 0.02, 0.12 \pm 0.01,$ and $0.14 \pm 0.03 \text{ AU/mm Hg}; P_3 = 99 \pm 4, 103 \pm 4,$ and $103 \pm 4 \text{ mm Hg};$ and $P_4 = 2 \pm 2, 2 \pm 2,$ and $3 \pm 2 \text{ AU in muscle, renal, and cardiac SNAs, respectively.}$

**Discussion**

Despite accumulated data of muscle SNA as measured by microneurography in human studies, whether muscle SNA parallels other SNAs controlling cardiovascular organs remains unclear. The major new finding in this study is that 1-minute muscle SNA was correlated strongly with both renal and cardiac SNAs, with $r$ at nearly unity, in both baroreflex closed- and open-loop conditions. This finding supports our hypothesis that muscle SNA averaged over 1 minute parallels renal and cardiac SNAs in response to baroreflex forcing. Our finding suggests that microneurographic muscle SNA is a useful proxy for renal and cardiac SNA in addressing baroreflex control of SNA.

Earlier human studies reported that microneurographic muscle SNA was correlated with noradrenaline spillovers in the kidney ($r^2 = 0.58$) and heart ($r^2 = 0.49$) at rest, suggesting a correlation between muscle SNA and cardiac or renal SNA. However, because spillover values are affected by neurotransmitter kinetics in synapses (release and uptake) and circulating noradrenaline independent of SNA, these results are not definitive. The present study complemented and extended the human studies by recording these SNAs directly and demonstrated stronger correlations ($r > 0.95$) between muscle SNA and cardiac or renal SNA than earlier studies of spillover technique.

Previous studies reported a greater response of splenic SNA to baroreceptor pressure changes than those of cardiac and renal SNAs in cats, suggesting regional differences in SNAs, but those studies did not investigate muscle SNA. Additionally, these regional differences were detected in faster SNAs averaged over 4 to 8 seconds. The present study investigated 1-minute SNA and hence did not address the relation between faster muscle SNA and renal or cardiac SNA.

The present study does not contradict earlier findings that indicated regionally different SNA responses to physiological stresses other than baroreceptor pressure changes. For example, the human cold pressor test increased muscle SNA but not heart rate.

**Limitations**

The anesthetic, artificial respiration, and surgical procedures used in this study may affect SNAs. In addition, experiment 2 was performed under a nonphysiological condition and did not investigate baroreflex hysteresis. We bandpass filtered all SNAs at the same condition (150 to 1000 Hz) except muscle SNA in experiment 2 (480 to 5000 Hz, human study condition). However, this did not affect the interpretation of data, because both experiments 1 and 2 showed strong correlations between muscle SNA and renal or cardiac SNA.

**Conclusion**

Muscle SNA averaged over 1 minute parallels renal and cardiac SNAs in response to a forced baroreceptor pressure change.

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