Static interaction between muscle mechanoreflex and arterial baroreflex in determining efferent sympathetic nerve activity

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Yamamoto, Kenta, Toru Kawada, Atsunori Kamiya, Hiroshi Takaki, Masaru Sugimachi, and Kenji Sunagawa. Static interaction between muscle mechanoreflex and arterial baroreflex in determining efferent sympathetic nerve activity. Am J Physiol Heart Circ Physiol 289: H1604–H1609, 2005. First published May 20, 2005; doi:10.1152/ajpheart.00053.2005.—Elucidation of the interaction between the muscle mechanoreflex and the arterial baroreflex is essential for better understanding of sympathetic regulation during exercise. We characterized the effects of these two reflexes on sympathetic nerve activity (SNA) in anesthetized rabbits (n = 7). Under open-loop baroreflex conditions, we recorded renal SNA at carotid sinus pressure (CSP) of 40, 80, 120, or 160 mmHg while passively stretching the hindlimb muscle at muscle tension (MT) of 0, 2, 4, or 6 kg. The MT-SNA relationship at CSP of 40 mmHg approximated a straight line. Increase in CSP from 40 to 120 and 160 mmHg shifted the MT-SNA relationship downward and reduced the response range (the difference between maximum and minimum SNA) to 43 ± 10% and 19 ± 6%, respectively (P < 0.01). The CSP-SNA relationship at MT of 0 kg approximated a sigmoid curve. Increase in MT from 0 to 2, 4, and 6 kg shifted the CSP-SNA relationship upward and extended the response range to 133 ± 8%, 156 ± 14%, and 178 ± 15%, respectively (P < 0.01). A model of algebraic summation, i.e., parallel shift, with a threshold of SNA functionally reproduced the interaction of the two reflexes (γ = 1.00x − 0.01; r2 = 0.991, root mean square = 2.6% between estimated and measured SNA). In conclusion, the response ranges of SNA to baroreceptor and muscle mechanoreceptor input changed in a manner that could be explained by a parallel shift with threshold.

ARterial PRESSure (AP) during exercise is regulated by neural inputs from three principal sources (19): efferent inputs from supramedullary regions, known as the central command; afferent inputs from contraction-sensitive skeletal muscle receptors, known as the exercise pressor reflex; and afferent inputs from baroreceptor populations such as the arterial and cardiopulmonary baroreflexes. Elucidation of the interaction among these inputs is essential for understanding the AP regulation during exercise, and it has been extensively studied (2–6, 11, 14–18, 22, 26). We previously demonstrated (26) that activation of muscle mechanoreceptors (muscle mechanoreflex) resets the arterial baroreflex control of sympathetic nerve activity (SNA), possibly compensating for a reduction in AP resulting from exercise-induced vasodilation. However, how these reflexes quantitatively interact with each other in regulating SNA over a wide range of inputs remains unknown.

Recent studies (13, 26) demonstrated that treadmill exercise or the muscle mechanoreflex extends the response range of SNA (i.e., the difference between maximum and minimum SNA) in the arterial baroreflex. The extension of the response range was mainly attributed to an increase in maximum SNA but not to changes in minimum SNA. On the other hand, Potts and Li (16) showed that higher carotid sinus pressure (CSP) attenuates the pressor response induced by the muscle mechanoreflex compared with lower CSP. We therefore hypothesized that the response range of SNA to either the muscle mechanoreflex or the arterial baroreflex would be changed depending on the afferent inputs from the other reflex.

To test the above-described hypothesis, we examined the static SNA responses to a combination of a wide range of inputs (4 different levels of baroreceptor input and 4 different levels of muscle mechanoreceptor input) in anesthetized rabbits. The results indicated that the response ranges of SNA to baroreceptor and muscle mechanoreceptor input can change depending on the input from the other reflex.

MATERIALS AND METHODS

Surgical preparations. Animals were cared for in strict accordance with the “Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences” approved by the Physiological Society of Japan. All protocols were approved by the Animal Subjects Committee of the National Cardiovascular Center. Seven Japanese White rabbits weighing 2.6–3.0 kg were anesthetized via intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml) and were mechanically ventilated with oxygen-enriched room air. Supplemental anesthetics (0.2–0.3 ml/kg) were administered continuously to maintain stable AP and heart rate levels during intervals of experimental protocols, which were indicative of an appropriate level of anesthesia. Arterial blood was sampled from the left common carotid artery. The rabbits were slightly hyperventilated to suppress chemoreflexes (arterial PCO2 ranged from 30 to 35 mmHg, arterial P02 > 300 mmHg). Arterial blood pH was within the physiological range when examined at the end of surgical preparation, as well as at the end of the experiment. The body temperature of each animal was maintained at ~38°C with a heating pad. AP was measured with a high-fidelity pressure transducer (Millar Instruments, Houston, TX) inserted from the right femoral artery.

We isolated bilateral carotid sinuses from the systemic circulation by ligating the internal and external carotid arteries and other small branches originating from the carotid sinus region. The isolated

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Fig. 1. Typical time series of intracarotid sinus pressure (CSP), muscle tension (MT), sympathetic nerve activity [SNA; in arbitrary units (a.u.)], and arterial pressure (AP) obtained from 1 animal. The 4 panels correspond to MT of 0, 2, 4, and 6 kg, in that order. SNA and AP decreased in response to increments in CSP at all MT levels. SNA and AP increased in response to the increments in MT at CSP below 120 mmHg in this animal. Data were resampled at 10 Hz.

carotid sinuses were filled with warmed physiological saline via catheters inserted through the common carotid arteries. CSP was controlled by a servo-controlled piston pump (model ET-126A, Labcatheters inserted through the common carotid arteries. CSP was controlled by a servo-controlled piston pump (model ET-126A, Lab
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RESULTS

Figure 1 shows a typical time series of CSP, MT, SNA, and AP obtained from one animal. Although the panels are arranged in Fig. 1 in increasing order of MT, the MT levels were applied randomly in the experiments. SNA and AP decreased in response to the increments in CSP with all MT levels. SNA and AP increased in response to the increments in MT at CSP below 120 mmHg in this animal.

Figure 2A illustrates the mean MT-SNA relationship at each CSP level. SNA proportionally increased in response to the increments in MT at CSP of 40 and 80 mmHg. However, SNA did not increase at CSP of 120 mmHg, except at MT of 6 kg. Furthermore, the level of MT did not affect SNA at CSP of 160 mmHg.

Figure 2B illustrates the mean CSP-SNA relationship at each MT level. SNA decreased in response to increments in CSP with all MT levels. The CSP-SNA relationship approximated a sigmoid curve and was shifted upward with increasing MT. The increase in MT extended the response range of SNA to the carotid sinus baroreflex.

Two-way ANOVA indicated a significant interaction between MT and CSP in determining SNA (P < 0.001), suggest-
that the effects of the muscle mechanoreflex and the arterial baroreflex could not be explained by algebraic summation (15, 16).

The response range of SNA to the muscle mechanoreflex obtained at each CSP level is shown in Fig. 3A. The response range of SNA was significantly smaller at CSP of 120 and 160 mmHg than at CSP of 40 mmHg.

The response range of SNA to the carotid sinus baroreflex obtained at each MT level is shown in Fig. 3B. The response range of SNA was significantly greater at MT of 2, 4, and 6 kg than at 0 kg.

Figure 4 illustrates the relationship between SNA and AP obtained by 16 combinations of 4 levels of CSP and 4 levels of MT. The relationship between SNA and AP can be characterized by a single sigmoid curve, indicating that the relationship between SNA and AP does not differ between the muscle mechanoreflex and the carotid sinus baroreflex.

**DISCUSSION**

The key findings of the present study were as follows. First, an increase in CSP from 40 to 80 mmHg caused a parallel downward shift in the MT-SNA relationship, and a further increase in CSP reduced the response range of SNA for the muscle mechanoreflex. Secondly, an increase in MT shifted the CSP-SNA relationship upward, extending the response range of SNA for the carotid sinus baroreflex. These results suggest that the response ranges of SNA to baroreceptor and muscle mechanoreceptor inputs can change depending on the input from the other reflex.

**Interaction between muscle mechanoreflex and arterial baroreflex.** We determined the maximum MT based on a preliminary study in which the SNA response to MT did not saturate at 6 kg. The accurate range for MT to mimic the physiological activation of muscle mechanoreceptor afferents was unclear. The maximum MT in the present study was threefold as strong as that which could occur if the configuration of Achilles tendon and calcaneus bone was kept intact (23). Although the maximum MT of 6 kg was nonphysiological and might have recruited nociceptive or nonspecific fiber activation, the SNA increased linearly with MT at CSP of 40 and 80 mmHg (Fig. 2A). Accordingly, the transition of physiological nociceptive stimulation to nonphysiological nociceptive stimulation was not clearly determined in the present experimental settings. The muscle mechanoreflex is mediated by group III and IV afferents (10, 12). The proportion of contraction-sensitive units with presumably mechanical mechanism of activation is higher among group III than group IV afferents (7). Discharge of group IV afferents is enhanced when the muscle is made ischemic. The dominant fiber type might have changed when the stimulation changed from non-nociceptive to nociceptive. Another concern is that because nociceptive stimulation of muscle afferents by metabolic products of contraction is likely to be related to exercise but stimulation by nonphysiological levels of stretch is not, the physiological significance of the present results should be interpreted carefully.

The effect of baroreceptor input on muscle mechanoreflex control of SNA has never been analyzed quantitatively over a wide range of inputs. SNA proportionally increased in response to increments in MT at CSP of 40 and 80 mmHg (Fig. 2A). However, SNA did not increase at CSP of 120 mmHg until MT of 6 kg was applied (Fig. 2A). As a result, the response range of SNA to MT was reduced by an increase in CSP (Fig. 3A). These data suggest that greater tension development above a certain level is necessary to evoke sympathoexcitation by the muscle mechanoreflex at higher CSP. Stewbins et al. (23) demonstrated that mean AP increased with increasing passive muscle stretch up to 8 kg, which suggests the SNA increase during passive muscle stretch. However, the AP response to passive muscle stretch might be modified by the accompanying arterial baroreflex in their study, because they did not open the arterial baroreflex negative-feedback loop. Potts and Li (16) demonstrated that higher CSP attenuated the sympathoexcitatory responses induced by muscle mechanoreflex. The present study extended the results by Potts.
Elevation of MT increased the response range of SNA to CSP to ~130%, 160%, and 180% at MT of 2, 4, and 6 kg, respectively, relative to that observed under MT of 0 kg (Fig. 3B). These results are consistent with results by Miki et al. (13), who demonstrated that treadmill exercise increases the response range of SNA in the arterial baroreflex. Muscle mechanoreflex may contribute to the extended response range of SNA in the arterial baroreflex during exercise. The pressor response was observed during tetanic contraction of the hind-limb induced by femoral nerve stimulation at 100 Hz in anesthetized and baroreceptor-deafferentiated rabbits (24). The static contraction also induces the pressor response in decerebrated rabbits (25). However, rhythmic contraction of the hind-limb by 3-Hz stimulation of the femoral nerve decreases mean AP (24). Both pressor and depressor responses were initiated from the contracting limbs, as both responses were eliminated after sectioning of the somatic nerves. To what extent the opposing reflexes participate in the regulation of SNA and AP during exercise awaits further investigation.

Our data are the first to demonstrate that sympathoexcitation induced by the muscle mechanoreflex requires development of a strong tension when CSP is high. On the other hand, weak tension development is sufficient to evoke sympathoexcitation at a lower CSP, possibly antagonizing a further reduction in AP during exercise (1, 16). An increased response range of SNA to CSP by muscle mechanoreceptor activation may also improve the pressure-stabilizing capacity of the arterial baroreflex against larger pressure disturbances such as those occurring during exercise (26). Furthermore, the muscle mechanoreflex and the carotid sinus baroreflex share a common output variable of SNA with regard to the regulation of AP, because the SNA-AP relationship cannot be discriminated between MT and CSP perturbations (Fig. 4). Together, these findings suggest that interaction of the two reflexes is beneficial to compensate for AP decreases resulting from exercise-induced vasodilation while maintaining the stabilization of AP against pressure disturbances.

**Functional model for interaction between muscle mechanoreflex and arterial baroreflex.** A functional model of a given system is useful for understanding the physiological system through a simulation study. One can examine the performance of a given physiological system by simulating what would happen if the parameters of the model deviate from their normal physiological values. For instance, we have reported (8) the importance of high-cut baroreflex neural arc transfer characteristics in AP regulation by removing the high-cut characteristics in the simulation. Another application of a functional model is that it can provide a basis for development of an artificial device to support or replace the impaired physiological system. For instance, we have identified dynamic characteristics of the arterial baroreflex system and developed a framework of an artificial baroreflex center that can replace the failed vasomotor center (20, 21, 27). Currently, the artificial baroreflex center does not take account of any interactions from afferent inputs other than the baroreceptors. Quantitative analysis of interaction between the mechanoreflex and the arterial baroreflex is the first step toward the future improvement of the artificial baroreflex center, when the artificial baroreflex center will be able to adjust its function during exercise.

We constructed a functional model to reproduce the interaction between the muscle mechanoreflex and the carotid sinus arterial baroreflex. The CSP-SNA relationship has been modeled by a sigmoid curve as follows (9):

$$\text{SNA}_b(\text{CSP}) = \frac{P_1}{1 + \exp[P_2(\text{CSP} - P_3)]} + P_4$$

where SNA\(_b\) is SNA derived from the baroreflex, P\(_1\) denotes the response range (i.e., the difference between the maximum and minimum values of SNA), P\(_2\) is the coefficient of gain, P\(_3\) is the midpoint of the logistic function on the CSP axis, and P\(_4\) is the minimum value of SNA.

The MT-SNA relationship can be modeled by a linear function as follows:

$$\text{SNA}_m(\text{MT}) = A_1 \cdot \text{MT} + A_2$$

where SNA\(_m\) is SNA derived from the mechanoreflex, and A\(_1\) and A\(_2\) represent the slope and intercept, respectively. The linear model was based on the MT-SNA relationship at CSP of 40 and 80 mmHg (Fig. 2A).

We then constructed an integrative model from the above two models. We first constructed an algebraic summation model based on the MT-SNA relationship, which showed a parallel shift between CSP of 40 and 80 mmHg. To remove apparent changes in parameters in Eq. 1 for different MT and nonlinearity observed in the MT-SNA relationship for higher CSP, we introduced threshold in the summation model as follows:

$$\text{SNA}(\text{CSP, MT}) = \max(\text{SNA}_b(\text{CSP}) + \text{SNA}_m(\text{MT}), \text{Th})$$

where Th is a threshold value for SNA. The function max(a, b) gives the greater or equal value between a and b.

Figure 5 illustrates a hypothetical interaction between the muscle mechanoreflex and the arterial baroreflex in a model of algebraic summation with threshold (Eq. 3). Figure 5A is a simplified block diagram of the functional integration of two reflexes. The SNA control signals derived from the muscle mechanoreflex and the arterial baroreflex are summed, and then SNA is evoked if the sum exceeds a threshold Th. In the muscle mechanoreflex analysis (Fig. 5B), the increase in CSP input induces a parallel downward shift in the MT-SNA relationship from the solid thin line to the dashed line. Because of the threshold, SNA does not respond up to ~4 kg of MT, resulting in the MT-SNA relationship shown by the solid thick line in Fig. 5B. In the arterial baroreflex analysis (Fig. 5C), the increase in MT input induces a parallel upward shift in the CSP-SNA relationship from the dashed line to the solid thick line. The observed CSP-SNA relationship at a low MT is shown as the solid thin line rather than the dashed line in Fig. 5C because of the threshold for SNA. Because of the subliminal fringe (gray area in Fig. 5, B and C), the response ranges of SNA for the muscle mechanoreflex and the arterial baroreflex can change depending on the input of the other reflex.

An iterative nonlinear least-squares fitting of Eq. 3 was performed on 16 combinations of SNA data for 4 CSP levels and 4 MT levels to determine 7 parameters (P\(_1\)–P\(_4\), A\(_1\), A\(_2\), and Th) in each animal. The model successfully reproduced the
characteristics of the interaction between the two reflexes (Fig. 6, A and B). Figure 6C shows the relationship between SNA estimated from the model and SNA that was actually measured. A linear regression analysis indicated that the estimated SNA in the model was similar to the measured SNA. This result reinforces our summation-threshold model of interaction between the muscle mechanoreflex and the arterial baroreflex.

**Limitations.** The first limitation of the present study is that we performed the experiment in anesthetized animals. Anesthesia might have modified both the carotid sinus baroreflex and the muscle mechanoreflex.

Second, we only focused on the static interaction and did not investigate the dynamic interaction between the muscle mechanoreflex and the arterial baroreflex in the present study.
Further investigations focusing on the dynamic interaction are required.

Third, stretch of skeletal muscle provides a stimulus for activation of mechanoreceptors that is different from that which occurs during muscle contraction. During contraction, mechanoreceptors are activated by a shortening of skeletal muscle and by compression of the receptors. Thus mechanoreceptors may be stimulated in a very different manner during stretch, which would likely affect the magnitude of the corresponding reflex response. In addition, stretch may activate different afferents than contraction. Further studies are required to elucidate the interactions between baroreflex and muscle mechanoreflex induced by different modes of activation.

In conclusion, activation of afferents from baroreceptors shifted the MT-SNA relationship downward and reduced the response range. The activation of mechanosensitive afferents from skeletal muscles shifted the CSP-SNA relationship upward and extended the response range. A model of algebraic summation with a threshold may explain the integration of the two reflexes. The existence of the subliminal fringe may increase the capacity of the arterial baroreflex to stabilize AP during exercise and express the sympathoexcitatory responses induced by weak muscle mechanoreceptor input at lower AP.

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REFERENCES


