Central interaction between carotid baroreceptors and skeletal muscle receptors inhibits sympathoexcitation

JEFFREY T. POTTS,1 GREGORY A. HAND,3 JIANHUA LI,2 AND JERE H. MITCHELL2

Departments of 1Physiology and 3Internal Medicine, Harry S. Moss Heart Center, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9034; and 2Department of Exercise Science, University of South Carolina, Columbia, South Carolina 29208

Potts, Jeffrey T., Gregory A. Hand, Jianhua Li, and Jere H. Mitchell. Central interaction between carotid baroreceptors and skeletal muscle receptors inhibits sympathoexcitation. J. Appl. Physiol. 84(4): 1158–1165, 1998.—To determine the potential of an inhibitory interaction between the carotid sinus baroreflex (CSB) and the exercise pressor reflex (EPR), both pathways were activated to produce sympathoexcitation. It was hypothesized that, under conditions when the baroreflex increased sympathetic output, the interaction between CSB and EPR would be inhibitory. Bilateral carotid occlusion (BCO), electrically induced muscle contraction (EMC), and passive muscle stretch (PMS) were used to evoke sympathoexcitation. BCO decreased sinus pressure 50 ± 5 mmHg, and the levels of muscle tension generated by EMC and PMS were 7 ± 2 and 8 ± 1 kg, respectively. This resulted in significant increases in mean arterial pressure (MAP) of 55 ± 9, 50 ± 7, and 50 ± 6 mmHg (P = not significant, BCO vs. EMC vs. PMS) and in heart rate (HR) of 7 ± 2, 19 ± 4, and 17 ± 2 beats/min (P < 0.05, BCO vs. EMC and PMS). When BCO was combined with EMC or PMS, the reflex increase in MAP was augmented (80 ± 8 and 79 ± 10 mmHg; BCO + EMC and BCO + PMS, respectively; P < 0.05). However, summation of the individual MAP responses was greater than the response evoked during coactivation (106 ± 11 and 103 ± 12 mmHg, respectively; P < 0.05). Because summing the individual blood pressure responses exceeded the response during coactivation, the net effect was that the CSB and EPR interacted in an occlusive manner. In contrast, summation of the individual chronotropic responses was the same as the response evoked during coactivation. Moreover, there was no difference in summation of the individual MAP or HR responses when muscle afferents were activated by either EMC or PMS. In conclusion, the interaction between the CSB and the EPR in control of MAP was occlusive when both reflexes were stimulated to evoke sympathoexcitation. However, summation of the reflex changes in HR was simply additive.

Static muscle contraction; baroreceptor afferents; somatic afferents; sympathetic nerve activity; heart rate; blood pressure; exercise

Neural input from three principal sources establishes the autonomic and cardiovascular adjustments to exercise (19, 27, 34). These sources include 1) descending input from supramedullary regions (central command), 2) ascending input from contracting skeletal muscle (exercise pressor reflex), and 3) afferent input from peripheral baroreceptor populations (arterial and cardiopulmonary baroreceptors). The cardiovascular responses mediated by each of these neural pathways have been well described (3, 17, 19, 22, 25, 27, 34, 36, 38). However, the effect of simultaneously activating two or more of these pathways is complex, and the central integration of these neural inputs is not well understood.

Previous studies have reported that tetanic (35) and rhythmic muscle contraction (31, 36) potentiates the reflex sympathoexcitation when afferent input from arterial baroreceptors was prevented by acute baroreceptor deafferentiation. From this finding, it has been suggested that arterial baroreceptor afferent input acts as an inhibitory signal during exercise to oppose sympathoexcitation (26, 31, 32, 35, 36). However, others have shown that systemic pressure falls in the absence of afferent input from arterial baroreceptors (2, 7, 13, 16). This has been taken as evidence that neural input from arterial baroreceptors acts as an excitatory signal and, together with the exercise pressor reflex and central command, increases sympathetic outflow during exercise. Neural input from arterial baroreceptors and skeletal muscle receptors is conveyed to the central nervous system (CNS) via separate afferent pathways. However, the central projections of these two cardiovascular reflexes synapse in similar regions of the medulla (9, 10, 14, 33), and they share common efferent sympathetic pathways and effector organs (3, 17, 19, 28). Therefore, summation of the sympathoexcitatory responses evoked by these two reflexes will depend on the degree of overlap between these central and efferent neural pathways. The motivation for this study was to determine whether the interaction between the arterial baroreflex and the exercise pressor reflex was inhibitory when both pathways evoked sympathoexcitation. In this context, the baroreflex and the exercise pressor reflex represent two redundant sympathoexcitatory reflex pathways, and the inhibitory interaction between them may occur at a central or a peripheral site. To evoke a sympathoexcitatory response, the carotid baroreflex was selectively inhibited by decreasing the perfusion pressure to the carotid sinus regions (bilateral carotid occlusion), and the exercise pressor reflex was activated by passive stretch and electrically induced contraction of the triceps surae. We tested the hypothesis that, under the condition when both reflex pathways increased sympathetic outflow, the interaction between the baroreflex and the exercise pressor reflex would be inhibitory. To determine whether the interaction occurred at a peripheral (i.e., level of the effector organs) or at a central (i.e., common central/efferent pathway) site, the reflex cardiovascular responses were compared with the responses evoked by CNS ischemia. It was reasoned that if the interaction was of central origin, the reflex cardiovascular responses evoked by both reflexes would be less than the response evoked during CNS ischemia (a maneuver
known to elicit maximal changes in blood pressure and heart rate (HR)]. Furthermore, this would eliminate the possibility that the inhibitory interaction between these two reflexes was caused simply by saturation of the common effector organs (i.e., heart, resistance vessels) that produced the increase in blood pressure and HR. A preliminary report of these findings has been published (24).  

**METHODOLOGY**

Surgical procedures. The experiments were conducted on 11 mongrel cats of either sex (body wt 3.0–5.5 kg). After initial induction of anesthesia with a gas mixture [3–5% halothane in oxygen (1–2 l/min)], a solution of α-chloralose (80 mg/kg) and urethane (200 mg/kg) was administered intravenously via a femoral vein. Catheters (polyethylene tubing, PE-60) were inserted into the left femoral vein for the administration of drugs and the left femoral artery for measurement of systemic arterial pressure. Animals were artificially ventilated by a mechanical respirator (model 661, Harvard Apparatus, South Natick, MA). Arterial blood gases and pH were measured every 45–60 min by an automated blood-gas analyzer (model ABL-3, Radiometer) and maintained within normal ranges (arterial Po2 80–100 Torr, arterial PCO2 35–45 Torr, pH 7.3–7.4). If necessary, 100% oxygen was supplemented to maintain arterial Po2 above 80 Torr. Rectal temperature was continuously monitored throughout each experiment and was maintained between 37 and 38°C by a temperature-controlled water-perfused heating pad and a near-infrared-heat lamp. Gradual increases in baseline HR and blood pressure over the course of the experiment were used to indicate the need for additional anesthesia. When supplemental anesthesia was required, a solution of α-chloralose (15 mg/kg) and urethane (75 mg/kg) was administered intravenously. Next, a laminectomy was performed, exposing the lower lumbar and upper sacral portions of the spinal cord from roughly L5 to S2.

Before the cat was placed into the head and spinal units, the carotid sinus regions were exposed via a midline incision on the ventral surface of the neck. Superficial tissues were cauterized to expose the common carotid artery and the carotid bifurcation. The ascending pharyngeal and lingual arteries were ligated, and retrograde cannulation of the external carotid artery with polyethylene tubing (PE-50) was used to measure carotid sinus pressure (CSP). A 2.0-mm-ID vascular occluder (model OC2A, In Vivo Metric, Healdsburg, CA) was placed around each common carotid artery proximal to the sinus region, and when inflated it reduced CSP to deactivate carotid baroreceptors and evoke an excitatory cardiovascular response. The vagosympathetic trunks were ligated and cut bilaterally to remove reflex buffering from aortic and cardiopulmonary baroreceptor afferents. Thus, neural changes in HR and mean arterial pressure (MAP) were evoked exclusively by reflex changes in sympathetic nerve activity (SNA).

The incision on the neck was sutured, and the external carotid artery cannulas were conjoined and connected to a pressure transducer for measurement of CSP. Finally, the carotid bifurcation was placed into the head and spinal units (David Kopf Instruments, Tujunga, CA). The dura was opened longitudinally, and the L7 and S1 spinal roots were identified. The dorsal and ventral roots of L7 and S1 were carefully dissected, and the ventral roots were sectioned and positioned over a pair of bipolar platinum stimulating electrodes. The stimulating electrodes were covered in a pool of warmed mineral oil (37°C) and connected to a stimulator (model S88, Grass Instruments, Quincy, MA). The calcaneal bone was cut, and the pelvis was stabilized in a spinal unit (David Kopf Instruments) with the lower limb secured by attaching the patellar tendon to a steel post, and the Achilles tendon was connected to a force transducer (model F10, Grass Instruments) to measure the amount of tension generated during electrically induced contraction of the triceps surae.

Data acquisition. Systemic arterial pressure and CSP were measured by connecting the femoral artery and external carotid artery catheters to separate pressure transducers (model P23ID, Statham, Oxnard, CA). MAP was calculated from an algorithm run on a laboratory minicomputer (model PDP-11/23, Digital Equipment, Maynard, MA), which integrated the area under the arterial pressure waveform. HR was derived by a biotachometer (Gould Instruments, Cleveland, OH) from the systemic arterial pulse pressure as well as from the sequential timing of R-R intervals from surface electrocardiogram. All data were simultaneously recorded on an eight-channel physiological recorder (model 2800S, Gould Instruments) as well as a videotape multiplex adapter (model 4000, Vetter, Rebersburg, PA) and recorder (model PV-4760, Panasonic) system. The cardiovascular signals were acquired by a laboratory minicomputer (model PDP-11/23, Digital Equipment) at a sampling frequency of 100 Hz by an asynchronous data-acquisition program for subsequent analysis. Offline analyses were performed by sorting the data into 6-s bins and averaging the beat-to-beat changes in HR and MAP over the course of each experimental trial.

Experimental protocol. On completion of the surgery and positioning the animal in the head and spinal units, a period of 60 min was used to permit MAP and HR to stabilize. Reflex changes in HR and MAP were measured during 1) activation of muscle mechano- and metaboceptors by static muscle contraction and/or passive muscle stretch and 2) inhibition of the carotid sinus baroreflex by occlusion of the common carotid arteries. First, electrically induced static muscle contraction of the triceps surae was performed by stimulating the L7 and S1 ventral roots for 1 min at a frequency of 30–40 Hz, a pulse duration of 0.1 ms, and a voltage representing 2.5–3.0 times the motor threshold with the muscle preloaded with 0.8–1.0 kg of tension. Use of these stimulation parameters in conjunction with determination of the motor threshold before each tetanic contraction has been shown to elicit consistent muscular force generation during electrically induced tetanic contraction that is mediated exclusively by group III and group IV muscle afferents (17). Passive stretch of the triceps surae was performed to the same level of muscle tension generated during ventral root stimulation. A period of no less than 15 min separated each condition to permit HR and MAP to return to their prestimulus baseline values. Second, the carotid baroreceptor reflex was activated for 1 min by simultaneously inflating the vascular occluders on the common carotid arteries, which rapidly reduced CSP below the threshold of the baroreflex (28). Third, the carotid baroreflex and the exercise pressor reflex were simultaneously activated for 1 min as previously outlined. Fourth, static muscle contraction, passive muscle stretch, and bilateral carotid occlusion (BCO) were again performed to determine the extent of deterioration of the preparation over the duration of the experiment. In the event that the reflex change in blood pressure during muscle contraction/stretch was <80% of the initial response, it was deemed that the preparation had deteriorated, and no further trials were performed. If, however, the cardiovascular responses had not deteriorated, the above-mentioned sequence was repeated. On average, this sequence was repeated twice, and the reflex cardiovascular responses were averaged to provide a mean response for...
each animal. The order of presentation of these four experimental treatments was randomized. Because the order did not appear to have an effect on the reflex-evoked cardiovascular responses, these data were combined. Finally, an intravenous injection (200 μg/kg) of the neuromuscular-blocker pancuronium bromide (Elkins-Sinn, Cherry Hill, NJ) was administered to confirm that the induced cardiovascular response was a reflex originating in the hindlimb skeletal muscle. The paralyzing agent was given 5 min before electrically induced muscle contraction.

Temporary occlusion of the vertebral and common carotid arteries was performed for 15–20 s to evoke CNS ischemia. This maneuver was performed to evoke maximal sympathoexcitation to determine whether the response of the effector organs (i.e., heart, vascular smooth muscle) was saturated during high levels of sympathoexcitation. This procedure was repeated twice, and the changes in MAP and HR were averaged to obtain a mean response for each animal.

Statistical analyses. The reflex changes in MAP, CSP, HR, and developed muscle tension during electrically induced muscle contraction/passive muscle stretch and baroreflex activation were averaged in 10-s time bins during a period of 40 s preceding reflex activation, continuously over the 60 s of activation, and over the 20 s immediately after reflex activation. Changes in these variables from control levels were compared by a two-way analysis of variance (ANOVA) with repeated-measures [experimental condition (3 levels) × time (12 levels)]. When a significant main effect was found, differences were identified by using a Student-Newman-Kuels multiple-comparison test.

To identify the nature of the interaction between the carotid baroreflex, and the skeletal muscle reflex the peak changes in HR and MAP elicited during coactivation were compared by summing the individual peak cardiovascular responses evoked when each reflex was activated separately. The peak cardiovascular responses evoked by baroreceptor afferents, skeletal muscle afferents, and algebraic summation and during CNS ischemia were compared by a one-way ANOVA. Data are presented as means ± SE. The level of significance was set at \( P < 0.05 \).

RESULTS

Reflex changes in MAP and HR by carotid sinus baroreceptors and skeletal muscle mechanod- and metabo-

Table 1. Baseline and peak reflex changes in heart rate and mean arterial pressure to baroreceptor activation and electrically induced skeletal muscle contraction

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<th>Baseline</th>
<th>Peak Change</th>
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<tr>
<td></td>
<td>HR, bemts/min</td>
<td>MAP, mmHg</td>
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<tr>
<td>Baroreceptor reflex</td>
<td>195 ± 11</td>
<td>100 ± 6</td>
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<tr>
<td>Skeletal muscle reflex</td>
<td>197 ± 10</td>
<td>102 ± 6</td>
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<tr>
<td>Coactivation</td>
<td>192 ± 10</td>
<td>94 ± 5</td>
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Values are means ± SE for 11 cats. HR, heart rate; MAP, mean arterial pressure; Tension, contraction-induced tension development.
*Significantly different from baroreceptor reflex only, \( P < 0.05 \).
†Significantly different from baroreceptor and skeletal muscle reflexes, \( P < 0.05 \).

Table 2. Reflex changes in heart rate and mean arterial pressure to baroreceptor activation and skeletal muscle reflexes

<table>
<thead>
<tr>
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<th>HR, beats/min</th>
<th>MAP, mmHg</th>
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<tr>
<td>Baseline</td>
<td>100 ± 6</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>Coactivation</td>
<td>80 ± 8†</td>
<td>7.6</td>
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Fig. 1. Summary of reflex changes (Δ) in mean arterial pressure (MAP; A) and heart rate (HR; B) from 11 cats to 1) activation of skeletal muscle receptors by muscle contraction (□), 2) activation of carotid baroreceptors by bilateral carotid occlusion (○), and 3) activation of both reflexes simultaneously (△). Brackets show periods of baroreflex and skeletal muscle reactivation. Values are means ± SE, bpm, Beats/min. *Significantly different from control, \( P < 0.05 \).
*Significant difference between coactivation and activation of each reflex separately, \( P < 0.05 \). Values are means ± SE.

Experimental conditions (i.e., BCO, muscle contraction, reflex coactivation) or in the level of developed muscle tension during contraction alone and coactivation [\( P = \) not significant (NS)]. The time course and characteristic profile of reflex responses evoked by activation of skeletal muscle receptors and carotid baroreceptors by electrically induced tetanic muscle contraction and BCO are depicted in Fig. 1. There was a gradual increase in MAP and HR, and the maximal change in each variable was reached ~30–40 s after onset of the stimulus (time = 0 s). The peak changes in MAP and HR to muscle contraction and BCO are presented in Table 1 and illustrated in Fig. 2. The peak increase in MAP and HR (10-s epochs) to muscle contraction was 50.2 ± 7.0 mmHg and 18.6 ± 3.5 beats/min, respectively (\( P < 0.05 \)). The reflex increase in MAP evoked by BCO was similar to the response to muscle contraction (54.7 ± 8.5 mmHg, \( P < 0.05 \)). However, the reflex tachycardia to BCO was significantly less than that produced by muscle contraction (8.1 ± 2.3 beats/min; \( P < 0.05 \)). Coactivation of carotid baroreflex and the exercise pressor reflex augmented the reflex changes in MAP and HR. The peak rise in MAP and HR (79.5 ± 7.6 mmHg and 26.0 ± 4.0 beats/min, respectively) was significantly greater than the changes evoked when each reflex was activated separately (\( P < 0.05 \)).

Baseline values and peak changes in MAP and HR to baroreceptor activation and passive stretch of the hindlimb are summarized in Table 2 (useable data were available from 6 animals). No significant difference was
found in baseline HR and MAP between the experimental conditions (i.e., BCO, muscle stretch, reflex coactivation) or in the level of developed muscle tension during passive stretch alone and coactivation. A similar time course for the cardiovascular responses evoked by electrically induced muscle contraction was found during passive stretch of the hindlimb (Fig. 3).

The peak changes in MAP and HR evoked by muscle stretch and BCO are shown in Fig. 4. Passive stretch of the triceps surae and BCO produced a similar increase in MAP (54.2 ± 8.0 vs. 49.8 ± 6.4 mmHg). However, the reflex tachycardia to BCO was less than that evoked by muscle stretch (6.1 ± 1.2 vs. 16.8 ± 2.2 beats/min, P < 0.05). Simultaneous activation of both pathways potentiated the increase in MAP and HR (78.5 ± 9.9 mmHg and 19.7 ± 1.6 beats/min). These responses were not different from those evoked during muscle contraction and BCO.

Effect of CNS ischemia and muscle paralysis on reflex cardiovascular responses. We evoked CNS ischemia to induce a maximal level of sympahtoexcitation and contrasted the changes in MAP and HR with those produced during activation of the baroreflex and the exercise pressor reflex. CNS ischemia increased MAP and HR (133.3 ± 5.6 mmHg and 35.2 ± 4.0 beats/min, respectively; P < 0.05). These responses were significantly larger than both the evoked responses during simultaneous activation of both reflexes and the algebraic summation of the individual responses (see Figs. 2 and 4).

To determine whether the cardiovascular response elicited by electrical stimulation of L7 and S1 ventral roots was mediated by activation of sensory receptors originating in the contracting skeletal muscle, the effect of muscle paralysis with pancuronium bromide (200 µg/kg) was examined. After intravenous injection of the neuromuscular-blocking agent, the reflex increase in MAP and HR to electrical stimulation of L7 and S1 ventral roots was abolished. However, the reflex responses to BCO were preserved during paralysis.
DISCUSSION

The interaction between arterial baroreceptors and skeletal muscle has previously been examined (1, 26, 31, 32, 35, 36). However, the anatomic substrate(s) mediating this interaction remains unknown. The present study found an inhibitory interaction in the regulation of arterial blood pressure when the baroreflex and the exercise pressor reflex were activated to evoke excitatory sympathetic responses. Because the cardiovascular response to CNS ischemia exceeded the response evoked by simultaneous activation of both reflexes, saturation of effector organs (i.e., chronotropic/inotropic responses and vascular smooth muscle vasoconstriction) was excluded as the primary site for inhibition between these two pathways. Therefore, the major new finding of this study is that the likely site for inhibition between these two reflexes is within the CNS.

Inhibitory summation for blood pressure control. The present study found that the sympathetically mediated responses summed in an inhibitory manner. This supports the findings from earlier studies (31, 35). However, Walgenbach and Donald (36) reported that when carotid baroreceptors were surgically isolated and perfused at a constant pressure the exercise-induced increase in blood pressure was potentiated when the dogs ran on a treadmill. They attributed this potentiated response to a marked vasoconstriction within the nonexercising vascular beds mediated by an increase in sympathetic neural activity. Thus, when carotid baroreceptors remain intact and are unable to respond to changes in blood pressure, the increase in blood pressure evoked during exercise was augmented. This exaggerated sympathetic neural response was supported by our finding that the increase in MAP and HR was greater when the exercise pressor reflex and the carotid sinus baroreflex were activated to mutually evoke sympathoexcitation.

However, the combined effect of inhibiting the carotid sinus baroreflex and activating the skeletal muscle receptors yielded responses that were significantly less than when each afferent pathway was activated separately. The summation of inputs from multiple neural pathways depends on whether the sensory inputs are excitatory or inhibitory (1, 28). Sagawa (28) found that the interaction between selected baroreceptor populations was dependent on whether the reflex was decreasing or increasing SNA. To address these issues, we have proposed a model to predict summation of sensory input from the baroreflex and the exercise pressor reflex (Fig. 5). The carotid baroreflex is considered an excitatory input signal to the CNS that increases SNA despite the elevation in arterial blood pressure. However, for the baroreflex to function as an excitatory input it must first rapidly reset to a higher arterial pressure. Classic resetting of the carotid baroreflex during dynamic exercise has

Fig. 4. Summary of average peak change in MAP (A) and HR (B) from 6 cats when muscle stretch and bilateral carotid occlusion were evoked 1) separately, 2) simultaneously, 3) by algebraic summation of the separate responses, and 4) by CNS ischemia. Values are means ± SE. *Significantly different from control, $P < 0.05$. **Significantly different from baroreflex and/or muscle stretch, $P < 0.05$. †Significantly different from coactivation, $P < 0.05$. ‡Significantly different from algebraic summation, $P < 0.05$.

Fig. 5. Hypothetical model to predict summation of sympathetic nerve activity (SNA) between carotid baroreceptor reflex (Baroreflex) and exercise pressor reflex (Muscle reflex). Both reflexes are shown as an excitatory input signal that, when activated, will produce sympathoexcitation. Inhibition of baroreflex (top) by bilateral carotid occlusion increased sympathetic activity (+++ SNA). Magnitude of increase in SNA is depicted by “+” signs. Activation of muscle reflex (middle) by muscle contraction and passive stretch produced similar increases in sympathetic activity (+++ SNA). When both reflexes were evoked simultaneously (bottom), SNA response was augmented (++++ SNA). Because SNA response produced by both reflexes (++++ SNA) is less than summation of individual SNA responses (++++ SNA), this shows that interaction between baroreflex and muscle reflex is inhibitory. Thus summation of a response produced by 2 separate reflex pathways cannot simply be added together to predict response when both pathways are activated simultaneously. See DISCUSSION for further details.
been demonstrated by Potts et al. (25) and Paplier and colleagues (22). Although the time course for baroreflex resetting has not been determined, several studies have shown that the cardiovascular responses during the initial onset of exercise were altered when pharmacologically induced changes in blood pressure were used to perturb the baroreflex (6, 29). In these studies, it was shown that, if the baroreceptor signal is considered an excitatory input, activation of both reflexes would produce a larger increase in SNA. This finding was supported by the present study. Because summing the individual blood pressure responses exceeded the response during coactivation, the net effect was that the carotid baroreflex and the exercise pressor reflex interacted in an occlusive manner. Thus this model illustrates that summation of a response produced by two separate reflex pathways cannot simply be added together to predict the response when both pathways are activated simultaneously. Furthermore, this study demonstrates that the interaction between two reflex systems that were mutually activated to increase sympathetic outflow was occlusive.

This interaction may have resulted from redundancy in the common shared components (i.e., central/efferent pathways, inotropic/chronotropic responses, vascular smooth muscle responses) of these two pressure-raising reflexes (1, 5, 10, 34). To determine whether the inhibitory interaction was produced at a peripheral (i.e., saturation of effector organs) or a central (i.e., common central and efferent pathways) site, the reflex cardiovascular response to transient CNS ischemia was compared with the response evoked during activation of both reflex pathways. The rationale was that if the HR and blood pressure response to CNS ischemia was equal to or less than the responses during coactivation, then the inhibitory interaction could be ascribed to saturation of the end organs (i.e., heart, resistance vessels) that were responsible for generating the increases in HR and blood pressure. However, the resulting increases in MAP and HR to this maneuver were significantly greater than the responses obtained by coactivation and summation (see Figs. 2 and 4, Table 2). Therefore, the inhibitory interaction between these two reflexes was not produced by a reduction in the capacity of the heart and resistance vessels to increase MAP. This suggests that site(s) within the CNS (central autonomic pathways, efferent preganglionic sympathetic pathways, spinal cord) were involved in mediating the inhibitory interaction between the baroreflex and the exercise pressor reflex. Therefore, this model can be used to explain summation of the cardiovascular responses when both the exercise pressor reflex and the arterial baroreceptor reflex are considered “excitatory” sensory inputs to the CNS.

Additive summation for HR control. In the present study we reported an inhibitory interaction for the reflex control of MAP. However, summation of the reflex tachycardia was simply additive. That is, the combined effect of reflex activation on the increase in MAP was only 66% of the summated response (80 vs. 106 mmHg; coactivation vs. summation, respectively), whereas summation of the reflex tachycardia during combined activation was equal to the summated HR response (26 vs. 26 beats/min, coactivation vs. summation, respectively). A possible explanation for this finding may have been the absence of parasympathetic control of the heart in this study. Bilateral cervical vagotomy was performed to eliminate the reflex buffering by both aortic and cardiopulmonary baroreceptors. If aortic baroreceptors remained intact, the cardiovascular responses produced by the carotid baroreflex and the exercise pressor reflex would have been attenuated (28, 31, 35). Although vagotomy prevented vagally mediated changes in HR, we felt that this would not affect the interaction because it has been shown that α-chloralose anesthesia virtually eliminates vagal control of HR (4). Furthermore, it is likely that complete expression of a chronotropic response requires both withdrawal of vagal tone and an increase in cardiac SNA (20). Therefore, in the absence of vagal control of HR reported in this study, it is difficult to reconcile the additive summation between these two reflex pathways.

Several other possibilities may explain the additive summation for HR. Viscerotropism of central and efferent sympathetic pathways may have also contributed to the difference in summation between the reflex control of HR and blood pressure (14, 33). It is well documented that the discharge of sympathetic efferent activity to different peripheral vascular beds and organs is nonuniform (5, 9). Therefore, activation of carotid baroreceptor and skeletal muscle afferents may have resulted in a differential response in SNA directed to the heart and selected vascular beds. This differential regulation of efferent sympathetic activity may have contributed to the difference in summation between HR and blood pressure reported in this study.

Finally, summation of skeletal muscle and baroreceptor responses may differ between the sympathetic and parasympathetic branches of the autonomic nervous system. There is a clear separation in the central projections between nuclei controlling sympathetic and parasympathetic preganglionic motoneurons (9, 33). Furthermore, the neurochemical transmitters mediating central neurotransmission are different between the parasympathetic and sympathetic nervous systems. Therefore, differences in the central interaction of HR and MAP may have arisen from dissimilarities in the anatomic organization and the neurochemical transmission between the sympathetic and parasympathetic nervous systems. On the basis of the findings from this study, it is not possible to distinguish between these mechanisms.

Potential limitations of the study. First, lack of complete surgical isolation of the carotid sinus regions represents a potential problem in the interpretation of these findings. We found that, accompanying the increase in blood pressure produced by bilateral carotid occlusion and muscle contraction/stretch, the pressure in the carotid sinus region also increased gradually during this period. Therefore, the afferent signal from carotid baroreceptors was not constant over the period
of muscle contraction and this may have influenced our results. However, the change in sinus pressure during BCO was similar to that produced when carotid occlusion was accompanied by muscle contraction or stretch (48 ± 7 mmHg vs. 55 ± 8 mmHg, baroreflex vs. coactivation, respectively, t = −0.745, df = 20, P = 0.465). Hence, the increase in sinus pressure was equivalent during each perturbation, and therefore, this effect likely contributed to a similar degree in determining the integration between these two reflexes.

Second, the paradigm that we used to determine the interaction between these two reflexes only evaluated summation of the cardiovascular responses from a single point (operating point) on the stimulus-response relationship of each reflex. Numerous studies have shown that the stimulus-response relationship of the arterial baroreflex is essentially nonlinear (for review see Ref. 28). However, less is known of the stimulus-response profile of the skeletal muscle reflex. It has been shown that this reflex 1) is exclusively excitatory, 2) can be activated in a "dose-dependent" manner, and 3) has a saturation plateau (4, 17, 19). On the basis of these facts, our discussion of the inhibitory interaction between these two reflex systems must be restricted to the following caveats: 1) that the baroreflex is deactivated to a point below its threshold pressure that will evoke maximal sympathoexcitation (assuming the operating point of the reflex is at the middle of the baroreflex curve) (28) and 2) that the skeletal muscle reflex is not fully activated, and, therefore, sympathoexcitation is not maximal. Whether the interaction between these two reflex pathways is also inhibitory under other conditions (i.e., at threshold or maximal levels) is currently under investigation.

Third, hindlimb perfusion may have been altered when electrically induced muscle contraction was combined with activation of the baroreflex. Coactivation potentiated the pressor response (ΔMAP 30 mmHg), which may have increased perfusion to the contracting hindlimb, and, therefore, reduced the afferent "signal" from skeletal muscle by washing out the metabolic by-products that are known to activate metabolically sensitive receptors (19). Electrically induced muscle contraction has been reported to increase hindlimb blood flow (35). However, Waldrop and Mitchell (35) found that blood flow to the contracting hindlimb was not affected after acute baroreceptor deafferentation that significantly increased the pressor response during muscle contraction. Furthermore, the possibility that the increase in blood pressure affected the integration of sensory input from these two reflexes is unlikely because the interaction between the baroreflex and activation of the exercise pressor reflex by passive muscle stretch (a stimulus that does not alter skeletal muscle perfusion or muscle oxygenation) was the same as the interaction that resulted during electrically induced muscle contraction. Therefore, any change in muscle blood flow that may have occurred during activation of either reflexes was not a sufficient stimulus to alter the interaction between the baroreflex and the exercise pressor reflex.

Finally, although single fiber recordings have shown that group III/IV muscle afferents discharge during electrically induced muscle contraction and passive stretch (11, 18), some group III/IV afferents also exhibit nociceptive properties (12). At least a portion of these muscle afferents are polymodal, thereby precluding precise categorization of these fibers. Therefore, although the responses in the present study are thought to have resulted from ergoreceptor activation, we cannot rule out the possibility that some of these responses may have been mediated by contraction- and stretch-induced muscle nociceptors.

Summary. Findings from the present study demonstrate a central neural occlusive interaction between the carotid baroreflex and the exercise pressor reflex. When both reflexes were activated to increase sympathetic outflow, the reflex cardiovascular responses were attenuated 33% compared with when each reflex was activated separately and the responses summated. This result suggests an occlusive interaction between the exercise pressor reflex and the carotid baroreceptor reflex. Moreover, inhibition of sympathetic outflow occurred at site(s) located in the CNS and was not attributed simply to the inability of effector organs to generate increases in HR and blood pressure. However, within the constraints of the present study, summation of the chronotropic response was simply additive. This contrast in summation may be attributed to the absence of parasympathetic innervation of the heart and/or to differences in the central circuitry and descending effenter pathways that project to the heart and the peripheral vasculature.

In conclusion, these data indicate that reflex sympathoexcitation evoked by inhibition of the carotid baroreflex and activation of the exercise pressor reflex is integrated in an occlusive manner. A similar degree of inhibition was found between these two reflexes when muscle afferents were activated by either muscle contraction or passive stretch. This suggests that central integration of somatic input from mechanosensitive receptors (passive muscle stretch) and combined mechano- and metaboreceptors (electrically induced muscle contraction) is similar. The anatomic substrates and the electrophysiological/neurochemical mechanisms mediating the central neural occlusive interaction between arterial baroreceptors and the skeletal muscle receptors await further investigation.

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Address for reprint requests: J. T. Potts, Dept. of Physiology, Harry S. Moss Heart Center, Univ. of Texas Southwestern Medical Center, 5323 Harry Hines Blvd. Dallas, TX 75235-9034.

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