Exaggerated sympathetic and cardiovascular responses to stimulation of the mesencephalic locomotor region in spontaneously hypertensive rats

Liang N, Mitchell JH, Smith SA, Mizuno M. Exaggerated sympathetic and cardiovascular responses to stimulation of the mesencephalic locomotor region in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 310: H123–H131, 2016. First published November 6, 2015; doi:10.1152/ajpheart.00479.2015.—The sympathetic and pressor responses to exercise are exaggerated in hypertension. However, the underlying mechanisms causing this abnormality remain to be fully elucidated. Central command, a neural drive originating in higher brain centers, is known to activate cardiovascular and locomotor control circuits concomitantly. As such, it is a viable candidate for the generation of the augmented vascular response to exercise in this disease. We hypothesized that augmentations in central command function contribute to the heightened cardiovascular response to exercise in hypertension. To test this hypothesis, changes in renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) in response to electrical stimulation of mesencephalic locomotor region (MLR; 20–50 μA in 10-μA steps evoking fictive locomotion), a putative component of the central command pathway, were examined in decerebrate, paralyzed normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR). Tibial nerve discharge during MLR stimulation significantly increased in an intensity-dependent manner in both WKY and SHR but was not different between groups. Stimulation of the MLR evoked significantly larger increases in RSNA and MAP with increasing stimulation intensity in both groups. Importantly, the increases in sympathetic and pressor responses to this fictive locomotion were significantly greater in SHR compared with WKY across all stimulation intensities (e.g., at 50 μA, ΔRSNA: WKY 153±31%, SHR 287±42%; ΔMAP: WKY 87±9 mmHg, SHR 139±7 mmHg). These findings provide the first evidence that central command may be a critical contributor to the exaggerated rise in sympathetic activity and blood pressure during exercise in hypertension.

hypertension; exercise; central command; arterial blood pressure; sympathetic nervous system

NEW & NOTEWORTHY

The data suggest that the exaggerated cardiovascular and sympathetic responses to physical activity characteristic of hypertension are mediated, in part, by augmentations in central command function. These findings identify the central command pathway as a potential target for the treatment of exercise-induced circulatory hyperexcitability in hypertensive individuals.

HYPERTENSION is a major risk factor contributing to a number of life-threatening cardiovascular-related disorders such as a

myocardial ischemia, myocardial infarction, heart failure, cardiac arrest, and stroke. Cardiovascular hemodynamics in hypertension are abnormal not only at rest but also during physical exercise. An increasing number of studies have demonstrated that the arterial blood pressure (ABP), heart rate (HR) and sympathetic nerve activity (SNA) responses to exercise are abnormally exaggerated in hypertensive individuals (1, 42, 47, 55). This heightened responsiveness increases the risk for occurrence of an adverse cardiovascular event during and immediately after physical activity (12, 31). However, the mechanisms underlying this overactive cardiovascular responsiveness to exercise have not been fully established.

Central signals originating in higher brain centers, termed central command, play a crucial role in mediating the cardiovascular response to exercise (11, 24, 29). Central command activates cardiovascular and locomotor control circuits concomitantly (2, 9, 10, 26, 36, 54). It has been proposed that the mesencephalic locomotor region (MLR), subthalamic locomotor region, cerebellar locomotor region, and several cortical areas are putative components of the central command pathway (2, 3, 6, 40, 48, 53, 57, 58). Specifically, stimulation of the MLR or subthalamic locomotor region is often used to determine the role of central command in cardiovascular and sympathetic regulation in rodents (2, 14–17).

Autonomic dysfunction is one of the hallmarks of hypertension. Autonomic adjustments regulating the cardiovascular system during exercise are determined by integrating input within the brain stem from central command (29), the arterial baroreflex (a negative feedback system maintaining stable blood pressure) (7, 43), and the exercise pressor reflex (EPR, a peripheral reflex originating in skeletal muscle) (27, 29). It has been shown that baroreflex sensitivity is reduced in hypertension (19, 30, 34). Further, it has been demonstrated that selective activation of the EPR elicits markedly greater increases in mean arterial pressure (MAP) and renal SNA (RSNA) in hypertensive compared with normotensive rats (22, 32, 33, 35, 52). In addition to a decrease in baroreflex sensitivity and the pathogenesis of EPR overactivity, it is quite possible that the heightened cardiovascular response to exercise in hypertension is due to the development of central command dysfunction as well. In support of this contention, sympathetic activation elicited by central command is potentiated in animals with chronic heart failure, a disease state that often develops from prolonged exposure to high blood pressure (14, 15). Specifically, it has been suggested that oxidative stress within the medulla oblongata of heart failure animals mediates the central command dysfunction manifest (15). However, to date, no studies have examined the possible contribution of...
central command to the abnormal cardiovascular response to exercise in hypertension.

We, therefore, hypothesized that augmentations in central command function contribute to the heightened cardiovascular response to exercise in hypertension. To test this hypothesis, we examined ABP, HR, and renal SNA (RSNA) responses to stimulation of the MLR in decerebrate, paralyzed normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive (SHR) rats.

MATERIALS AND METHODS

Experiments were performed using age-matched (13–15 wk) male WKY (n = 31) and SHR (n = 31). Animals were maintained in a temperature-controlled environment, fed ad libitum, and kept on a 12:12-h light-dark cycle. All studies were performed in accordance with the US Department of Health and Human Services NIH Guide for the Care and Use of Laboratory Animals. The procedures outlined were approved by the Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center. The general surgical procedures used have been described previously (50). Briefly, rats were anesthetized with isoflurane gas (4% in 100% oxygen, 1.5–2% during surgery) and intubated for mechanical ventilation. Fluid-filled polyurethane catheters were inserted into the right external jugular vein for the administration of drugs and into both common carotid arteries for the measurement of ABP and MAP (MLT0380/D; ADInstruments). To stabilize fluid balance and maintain baseline ABP, a continuous infusion of 1 M NaHCO₃, 5% dextrose Ringer solution was continuously established via the jugular vein at a rate of 3–5 ml·h⁻¹·kg⁻¹ (44). Needle electrodes were placed on the back of the animal to record electrocardiograph signals (ECG). HR was derived from the R wave of the ECG recording. ABP and HR were continuously monitored, and respiratory thoracic movement was visually observed. Rectal temperature was maintained between 36.5 and 38.0 °C with a heating pad and an external lamp. To record RSNA, the left kidney was exposed via a retroperitoneal approach to isolate a renal nerve bundle along the renal artery and vein. The renal nerve bundle was attached to a pair of stainless steel wire electrodes (Bioflex wire AS633; Cooner Wire), and the nerve and electrodes were covered with silicone glue (Kwik-Sil; World Precision Instruments, Sarasota, FL) for insulation and fixation. To quantify RSNA, the preamplified nerve signal was band-pass filtered at 150–1,000 Hz (Neuro Amp EX; ADInstruments), then full-wave rectified and low-pass filtered with a cut-off frequency of 30 Hz. All animals were held in a stereotaxic head unit (Kopf Instruments), and a precollcularic decerebration was performed rendering the animals insentient. Dexamethasone (0.2 mg) was given intravenously to minimize brain edema. The upper skull and dura were removed. Subsequently, the cerebral cortex and neural tissue rostral to the superior colliculus were removed by aspiration. The cranial vault was filled with cotton gauze to arrest brain bleeding. Gas anesthesia was discontinued immediately following the decerebrate procedure. After the cessation of isoflurane anesthesia, animals were artificially ventilated with 100% oxygen by a respirator. Arterial blood gases and body temperature were checked periodically and maintained within normal ranges throughout the experiment. Experimental protocols were performed at least 1.25 h thereafter (18). MLR stimulation. A concentric bipolar electrode (outer pole diameter: 200 µm, stainless steel; inner pole wire diameter: 50 µm, platinum/iridium; FHC) connected to a photoelectric stimulus isolation unit and stimulator (Grass S88, Grass Instrument) was used to electrically stimulate the MLR. The tip of the electrode was placed 1.7–2.0 mm lateral, 0.3–0.8 mm anterior, and 3.5–4.5 mm deep from the surface junction of the superior and inferior colliculus (2, 14, 16, 17). The motor threshold of MLR stimulation (i.e., the minimum current intensity required to induce reciprocal extremity movements) was determined by slightly increasing the current intensity until the movement of the animal was observed. The site of the MLR stimulation was identified by physiological criteria as previous reported (2, 14, 16, 17). After determination of the location of the MLR, the rat was paralyzed with pancuronium bromide (1 mg/kg iv), and the lungs were artificially ventilated with a respirator.

Recordings of tibial nerve discharge. Tibial nerve discharge (TND) was recorded to assess motor activity induced by electrical stimulation of the MLR (WKY, n = 11; SHR, n = 9). The left tibial nerve innervating the triceps surae muscle was separated from the sciatic nerve at the knee joint. The distal portion of the tibial nerve was ligated to eliminate afferent discharge. The nerve bundle was mounted on a bipolar electrode of Ag-AgCl wires in a warm mineral oil pool surrounded with connective tissue and skin. The original TND was amplified with a band-pass filter at 100–4,000 Hz, then full-wave rectified.

Sinoaortic barodenervation. To minimize the effect of the arterial baroreflex on the sympathetic and cardiovascular responses to MLR stimulation, sinoaortic baroreceptor denervation was performed in a subset of rats (WKY, n = 7; SHR, n = 8). A midline incision was made in the ventral region of the neck and the common carotid artery and carotid bifurcation exposed. The cervical sympathetic nerve, aortic depressor nerve, and vagus nerve were bilaterally cut, and the carotid body was removed. Sinoaortic denervation was confirmed by absence of reflex HR changes in response to changes in ABP induced by intravenous phenylephrine injection (5 µg/kg iv).

Experimental protocols. Current intensity of 20, 30, 40, and 50 µA (pulse duration of 1 ms at 60 Hz, for 30 s) was used to electrically stimulate the MLR evoking fictive locomotion in the paralyzed, decerebrate rats. The stimulation parameters were determined based on earlier studies (2, 4, 14–17). The order of the current intensities was randomized. The interprotocol interval was at least 5 min between stimulations. If voluntary ventilation and/or movement was observed, supplemental doses of pancuronium bromide (0.5–0.75 mg/kg iv) were administered. By conducting the experiments in paralyzed animals, input from the skeletal muscle EPR was effectively eliminated. At the conclusion of all experiments, the insentient animals were humanely killed by intravenous injection of saturated potassium chloride (4 M, 2 ml/kg iv). The heart and lungs were excised and weighed. For measurement, the tibia was harvested, weighed, and measured.

Data acquisition and analysis. ABP, MAP, HR, RSNA, TND, and stimulation pulse data were recorded and analyzed using data-acquisition software (LabChart, ADInstruments) for the Powerlab analog-to-digital converter (Powerlab8/30; ADInstruments) at a 1-kHz sampling rate. TND was recorded at a sampling rate of 4 kHz. To analyze RSNA, full-wave rectified signals of RSNA as well as background noise signals were obtained. The noise signal component, which was defined as the signal recorded postmortem, was subtracted from rectified RSNA. To quantify RSNA responses to MLR stimulation, baseline values were calculated by averaging 30 s of data immediately prior to the onset of stimulation and were considered 100% of basal RSNA. Subsequently, changes in RSNA were expressed as a percent of baseline and the relative changes in RSNA (ΔRSNA, %) from baseline were evaluated. To analyze TND, the original signal was full-wave rectified. The baseline value was calculated by averaging 30 s of data immediately prior to the onset of MLR stimulation and was considered 100% of basal tibial nerve activity. Relative changes in TND were assessed in the same manner as RSNA. Data sets of 1-s averages for MAP, HR, RSNA, and TND were analyzed. Baseline values for all variables were determined by evaluating 30 s of recorded data immediately before MLR stimulation. The maximum response of each variable was defined as the peak change from baseline elicited by MLR stimulation.

Statistical analysis. Data were analyzed using Student’s unpaired t-tests (WKY vs. SHR), two-way repeated-measures ANOVA (rat group and MLR stimulation intensity) with “rat” (WKY and SHR) as a within-subject factor. If significant interaction and main effects were
RESULTS

Morphometric characteristics and baseline hemodynamics for WKY and SHR are summarized in Table 1. There were no significant differences in body weight or lung weight-to-body weight ratios among groups. As previously reported (22, 32, 33, 35, 52), heart weight-to-body weight ratios as well as heart weight-to-tibial length ratios were significantly greater in SHR than WKY. There were no statistical differences in motor threshold for MLR stimulation between groups. In both barointact and -denervated animals, baseline HR was significantly lower and MAP significantly higher in SHR compared with WKY. Sinoaortic denervation significantly increased baseline RSNA compared with barointact animals in both groups. Baseline signal-to-noise ratios for RSNA did not differ among groups.

Representative TND recordings from both groups of animals in response to MLR stimulation are demonstrated in Fig. 1A. MLR stimulation significantly increased TND in an intensity-dependent manner (Fig. 1B). Notably, there were no differences in TND between WKY and SHR (Fig. 1B).

Original ABP, HR, and RSNA tracings in response to MLR stimulation in representative WKY and SHR are presented in Fig. 2. Importantly, the magnitude of the increases in ABP and RSNA responses to MLR stimulation were markedly greater in SHR compared with WKY across all stimulation intensities. MLR stimulation slightly increased HR in both groups of animals.

Figure 3 summarizes group mean responses to MLR stimulation in barointact animals. In hypertensive animals, MAP and RSNA responses to stimulation of the MLR were significantly greater compared with normotensive rats (Fig. 3, A and B). The HR response to MLR stimulation was not statistically different between SHR and WKY. In addition, the pressor as well as the sympathetic responses to MLR stimulation were step-wise increased with each elevation in stimulus intensity in both SHR and WKY (Fig. 3B) (WKY, MAP: $F = 24.737, P < 0.0001$; RSNA: $F = 9.773, P < 0.001$; SHR, MAP: $F = 13.542, P < 0.0001$; RSNA: $F = 5.205, P < 0.01$).

Figure 4 summarizes group averaged sympathetic and cardiovascular responses during central command activation in barodenervated animals. The pressor responses to electrical activation of the MLR were likewise exaggerated in SHR compared with WKY (Fig. 4, A and B) in sinoaortic-barodenervated animals. Although the changes in RSNA during MLR stimulation tended to be larger in SHR than WKY, statistical significance was not reached by sequential Bonferroni correction. No significant difference in the tachycardic response to MLR stimulation was observed between groups of animals.

To simplify quantification of the effect of sinoaortic denervation on the cardiovascular and sympathetic responses to MLR stimulation, data from barointact (Fig. 3B) and barodenervated (Fig. 4B) animals are combined in Fig. 5. The changes evoked by barodenervation in both groups of animals were relatively modest. As such, there were no statistical differences for any variable between barointact and -denervated animals within either WKY or SHR.
DISCUSSION

The major finding from this investigation was that the pressor and sympathetic responses to matched-intensity stimulation of the MLR were significantly larger in SHR than WKY. Further, these larger ABP and RSNA responses to MLR-induced fictive locomotion were likewise observed in sinoaortic-barodenervated SHR. To the best of our knowledge, this investigation provides the first evidence, in animals or humans, that alterations in central command function may importantly contribute to the generation of the exaggerated cardiovascular response to exercise in hypertension.

TND response to MLR stimulation. Since central command activates neural circuits simultaneously modulating locomotion and cardiovascular function, it was important to ensure that MLR-induced fictive locomotion was equivalent at all levels of intensity between WKY and SHR. If locomotor activity (i.e., TND or motor threshold) during MLR stimulation was not the same between groups, it could account for the larger sympathetic and pressor responses to fictive locomotion observed in hypertensive animals. To address and control for this issue, motor threshold and TND were assessed in WKY and SHR during MLR stimulation. It was determined that no differences in either variable existed between the two groups of animals at any stimulus intensity (Table 1 and Fig. 1). This suggests that the motor command induced by MLR stimulation was similar among groups. Therefore, the larger sympathetic and pressor responses in hypertensive animals during MLR stimulation were unlikely mediated by unequal experimental activation of the central command pathway between groups. Based on previous work (2), we carefully identified the site of the MLR using physiological criteria. The motor threshold in the present study was the same, and in some cases lower, than in earlier studies (14–17). This finding increases confidence that the motor and cardiovascular responses obtained in this investigation were induced by stimulation of the locomotor region located in the mesencephalon.

Pressor and sympathetic responses to MLR stimulation. There are a few viable possibilities for the enhanced pressor and sympathetic responses to MLR-induced fictive locomotion in hypertensive animals. For example, the rostral ventrolateral medulla (RVLM) within the brain stem is well known to play an important role in the control of cardiovascular system during exercise (38). It has been reported that cholinergic projections from the pedunculopontine tegmental nucleus to the RVLM are an integral component of the central command pathway regulating cardiovascular function during exercise (39). It has also been demonstrated that increased production of reactive oxygen species contributes to sympathoexcitatory responses by altering synaptic transmission in the RVLM of SHR (37). Indeed, in animals with chronic heart failure, a disease state that often develops from prolonged hypertension, it has been recently reported that abnormal sympathetic and cardiovascular responses to activation of central command are mediated by oxidative stress within the RVLM (15). Speculatively, it is possible that the exaggerated RSNA and ABP responses to MLR stimulation observed in the current study were mediated by similar hypertension-induced increases in oxidative stress within the RVLM. As another possibility, the RVLM is known to receive input from the nucleus tractus solitarius (NTS), a shared signal processing center for central command, the arterial baroreflex and the EPR within the brain stem (4). We have previously shown that nitric oxide (NO) within the NTS modulates both the arterial baroreflex and the EPR (51). Moreover, in hypertensive rats, expression of NO synthase protein (required for the enzymatic production of NO) is significantly lower within NTS neurons excited by the EPR (35). Further evidence suggests that these reductions contribute significantly to abnormal NO signaling within the NTS of hypertensive animals (20, 21, 49). Abnormal signal processing within the NTS could affect sympathetic regulation from the RVLM accounting for the exaggerated increases in RSNA and ABP in SHR during fictive locomotion. As an equally compelling possibility, the activity of neurons within the MLR region itself might be negatively impacted by the pathogenesis of hypertension accounting for the abnormally large sympathetic and pressor responses to stimulation. Clearly, further research is needed before definitive conclusions can be drawn.

It has been reported that in decerebrate rats with myocardial infarction as well as sham controls, MLR stimulation causes

Fig. 2. Original tracings demonstrating arterial blood pressure (ABP), heart rate (HR), and renal sympathetic nerve activity (RSNA) responses to stimulation of the MLR in barointact WKY and SHR. Horizontal bars indicate the 30-s period of MLR stimulation.
increases in sympathetic and blood pressure responses with no significant changes in HR (14, 15). Consistent with these studies, there was no significant difference in the peak HR response to MLR stimulation between WKY and SHR (Figs. 3B and 4B). In barointact animals, HR responses varied depending on the established arterial blood pressure during MLR stimulation (Fig. 3A). However, although not statistically significant, time-course HR responses to MLR stimulation were consistently greater in SHR compared with WKY in sinoaortic-barodenervated animals (Fig. 4A). Since baseline HR in decerebrate animals is much higher than that in conscious or anesthetized animals (i.e., sympathetic dominance), it may have been difficult to detect differences in the tachycardia response to central command activation in the current study accounting for the lack of statistical significance. Cleary, further research is needed to definitively determine whether the HR response to central command activation is altered in hypertension.

Baroreflex effects on the cardiovascular responses to MLR stimulation. It has been reported that stimulation of the MLR modulates arterial baroreflex function (4, 28). Specifically, it has been suggested that central command blunts the sensitivity of the arterial baroreceptor-HR reflex at the onset of exercise. This decrease in sensitivity allows larger increases in HR for any given level of exercise-induced elevation in blood pressure (24). Further, it has been reported on several occasions that baroreflex function is impaired in hypertension (19, 30, 34) although its ability to buffer reflex-induced augmentations in blood pressure (e.g., EPR-induced increases in ABP) remains operative (52). Thus, to minimize the possibility of interactions between central command and the arterial baroreflex influencing data interpretation, sinoaortic barodenervation was performed in a subset of animals. The results of these experiments clearly demonstrated that the enhanced sympathetic and pressor responses to activation of the MLR were present in both barointact and barodenervated SHR (Fig. 4). Moreover, there were no within-group differences in the MAP, HR, and RSNA responses to MLR stimulation between barointact and barodenervated WKY or SHR (Fig. 5). Given these findings, it is unlikely that the heightened MAP and RSNA responses to fictive locomotion in barointact SHR were appreciably influenced by the baroreflex and/or its interactive effects with central command.

Methodological and analytical considerations. It is acknowledged that, since catheters were inserted into the bilateral common carotid arteries to measure ABP, the peripheral ends of these arteries were experimentally ligated. As a result, carotid baroreflex function may have been compromised in animals in which the aortic baroreflex remained intact. Despite this limitation with the experimental preparation used, evidence suggests that the aortic baroreflex is dominant to the carotid baroreflex in the maintenance of blood pressure (41, 45, 46). As such, limiting carotid baroreflex input during MLR stimulation would not be anticipated to significantly alter the findings reported in this investigation. In support of this contention, it has recently been demonstrated that fictive motor activity selectively inhibits the cardiomotor component of the
aortic, but not the carotid, baroreflex (25). It is likewise noted that, although there were no statistically significant differences between barointact and barodenervated animals, the RSNA response to activation of the MLR tended to be lower postdenervation in both WKY and SHR (Fig. 5). This may have resulted from the finding that baseline signal-to-noise ratio for RSNA was significantly higher in barodenervated compared with barointact animals, suggesting denervation augmented baseline SNA (Table 1). This is consistent with a previous study demonstrating similar results in both WKY and SHR (5). Given that the changes in RSNA were calculated as a percent of baseline activity, the higher baseline SNA in barodenervated animals most likely accounted for the smaller relative increases in RSNA in response to MLR stimulation. Moreover, it should be noted that baseline blood pressure in decerebrate animals is known to be relatively lower than that in conscious and/or anesthetized animals. This was observed in the present study (Table 1). It is possible that the lower pressures manifest postdecerebration could impact the reported results and interpretation of data. That being stated, the decerebrate model has been widely used to examine autonomic nervous system function in normal and diseased animals, and thus its use is most appropriate for direct comparison with such studies (2, 4, 14–17, 20–22, 25, 28, 32, 33, 35, 50–52, 54).

The central command-mediated tachycardia response to exercise is predominantly regulated through cardiac autonomic nerves (25). However, compared with the MAP and RSNA responses to stimulation of the MLR, the HR responses were relatively small in the present investigation (less than a 5% change from baseline on average). It is possible that stimulation of the MLR influences renal and vascular sympathetic outflow to a greater extent than cardiac sympathetic outflow. Interestingly, in different experimental settings, HR has been reported to increase (2) or remain unchanged (16, 17) in response to electrical MLR stimulation. The inconsistencies between investigations may be due to differences in animal species or experimental preparations utilized. Alternatively, the precollicular decerebration model may limit the maximum increases in HR that can be obtained by physically disconnecting the neural fibers between higher brain centers and the brain stem. Additional studies are warranted to address these potential issues.

Although evidence suggests that central command activates cardiovascular and locomotor control circuits concomitantly, whether the firing threshold of neurons in each circuit is similar is unknown. For example, the motor threshold of the SHR presented in Fig. 2 was 24.1 μA. MAP as well as RSNA increased in response to 20 μA MLR stimulation before locomotion activity was observed. In fact, when 10-μA stimulation was applied in a testing trial to the SHR presented in Fig. 2, MAP and RSNA responses were produced that were approximately 50–60% of those evoked with 20 μA. Although speculative, the “cardiovascular” threshold might be lower than the “locomotor” threshold. Related to this issue, since the stimulating intensity was fixed ranging from 20 to 50 μA in 10-μA steps in the present study, the variability in...
the responses at each point of stimulation would be expected to be larger than when adjusting the stimulation intensity according to the motor threshold. Regardless of this technical issue, as described in the results, intensity-dependent pressor and sympathetic responses to MLR stimulation were observed.

**Future directions.** We previously demonstrated that the skeletal muscle EPR is exaggerated in hypertensive animals (22, 32, 33, 35, 52). To determine the effects of activation of the central command pathway independent of the EPR, the cardiovascular and sympathetic responses to MLR stimulation were assessed only after the induction of skeletal muscle paralysis. The lack of whole body movement and/or individual muscle contraction was carefully confirmed during stimulation of the MLR eliminating the possibility of inadvertently stimulating the EPR. Therefore, contributions from the EPR to the cardiovascular and sympathetic responses elicited during fictive locomotion were effectively excluded using this preparation. Assessing central command activity in isolation was initially critical to establish its potential contribution to the pathogenesis of autonomic dysfunction in hypertension. That being stated, central command and the EPR are known to modify one another functionally. To fully understand the mechanisms underlying the exaggerated cardiovascular response to exercise in hypertension, it will be essential in the future to determine whether the interactive relationship between central command and the EPR is altered with the advent of this disease.
Perspectives and clinical significance. The blood pressure response to exercise is clinically important. For example, normotensive individuals that exhibit an abnormally large blood pressure response to exercise are more likely to develop future hypertension (56). In hypertensive patients, exercise-induced exaggerations in blood pressure elevate the risk for adverse cardiovascular or cerebrovascular events during or immediately following physical activity. As such, understanding the pathophysiology underlying the abnormally cardiovascular response to exercise is requisite to developing novel therapeutic strategies for treatment. To this end, the current study suggests that alterations in central command function may contribute to the heightened cardiovascular response to exercise in hypertension. This is not surprising as human studies have demonstrated that central command significantly drives the cardiovascular response to voluntary exercise even at relatively low intensities (23) making it a logical contributor to the abnormal response to physical activity in this disease. Interestingly, exercise training has been demonstrated to evoke positive adaptations in central command in healthy subjects (8). Moreover, it has been reported that exercise training is capable of normalizing central command dysfunction in chronic heart failure rats through its antioxidant effects in the medulla oblongata (15). Considering these findings collectively, central command could prove a novel target for the treatment of the cardiovascular hyperexcitability that accompanies exercise in hypertension. Moreover, putative therapeutic interventions for the treatment of central command dysfunction could include antioxidant therapies and/or controlled exercise training programs.

Conclusions. In summary, the pressor and sympathetic responses to electrical stimulation of the MLR are abnormally exaggerated in spontaneously hypertensive rats compared with normotensive animals. The data suggest that central command mediates, at least in part, the exaggerated cardiovascular response to exercise in hypertension.

ACKNOWLEDGMENTS

We thank Dr. K. Matsukawa for invaluable scientific input as well as M. Romero and J. Lamar, Jr., for expert technical assistance.

GRANTS

This research was supported by grants from the National Institutes of Health Heart, Lung, and Blood Institute (HL-088422 to S. A. Smith) and the Lawson & Rogers Lacey Research Fund in Cardiovascular Disease (to J. H. Mitchell). N. Liang was supported by a research fellowship (Institutional Program for Young Researcher Overseas Visits) from the Japan Society for the Promotion of Science.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: N.L., J.H.M., S.A.S., and M.M. conception and design of research; N.L. and M.M. performed experiments; N.L. and M.M. analyzed data; N.L., J.H.M., S.A.S., and M.M. interpreted results of experiments; N.L. and M.M. prepared figures; N.L. and M.M. drafted manuscript; N.L., J.H.M., S.A.S., and M.M. edited and revised manuscript; N.L., J.H.M., S.A.S., and M.M. approved final version of manuscript.

REFERENCES

4. Degtyarenko AM, Kaufman MP. MLR-induced inhibition of barorece-
7. Fadel PJ, Raven PB. Human investigations into the arterial and cardio-
11. Goodwin GM, McCloskey DI, Mitchell JH. Cardiovascular and respira-
17. Koba S, Yoshida T, Hayashi N. Sympathetically induced renal vasocon-
19. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovas-
23. Liang N, Nakamoto T, Mochizuki S, Matsukawa K. Differential contribu-