Central Command Increases Sympathetic Nerve Activity During Spontaneous Locomotion in Cats

George Hajduczok, Jon S. Hade, Ally L. Mark, John L. Williams, and Robert B. Felder

A controversial issue in exercise physiology is the relative contribution of central command versus afferent input from contracting muscles and baroreceptors in the regulation of sympathetic nerve activity (SNA) during exercise. Recent studies of exercising humans have suggested that central command increases cutaneous sympathetic sudomotor nerve activity but have challenged the concept that central command contributes importantly to increases in vasomotor nerve activity to skin and skeletal muscle. The purpose of this study was to examine the influence of central command on renal SNA and lumbar SNA during spontaneous locomotion in decorticate cats. Unanesthetized decorticate cats that developed locomotion spontaneously or during electrical stimulation of the subthalamic locomotor region were studied in the presence and absence of input from skeletal muscle and baroreceptor afferents. Spontaneous rhythmic locomotion in the unparalyzed state was associated with significant increases in mean arterial pressure (MAP) from 106±10 to 133±11 mm Hg (p<0.05) and increases in renal SNA of 301±100% (p<0.05). During spontaneous fictive locomotion in paralyzed cats, there were also significant (p<0.05) increases in MAP (43±6%), renal SNA (183±32%), and lumbar SNA (223±83%). Baroreceptor denervation did not attenuate increases in MAP, renal SNA, and lumbar SNA during locomotion. During electrical stimulation of the subthalamic locomotor region in paralyzed cats, MAP increased by 43±17% (p<0.05), and renal SNA increased by 175±47% (p<0.05). These findings indicate that central command is capable of increasing sympathetic neural drive in unanesthetized decorticate cats. This increase in sympathetic drive occurs even in the absence of feedback from contracting muscles or from arterial and cardiopulmonary baroreceptors. (Circulation Research 1991;69:66–75)

Increases in heart rate, myocardial contractility, arterial pressure, and ventilation occur with the onset of exercise.1–3 Peripheral feedback and central command are mechanisms that have traditionally been proposed to account for the autonomic cardiovascular and respiratory changes associated with muscular exercise.4

The concept of central command invokes a feedback mechanism by which activation of cardiovascular and respiratory centers is accomplished by descending signals from the suprapontine regions that initiate somatomotor activity.5–7 Chemical or electrical stimulation of the subthalamic locomotor region (STLR) in the hypothalamus in animals produces both locomotion and increases in cardiopulmonary function,8–11 which simulate the responses to voluntary exercise in humans. Similar findings have been reported during spontaneous locomotion in unanesthetized decorticate cats.8–10

Although these studies5–11 have provided support for a role of central command in the cardiorespiratory adjustments to exercise, an area of recent controversy has been the role of central command in the sympathetic nerve responses to exercise. This controversy originated several years ago from studies in humans involving direct intraneural recordings of sympathetic nerve activity during exercise.12 These and subsequent studies13–15 demonstrated that central command increases heart rate but elicits no or only modest increases in muscle sympathetic nerve activity in humans. A recent study16 suggested that

From the Department of Internal Medicine and the Cardiovascular Center, University of Iowa College of Medicine and VA Medical Center, Iowa City, Iowa.

Supported by the American Heart Association, Iowa Affiliate (G.H.), National Institutes of Health grants HL-36224 (A.L.M.), HL-25488 (A.L.M.), HL-29302 (R.B.F.), and HL-14388 (R.B.F.), and research funds from the VA Medical Center (A.L.M.). R.B.F. was an Established Investigator of the American Heart Association at the time these studies were performed.

Address for correspondence: Robert B. Felder, MD, Cardiovascular Division, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA 52242.
central command increases skin sympathetic activity in humans, but this increase consisted of sympathetic sudomotor activity and not vasoconstrictor activity. Thus, studies in humans in the past six years have failed to demonstrate that central command plays a major role in regulation of sympathetic neural vasoconstrictor activity in humans.

Sympathetic nerve activity has been recorded recently in response to posterior hypothalamic stimulation in cats17 and rats.18 Microinjection of the γ-aminobutyric acid (GABA) antagonist picrotoxin into the posterior hypothalamus produced a marked increase in cervical17 and splanchnic18 sympathetic nerve activity along with increases in arterial pressure and heart rate. The site of injection of picrotoxin in the study performed on cats17 was the same as that described for the location of the STLR,8-10 but locomotor activity was not documented. It cannot be concluded from this study that the sympathetic nerve responses emanated from activation of the locomotion neurons in the STLR as opposed to other neurons in the posterior hypothalamus. In addition, it should be noted that there have been no reports of sympathetic nerve responses to spontaneous fictive locomotion in animals. Thus, the role of central command in regulation of sympathetic nerve activity with animals has not been definitively addressed.

Since the relative contribution of central command and peripheral feedback to the cardiovascular response to exercise remains controversial, we sought to determine if central command alone can increase sympathetic nerve activity during spontaneous locomotion and fictive locomotion in decorticate cats. Cats that developed locomotion spontaneously or during electrical stimulation of the STLR were studied in the presence and absence of input from skeletal muscle and baroreceptor afferents.

Materials and Methods

General Preparation

Experiments were performed on cats weighing between 2.2 and 5.8 kg. Anesthesia was induced with halothane (4%). The trachea was then cannulated, and the cat was connected to a respirator (model 611, Harvard Apparatus, South Natick, Mass.) for controlled ventilation. Anesthesia was maintained with 2.5% halothane. The left femoral vein and external carotid artery were cannulated for injection of drugs and for measurement of arterial pressure, respectively. The carotid sinus nerves and vagosympathetic trunks were isolated bilaterally and surrounded with ligatures for later sectioning. Body temperature was maintained at 37–38°C with a heating pad and heat lamp. Arterial blood gases were maintained within the normal range by adjusting the ventilator or by administering sodium bicarbonate.

The cats were placed in a stereotaxic device (David Kopf Instruments, Tujunga, Calif.) with the head flexed ventrally. The spinal processes of the lower cervical (C-7 through T-2) and lumbar (L-4 and L-5) regions were exposed and clamped, and the cats were suspended above the table to allow the limbs to move freely during locomotion. After ligature of the remaining external carotid artery, the cranium was removed, and decortication was performed according to the method described by Eldridge and colleagues.10 Briefly, the brain was sectioned transversely ~10–12 mm anterior to the superior colliculi. The brain rostral to this section was removed by suction, and bleeding was controlled with Gelfoam (The Upjohn Co., Kalamazoo, Mich.). After decortication, no additional anesthesia was required. The cats were disconnected from the ventilator when they began to breath spontaneously.

Nerve recordings. Efferent sympathetic nerve activity was recorded from renal and/or lumbar sympathetic nerves (L-2 or L-3) that were exposed and isolated via a left lateral flank incision. After cutting the nerve, the sheath was removed from the proximal end, and the nerve was placed on bipolar platinum electrodes and covered with a mixture of paraffin oil and vacuum grease to avoid desiccation. In the unparalyzed cats, the nerves were secured to the electrodes with dental epoxy (Replosil, Dentsply International, Milford, Del.) to prevent nerve damage and minimize motion artifact during locomotion. The multiple fiber nerve signals were passed through a high-impedance probe (model HIP 511E, Grass Instrument Co., Quincy, Mass.) and band-pass amplifier (model P511K, Grass Instrument), and nerve activity was monitored on a storage oscilloscope (model 5115, Tektronix Inc., Beaverton, Ore.) and an audioamplifier (model AM8, Grass Instrument).

Hind limb motor nerve activity was monitored in the paralyzed cats to permit recognition of spontaneous central locomotor drive. The biceps femoris nerves were exposed bilaterally in the upper thigh and placed on bipolar recording electrodes. The techniques used for recording and quantitating motor nerve activity were similar to those described above for sympathetic nerve recording. The motor nerves were identified before the recording session by electrically evoking contractions of the biceps femoris muscle during single-pulse electrical stimulation. The absence of sympathetic nerve activity in the motor nerve recordings was determined in some cats (n=5) by the failure to reflexly activate or inhibit nerve activity in response to bolus injections of nitroglycerin or phenylephrine, respectively.

In five studies, phrenic nerve activity was recorded as an index of central respiratory drive in paralyzed cats. Phrenic nerve recordings were obtained from the C-5 root of the phrenic nerve via a right lateral cervical approach as previously described.19

Electromyographic recordings. Spontaneous locomotion in the unparalyzed condition was monitored by recording electromyographic (EMG) activity from the hind limb biceps femoris muscles. Hook electrodes were placed in the exposed muscles, and the signals were amplified and recorded in a manner similar to that described above.
**Protocols**

Cats decorticated rostral to the STLR began to locomote spontaneously and intermittently 30–60 minutes after cessation of anesthesia. When the cats were hemodynamically stable and spontaneously locomoting, arterial pressure, heart rate, renal and/or lumbar sympathetic nerve activity, and, in some cats, phrenic nerve activity were recorded under the following experimental conditions.

**Protocol 1: Spontaneous locomotion with peripheral feedback intact.** In six cats, the cardiovascular and sympathetic nerve responses to spontaneously occurring rhythmic, coordinated movement of all four limbs were examined. This activity was presumed to originate from the STLR, since mesencephalic cats (i.e., those with STLR removed) do not develop spontaneous locomotion. Quadriceps muscle EMG activity served as a marker for locomotion when the limbs were freely moving.

**Protocol 2: Spontaneous locomotion with baroreceptor input eliminated.** Five cats from protocol 1 were also studied after baroreceptor and chemoreceptor denervation, which was accomplished by severing the carotid sinus nerves and the vagosympathetic trunks bilaterally. In all five cats, complete baroreceptor denervation was confirmed by demonstrating that inhibition of renal nerve activity in response to a phenylephrine-induced pressor response was eliminated.

**Protocol 3: Spontaneous fictive locomotion with muscle afferent input eliminated.** Twenty cats that exhibited spontaneous locomotor behavior were paralyzed with gallamine triethiodide (3 mg/kg initially and supplemented with 3 mg/kg/hr) to eliminate skeletal muscle activity and, thus, afferent input from exercising muscle. Ventilation was controlled with a respirator. The occurrence of central locomotor drive was monitored in this “fictive” locomotor state by recording hind limb motor nerve activity.

**Protocol 4: Spontaneous fictive locomotion with both muscle afferent and baroreceptor input eliminated.** For 17 cats, the responses to spontaneous fictive locomotion were also examined after baroreceptor and chemoreceptor denervation.

**Protocol 5: Electrical activation of STLR.** In four cats, locomotion was induced by electrical stimulation in the STLR. The STLR was identified using a combination of stereotaxic coordinates and characteristic responses to electrical stimulation. This approach has been followed previously using the same animal model and is briefly described below. A bipolar stimulating electrode (100 kΩ, Frederick Haer and Co., Brunswick, Me.) was inserted into the STLR using the following stereotaxic coordinates: A9, L1-L2, and H-3.8 Stimulus trains were delivered by passing current ranging from 25 to 300 μA with a 200-μsec pulse duration at a frequency of 50 Hz. If coordinated limb movement did not occur with stimulation at this site, the electrode was repositioned dorsoventrally within a tract or moved to another position within a 1-mm radius of this location until a responsive site was found. Sympathetic and hind limb nerves were then placed on recording electrodes, and the cat was ventilated with a respirator and then paralyzed with gallamine triethiodide to eliminate feedback from the exercising muscle. Locomotion in these baroreceptor intact cats was monitored under these conditions by recording hind limb motor nerve activities.

**Data Analysis**

Arterial pressure, renal sympathetic nerve activity (RSNA), lumbar sympathetic nerve activity (LSNA), phrenic nerve activity, and EMG or motor nerve activity were recorded and stored on FM (model G Recorder, A.R. Vetter Co., Rebersburg, Pa.) or VHS (model 4000 PCM digital processor, A.R. Vetter) tape for off-line analysis. The output from the tape was played back to an electrostatic recorder (model ES1000, Gould Inc., Cleveland, Ohio) for data analysis and figures. Control values for the above variables were obtained over 10–30 seconds during steady-state conditions before the onset of locomotion. The data from multiple (two to four) bouts of locomotion for each cat were averaged to obtain a single value for each cat, and entries represent the average response for each cat. RSNA and LSNA were integrated after full-wave rectification of the nerve signal and placed into 1-second bins. Control values were averaged over 10–30 seconds and compared with the peak mean arterial pressure (MAP), RSNA, and LSNA responses during locomotion. The voltage from phrenic nerve activity was integrated using 100-msec time bins, and minute activity was calculated as the product of tidal activity (peak phrenic activity) and respiratory frequency.

The timing of the activation of RSNA with respect to the onset of rhythmic locomotor activity was analyzed in cats in which bilateral hind limb EMG or motor nerve activity was recorded. Recordings were examined visually for an obvious burst of sympathetic nerve activity correlated with the onset of locomotion. Two investigators independently inspected each recording to determine the relation between onset of EMG or muscle nerve activity and sympathetic nerve activity. Time zero was taken at the beginning of the locomotor burst from the hind limb that first exhibited locomotion. Negative values indicate that RSNA preceded locomotor activity; positive values reflect activation of RSNA after the onset of locomotor activity.

Statistical analysis was performed using analysis of variance and Fisher’s protected least significant difference post hoc test for multiple comparisons. Values of *p*<0.05 were considered significant. Results were expressed as mean±SEM.

All experiments performed in this study complied with the guiding principles of the American Physiological Society on animal experimentation.
Patterns of Locomotor Activity

Several patterns of spontaneously occurring locomotor activity were observed. Some cats (n=14) exhibited coordinated, rhythmically alternating limb motion (rate, 0.5–2.5 steps/sec) in the unparalyzed state and rhythmic alternating discharge in the hind limb motor nerves during paralysis. Other cats (n=7) demonstrated coordinated rhythmically synchronous limb motion (rate, 0.5–2.8 steps/sec) in the unparalyzed state and rhythmic hind limb motor nerve activity in the paralyzed state. Cats displaying either of these two patterns of activity were assigned to the “rhythmic” category of spontaneous locomotion. A second group of cats (n=9) displayed spontaneous episodic nonrhythmic limb motion or hind limb motor nerve discharge. Motor nerve activity in this group was characterized by the sudden onset of continuous discharge with prolonged bursts of activity. These cats were assigned to the “static” category of locomotion. Animals with static patterns of limb muscle activity also occasionally exhibited coordinated rhythmic locomotor activity as defined above. Thus, data from some cats (n=2) appear in both the rhythmic and static categories.

The results are reported from 34 cats. In all cats analyzed, there was coordinated four-legged walking in the unparalyzed condition, with a walking frequency of ~2 steps/sec/limb. The duration of the locomotor episodes ranged from 5 seconds to more than 30 minutes.

Responses During Spontaneous Rhythmic Locomotion

Figure 1 illustrates a typical response to the onset of spontaneous locomotion in a cat with intact baroreceptors and with functioning skeletal muscle. The onset of exercise was associated with an immediate increase in RSNA and a gradual increase in arterial pressure. Figure 2 shows the grouped data for six cats. With intact baroreceptors, spontaneous rhythmic locomotion increased MAP by 29±12% from a baseline of 106±10 mm Hg and increased RSNA by 301±100%. After barodenervation, MAP increased by 28±11%, and RSNA increased by 249±67% from a baseline of 93±12 mm Hg during locomotion. Baseline MAP was not significantly different before or after barodenervation.

Responses During Spontaneous Rhythmic Fictive Locomotion

The responses during spontaneous rhythmic fictive locomotion are shown in Figures 3 and 4. With the onset of fictive locomotion (Figure 3), evidenced by the increased bilateral motor nerve activity, there were abrupt increases in RSNA and LSNA, followed by a slower rise in arterial pressure. With the cessation of fictive locomotion, sympathetic nerve activity returned promptly to or below control levels with a slower return of arterial pressure to control.

With spontaneous rhythmic fictive locomotion before barodenervation (Figure 4), MAP increased by 43±6%, RSNA increased by 183±32%, and LSNA increased by 223±83%. During fictive locomotion after barodenervation, MAP, RSNA, and LSNA increased significantly by 56±14%, 226±42%, and 169±25%, respectively (Figures 3 and 4). Minute phrenic nerve activity increased during spontaneous fictive locomotion before (446%, n=2) and after

![Figure 1](image1.png)

**Figure 1.** Experimental recordings showing the increase in renal sympathetic nerve activity (RSNA) in a decorticate cat with baroreceptors intact during spontaneous rhythmic locomotion. With the onset of bilateral locomotion, as seen in the alternating rhythmic hind limb biceps femoris electromyograms (EMGs), RSNA increased immediately with a gradual rise in arterial pressure. Integrated RSNA (third tracing) was obtained after full-wave rectification of the raw renal voltage neurogram and was reset every second.

![Figure 2](image2.png)

**Figure 2.** Bar graphs showing increases of mean arterial pressure (MAP, left panel) and renal sympathetic nerve activity (RSNA, right panel) during spontaneous rhythmic locomotion with baroreceptors intact (open bars) and after baroreceptor denervation (shaded bars). Baroreceptor denervation did not alter the magnitude of the MAP and RSNA increases. Values are presented as percent change from prelocomotion control (mean±SEM). Numbers within the bars represent the number of cats. *p<0.05 compared with prelocomotion control values.
(541%, n=2) barodenervation. No significant differences were observed in the MAP, RSNA, or LSNA responses during fictive rhythmic locomotion before versus after barodenervation.

Responses During Static Fictive Locomotor Activity

In cats that responded with a continuous burst of motor nerve discharge, there were similar significant increases in MAP (50±5% versus 57±6%) and RSNA (145±17% versus 190±47%) before and after barodenervation, respectively (Figure 5). There were no differences in these responses during fictive locomotion before versus after barodenervation. In two cats, LSNA increased by 495% and 461%, and minute phrenic nerve activity increased by 87% and 138% before and after barodenervation, respectively.

Responses to Electrical Stimulation of STLR

During stimulation of the STLR, MAP increased significantly by 43±17%, and RSNA increased by 175±47% (Figures 6 and 7). The responses were similar to those seen during spontaneous locomotion.

Timing of Locomotor and Sympathetic Changes

We found no significant differences in the time of onset of hind limb locomotor activity and RSNA. During spontaneous rhythmic locomotion, values for this relation were −170±550 msec in intact (n=6) and −10±210 msec in denervated (n=5) cats. No significant differences between RSNA and motor nerve activity were observed during spontaneous rhythmic fictive locomotion in intact (−100±260 msec, n=5) and denervated (−240±410 msec, n=5) cats.

Discussion

In recent years, the role of central command in regulation of sympathetic nerve activity has been controversial. From previous studies4–7,22 using measurements of heart rate and arterial pressure, it has been assumed that central command plays a major role in augmenting sympathetic neural drive. For instance, Freund et al22 demonstrated that cardiac output or arterial pressure responses to muscle contraction were not attenuated when the sensory input

![Figure 3](image-url)

*Figure 3. Experimental recordings showing the increases in renal sympathetic nerve activity (RSNA) and lumbar sympathetic nerve activity (LSNA) with baroreceptors intact (left recordings) and after baroreceptor denervation (right recordings) in the same cat with the onset of spontaneous fictive locomotion. RSNA and LSNA increased abruptly with the onset of bilateral hind limb motor nerve activity while arterial pressure increased gradually. The responses of mean arterial pressure, RSNA, and LSNA during locomotion were similar after baroreceptor denervation (right recordings).*

![Figure 4](image-url)

*Figure 4. Bar graphs showing that spontaneous fictive rhythmic locomotion produced increases of mean arterial pressure (MAP, left panel), renal sympathetic nerve activity (RSNA, center panel), and lumbar sympathetic nerve activity (LSNA, right panel) in cats with baroreceptors intact (open bars) and after baroreceptor denervation (shaded bars). Control values for MAP were 105±6 mm Hg in the intact and 96±10 mm Hg in the denervated state. Baroreceptor denervation did not alter the magnitude of the MAP, RSNA, or LSNA increases. Values are presented as percent change from prelocomotion control (mean±SEM). Numbers within the bars represent the number of cats. *p<0.05 compared with prelocomotion control values.*
from exercising muscle was blocked by epidural anesthesia in humans. With attempted handgrip during neuromuscular blockade, increases in heart rate, arterial pressure, and muscle sympathetic nerve activity have also been shown. However, recent studies in humans involving direct recording of sympathetic nerve activity have suggested that central command does not play a major role in increases in sympathetic neural vasoconstrictor activity to muscle or skin. Mark et al. concluded that central command does not increase and may actually inhibit slightly sympathetic activity to nonexercising muscle during static handgrip in humans. In a study in which exercise was attempted during partial neuromuscular blockade, Victor et al. concluded that central command produces modest increases in sympathetic nerve activity during static handgrip. It has recently been shown that central command may play an important role in increases in sympathetic neural sudomotor activity in skin but not in sympathetic neural vasoconstrictor activity to muscle. Thus, recent studies in humans have renewed interest in the role of central command in the regulation of sympathetic nerve activity. In light of these recent observations, we sought to determine whether central command alone can increase sympathetic nerve activity during spontaneous fictive locomotion in a decorticate cat model in which confounding sensory inputs from muscle afferents and cardiovascular receptors could be effectively excluded.

The major finding of the present study is that sympathetic nerve activity increased substantially during actual and fictive spontaneous locomotion and during electrical stimulation of the STLR in unanesthetized decorticate cats. This increase in sympathetic drive occurred in the absence of feedback from contracting muscles, arterial and cardiopulmonary baroreceptors, and arterial chemoreceptors. We observed both rhythmic and static patterns of motor activity during fictive locomotion. The responses of arterial pressure, RSNA, and LSNA were similar regardless of the pattern of motor activity. In the following discussion, these results are considered in the context of the potential contribution of "central command" to the autonomic responses to exercise.

**Central Command and the Decorticate Cat Model of Exercise**

The onset of exercise is associated with characteristic changes in autonomic outflow, which result in increases in arterial pressure and heart rate and in central respiratory drive. In the decorticate cat...
model, similar changes have been observed during activation of the STLR, whether occurring spontaneously or in response to electrical stimulation.9,10,20 Thus, spontaneous or electrical activation of the STLR has been used as a model to investigate the potential role of central command in the exercise response.9,10,20 In our study, pronounced increases in arterial pressure and the discharge in renal and lumbar sympathetic nerves as well as an increase in phrenic motor nerve activity were associated with the onset of either rhythmic or static locomotion in this model.

The responses to spontaneous locomotion in the unanesthetized decorticate cat may not mimic the total contribution of central command during voluntary exercise in intact humans. Cortical sites are involved in the voluntary decision to exercise. In the decorticate cat model for locomotor studies, the connections with cortical neurons have been severed. The decorticate animal is subject to episodes of spontaneous locomotion, often cyclical in pattern, without regulation by higher centers. It is well established that this locomotor behavior originates from neurons of the subthalamic locomotor center when the tonic inhibitory influence from higher centers is removed. It is conceivable that, under intact conditions, signals originating at the cortical level during exercise might importantly modulate the contribution of STLR neurons and central command. Thus, it is possible that the role of central command in this model might differ from that in intact animals or humans. In fact, the influences from higher centers may partially account for the differences in the response of sympathetic nerve activity observed between our study and those in humans (see below). Despite this caveat, insights concerning the role of central command have emerged from the decorticate cat model.

Central Command Increases Sympathetic Nerve Activity Independent of Feedback From Contracting Muscle

Previous studies24–28 have attributed the autonomic responses during exercise to activation of muscle afferents. Muscle mechanoreceptors, with type III afferents in particular, have been reported to increase renal sympathetic nerve activity.29 Metaboreceptors responding to cellular metabolites from contracting muscle are also capable of activating sympathetic nerve activity.30 Moreover, Waldrop and Stremel31 have recently demonstrated that neurons in the STLR can be activated by stimulation of muscle afferents, suggesting that there may be direct feedback from exercising muscle to this locomotor center.

We observed striking increases in RSNA and LSNA as well as arterial pressure during spontaneous locomotion and fictive locomotion after paralysis. In the fictive state, respiratory drive, as indicated by phrenic motor nerve activity, also increased, consistent with earlier studies.9,10 Similarly Eldridge et al10 have noted that increases in respiratory and arterial pressure did not differ during spontaneous locomotion versus fictive locomotion in this model. We observed that sympathetic nerve activity responses did not differ during spontaneous locomotion and fictive locomotion. The observation that muscle afferents do not contribute importantly to the sympathetic and pressure responses in this preparation is not surprising since the locomotion occurred without limb resistance. In the absence of a substantial workload, the stimulus to muscle metaboreceptors or to muscle mechanoreceptors would be minimal. Thus, our results do not totally exclude a role for muscle afferents in the exercise response. However, the results do indicate that signals originating from the STLR, when operating in isolation, are capable of engendering a prominent sympathoexcitatory response. This response might be construed to be representative of events occurring at the initiation of exercise before the development of substantial metabolic or mechanical stresses in exercising muscle.

Central Command Increases Sympathetic Nerve Activity Independent of Feedback From Baroreceptors

The precise role of the arterial and cardiopulmonary baroreceptors in the cardiovascular adjustments to exercise is controversial and undoubtedly complex. Earlier studies32,33 suggested that exercise was accompanied by inhibition of baroreceptor reflexes. Ludbrook and Graham34 observed that the baroreflex control of systemic vascular resistance is suppressed at the onset of exercise but that, as exercise continues, the arterial baroreceptors regain their capacity to control the circulation. Moreover, evidence indicates that baroreceptor influences remain operative but are reset to a higher pressure during steady-state exercise.35,36 In theory, this upward resetting of the baroreflex might account in part for the sympathetic response to exercise, since upward resetting would result in an increase in sympathetic drive for a given level of arterial pressure.

In the decorticate cat, we found that denervation of sinoaortic and cardiopulmonary baroreceptors had no effect on the magnitude of the peak increases in sympathetic nerve activity and arterial pressure. This observation indicates that central command can increase sympathetic nerve activity independent of baroreceptor reflexes. Our study was not designed primarily to determine the interaction of baroreceptor reflexes and central command during exercise, and we cannot exclude a role of baroreceptors in modulating the responses of central command during steady-state exercise. Nevertheless, our studies indicate that the baroreflexes are not essential for the sympathetic nerve activity response to central command.

During the denervation procedure, peripheral chemoreceptor and pulmonary receptor inputs also were eliminated. Although these receptor regions could potentially modulate the responses to exercise, their elimination had no effect on the magnitude of the peak increases in sympathetic activity in our preparation. In fact, the increased ventilation and
slight hypocapnia that may occur during exercise in the spontaneously breathing unparalyzed cats would tend to minimize rather than enhance the increase in sympathetic nerve activity. In addition, in the paralyzed cats, ventilation was controlled, and any stimuli to the chemoreceptors would be further minimized. These data suggest that neither baroreceptors, chemoreceptors, nor pulmonary receptors account for the sympathetic nerve activity response to the onset of exercise in our study.

**Timing of Locomotor and Sympathetic Changes**

The onset of spontaneous rhythmic locomotion (actual and fictive) was associated with a virtually simultaneous increase in RSNA. Occasionally, sympathetic nerve activity preceded locomotion by a matter of milliseconds, but this was not a consistent finding. Since motor nerve or EMG activity was recorded only from the hind limbs, it is still conceivable that motor activity to forelimb muscles might have preceded any change in sympathetic discharge. Increases of arterial pressure, on the other hand, always followed the onset of locomotion and sympathetic nerve activity. Our results suggest that the onset of locomotion is associated with a parallel activation of sympathetic drive.

In the recording shown in Figure 6, electrical stimulation of the STLR appears to activate RSNA before the onset of locomotion. Earlier activation of sympathetic nerve activity in this protocol would be consistent with the idea that mild electrical stimulation might first activate systems that are tonically active and above threshold (cardiovascular neurons) and then activate motor neurons that are normally below threshold. However, this finding is not conclusive, because only unilateral hind limb motor nerve activities were obtained in this series of studies.

Eldridge et al. noted that respiratory and circulatory changes often slightly preceded the development of actual or fictive locomotion. However, these changes were not quantitated, and only one example each of actual and fictive locomotion was provided in support of their conclusion so that a direct comparison with our findings is difficult. Electrical stimulation of the STLR in this same study also appeared to activate respiratory activity and arterial pressure before the onset of locomotion, with a variable time lag. Despite the slight differences between our study and that of Eldridge et al, both studies support the conclusion that signals originating from the hypothalamus are responsible for locomotor, respiratory, and cardiovascular adjustments at the onset of exercise.

**Physiological Implications**

The augmentation of sympathetic drive in renal and lumbar nerves during locomotion may have important functional implications. An increase in RSNA by central command would be expected to increase renal vascular resistance and arterial pressure and thereby promote perfusion of contracting muscle. In studies of regional blood flow responses during electrical stimulation of the STLR, Waldrop et al. observed increases in vascular resistance to the renal and gastrointestinal regions, with increases in blood flow to heart, diaphragm, and skeletal muscle. The increases in renal vascular resistance accompanying the pressor response to STLR stimulation could be caused by autoregulation or by sympathetic stimulation of the renal vasculature. Our findings suggest that the increased renal vascular resistance can be attributed to a pronounced increase in sympathetic drive to the renal vascular bed.

LSNA also increased during spontaneous fictive locomotion in our study. In this study, we measured LSNA at the L-2 and L-3 sympathetic chain region. At this level, lumbar sympathetic outflow supplies innervation to the hind limb skin and skeletal muscle as well as to abdominal visceral organs. Sympathetic outflow to skin regulates vasoconstriction and pilomotor and sudomotor activity. Sympathetic outflow to muscle regulates both cholinergic vasodilator and adrenergic constrictor influences. Our results might be consistent with the view that activity increases to vasoconstrict inactive regions and to vasodilate active muscles during exercise. However, Vissing and Victor have recently reported that, in humans, central command increases sympathetic sudomotor but not vasoconstrictor activity to skin. Other findings in humans indicate that central command increases sympathetic cholinergic vasodilator activity to muscle but does not contribute importantly to increases in sympathetic vasoconstrictor activity to muscle. The present study does not address the exact nature of the lumbar sympathetic pathways activated during spontaneous locomotion.

Our results indicating a relation between engagement of central command and striking increases in sympathetic nerve discharge with exercise should be discussed in comparison with recent studies in humans. First, a direct comparison between human and animal studies is rendered difficult by the fact that visceral nerves are not accessible for study in humans and also because selective sympathetic outflow to muscle beds has not been examined in an animal model.

Second, there is a lack of modulatory influences of higher brain centers on the STLR in the decorticate cat. The volitional component of exercise in humans is absent in this model. Although the potential influences of cortical sites on the cardiovascular responses to exercise have not been explored, it is clear that cortical sites can effect indexes of cardiovascular function. For instance, Oppenheimer and Cechetto noted that a chronotropic organization exists within the insular cortex. Electrical stimulation of the rostral posterior or caudal posterior insular regions results in a tachycardia or bradycardia, respectively, in rats. These changes occur in the absence of any changes in blood pressure or respiration. Oppenheimer et al. hypothesized that the insular cortex, which has extensive connections with the limbic system, the hypothalamus, and other areas involved
in autonomic control, integrates emotional and autonomic states. Thus, activation of cortical neurons during exercise in humans could account for a selective tachycardia with no appreciable change in muscle sympathetic nerve activity.

Third, the nature of the "exercise" stimulus might contribute to the different responses to exercise observed in humans and in the decorticate cat model. In the decorticate cat, the onset of locomotion appears to be associated with a diffuse activation of the sympathetic nervous system, as evidenced by increases in RSNA and LSNA in this study. That view is supported by the observation that cardiovascular and sympathetic responses can be elicited by micro-injection of GABA antagonists in posterior hypothalamus. The association between enhanced sympathetic activity and locomotion was not examined in these latter studies.\(^{17,18}\) In human studies measuring sympathetic nerve activity, the exercise has usually been limited to a relatively small muscle mass, and sympathetic nerve activity is commonly recorded from muscle regions that are voluntarily maintained in an inactive state. Under these conditions, the hypothalamic neurons effecting changes in autonomic activity may be more selectively engaged.

**Conclusion**

This study indicates that central command originating in the STLR in the unanesthetized decorticate cat model increases renal and lumbar sympathetic nerve activity. This increase in sympathetic drive can occur in the absence of feedback from contracting muscle and arterial and cardiopulmonary baroreceptors.

**Acknowledgments**

We would like to thank Harold D. Brinegar for research assistance, Carolyn Wagner and Deb Schiek for the preparation of the figures, and Nancy Stamp for secretarial assistance.

**References**


**KEY WORDS** • exercise reflex • peripheral feedback • baroreflex • subthalamic locomotor region