Rapid resetting of carotid baroreceptor reflex by afferent input from skeletal muscle receptors

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Potts, Jeffrey T., and Jere H. Mitchell. Rapid resetting of carotid baroreceptor reflex by afferent input from skeletal muscle receptors. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H2000–H2008, 1998.—Resetting of the arterial baroreflex is mediated by central (central command) or peripheral (exercise pressor reflex) mechanisms. The purpose of this study was to determine the effect of somatosensory input from skeletal muscle receptors on resetting of the carotid baroreceptor reflex. Resetting of the baroreflex was determined by measuring carotid sinus threshold pressure (Pth) during a ramp protocol that consisted of a linear increase in sinus pressure from 50 to 250 mmHg at −3 mmHg/s. Experiments were performed in seven α-chloralose-anesthetized and vagotomized dogs. To determine the effect of skeletal muscle afferent input on resetting, electrically induced muscle contraction was used to activate predominantly mechanically and metabolically sensitive skeletal muscle afferent fibers, whereas passive stretch of the hindlimb was used to activate predominantly mechanically sensitive afferent fibers. Pth for heart rate (HR) and arterial blood pressure (BP) during the control ramp protocol was 110 ± 4 and 118 ± 7 mmHg, respectively. Electrically induced muscle contraction increased hindlimb tension (5.7 ± 0.4 kg) and significantly increased Pth-HR and Pth-BP above control (135 ± 6 and 141 ± 5 mmHg, respectively; P < 0.05). Muscle paralysis prevented the increase in Pth-HR and Pth-BP during ventral root stimulation (104 ± 7 and 116 ± 5 mmHg, respectively; P = not significant). Passive muscle stretch (n = 3) increased hindlimb tension (5.9 ± 0.9 kg) and significantly increased Pth-BP (125 ± 21 vs. 159 ± 16 mmHg, control vs. contraction; P < 0.05). There was no difference in the magnitude of Pth, resetting between muscle contraction or stretch. The present study demonstrates that activation of skeletal muscle afferent fibers, by either muscle contraction or stretch, increases Pth of the carotid baroreflex. Therefore, neural input from skeletal muscle receptors resets the carotid baroreflex in a manner similar to that ascribed by central command.

Cardiovascular regulation; exercise; arterial blood pressure; heart rate; ergoreceptors; medullary neurons; nucleus tractus solitarius

The cardiovascular responses evoked by muscular exercise have been intensely investigated in the past (9, 18, 27). Two neural mechanisms have been proposed to mediate the cardiovascular responses during exercise. A feedforward mechanism, referred to as central command, activates central neuronal circuits that control somatomotor and cardiovascular motor systems (6, 27, 33). Second, a feedback mechanism, referred to as the exercise pressor reflex or the muscle chemoreflex, controls cardiovascular motor outflow by transmitting mechanical and metabolic signals generated by contracting skeletal muscle to the brain stem (9, 11, 18, 26, 27). Both of these mechanisms have been reported to control the level of autonomic outflow during exercise. In addition, neural input from arterial baroreceptors has been shown to be essential in producing the cardiovascular responses evoked by exercise (2, 24). Many investigators have studied the effect of exercise on the arterial baroreceptor reflex (2, 4, 7, 12–16, 20, 24, 29, 34). Several of these reports suggested that resetting of the arterial baroreflex mediates the autonomic adjustments to exercise (4, 29). Recently, two studies confirmed this notion by showing that the carotid baroreflex is reset to the prevailing level of arterial pressure during dynamic exercise in human subjects (20, 24). These findings, in conjunction with previous studies, have now established that afferent input from arterial baroreceptors plays a pivotal role in regulating the cardiovascular responses during exercise.

To date, the neural mechanism(s) that modulate the arterial baroreflex during exercise remains unknown. Rowell and colleagues (26, 27) suggested that neural input from central command was the stimulus that reset the arterial baroreflex during exercise. Recently, Iellamo et al. (7) reported that neural input from both central command and reflex drive of skeletal muscle together shifted the arterial baroreflex to higher operating pressures during exercise in human subjects. However, because volitional exercise simultaneously activates central command and skeletal muscle reflexes, it is difficult to partition the contribution of each to resetting the baroreflex.

The purpose of the present study was to determine the effect of peripheral sensory input from skeletal muscle receptors on resetting of the carotid baroreflex. The threshold pressure (Pth) of the carotid baroreflex was determined using a vascularly isolated and perfused carotid sinus preparation in anesthetized dogs. To separate the contribution of mechanically and metabolically sensitive skeletal muscle afferent input, electrical stimulation of L7–S1 ventral roots was used to activate both afferent populations, whereas passive stretch of the hindlimb was used to activate predominantly mechanically sensitive muscle receptors. We tested the hypothesis that Pth was rapidly reset to higher sinus pressures when skeletal muscle afferent fibers were activated by muscle contraction or stretch. A preliminary report has been published (22).
METHODS

Surgical preparation. Studies were conducted in seven α-chloralose-urethane-anesthetized dogs (10–15 kg) of either sex. Induction of anesthesia was performed with thiopental sodium (10–12 mg/kg iv), and anesthesia was maintained with α-chloralose (80 mg/kg) and urethane (200 mg/kg). Supplemental anesthesia was administered every 90 min (α-chloralose, 15 mg/kg; urethan, 75 mg/kg) via a catheter in the femoral vein. An endotracheal tube was inserted and connected to a piston-type respirator (model 613, Harvard) set at 20 ml/kg tidal volume and respiratory frequency of 15–20 breaths/min. The animals were ventilated with room air, and the adequacy of ventilation was determined from arterial blood gas measurements (ABL3 Acid Base Laboratory, Radiometer, Copenhagen) obtained approximately every 30–45 min. Arterial PO₂ and PCO₂ were kept within normal limits by enriching the inspired O₂ supply and adjusting the ventilatory rate or volume. In cases of metabolic acidosis, sodium bicarbonate (8.4% solution) was infused to maintain an arterial pH of 7.4 ± 0.05. Body temperature was monitored with a rectal probe and maintained at 38.0 ± 0.5°C with a water-perfused heating pad and a near-infrared heating lamp.

Vascular isolation of carotid baroreceptors. The left and right carotid sinuses were vascally isolated from the remainder of the circulation and were perfused with varied levels of static pressure. Briefly, the internal and external carotid arteries and any small branches originating from the carotid bifurcation were completely ligated. The occipital arteries were cannulated and connected to a pressure transducer (Statham P23 Db) for the measurement of carotid sinus pressure (CSP). The left and right common carotid arteries were cannulated proximal to the carotid bifurcation with a three-way connector, and the free end of the connector was attached to a servo-controlled nonpulsatile pressure-generating system (Harvard Apparatus). In addition, the left common carotid artery was cannulated with polyvinyl chloride catheter tubing (1D, 0.059 in; OD, 0.128 in.) and advanced to the junction of the brachiocephalic artery and the aorta for the measurement of systemic arterial blood pressure (BP). All pressure transducers were calibrated with known reference pressures before and after each experiment. The perfusate used in the extracorporeal circuit (lactated Ringer, Baxter) was buffered to pH 7.4 and equilibrated with 95% O₂-5% CO₂. Because the extracorporeal circuit was not a follow-through system, the perfusate was exchanged with new stock every 30 min to maintain the desired PO₂, PCO₂, and pH in the carotid sinus regions. This was achieved by opening the lingual arterial cannula to permit new perfusate to flow into the sinus regions. We found that this procedure preserved the baroreflex-evoked responses for >6 h of extracorporeal perfusion. The vago sympathetic trunks were tied and cut bilaterally proximal to the carotid bifurcation to eliminate buffering from the aortic and cardiopulmonary baroreceptors.

Activation of skeletal muscle receptors. A limited laminectomy was performed to expose the spinal cord at the level of the lower lumbar-upper sacral region. Care was taken to remove only those vertebrae necessary to expose the dorsal and ventral spinal rootlets at the L7 and S1 levels. The dog was positioned into a head and spinal unit (David Kopf Instruments, Tujunga, CA), and the pelvis was secured with stabilizing pins. The dura was opened longitudinally, and the L7 and S1 spinal roots were identified. The ventral roots were carefully dissected from the dorsal roots, sectioned, and placed on bipolar platinum stimulating electrodes. The stimulating electrodes were covered in a pool of warmed mineral oil (37°C) and connected to a high-impedance signal isolation unit (model F-HIPS11G, Grass Instruments, Quincy, MA) and a stimulator (model S88, Grass Instruments). The skin covering the ipsilateral lower limb was removed, the calcaneal bone was sectioned, and the Achilles tendon was connected to a force transducer (model F.10, Grass Instruments) to measure the amount of tension generated during electrical-induced contraction and mechanical stretch of the gastrocnemius. Finally, the patellar tendon was secured to a steel post to stabilize to hindlimb.

Experimental protocol. After the surgery was completed, we allowed 60-min stabilization period. CSP was initially set at 50 mmHg. After steady-state cardiovascular responses were attained, CSP was increased at a constant rate from 50 to 200 mmHg using a servo-controlled pressure circuit. From preliminary studies, CSP was increased at a constant rate that varied between 2 and 5 mmHg/s from animal to animal, and the average perfusion rate was 3.4 mmHg/s. The use of a ramp of nonpulsatile baroreceptor-forcing pressures has been reported in previous studies to be a specific stimulus to activate carotid baroreceptors (30). During the ramp protocol, efferent HR and BP responses were continuously recorded. After control ramp experiments, the ramp protocol was repeated during activation of skeletal muscle receptors. Skeletal muscle afferent fibers were activated using two separate paradigms. First, contraction-sensitive muscle afferent fibers were activated by electrically stimulating the L7 and S1 ventral roots (3× motor threshold, a stimulus frequency of 30 Hz, and a pulse duration of 0.1 ms) to contract the gastrocnemius. Second, stretch-sensitive muscle afferents were activated by passive mechanical stretch of the hindlimb. The level of hindlimb tension generated by electrically induced contraction was matched during passive stretch of the hindlimb. The timing of muscle contraction or stretch with the onset of the ramp protocol was determined from preliminary studies (14, 15). In addition, we found that consistent results could be obtained when contraction and/or stretch was initiated simultaneously with the onset of the ramp. The sequence of experiments (control ramp vs. ramp protocols during activation of muscle afferent fibers) was randomized.

To confirm that the effect of muscle contraction was due to afferent input from contraction-sensitive skeletal muscle receptors, the ramp protocol during ventral root stimulation was also performed after the animal was pretreated with a neuromuscular-blocking agent (pancuronium bromide, 500 µg iv).

Determination of Pth for carotid baroreflex. The Pth for the baroreflex was identified using a data-smoothing and break-point identification algorithm. Data were sampled at 100 Hz and analyzed using an algorithm that performed three separate functions (Symbolic Logic, Grapevine, TX). Outlier data points were first identified and replaced by linear interpolation. The data set was recursively searched, and all data points that deviated from the mean of a selected data segment were identified. On average, 100–400 data points were used to calculate the mean for each identified segment. When a data point was greater than ±2 SD from the calculated mean, the data point was replaced by linear interpolation. The data set was then smoothed using a boxcar averaging technique. The number of points used for this smoothing step varied between 100 and 200 data points. After the data replacement and smoothing steps, break-point analysis was performed. Briefly, the algorithm first identified a linear segment of data and computed its slope by linear regression. The algorithm then recursively searched for the next data segment and...
repeated this calculation. A break point was identified when the slope of one data segment deviated from the slope of the next segment. The program searched the entire data set until all of the break points were identified. The break point that best predicted the decrease in heart rate (HR) and BP produced during the ramp protocol was chosen. An example of the performance of these algorithms in identifying the break points is shown in Fig. 2. Using this approach, it was possible to obtain an accurate and unbiased measure of $P_{th}$.

Statistical analyses. All cardiovascular signals were recorded directly by an eight-channel physiological recorder (model 2800S, Gould Instruments). These signals were also sampled at 100 Hz by commercially available data acquisition software (Global Lab 3, Data Translation) and stored by a videotape multiplex adaptor (model 4000, Vetter) and recorder (model PV-4760, Panasonic) for subsequent analyses.

The effect of induced muscle contraction and passive muscle stretch on $P_{th}$ of the carotid baroreflex was determined by paired $t$-test. Data are presented as means ± SE. Significant difference was determined as $P < 0.05$.

RESULTS

An example of one experiment used to determine the effect of muscle contraction on $P_{th}$ is shown in Fig. 1. In this experiment, CSP was increased at a rate of 5 mmHg/s from 50 to 200 mmHg while HR and BP were recorded continuously. During the ramp, both HR and BP decreased as CSP was linearly increased to its maximum (Fig. 1). The effect of the HR and BP responses evoked by the CSP ramp was repeated during electrically induced muscle contraction.

An example of the methods used to quantify $P_{th}$ is shown in Fig. 2. In this figure, BP, HR, CSP, and the corresponding outlier boundaries for each variable are plotted in the left-hand panels, whereas the smoothed and interpolated data are plotted in the right-hand panels. Figure 2, A and B (right panels), shows the break points that were identified by the algorithm. The right panel of Fig. 2C shows the $P_{th}$ that corresponded with the two break points (indicated by downward arrow). In this example, the CSP ramp began at 22 s and increased at a rate of 1.2 mmHg/s. The break points for HR and BP occurred at 87 and 82 s, respectively. When these time values were applied to the smoothed CSP data set, the $P_{th}$ for HR ($P_{th}$-HR) and arterial pressure ($P_{th}$-BP) was estimated to be 111 and 98 mmHg, respectively.

A summary of the cardiovascular responses evoked by the CSP ramp in the presence and absence of skeletal muscle receptor activation is presented in Table 1. Before the ramp protocol, baseline HR and mean arterial pressure (MAP) were 192 ± 10 beats/min and 169 ± 15 mmHg, respectively. During the ramp protocol, HR and MAP decreased to a nadir of 147 ± 6 beats/min and 98 ± 12 mmHg, respectively ($P < 0.05$). Control $P_{th}$ was $110 ± 4$ and $118 ± 7$ mmHg ($P_{th}$-HR and $P_{th}$-BP, respectively). When the ramp protocol was repeated during electrically induced muscle contraction, hindlimb tension increased from 0.7 ± 0.1 to 5.7 ± 0.4 kg ($P < 0.05$). Likewise, $P_{th}$-HR significantly increased from $110 ± 4$ to $135 ± 6$ mmHg, and $P_{th}$-BP increased from $118 ± 7$ to $141 ± 5$ mmHg ($P < 0.05$). $P_{th}$-HR and $P_{th}$-BP were significantly greater during muscle contraction than during the ramp protocol alone.

To assess the effect of mechanically sensitive muscle afferent fibers on $P_{th}$, the ramp protocol was repeated during passive muscle stretch ($n = 3$). These results are shown in Table 1. The increase in hindlimb tension during passive muscle stretch was similar to the level of CSP.
of tension development during electrically induced muscle contraction (5.7 ± 0.4 vs. 5.9 ± 0.9 kg, contraction vs. stretch, P = not significant (NS)). During passive stretch, \( P_{th}-BP \) increased 27% (125 ± 21 to 159 ± 16 mmHg, P < 0.05). On the other hand, although there was a 26% increase in \( P_{th}-HR \) (123 ± 24 to 155 ± 21 mmHg), this did not attain statistical significance (\( P = 0.19 \)).

Figure 3 summarizes the effect of skeletal muscle receptor activation on \( P_{th}-HR \) (left) and \( P_{th}-BP \) (right). In the left panel, static contraction of the hindlimb significantly increased \( P_{th}-HR \) (\( t = 5.97, P = 0.001 \)). A similar effect was observed during passive muscle stretch; however, this did not attain statistical significance (\( t = 1.92, P = 0.19 \)). On the other hand, \( P_{th}-BP \) was increased by both muscle contraction (\( t = 5.81, P = 0.001 \)) and stretch (\( t = 5.07, P = 0.037 \)).

To confirm that the changes in \( P_{th} \) were produced by afferent input from contraction-sensitive skeletal muscle receptors, muscle paralysis was used to prevent hindlimb contraction, and ventral root stimulation was then repeated (\( n = 3 \)). The results are presented in Table 1. After paralysis, \( P_{th}-HR \) (104 ± 7 vs. 110 ± 4 mmHg, control vs. paralysis, \( P = NS \)) and \( P_{th}-BP \) (116 ± 5 vs. 118 ± 7 mmHg, control vs. paralysis, \( P = NS \)) were not significantly different. Thus neuromuscular blockade prevented the increase in both \( P_{th}-HR \) and \( P_{th}-BP \).

There was no significant difference in the rate at which CSP was increased during the five ramp protocols (see Table 1). On average, CSP was increased from 45 to 226 mmHg and CSP perfusion rates varied between 1 and 5 mmHg/s. For all experiments (\( n = 23 \)) the average rate was 3.4 ± 0.8 mmHg/s.

**DISCUSSION**

The major finding from this study is that activation of skeletal muscle receptors by electrically induced muscle contraction or passive muscle stretch rapidly resets the carotid baroreflex. Resetting was defined as an increase in the minimal level of CSP (\( P_{th} \)) necessary to evoke reflex bradycardia and hypotension during a ramp increase in sinus pressure. Utilizing an algorithm designed to identify break points in the HR and BP data sets, we found that activation of skeletal muscle receptor afferent fibers by electrically induced muscle contrac-
tion (ventral root stimulation) or passive stretch of the gastrocnemius resets Pth to higher sinus pressures. Moreover, this effect was produced within the first 60 s of muscle contraction and stretch. Therefore, these findings demonstrate that neural input from skeletal muscle receptors reset the carotid baroreflex to a higher BP.

Resetting of the arterial baroreflex during exercise is of fundamental importance. This was initially demonstrated by Walgenbach and Donald (34). They reported that when carotid baroreceptor activity was held constant and afferent input from arterial/cardio pulmonary baroreceptors was eliminated, arterial BP and HR increased to a greater extent compared with when CSP was allowed to follow the changes in arterial BP. This finding has been used to show that the baroreflex is progressively reset to a higher operating pressure and that upward resetting of the baroreflex contributes to the autonomic adjustments that accompany exercise. Two other groups have used somewhat different experimental approaches to reproduce this finding. Scherrer et al. (29) showed that the increase in muscle sympathetic nerve activity during static handgrip exercise was dependent on the level of arterial baroreceptor afferent activity. When phenylephrine was infused to raise arterial BP and increase baroreceptor activity, the increase in muscle sympathetic nerve activity evoked by static handgrip exercise was attenuated. Conversely, when nitroglycerin was used to lower arterial BP and decrease baroreceptor activity, the increases in muscle sympathetic nerve activity and HR were potentiated. From these results they concluded that the act of performing volitional exercise resulted in an upward resetting of the arterial baroreceptor reflex that contributed to the autonomic adjustments that accompany exercise. Similarly, DiCarlo and Bishop (4) used intravenous infusion of nitroglycerin to attenuate the rise in arterial BP evoked by treadmill exercise in rabbits. The rationale was that by preventing the increase in BP, the sensory input from arterial baroreceptors will remain essentially constant. Resetting of the baroreflex will produce a centrally perceived pressure error signal that will augment the sympathoexcitatory and cardiovascular responses during exercise. When the rise in arterial BP was prevented, they found that the increases in renal sympathetic nerve activity and HR were augmented. However, because volitional exercise activates central motor command signals as well as afferent input from mechanically and metabolically sensitive skeletal muscle receptors, it is difficult to determine from these studies whether resetting of the baroreflex was mediated by central command or neural input from contracting skeletal muscle.

The relative contribution of these mechanisms to reset the arterial baroreflex during exercise remains
unknown. Rowell and colleagues (26, 27) proposed that centrally generated neural motor command resets the arterial baroreflex to a higher operating pressure range. Because central command is a feedforward mechanism and does not require an error signal (6), resetting of the baroreflex could conceivably occur before or immediately after the initiation of the motor command signal. However, whereas this hypothesis has been used to explain the effect of volitional exercise on the arterial baroreflex, there is a lack of direct evidence demonstrating that central command resets the reflex. Recently, two human studies have investigated the contribution of central command and skeletal muscle reflexes on the arterial baroreflex. Papelier et al. (21) utilized the technique of postexercise circulatory arrest to determine the effect of activating metabolically sensitive skeletal muscle afferent fibers on the carotid baroreflex. They reported that the linear slope for the relationship between carotid sinus transmural pressure and BP was significantly reduced during postexercise circulatory arrest, whereas the relationship for HR was unaffected. In addition, the authors reported that the baroreflex responses to a hypotensive and hypertensive challenge were differentially affected by postexercise circulatory arrest. This apparent paradox suggests that the interaction between the muscle chemoreflex and the carotid baroreflex may be nonlinear. Unfortunately, the modulating influence of the muscle chemoreflex was not examined during exercise. Iellamo et al. (7) determined the effect of volitional exercise and electrically induced dynamic knee exercise under free-flow and arrested-flow conditions on an index of the integrated arterial baroreflex control of HR. They found that neural input from both central command and skeletal muscle receptors modified the arterial baroreflex in a manner that has previously been reported during exercise (20, 24). Whereas there are obvious technical differences between these studies that may make the direct comparison of results difficult, they suggest that central command and skeletal muscle reflexes have a modifying effect on the arterial baroreflex.

Results from the present study add new information to our understanding of the neural mechanisms that modulate the arterial baroreflex during exercise. We found that afferent input arising from contracting skeletal muscle resets the carotid baroreflex to a higher operating pressure in the absence of central command motor signals. Others, however, have reported that reflex drive from contracting skeletal muscle acts to reduce the sensitivity of the baroreflex (7, 14, 15). This observation was first reported by McWilliam and colleagues (14, 15). They found that direct electrical stimulation of the peroneal nerve, as well as electrically evoked contraction of the hindlimb, decreased the sensitivity of the carotid-cardiac baroreceptor reflex. From this finding, they concluded that muscle contraction attenuated the overall sensitivity or gain of the carotid baroreflex. However, because of the method used to quantify baroreflex sensitivity, it was not possible to determine whether the blunted HR response was due to a reduction in reflex sensitivity or whether it may have resulted from resetting of the baroreflex. Because the present study found that reflex drive from contracting skeletal muscle reset the carotid baroreflex to a higher pressure, we propose that rapid resetting of the baroreflex may account for the attenuated HR responses reported by McWilliam and colleagues (14, 15). Figure 4 illustrates two possible effects of muscle contraction on the carotid baroreflex. Figure 4A depicts a decrease in baroreflex sensitivity. If the gain (or slope) of the baroreflex is reduced, then the reflex bradycardia (\(\Delta HR\) vs. \(\Delta HR'\)) will be attenuated when CSP is increased (arrow along abscissa). This corresponds to the mechanism proposed by McWilliam et al. (14, 15). Alternatively, the reflex bradycardia will also be attenuated if the baroreflex is reset to a higher pressure (\(P_{th} \rightarrow P_{th}'\)) (see Fig. 4B). This finding is supported by the present study. However, because we did not examine the complete stimulus-response relationship of the baroreflex, it was not possible to determine whether the gain of the reflex was also altered.

Because passive muscle stretch increased \(P_{th}\) to the same extent as muscle contraction, it would appear
that resetting of the baroreflex was predominantly mediated by mechanically sensitive skeletal muscle afferent fibers. Several points lend support to this idea. First, the contribution of metabolically sensitive muscle afferent fibers was likely minimal because local muscle ischemia does not occur during contraction while the hindlimb remains arterially perfused (9, 18). Second, the firing patterns of group III afferent fibers show that they fire transiently at the onset of contraction, whereas group IV fibers fire robustly during muscle ischemia (10, 17). Furthermore, because the change in P_{th} occurred within the first 30–60 s of contraction, it seems unlikely that a change in metabolism would have been sufficient to activate metabolically sensitive muscle afferent fibers. This is consistent with a predominant mechanosensitive role for group III afferent fibers. Therefore, it appears that rapid resetting of the carotid baroreflex was mediated predominantly by mechanosensitive skeletal muscle afferent fibers.

Perspectives. This study was specifically designed to investigate the effect of neural input from contraction-sensitive skeletal muscle afferent fibers on an important functional characteristic of the carotid baroreflex, namely, carotid sinus P_{th}. The question of baroreflex resetting during exercise has been argued for decades; however, not until very recently has there been strong evidence supporting the claim that the arterial baroreflex is reset (and not inhibited) during exercise (20, 24). Resetting has important functional consequences on the baroreflex, because an alteration in threshold will determine the pressure range over which the reflex can regulate BP. Furthermore, owing to the nonlinear behavior of the baroreflex, resetting may optimize the location of the operating point on the stimulus-response relationship so that the high gain characteristics of the reflex are retained during exercise. However, despite the recent evidence showing that the reflex is reset, the electrophysiological and neurochemical mechanisms that modulate the arterial baroreflex during exercise remain unknown.

To date, there is growing evidence suggesting that the nucleus tractus solitarius (NTS) is the central anatomical substrate that mediates these changes in baroreflex function (31). This is based on neuroanatomical and electrophysiological evidence showing that the afferent fibers from baroreceptors and skeletal muscle receptors synapse in the NTS (8, 13, 19, 23, 32). In the context of the present study, an attractive hypothesis to explain the effect of exercise on resetting is that activation of contraction-sensitive skeletal muscle afferent fibers inhibits the firing of barosensitive NTS neurons. If NTS neurons are inhibited, then a greater input stimulus will be needed to activate the baroreflex. This would result in a reflex that operates at a higher pressure range with no change in overall reflex sensitivity (acute resetting). McMahon et al. (13) investigated the effect of stimulating the peroneal nerve on the firing patterns of NTS neurons. They found that barosensitive NTS neurons were inhibited by somatosensory input. Furthermore, this involved a GABAergic mechanism, because the inhibition of NTS neurons was blocked by bicuculline. Therefore, neural input from skeletal muscle receptors may modulate the arterial baroreflex by altering the excitability of barosensitive neurons. Recently, Toney and Mifflin (32) demonstrated that the excitability of NTS neurons was also affected by the timing of incoming synaptic inputs. They reported that when paired electrical stimuli were delivered to hindlimb somatic afferent fibers, the unit response of a NTS neuron to a second stimulus was significantly reduced compared with the response evoked by the first stimulus. This temporal response pattern, termed time-dependent inhibition, may also be involved in mediating the effects of muscle contraction on resetting of the arterial baroreflex, because afferent fibers from skeletal muscle converge on barosensitive NTS neurons.

The precise role for inhibition of barosensitive NTS neurons on “overall” baroreflex function remains in question. Inhibition of barosensitive neurons has been suggested to decrease the sensitivity of the arterial baroreflex (13, 14). However, there is now compelling evidence showing that the sensitivity (or gain) of the carotid baroreflex is unaltered during exercise (16, 20, 24, 34). Therefore, a frank reduction in baroreflex sensitivity during muscular activity is not supported by these findings. Alternatively, we hypothesize that inhibition of barosensitive NTS neurons may result in a change in baroreflex function that is characterized by resetting of the stimulus-response relationship. This hypothesis is currently under investigation (23).

Although the scope of the present study was to examine the modulatory effects of somatosensory input on carotid baroreflex function, the well-documented effect of central command must not be overlooked. It has been reported that activation of putative sites for central command, including the motor cortex, insular cortex, and the posterior hypothalamus, alters baroreflex control of HR (1, 5, 28, 33). Some of these effects are similar to those evoked by the defense reaction (31). Therefore, activation of central command neurons may also modulate the arterial baroreflex during exercise.

Interestingly, a feature common to both central command and the skeletal muscle reflex is that medullary neurons forming the central baroreceptor pathways receive synaptic input from both sources (8, 13, 19, 23, 31–33). However, it should be appreciated that other mechanisms, such as local paracrine factors that alter the mechanical transduction properties of baroreceptor endings (3), likely contribute to resetting of the baroreflex during volitional exercise in neurally intact animals and humans.

In summary, the arterial baroreceptor reflex should not be viewed as a controller of an absolute level of arterial BP. Despite its high-gain characteristics, the baroreflex functions most effectively as a negative feedback control mechanism over a limited range of BPs owing to its nonlinear properties. Thus, to retain its high-gain characteristics during exercise, the baroreflex must reset to the prevailing level of arterial pressure. Therefore, rapid resetting of the arterial baroreflex likely serves two purposes during exercise:
1) to aid in the initiation of autonomic adjustments following the onset of exercise (4, 26, 27, 29); and 2) to extend the range over which the baroreflex can operate as a negative feedback controller at high gain (24).

In conclusion, the results from the present study show for the first time that skeletal muscle activity rapidly resets the carotid baroreflex to a higher operating pressure in the absence of central command motor signals. Specifically, activation of mechanically sensitive skeletal muscle afferent fibers, by either muscle contraction or stretch, increases the \( P_{th} \) of the reflex. Because electrically induced muscle contraction and passive muscle stretch produced the same degree of resetting, it is proposed that activation of mechanically sensitive muscle afferent fibers mediated this effect. Therefore, neural input from skeletal muscle receptors appears to reset the carotid baroreflex in a manner similar to that of central command (4, 26, 27). Future investigations are needed to partition the exact contribution of mechanically and metabolically sensitive muscle afferent fibers, as well as the precise role for inhibition of NTS neurons, on the resetting process.

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