Differential effect of central command on aortic and carotid sinus baroreceptor-heart rate reflexes at the onset of spontaneous, fictive motor activity

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Matsukawa K, Ishii K, Kadowaki A, Liang N, Ishida T. Differential effect of central command on aortic and carotid sinus baroreceptor-heart rate reflexes at the onset of spontaneous, fictive motor activity. Am J Physiol Heart Circ Physiol 303: H464–H474, 2012. First published June 22, 2012; doi:10.1152/ajpheart.01133.2011.—Our laboratory has reported that central command attenuates the sensitivity of the carotid sinus baroreceptor-HR reflex at the onset of voluntary static exercise in conscious cats and spontaneous contraction in decerebrate cats. The purpose of this study was to examine whether central command attenuates the sensitivity of the carotid sinus baroreceptor-HR reflex at the onset of spontaneous motor activity. Although the baroreflex bradycardia by electrical stimulation of the carotid sinus nerve (CSN) was suppressed ($P < 0.05$) to 86 ± 5.6% of the control (38 ± 1.2 beats/min), the inhibitory effect of spontaneous motor activity was much weaker ($P < 0.05$) with CSN stimulation than with AN stimulation. The baroreflex bradycardia elicited by brief occlusion of the abdominal aorta was blunted to 36% of the control (36 ± 1.6 beats/min) during spontaneous motor activity, suggesting that central command is able to inhibit the cardiomotor sensitivity of arterial baroreflexes as the net effect. Mechanical stretch of the triceps surae muscle never affected the baroreflex bradycardia elicited by AN or CSN stimulation and by occlusion, suggesting that muscle mechanoreflex did not modify the cardiomotor sensitivity of aortic and carotid sinus baroreflex. Since the inhibitory effect of central command on the carotid baroreflex pathway, associated with spontaneous motor activity, was much weaker compared with the aortic baroreflex pathway, it is concluded that central command does not force a generalized modulation on the whole pathways of arterial baroreflexes but provides selective inhibition for the cardiomotor component of the aortic baroreflex.

bradycardia; exercise; muscle mechanoreflex; precollicular-premamillary decerebrate cats

ARTERIAL BARORECEPTORS in the aortic arch and the carotid sinuses convey afferent information about arterial blood pressure (AP)-evoked distension of the arterial vessels to the vasomotor centers and constitute the aortic baroreflex and carotid sinus baroreflex arc, respectively. The arterial baroreflexes represent a negative feedback mechanism to help AP maintain constant. However, since AP and heart rate (HR) simultaneously increase during exercise, sympathetic activation can override arterial baroreflex function without changing its characteristics, or otherwise the arterial baroreflex function can be modified during exercise. The effect of central command on the stimulus-response curve of the carotid sinus baroreflex during the steady-state period of static or dynamic exercise in humans and conscious dogs has been assessed by characterizing the threshold pressure, operating point, and gain of the carotid sinus baroreflex (2, 31, 38, 39, 41). Augmented central command during exercise in humans with partial neuromuscular blockade caused a resetting of the stimulus-response curve of the carotid baroreflex to a higher blood pressure without changing the gain (13, 42, 46). This type of resetting of the carotid baroreflex was similarly observed during electrical stimulation of the mesencephalic locomotor region in decerebrate cats (29). However, dynamic beat-to-beat modulation by central command of the arterial baroreflex function during exercise, especially at the beginning of exercise, has been little identified.

Our laboratory recently reported that the baroreflex bradycardia due to stimulation of the aortic nerve (AN) is blunted immediately before or at the onset of voluntary static exercise in conscious cats (22) and also at the onset of spontaneous contraction in decerebrate cats (34). This is in agreement with previous studies (3, 49) that reduction in the arterial baroreflex sensitivity occurred at the onset of ergometer exercise in humans. In particular, the attenuating effect on the baroreflex bradycardia, seen immediately before the onset of exercise, leads to an assumption that central command plays an important role in blunting the sensitivity of the aortic baroreceptor-HR reflex and thereby contributes to an instantaneous increase in HR (25, 28). In contrast, neither electrically evoked contraction nor passive mechanical stretch of skeletal muscle altered the baroreflex bradycardia due to AN stimulation in decerebrate cats, indicating that exercise pressor reflex does not affect the sensitivity of the aortic baroreflex function (34). The blunted baroreflex bradycardia due to AN stimulation, immediately before or at the onset of voluntary static exercise, appeared with a relatively low exercise intensity lifting ~20–30% of body weight in conscious cats (22, 26). On the other hand, regarding the carotid sinus baroreflex, the bradycardia response to a step increase in carotid sinus transmural pressure was not altered during static handgrip with a low intensity of 15–30% of maximal voluntary contraction (MVC) in humans (12). The blunted response of the carotid sinus baroreflex bradycardia required a higher intensity of isometric handgrip exercise with 45–65% of MVC (12, 23, 24). Taken together, it is hypothesized that central command imposes differential influence on the cardiomotor components of aortic and carotid sinus baroreflexes at the onset of exercise.

To test this hypothesis, we examined the effects of central command on the aortic and carotid sinus baroreflex function using unanesthetized, decerebrate cats, which were able to...
elicit spontaneous motor activity under muscle paralysis and to represent the rapid cardiovascular responses associated with the spontaneous, fictive motor activity (10, 15, 27, 44). The aortic and carotid sinus baroreflex function was assessed by determining the bradycardia elicited by electrical stimulation of the AN or the carotid sinus nerve (CSN), respectively. The changes in the baroreflex bradycardia due to the AN or CSN stimulation given at the onset of spontaneous motor activity were considered to reflect the influences of central command on the cardiac limb of the aortic or carotid sinus baroreflex pathways within the brainstem.

METHODS

The present study was conducted using 13 cats weighing between 2.5 and 3.4 kg, in accordance with the Guiding Principles for the Care and Use of Animals in the Fields of Physiological Sciences approved by the Physiological Society of Japan and the Guideline for Animal Experiment in Hiroshima University. The experimental protocols were approved by the Committee of Research Facilities for Laboratory Animal Science, National Science Center for Basic Research and Development, Hiroshima University.

Preparations. The animals were anesthetized by inhaling of a halothane (4%)-N₂O-O₂ gas mixture so that the catheters could be implanted, decerebration surgery could be performed, and AN and CSN could be isolated. An endotracheal tube was inserted into the airway, and the lungs ventilated with 0.5–1.0% halothane through the endotracheal tube. Electrocardiogram (ECG), HR, and thoracic respiratory movements were monitored throughout the experiments. To maintain a surgical level of anesthesia, the concentration of halothane was increased to 1.5–2.5% if HR and/or respiration spontaneously increased and/or if limb withdrawal occurred in response to a noxious pinch of the paw. Polyvinyl catheters were inserted into the right cephalic vein or left external jugular vein for administering drugs and into the right brachial artery for measuring AP. The arterial catheter was connected to a pressure transducer (DPT-6100; Kawasumi Laboratories, Tokyo, Japan). HR was derived from the R wave of ECG or the arterial catheter and was connected to a pressure transducer (DPT-6100; Kawasumi Laboratories, Tokyo, Japan). Decerebration was performed by electrocoagulation at the precollicular-premammillary level as previously described (21, 27, 33, 34, 44). To do this, a stainless steel electrode with insulation removed 5 mm from the tip was inserted into the hypothalamic rostral to the mammillary bodies (coordinates from the midpoint of interaural line: anterior 13 mm, horizontal 6 mm, lateral 1–11 mm with an angle of 14° from perpendicular line; from stereotaxic atlases; Refs. 1, 47). A negative DC current (1 mA) was passed through the electrode for 30 s. The electrode was withdrawn 4 mm, and the current was passed again. This procedure was bilaterally repeated for a total of 42 tracks at 0.5-mm intervals. At the end of each experiment, the animal was killed with an overdose of pentobarbital sodium and the transected area of the brain was examined histologically. We confirmed that the cerebral cortex, the thalamus, and a rostral part of the hypothalamus (the anterior hypothalamic area, the supraoptic nucleus, and the rostral part of the lateral hypothalamic area) were disconnected from the brain stem as previously reported (27, 44).

After the decerebration was completed, the cat was removed from the stereotaxic frame and placed in the lateral posture. The AN (n = 10 cats) was isolated at the cervical level on the left side from the vago-sympathetic nerve bundle and surrounding connective tissue. In 9 of the 10 cats, the CSN was also separated from surrounding connective tissue at the cervical level on the left side (n = 1 cat) or the right side (n = 8 cats). Each nerve bundle was left intact and placed on a pair of Ag-AgCl electrodes for electrical stimulation. After confirmation of the characteristic baroreceptor discharges, each nerve-electrode complex was imbedded in a liquid paraffin pool. The left tibial nerve innervating the triceps surae muscle was dissected at the popliteal fossa in all 13 cats. For measurement of tibial motor nerve activity, the tibial nerve bundle was placed on a pair of Teflon-coated silver-wire electrodes and then the peripheral portion of the nerve bundle was ligated. The original tibial motor activity was amplified by a differential preamplifier (S-0476, Nihon Kohden, Tokyo, Japan) with a band-pass filter of 50 and 3,000 Hz. The amplified output was rectified and integrated with a resistance-capacitance integrator having a time constant of 20 ms. We simultaneously recorded bilateral tibial efferent nerve activities in additional five decerebrate cats. Spontaneous motor activity accompanied alternating rhythmic burst discharges between the tibial motor nerves, which lasted for 11 ± 4 s (n = 5 cats). The average interburst interval was 0.56 ± 0.10 s, which was within the normal range of the stepping cycle period during walking in conscious cats (43). Thus it is considered that tibial motor discharge reflected spontaneous fictive coordinated motor activity.

Baroreceptor stimulation. The AN or the CSN was electrically stimulated by using a train of electrical pulses at a frequency of 50 Hz for 1 s (pulse intensity, 3.2 ± 1.7 V or 0.26 ± 0.12 mA; pulse duration, 0.5 ms). The magnitude of the baroreflex bradycardia obtained during resting was defined as the control response. To determine the effect of central command during spontaneous motor activity on arterial baroreflex function, electrical stimulation of the AN or the CSN was then delivered during spontaneous motor activity in an individual cat with muscle paralysis. Furthermore, to determine the effect of muscle mechanoreflex on arterial baroreflex function, electrical stimulation of the AN or the CSN was delivered before, during, and after passive stretch of a hindlimb.

To naturally activate both aortic and carotid sinus arterial baroreceptors, the abdominal aorta was occluded for a brief period of 3.7 ± 0.1 s using a snare wound around the aorta above the left renal artery in eight cats. The baroreflex bradycardia in response to the brief occlusion of the abdominal aorta was examined before, during, and after spontaneous motor activity or passive muscle stretch.

Protocols. After all surgical and preparatory procedures were completed, inhalation anesthesia was stopped and then a neuromuscular blocker (pancuronium bromide, 2 ng) was intravenously administered. The experiments were started 2–3 h after the cessation of halothane anesthesia. Without any kind of artificial stimulation, the paralyzed, decerebrate cats were able to evoke spontaneous motor activity that was identified by recording tibial motor nerve activity. Therefore, the cardiovascular responses during the spontaneous motor activity were elicited by central command but not by exercise pressor reflex.

To evaluate the effects of central command on the cardiac components of the aortic and carotid sinus baroreflexes, either AN (n = 10 cats) or CSN stimulation (n = 9 cats) was delivered before spontaneous, fictive motor activity (n = 136 trials for AN; n = 204 trials for CSN); at the start of spontaneous motor activity (3.3 ± 0.1 s from the motor onset; n = 144 trials for AN; n = 221 trials for CSN); at the middle of spontaneous motor activity (11.5 ± 0.4 s from the motor onset; n = 48 trials for AN; n = 81 trials for CSN); immediately after spontaneous motor activity (4.4 ± 0.4 s from the cessation of motor activity; n = 52 trials for AN; n = 23 trials for CSN); and more than 10 s after spontaneous motor activity (31.7 ± 0.9 s from the cessation of motor activity; n = 132 trials for AN; n = 205 trials for CSN).

To identify the effects of a muscle mechanoreflex on aortic and carotid sinus baroreflex function, either AN (n = 6 cats) or CSN stimulation (n = 5 cats) was delivered during mechanical stretch of the left triceps surae muscle for 30 s (n = 25 trials for AN stimulation; n = 14 trials for CSN stimulation). The baroreceptor stimulation was delivered at the start of mechanical muscle stretch (5.4 ± 0.5 s from the stretch onset; n = 23 trials for AN; n = 14 trials for CSN); at the middle of mechanical muscle stretch (17.7 ± 1.0 s from the stretch onset; n = 13 trials for AN; n = 10 trials for CSN); and after...
mechanical stretch (n = 22 trials for AN; n = 13 trials for CSN). The changes in the hindlimb joint angles during mechanical stretch were traced with marks affixed on the joints. The hip and knee joints were manually extended during mechanical stretch of the hindlimb by 12 ± 4 and 48 ± 5°, respectively, and the ankle joint was maximally dorsiflexed by 36 ± 4°. The length of the lateral gastrocnemius muscle (114 ± 3 mm at rest) was not altered by extending the hip and knee joints but was increased to 128 ± 2 mm by subsequent dorsiflexion of the ankle joint when verifying muscle length with postmortem examination in accordance with our previous studies (20, 34).

The baroreflex bradycardia in response to the brief occlusion of the abdominal aorta, which naturally activated both aortic and carotid sinus arterial baroreceptors, was examined during spontaneous, fictive motor activity (n = 8 cats) or during mechanical stretch of the triceps surae muscle (n = 6 cats). Aortic occlusion was delivered before (n = 81 trials), at the start of (5.0 ± 0.5 s from the motor onset; n = 106 trials), and after spontaneous motor activity (n = 73 trials). Furthermore, aortic occlusion was delivered before (n = 20 trials), during (12.8 ± 1.3 s from the stretch onset; n = 21 trials), and after mechanical muscle stretch (n = 15 trials). The baroreflex sensitivity was defined from a ratio between the baroreflex bradycardia and the increase in systolic arterial blood pressure (SAP) or mean arterial blood pressure (MAP) due to the aortic occlusion.

Data treatment and statistical analysis. HR, AP, ECG, original and rectified tibial motor activity, and a marking signal for electrical stimulation of the AN or the CSN were continuously recorded on an eight-channel pen-writing recorder (Recti-8K; GE Marquette Medical Systems). The data were also stored in a computer with an analog-to-digital converter (MP150; BIOPACK Systems, Santa Barbara, CA) at a sampling frequency of 2 kHz. The beat-to-beat values of the cardiovascular variables were recalculated with the R wave of the ECG using a software program (AcqKnowledge 3.9.1; BIOPACK Systems). HR, AP, original and rectified tibial motor activity, and the signal marking the baroreceptor stimulation were displayed on a computer screen. The start and end of spontaneous motor activity were visually determined using the rectified tibial motor nerve activity. The baseline levels of the cardiovascular variables were defined as the mean values for >30 beats preceding the onset of spontaneous motor activity. The cardiovascular changes from the baseline levels in a given trial were aligned at the onset of spontaneous motor activity and further averaged. The average cardiovascular changes represented the responses to central command in association with spontaneous motor activity in the paralyzed condition. The average cardiovascular changes during mechanical muscle stretch were similarly analyzed and represented the reflex responses to stimulation of muscle mechanoreceptors. The time-course data of the cardiovascular responses during spontaneous motor activity or during mechanical muscle stretch were statistically analyzed by a one-way ANOVA with repeated measures. When a significant F value in the main effect of time was present, a Dunnett’s post hoc test was performed to detect a significant difference from the control.

The change in HR in response to the baroreceptor stimulation in a given trial of spontaneous motor activity or passive muscle stretch was defined as ΔHRstim. The time at which ΔHRstim was detected was defined as Tstim. The mean change in HR at Tstim during spontaneous motor activity or passive muscle stretch without the baroreceptor stimulation was defined as ΔHRref. Thus the net decrease in HR (ΔHRnet) due to the baroreceptor stimulation was calculated as (ΔHRnet = ΔHRref − ΔHRstim). The ΔHRref was also expressed as a relative percent value against the 100% control response to the baroreceptor stimulation observed during resting. The relative percent values of ΔHRnet were compared before, during (at the onset and in the middle of), and after each muscle intervention by a one-way ANOVA and the Dunnett’s post hoc test. Similarly, the average values of the baroreflex bradycardia and baroreflex sensitivity due to the aortic occlusion were statistically compared before, during, and after spontaneous, fictive motor activity or mechanical muscle stretch. The level of statistical significance was defined as P < 0.05. The data are expressed as means ± SE.

RESULTS

The cardiovascular responses during spontaneous, fictive motor activity. The preexercise baseline values of HR and MAP were 220 ± 2 beats/min and 137 ± 1 mmHg, respectively. The cardiovascular responses during spontaneous, fictive motor activity are represented in Figs. 1 and 2A. HR and MAP significantly (P < 0.05) increased at the start of spontaneous motor activity, the average duration of which was 87 ± 2.7 beats (21 ± 0.9 s). The increase in HR became significant at the 3rd beat from the motor onset and reached the peak value of 11 ± 0.8 beats/min at the 26th beat, while the rise in MAP became significant at the 9th beat and reached the peak value of 28 ± 1.5 mmHg at the 32nd beat (Fig. 1).

Effect of spontaneous motor activity on the baroreflex bradycardia by electrically-induced baroreceptor stimulation. Electrical stimulation of either the AN or the CSN transiently decreased HR during resting, as shown in Fig. 2. The size of

![Fig. 1. Beat-to-beat changes in heart rate (HR), mean arterial blood pressure (MAP), and tibial motor nerve activity during spontaneous motor activity in paralyzed, decerebrate cats. Data show means ± SE values. A vertical dotted line indicates the onset of spontaneous motor activity. A horizontal column and a small bar at the bottom indicate the mean ± SE value of the duration of spontaneous motor activity. AU, arbitrary unit.](http://ajpheart.physiology.org/)

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the AN-stimulation induced baroreflex bradycardia was $21 \pm 1.3$ beats/min with a latency of $4.4 \pm 0.1$ beats ($1.33 \pm 0.03$ s), while the size of the CSN-stimulation induced bradycardia was $38 \pm 1.2$ beats/min with a latency of $3.8 \pm 0.1$ beats ($1.26 \pm 0.02$ s). The AN stimulation-induced baroreflex bradycardia response was markedly attenuated at the onset and in the middle of spontaneous, fictive motor activity as demonstrated in Fig. 2B. On the contrary, the bradycardia response to the AN stimulation became exaggerated immediately after the cessation of the spontaneous motor activity. In contrast to the AN stimulation, the size of the CSN stimulation-induced baroreflex bradycardia was unaffected by spontaneous, fictive motor activity in the same cat (Fig. 2C).

The $\Delta HR_{net}$ elicited by electrical stimulation of the AN or the CSN, given during spontaneous motor activity, was quantitatively analyzed by subtracting the $\Delta HR_{ref}$ during spontaneous motor activity without the baroreceptor stimulation from the $\Delta HR_{stim}$ in response to the baroreceptor stimulation. The $\Delta HR_{net}$ value was further expressed as relative percent values against the preexercise control response to the baroreceptor stimulation.

Fig. 2. Effects of spontaneous motor activity on the baroreflex bradycardia evoked by electrical stimulation of the aortic nerve (AN) or the carotid sinus nerve (CSN) in the same paralyzed, decerebrate cat. Each arrow indicates the time at which nerve stimulation was applied. A: during spontaneous motor activity without stimulation. AN stimulation was given once at rest. B: during spontaneous motor activity with AN stimulation. C: during spontaneous motor activity with CSN stimulation. Baroreflex bradycardia evoked by AN stimulation was suppressed during spontaneous motor activity, whereas the baroreflex bradycardia evoked by CSN stimulation was unchanged.
Fig. 3. Effects of spontaneous motor activity on the baroreflex bradycardia evoked by stimulation of the AN (A) and the CSN (B) are summarized. Baroreflex bradycardia (ΔHRnet) evoked by AN stimulation was strongly suppressed during spontaneous, fictive motor activity. ΔHRnet evoked by CSN stimulation was slightly but significantly suppressed. Inhibitory effect of spontaneous motor activity on the baroreflex bradycardia was much greater (P < 0.05) with AN stimulation than with CSN stimulation. Onset, at the onset of spontaneous motor activity; middle, in the middle of spontaneous motor activity. *P < 0.05, significant changes from the control response before spontaneous motor activity. †P < 0.05, significant differences in the relative reflex bradycardia (%) between the AN and CSN stimulations.

Effects of spontaneous motor activity and mechanical muscle stretch on the baroreflex bradycardia by mechanically induced baroreceptor stimulation. As exemplified in Fig. 6, a brief occlusion of the abdominal aorta produced increases in SAP and MAP by 37 ± 1.3 and 26 ± 1.1 mmHg during resting, respectively, which simultaneously stimulated both aortic and carotid sinus baroreceptors. The natural increases in SAP and MAP caused the baroreflex bradycardia of 36 ± 1.6 beats/min, and the baroreflex sensitivity (defined as a ratio between the baroreflex bradycardia and the increase in SAP or MAP) was 1.05 ± 0.05 beats·min⁻¹·mmHg⁻¹ for SAP and 1.56 ± 0.08 beats·min⁻¹·mmHg⁻¹ for MAP. The effect of spontaneous, fictive motor activity on the baroreflex bradycardia in response to occlusion of the abdominal aorta is shown in Figs. 6 and 7. During spontaneous motor activity, the baroreflex bradycardia in response to the aortic occlusion was significantly (P < 0.05) blunted to 12.7 ± 1.9 beats/min, despite greater increases in SAP and MAP (43 ± 1.6 and 34 ± 1.3 mmHg, respectively). Accordingly, the baroreflex sensitivity was significantly (P < 0.05) reduced during spontaneous motor activity to 0.34 ± 0.06 beats·min⁻¹·mmHg⁻¹ for SAP and 0.48 ± 0.08 beats·min⁻¹·mmHg⁻¹ for MAP, respectively (Fig. 7). Following spontaneous motor activity, the sizes of the baroreflex bradycardia and sensitivity returned to the preexercise control values.

In contrast to spontaneous motor activity, mechanical stretch of the triceps surae muscle did not modify (P > 0.05) the baroreflex bradycardia in response to the brief occlusion of the abdominal aorta (Figs. 6 and 7). The sizes of the baroreflex bradycardia and its sensitivity were not significantly different.
Dicate that central command can evoke the differential effects during mechanical muscle stretch. These present findings in sinus baroreceptors, due to occlusion of the abdominal aorta, dia evoked by naturally stimulating both aortic and carotid sinus baroreflex function; and the triceps surae muscle influenced neither aortic nor carotid bradycardia by AN stimulation; bradycardia by CSN stimulation compared with the baroreflex motor activity, evoked weaker suppression of the baroreflex 1 that central command, associated with spontaneous, fictive motor activity under muscle paralysis and the centrally induced cardiovascular adjustment. Our new major findings are spontaneous motor activity occurred after the cessation of mechanical muscle stretch.

\[ P > 0.05 \] before, during, and after passive muscle stretch (Fig. 7).

**DISCUSSION**

The present study has examined for the first time the differential effects of central command on the aortic and carotid sinus baroreceptor-HR reflexes using identical premammillary-precollicular decerebrate cats, which were able to elicit spontaneous motor activity under muscle paralysis and the centrally induced cardiovascular adjustment. Our new major findings are 1) that central command, associated with spontaneous, fictive motor activity, evoked weaker suppression of the baroreflex bradycardia by CSN stimulation compared with the baroreflex bradycardia by AN stimulation; 2) that mechanical stretch of the triceps surae muscle influenced neither aortic nor carotid sinus baroreflex function; and 3) that the baroreflex bradycardia evoked by naturally stimulating both aortic and carotid sinus baroreceptors, due to occlusion of the abdominal aorta, was also blunted during spontaneous motor activity but not during mechanical muscle stretch. These present findings indicate that central command can evoke the differential effects on the cardiac components of the aortic and carotid sinus baroreflexes at the onset of spontaneous, fictive motor activity, whereas it is unlikely that a muscle mechanoreflex contributes to modulation of the aortic and carotid sinus baroreflexes. Indeed, central command blunts the sensitivity of the cardiac component of the aortic baroreflex but relatively preserves the sensitivity of the carotid sinus baroreflex. Furthermore, as the net effect, central command blunts the sensitivity of the cardiac limb of the arterial baroreflex function, because the baroreflex bradycardia elicited by occlusion of the abdominal aorta was blunted during spontaneous motor activity.

**Limitations of this study.** Several substantial limitations are involved in this study. First, we did not determine whether the AN or CSN stimulation recruited A-fibers alone or both A- and C-fibers. Since baroafferent nerve stimulation at a low voltage (<4–5 V) predominantly activates A-fibers and the stimulation at a higher voltage is needed to activate C-fibers in the cat and rat (11, 37), the present nerve stimulation (average voltage, 3.2 V) may predominantly activate A-fibers. In addition, since both the AN and the CSN contain not only barosensitive but also chemosensitive afferents in the cat, the nerve stimulation might excite chemosensitive afferents as well. It is known that a chemoreflex from the aortic and carotid sinus bodies increases HR and AP (5). When increasing the intensity of the AN or CSN stimulation, we observed tachycardia and pressor response instead of bradycardia. As long as the intensity of the baroreceptor nerve stimulation was kept low, barosensitive afferents are likely to be more stimulated than chemosensitive afferents. Second, the present data were taken in the intact baroafferent condition, including the stimulated baroafferent nerves. Therefore, there is a possibility that the ongoing baroreceptor activity might interfere with the nerve stimulation, although the data were taken in the intact baroreceptor condition and baroreceptor afferent activity could be recorded. However, the possibility was unlikely because the attenuating effect of central command on the aortic baroreceptor-HR reflex was detected at the onset of spontaneous contraction, irrespective of whether the aortic nerve remained intact (this study) or was cut (34). Furthermore, when electrical stimulation of the intact AN was started either independently of the cardiac cycle or in synchronization with the cardiac cycle, the size of the baroreflex bradycardia and the attenuating effect of voluntary exercise on the baroreflex bradycardia were not significantly different between the two stimulation conditions (22). Thus the ongoing baroreceptor activity might not interfere with the baroreceptor nerve stimulation, although the baroreceptor nerve stimulation was not tested in the sinoaortic denervated condition. Third, either the AN or CSN stimulation induced baroreflex bradycardia but failed to show a depressor response in most cats. The duration and frequency of electrical train pulses were identical with those in our previous study (34) using the same animal preparation, which clearly represented both baroreflex bradycardia and depressor response. Probably, the absence of the depressor response in this study is due to a lower intensity of electrical stimulation (average 3.2 v) than that (average 5.0 v) in the previous study (34). Fourth, although passive stretch of skeletal muscle stimulates mechanoreceptors and elicits pure muscle mechanoreflex without secreting metabolic products in venous blood (50), it is not always identical with the mechanical event of muscle contraction. Indeed, a correlation between group III mechanoreceptors that responded

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**Fig. 4.** Effects of mechanical stretch of the triceps surae muscle on the baroreflex bradycardia evoked by stimulation of the AN (A) or the CSN (B) in the same decerebrate cat. Each arrow indicates the time at which nerve stimulation was applied. Mechanical muscle stretch did not affect the baroreflex bradycardia irrespective of the AN stimulation or the CSN stimulation. ★Spontaneous motor activity occurred after the cessation of mechanical muscle stretch.
to stretch and those that responded to contraction was not strong (16). Accordingly, the effect of muscle mechanoreflex on the carotid baroreflex function remains to be studied using CSN stimulation given at the onset of evoked muscle contraction. Finally, the present data with the baroreceptor nerve stimulation suggest the sensitivity of the baroreflex curve around the operating point but do not provide information about the characteristics of the entire baroreflex curve. We (28) have already shown that when the MAP-HR baroreflex curve was plotted from the baseline conditions with different levels of MAP, the baroreflex curve was not shifted at the onset of voluntary exercise but its sensitivity was significantly blunted. In this study, when the simultaneous changes in MAP and HR during occlusion of the abdominal aorta (as shown in Fig. 6) were plotted, the slope of the MAP-HR curve over 130–200 mmHg of MAP was reduced during spontaneous motor activity but not during mechanical stretch of the triceps surae muscle (the preliminary data are not shown). Taken together, it is likely that the sensitivity of the MAP-HR curve, presumably the cardiac component of the aortic baroreflex, was actually reduced during spontaneous motor activity.

Central command-evoked inhibition of the aortic baroreflex sensitivity at the onset of exercise. The effect of central command on the stimulus-response curve of the carotid sinus baroreflex during the steady-state period of static or dynamic exercise in humans and animal models has been assessed by characterizing the threshold pressure, operating point, and gain of the carotid sinus baroreflex (2, 29, 31, 38, 39, 41). Central command caused a resetting of the stimulus-response curve of the carotid baroreflex to a higher blood pressure during exercise without changing the gain in humans (2, 38, 39, 41), conscious dogs (31), and decerebrate cats (29). However, dynamic beat-to-beat modulation by central command of the aortic and carotid sinus baroreflex function during exercise, especially at the beginning of exercise, has never been compared. Recently, Komine et al. (22) demonstrated that the baroreflex bradycardia induced by AN stimulation is temporarily attenuated to $62\% \pm 5\%$ of the control at the onset of voluntary static exercise in conscious cats. The most marked degree of baroreflex blunting occurred immediately before or at the onset of muscular activity associated with volitional exercise, demonstrating that central command produces the inhibition of the aortic baroreceptor-HR reflex at the onset of static exercise in conscious cats (22). Similarly, the AN stimulation-induced baroreflex bradycardia was blunted to $55\% \pm 4\%$ of the control at the onset of spontaneous muscle contraction in precollicular-premammillary decerebrate cats, indicating that central command, originating in some central site(s) in the caudal part of the diencephalon and the brainstem caudal to the transected area, caused the inhibition of the cardiac limb of the aortic baroreflex within the brainstem (34). Although it could not be denied that exercise pressor reflex from the contracting muscle might contribute to the blunted sensitivity of the aortic baroreflex, the present finding that the AN stimulation-induced baroreflex bradycardia was blunted to $26\% \pm 4\%$ of the control at the onset of spontaneous motor activity in paralyzed, decerebrate cats confirms that central command plays an important role in the blunted sensitivity of the cardiac component of the aortic baroreflex. When the stimulus-response curve of the arterial baroreflex was constructed by lowering AP due to nitroprusside or elevating AP due to phenylephrine, a threshold blood pressure of the baroreflex curve did not alter at the onset of exercise but the gain was reduced (28). We consider, therefore, that the gain of the
stimulus-response curve of the aortic baroreflex is actually suppressed at the onset of spontaneous exercise by central command.

Relative preservation of the carotid sinus baroreflex function at the onset of exercise. The decrease in the bradycardia by AN stimulation was observed at the onset of voluntary static exercise the intensity of which was so low as to lift ∼20–30% of body weight (22, 26). In contrast to this result, the increase in the R-R interval to a step increase in carotid sinus transmural pressure was not blunted at the beginning of isometric handgrip exercise with such low intensity (12). Since a higher intensity of 45–65% MVC was required for blunting the carotid sinus baroreflex-induced lengthening of R-R interval at the beginning of isometric handgrip exercise (12, 23, 24), it is conceivable that central command with a strenuous effort may blunt the cardiac components of the aortic and carotid sinus baroreflexes, whereas central command with a weaker effort may blunt selectively the cardiac component of the aortic baroreflex alone. Our laboratory (22, 34) has already reported that central command causes the differential effect on the cardiac and vasomotor limb of the aortic baroreflex (i.e., inhibition of the cardiac limb vs. preservation of the vasomotor limb). In addi-

Fig. 6. Effects of spontaneous motor activity and mechanical muscle stretch on the baroreflex bradycardia evoked by brief occlusion of the abdominal aorta (shown by small bars) in the same decerebrate cat. Brief occlusion of the abdominal aorta caused a transient increase in AP and thereby a baroreflex decrease in HR. Naturally evoked baroreflex bradycardia was suppressed during spontaneous motor activity but not mechanical muscle stretch. Spontaneous motor activity occurred at the end of mechanical muscle stretch.
tion to this, the present finding that central command relatively preserved the cardiac component of carotid sinus baroreflex compared with aortic baroreflex suggests that central command imposes another differential effect for the cardiomotor control of the arterial baroreflexes (carotid sinus baroreflex vs. aortic baroreflex).

When aortic and carotid sinus baroreceptors were simultaneously stimulated due to occlusion of the abdominal aorta during spontaneous motor activity, the evoked baroreflex bradycardia was blunted as similarly as the AN-stimulation-induced bradycardia (Figs. 6 and 7). Accordingly, it is conceivable that the aortic bradoreflex and bradycardia sensitivity evoked by mechanically stimulating aortic and carotid sinus baroreceptors due to occlusion of the abdominal aorta were not altered during mechanical muscle stretch as well (Figs. 6 and 7). Thus it is suggested that the sensitivity of the cardiac component of carotid sinus baroreflex is not changed throughout the mechanical stretch. However, mechanical stretch of skeletal muscle is not always identical with the mechanical event of isometric exercise pressor reflex. If inputs from muscle mechanoreceptors and/or metaboreceptors contribute to such modulation of the arterial baroreflexes, the sizes of the reflex bradycardia and depressor response induced by AN or CSN stimulation would be altered during electrically evoked contraction or during mechanical stretch of skeletal muscle. With respect to the aortic baroreflex, this possibility is unlikely because both the AN stimulation-induced baroreflex bradycardia and depressor response during electrically evoked contraction and during mechanical muscle stretch were not different from the control responses (34). The present study confirmed that the baroreflex bradycardia induced by AN stimulation was not affected by mechanical stretch of the triceps surae muscle under paralysis (Figs. 4 and 5).

On the other hand, regarding the effect of exercise pressor reflex on the carotid sinus baroreflex function, Gallagher et al. (14), McIlveen et al. (29), and Potts and Mitchell (40) suggest that the stimulus-response curve for carotid sinus baroreflex control of HR is shifted toward a higher blood pressure and a higher HR during the steady state period of evoked muscle contraction but the gain of the carotid baroreflex is unaltered by exercise pressor reflex. It cannot be denied, however, that the characteristics of the carotid arterial baroreflex are dynamically altered from moment to moment during evoked contraction, especially at the onset of contraction. In this study, the baroreflex bradycardia due to CSN stimulation was not affected by mechanical stretch of the triceps surae muscle at whatever phase CSN stimulation was given (Figs. 4 and 5). In addition, the baroreflex bradycardia and baroreflex sensitivity evoked by mechanically stimulating aortic and carotid sinus baroreceptors due to occlusion of the abdominal aorta were not altered during mechanical muscle stretch as well (Figs. 6 and 7). Thus it is suggested that the sensitivity of the cardiac component of carotid sinus baroreflex is not changed throughout the mechanical stretch. However, mechanical stretch of skeletal muscle is not always identical with the mechanical event of isometric exercise pressor reflex.
contraction. A possibility that a reflex originating muscle mechanoreceptors activated by actual contraction may modify the cardiac component of carotid sinus baroreflex cannot be excluded. Indeed, McWilliam et al. (30) reported that cardiac vagal bradycardia in response to carotid sinus pressure elevation was inhibited at the start of evoked muscle contraction in decerebrate cats. Drew et al. (9) also reported that passive calf muscle stretch with concurrent muscle metaboreflex activation following exercise reduced the maximal gain of the cardiac component of carotid sinus baroreflex in humans. Thus the dynamic effect of exercise pressor reflex on the carotid baroreflex function remains to be investigated with CSN stimulation during evoked muscle contraction.

Underlying mechanisms for the differential effects of central command on the arterial baroreflex circuits. Hilton (17) and Coote et al. (7) reported for the first time that electrical stimulation of the hypothalamic defense area inhibited the baroreflex bradycardia, depressor, and sympatho-inhibitory response evoked by raising carotid sinus pressure and by electrically stimulating the CSN in anesthetized cats. In addition, Nosaka et al. (35, 36) reported that electrical and chemical stimulation of neurons in the defense areas of the hypothalamus and midbrain periaqueductal gray matter (PAG) suppressed both baroreflex bradycardia and depressor response provoked by AN stimulation in anesthetized rats. Thus it has been generally thought that stimulation of the defense areas in the hypothalamus and midbrain suppressed both cardiomotor and vasomotor components of arterial baroreflexes, irrespective of the carotid sinus or aortic baroreflex, although it was recently reported that electrical and chemical stimulation of the dorsomedial nucleus of the hypothalamus or the dorsal PAG inhibited the cardiomotor component of the aortic baroreflex in anesthetized rats but not the vasomotor component (6, 45).

Since the central inhibition of the AN stimulation-induced baroreflex bradycardia is observed with β-adrenergic blockade but is markedly attenuated or abolished with muscarinic blockade (34, 36, 45), the modulation by central command of the aortic baroreceptor-HR reflex will take place on barosensitive neurons along the aortic baroreflex arc targeting the cardiac parasympathetic nervous system. Whether the inhibitory influence of central command is a direct action on cardiac parasympathetic preganglionic neurons and/or whether it involves an interaction with neurons in the nucleus tractus solitarius (NTS) are unknown at present. Nevertheless, speculations on the underlying mechanisms for the baroreflex modulation by central command, referring to the effects of stimulation of the hypothalamic or midbrain defense area, are worthy. First of all, a presynaptic inhibition on the baroafferent terminals is ruled out, because stimulation of the hypothalamic or midbrain defense area unchanged the excitability of the AN and CSN (18, 20, 36). Next, preganglionic cardiac vagal neurons are likely as a target site, because Inui and Nosaka (18) reported that vagal bradycardia evoked by microinjection of glutamate into the nucleus ambiguus was suppressed by PAG stimulation. Finally, barosensitive neurons in the NTS are more likely as a target site, because Inui and Nosaka (18) reported using intracellular recording that electrical stimulation of the hypothalamic defense area induced a long-lasting postsynaptic inhibition in NTS neurons, which received monosynaptic input from the CSN. The postsynaptic inhibitory action of the hypothalamic stimulation was antagonized by ionophoretic application of bicuculline on the neurons, suggesting a postsynaptic inhibition mediated with GABA_A receptors (19, 48).

Although primary aortic and carotid sinus baroreceptor afferents project to the same regions of the NTS, they do not converge on the same secondary neurons (4, 8). Most barosensitive neurons recorded in the NTS, however, respond to stimulation of both AN and CSN (48), indicating a convergence of aortic and carotid sinus baroreceptor input on the same higher order neurons in the NTS. Unlike stimulation of the defense areas, central command in association with spontaneous motor activity does not force a generalized modulation on the whole pathways of arterial baroreflexes but provides differential control of the cardiomotor and vasomotor components of the arterial baroreflexes during exercise. To do this, central command may organize highly specific modulation of the arterial baroreflex circuits at the onset of exercise as proposed in Fig. 8. Central command may postsynaptically inhibit the second-order neurons in the cardiomotor pathway of the aortic baroreflex arc, which receive monosynaptic input from the aortic nerve.

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