Role of paraventricular nucleus in the cardiogenic sympathetic reflex in rats

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Zahnerr, Matthew R., and Hui-Lin Pan. Role of paraventricular nucleus in the cardiogenic sympathetic reflex in rats. Am J Physiol Regul Integr Comp Physiol 288: R420–R426, 2005. First published October 7, 2004; doi:10.1152/ajpregu.00563.2004.—Myocardial ischemia stimulates cardiac spinal afferents to initiate a sympathoexcitatory reflex. However, the pathways responsible for generation of increased sympathetic outflow in this reflex are not fully known. In this study, we determined the role of the paraventricular nucleus (PVN) in the cardiogenic sympathetic reflex. Renal sympathetic nerve activity (RSNA) and blood pressure were recorded in anesthetized rats during epicardial application of 10 µg/ml bradykinin. Bilateral microinjection of muscimol (0.5 nmol), a GABAA receptor agonist, was performed to inhibit the PVN. In 10 vehicle-injected rats, epicardial bradykinin significantly increased RSNA 178.4 ± 48.5% from baseline, and mean arterial pressure from 76.9 ± 2.0 to 102.3 ± 3.3 mmHg. Microinjection of muscimol into the PVN significantly reduced the basal blood pressure and RSNA (n = 12). After muscimol injection, the bradykinin-induced increases in RSNA (111.6 ± 35.9% from baseline) and mean arterial pressure (61.2 ± 1.3 to 74.5 ± 2.7 mmHg) were significantly reduced compared with control responses. The response remained attenuated even when the basal blood pressure was restored to the control. In a separate group of rats (n = 9), bilateral microinjection of the ionotropic glutamate antagonist kynurenic acid (4.82 or 48.2 nmol in 50 nl) had no significant effect on the RSNA and blood pressure responses to bradykinin compared with controls. These results suggest that the tonic PVN activity is important for the full manifestation of the cardiogenic sympathoexcitatory response. However, ionotropic glutamate receptors in the PVN are not directly involved in this reflex response.

ACTIVATION OF CARDIAC SPINAL AFFERENTS during myocardial ischemia causes chest pain and an increase in sympathetic activity and blood pressure, referred to as the cardiogenic sympathoexcitatory reflex (15, 27, 34–36). During myocardial ischemia and infarction, this cardiogenic sympathetic reflex is important for the maintenance of blood pressure and perfusion of vital organs. However, increased sympathetic outflow also could be detrimental because it further increases the oxygen demand of the ischemic myocardium. The brain stem nuclei, such as the commissural nucleus tractus solitarius and rostral ventrolateral medulla (RVLM), play an important role in mediating the cardiogenic sympathoexcitatory reflex (15, 17). However, the role of supramedullary nuclei in the cardiogenic sympathetic reflex is not clear.

The paraventricular nucleus (PVN) of the hypothalamus is a key forebrain site for autonomic regulation (1, 27, 30, 37). In this regard, the PVN is one of five major autonomic premotor cell groups in the brain (28). The PVN sends projections to the RVLM, as well as intermediotegmental cell column (IML) of the spinal cord to influence sympathetic outflow (6, 10, 25, 26). Several physiological studies have demonstrated that the PVN controls the sympathetic nervous activity and blood pressure. For example, activation of PVN neurons with electrical stimulation and microinjection of the glutamate receptor agonists or the GABA_A receptor antagonist bicuculline induces a profound increase in the sympathetic nerve activity and blood pressure in anesthetized and conscious rats (12, 37). Conversely, inhibition of the PVN with GABA or the GABA_A receptor agonist muscimol suppresses basal sympathetic nerve discharges and lowers basal blood pressure (1). However, the potential role of the PVN in the generation of increased sympathetic drive during the cardiogenic sympathoexcitatory reflex remains unclear.

Anatomical studies have suggested that the hypothalamic nuclei, including the PVN, may receive visceral afferent inputs through the spinohypothalamic tract (8, 20). Because glutamate is the principal excitatory neurotransmitter that controls the excitability of PVN output neurons (9, 16, 19), the glutamatergic input to the PVN may be increased in response to stimulation of cardiac afferents and involved in the cardiogenic sympathetic reflex. Therefore, in this study, we tested the hypothesis that inactivation of the PVN attenuates the cardiogenic sympathoexcitatory reflex and that this reflex response is mediated by ionotropic glutamate receptors in the PVN.

MATERIALS AND METHODS

Surgical Preparations and Renal Nerve Recordings

Experiments were conducted on male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing between 250 and 300 g. The procedures and protocols were approved by the Animal Care and Use Committee of the Pennsylvania State University College of Medicine and adhered to the National Institutes of Health Guide for the Care and Use for Laboratory Animals. Rats were initially anesthetized using 2% halothane in O2 through a nose cone. Adequate depth of anesthesia was confirmed by the absence of a withdrawal response to painful stimuli (tail pinch). The trachea was cannulated for mechanical ventilation using a rodent ventilator (CWE, Ardmore, PA). Expired CO2 concentration was monitored with a CO2 analyzer (Capstar 100, CWE) and maintained at 4–5% by adjusting the ventilation rate and tidal volume throughout the experiment. The left carotid artery was cannulated, and arterial blood pressure was measured with a pressure transducer (PT 300, Grass Instruments, Quincy, MA). The left jugular vein was cannulated for intravenous injection of drugs. Halothane was discontinued after α-chloralose (50–60 mg/kg iv) and pentobarbital sodium (30 mg/kg, iv) were administered. Supplemental doses of pentobarbital sodium were administered as necessary to maintain an adequate depth of anesthesia.

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For epicardial application of bradykinin, a limited lateral thoracotomy was performed to expose the heart. The pericardium was removed, and bradykinin was applied to the anterior surface of the left ventricle with a cotton tip applicator through an exposed window in the left chest (15, 17, 36). Bradykinin was chosen to stimulate cardiac afferents because it is an endogenously produced metabolite during myocardial ischemia, and epicardial application of bradykinin excites cardiac afferents and induces a consistent sympathoexcitatory reflex in anesthetized animals (15, 18, 21, 23, 36). The pericardium was left in place just before the epicardial application of bradykinin to preserve the integrity of the epicardium. Body temperature was maintained at 37–38°C with a heating lamp. During renal nerve recordings, rats were briefly paralyzed with pancuronium bromide (1 mg/kg iv). Between protocols, the effect of pancuronium bromide was allowed to wear off, and the adequacy of anesthesia was verified by the absence of the withdrawal response to tail-pinch.

For renal nerve recordings, the left kidney was exposed through a left-flank incision via a retroperitoneal approach (15, 36). A small branch of the renal nerve was isolated and carefully dissected from the renal vasculature and surrounding tissue with the aid of an operating microscope. The renal nerve was cut distally to ensure thatafferent activity was not recorded. The renal nerve was then immersed in mineral oil and placed on a stainless steel recording electrode. The nerve signal was amplified (20,000–30,000) and band-pass filtered (100–3,000 Hz) by an alternating current amplifier (model P511, Grass Instruments). Renal sympathetic nerve activity (RSNA) was monitored through an audio amplifier (model AM 10, Grass Instruments). Renal nerve activity and arterial pressure were recorded using PowerLab data-acquisition system (model 4SP, Mountain View, CA), displayed, and stored on a Pentium computer. Heart rate was counted by triggering from the blood pressure pulse. Renal nerve activity was also fed into a second Pentium computer through an analog-to-digital interface for subsequent offline analysis. Discharge frequency was recorded and quantified using a software window discriminator (DataWave software). Nerve discharges were subtracted from the nerve recording using DataWave software as described previously (15, 36). This method allows us to directly isolate and analyze the nerve discharges. At the end of the experiments, the rat was killed by intracardiac perfusion with 10% formaldehyde for histology.

PVN Microinjections

Rats were placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA). The dorsal surface of the skull was exposed and a small hole drilled to expose the brain. A glass microinjection pipette (tip diameter 20–30 μm) was advanced to the PVN in the right hemisphere. The stereotaxic coordinates used were 1.6–2.0 mm caudal from bregma, 0.5 mm lateral to the midline, and 7.0–7.5 ventral to the dura (1, 37, 38). The sites of injection were verified in the PVN by the depressor response to microinjection of 5.0 nmol GABA (20 nl, 250 mM). This approach was chosen to identify the pressor regions of the PVN as described previously (1). GABA microinjections were separated by a 10–15-min period to allow recovery of the possible depressor effect. Drugs were mechanically injected over a 2-s period using a calibrated microinjection system (Nanoject II, Drumond Scientific, Broomall, PA) and monitored using an operating microscope. After microinjection, the glass pipette was left in place for 3–5 min to ensure adequate diffusion of the drug. The micropipette was then withdrawn and placed in the respective stereotaxic coordinates for injection into the contralateral PVN. No more than four microinjections of GABA were performed in each rat to elicit a decrease in blood pressure. The stereotaxic coordinates from the same rat in which the prior GABA microinjection elicited the greatest depressor response were used for the following microinjection (muscimol and kynurenic acid) experiments.

Experimental Design

Role of the PVN in blood pressure and RSNA responses to epicardial bradykinin. To determine if the PVN is involved in the cardio- genic sympathoexcitatory reflex, the PVN was inactivated bilaterally with the GABAA receptor agonist muscimol. Blood pressure and RSNA responses to epicardial bradykinin application were tested in vehicle- and muscimol-injected rats. After a high-quality nerve recording was obtained, a 30-min stabilization period was allowed. Then, baseline RSNA and blood pressure were recorded for 2 min. Bradykinin (10 μg/ml, Sigma, St. Louis, MO) was dissolved in normal saline and applied to the anterior surface (~1 cm²) of the left ventricle with a cotton applicator, as previously described (15, 17, 36). After bradykinin application, the RSNA and blood pressure responses were recorded continuously for 3 min. The RSNA and blood pressure responses to epicardial bradykinin were examined twice, separated by ~15 min, to ensure a reproducible response. After each bradykinin application, the heart was washed using cotton applicators soaked in normal saline, and the RSNA and blood pressure were allowed to return to baseline levels. Then, 0.5 nmol muscimol (50 nl, 10 mM; Sigma) or vehicle (saline) was injected bilaterally into the PVN. The effective concentration of muscimol to inhibit the PVN has been determined in a previous study (1). Because bilateral microinjection of muscimol into the PVN lowered the basal blood pressure and RSNA, the blood pressure was pharmacologically restored to the control level. To raise the blood pressure, we used a constant intravenous infusion of norepinephrine (0.4–1.0 μg/kg) or phenylephrine (0.4–1.0 μg/kg). After the blood pressure was restored, the RSNA and blood pressure responses to epicardial bradykinin were tested again as described above.

Role of ionotropic glutamate receptors in the PVN in blood pressure and RSNA responses to epicardial bradykinin. Because microinjection of muscimol attenuated the bradykinin-evoked reflex response (see RESULTS) and there is a potential connection from the heart to PVN, we next determined if the ionotropic glutamate receptors in the PVN play a role in the cardiogenic sympathoexcitatory reflex. In a separate group of rats, the blood pressure and RSNA responses to epicardial bradykinin (10 μg/ml) were tested before and ~15 min after bilateral microinjection of the ionotropic glutamate receptor antagonist kynurenic acid into the PVN. Rats received bilateral microinjections of 4.82 nmol kynurenic acid (50 nl, 96 mM; Sigma) into the PVN. The concentration of kynurenic acid was chosen based on previous studies showing that it is effective and lasts longer than 20 min (7, 13). Kynurenic acid was dissolved in saline, made basic by 1 N NaOH, and the pH was adjusted to 7.4 by adding 1 N HCl. The RSNA and blood pressure responses to epicardial application of bradykinin were determined before and ~15 min after completion of kynurenic acid microinjections.

Furthermore, because microinjection of 4.82 nmol kynurenic acid failed to attenuate the reflex response (see RESULTS), we also tested the response to epicardial bradykinin after bilateral microinjection of a higher concentration of kynurenic acid (48.2 nmol) into the PVN. Additionally, as a positive control, we performed the muscimol microinjection into the same coordinate in the PVN in some rats to verify that the injection site within the PVN was important for the reflex control of sympathetic outflow. After completion of kynurenic acid injections, we microinjected 50 nl muscimol (0.5 nmol) into the PVN bilaterally and repeated epicardial bradykinin application.

Histology

The location of the pipette tip and diffusion of the injectant within the PVN were examined and confirmed histologically in all rats. All muscimol, kynurenic acid, and vehicle microinjections contained 5% rhodamine-labeled fluorescent microspheres (0.04 μm, Molecular Probes, Eugene, OR) to identify the dispersion of the drug throughout
the PVN and its surrounding area. At the completion of experiments, brains were removed rapidly and fixed in 10% buffered formalin solution overnight. Frozen 50-μm coronal sections were cut on a freezing microtome and mounted on slides. Rhodamine-labeled regions were identified under an epifluorescence microscope and plotted on standardized sections from the Paxinos and Watson atlas (24). Rats with micropipette misplacement or injectants spreading outside of the PVN were excluded from analysis.

Data Analysis

Values are presented as means ± SE. Baseline RSNA and blood pressure were averaged during the 2-min control periods. Maximum RSNA and blood pressure responses were measured ~20 s after bradykinin application (15, 36). The RSNA response is presented as the percent change from the baseline activity because of the variability in baseline RSNA in each animal. Repeated-measures ANOVA with Dunnett’s post hoc test was used to compare the difference between group means. P < 0.05 was considered statistically significant.

RESULTS

Figure 1 shows the distribution of microinjection sites within the PVN for vehicle-, muscimol-, and kynurenic acid-injected rats. In all rats included for analysis, the size of the fluorescence microsphere spread was typically 0.3–0.5 mm around the injection site and did not penetrate the third ventricular ependymal lining. Nine rats in total were excluded from the study because of micropipette misplacement and injectants spreading outside of the PVN. In these nine rats excluded, pipette misplacement and injectant overspread occurred only in one hemisphere in eight rats. In the one remaining rat in which muscimol microinjection was ~1 mm dorsal to the edge of the PVN, bradykinin increased the baseline blood pressure from 72.8 to 100.6 mmHg and elicited a 172.4% increase in RSNA before muscimol injection. After muscimol microinjection, bradykinin increased the blood pressure from 78.3 to 104.6 mmHg and caused a 162.4% increase in RSNA.

Effect of Vehicle and Muscimol Microinjections Into the PVN on Blood Pressure and RSNA Responses to Epicardial Bradykinin

Figure 2 shows representative RSNA and blood pressure responses to epicardial bradykinin (10 μg/ml) before and ~15 min after bilateral microinjection of the vehicle into the PVN.
in a rat. During control and after vehicle injection, epicardial bradykinin induced an immediate and reproducible increase in the RSNA and blood pressure. The maximal increase in the RSNA and blood pressure occurred ~20 s after bradykinin application and gradually returned to baseline within 10 min. Before vehicle injection, epicardial bradykinin significantly increased RSNA 198.7 ± 26.7% from the baseline and mean arterial pressure from 75.0 ± 1.8 to 103.0 ± 3.0 mmHg (P < 0.05) in all 10 rats tested. However, heart rate was not significantly increased from the baseline (243.0 ± 11.5 to 244.6 ± 12.7 beats/min) after bradykinin application. In these rats, microinjection of the vehicle into the PVN did not significantly alter bradykinin-induced increases in the RSNA (188.4 ± 38.5% over baseline) and mean arterial pressure (from 76.9 ± 2.0 to 102.3 ± 3.3 mmHg), compared with the control response.

The effect of microinjection of muscimol into the PVN on the cardiogenic reflex was examined in 12 rats. Figure 3 shows representative RSNA and blood pressure responses to epicardial application of bradykinin (10 μg/ml) before and ~15 min after bilateral muscimol microinjection into the PVN in a rat. In all of the 12 rats examined, bilateral microinjection of 0.5 nmol muscimol into the PVN resulted in a significant decrease in basal RSNA (29.8 ± 5.1% decrease) and blood pressure (17.1 ± 2.6 mmHg decrease). After muscimol microinjection, epicardial bradykinin still significantly increased RSNA (111.6 ± 35.9% over baseline) and mean arterial pressure (from 61.2 ± 1.3 to 74.5 ± 2.7 mmHg; Fig. 4, A and B, P < 0.05). However, the magnitude of the RSNA and blood pressure responses to epicardial bradykinin was significantly reduced compared with those before muscimol microinjection (Fig. 4, A and B). Because muscimol microinjection into the PVN significantly lowered basal blood pressure, we also tested the RSNA and blood pressure response to epicardial bradykinin when the blood pressure was restored to the control level with intravenous norepinephrine or phenylephrine. In all rats tested, bradykinin-elicited RSNA and blood pressure responses remained significantly attenuated compared with the response during control (Figs. 3 and 4).

**Effect of Microinjection of Kynurenic Acid Into the PVN on Blood Pressure and RSNA Responses to Epicardial Bradykinin**

To determine if glutamate in the PVN is involved in the bradykinin-induced cardiogenic sympathetic response, the ionotropic glutamate receptor antagonist kynurenic acid was microinjected into the PVN (7, 13). At both low (4.82 nmol) and high (48.2 nmol) concentrations, bilateral microinjections of kynurenic acid had no significant effect on bradykinin (10 μg/ml)-induced increases in the RSNA and blood pressure in all nine rats tested (Figs. 5 and 6).
Because bradykinin-elicited reflex responses were not attenuated by kynurenic acid, we then microinjected muscimol into the same coordinate of the PVN where kynurenic acid was injected. After bilateral muscimol (0.5 nmol) microinjections, we again tested the RSNA and blood pressure responses to epicardial bradykinin. In six rats examined, muscimol microinjection caused a significant reduction in the basal RSNA (24.6 ± 9.5% decrease) and blood pressure (18.2 ± 3.1 mmHg decrease; Figs. 5 and 6). Furthermore, the bradykinin-induced increases in the RSNA (110.4 ± 31.8% increase) and blood pressure (75.9 ± 2.8 mmHg) were significantly reduced compared with the control response (Figs. 5 and 6).

DISCUSSION

This study focused on the potential role of the PVN in the cardiogenic sympathetic reflex caused by stimulation of cardiac afferents. We also determined whether glutamate in the PVN mediates this autonomic reflex response. We found that microinjection of the GABA<sub>A</sub> receptor agonist muscimol into the PVN significantly attenuated the cardiogenic sympathoexcitatory reflex. However, microinjection of the ionotropic glutamate receptor antagonist kynurenic acid into the PVN did not significantly alter this reflex response. Therefore, this study provides new information that the PVN tonic activity contributes importantly to the full increase in sympathetic outflow elicited by stimulation of cardiac afferents, but the ionotropic glutamate receptors in the PVN are not directly involved in this cardiogenic reflex.

Activation of cardiac afferents during myocardial ischemia in patients is associated with an increase in sympathetic nerve activity and blood pressure (34, 35). Myocardial ischemia increases the release of ischemic metabolites, including bradykinin to activate cardiac afferents (3, 23, 31). It has been shown that bradykinin activates the kinin B<sub>2</sub> receptors on cardiac capsaicin-sensitive afferents to produce a sympathoexcitatory reflex response (3, 15, 27, 31, 36). Also, the cardiogenic sympathetic reflex involves predominantly brain stem nuclei (15, 17, 33). Although the brain stem nuclei play a critical role in generation and regulation of the sympathetic activity, descending projections from supramedullary sites such as the PVN are also important to regulate sympathetic outflow (1, 19, 37). In this regard, the RVLM receives excitatory inputs from the PVN autonomic neurons, and blockade of these inputs to the RVLM attenuates the depressor response caused by PVN inactivation (1). On the basis of these previous studies, the PVN is likely another potentially important structure in this reflex. Thus the PVN is functionally positioned to regulate sympathetic outflow originating from the brain stem and spinal cord. However, there is little functional evidence showing that the PVN is directly involved in the cardiogenic sympathetic reflex.

To determine if the PVN is an important component for the cardiogenic sympathoexcitatory response, we inhibited the PVN by bilateral microinjection of the GABA<sub>A</sub> agonist muscimol.
the PVN in 6 rats. Data are presented as means ± SE. *P < 0.05 compared with the respective baseline; **P < 0.05 compared with the control baseline.

**Fig. 6.** Summary data showing the RSNA (A) and MAP (B) responses to epicardial bradykinin (10 μg/ml) before and after bilateral injection of kynurenic acid (4.82 and 48.2 nmol) into the PVN in 9 rats. The RSNA responses evoked by bradykinin were presented as percent change from the baseline before bradykinin application during control. The responses to bradykinin were also tested after bilateral injection of muscimol (0.5 nmol) into the PVN in 6 rats. Data are presented as means ± SE. *P < 0.05 compared with the respective baseline. **P < 0.05 compared with the control baseline.

cimol. Muscimol was used because of the long-lasting action of the agent (1). In our experiments, the muscimol-induced inhibition of the basal RSNA and blood pressure lasted several hours and did not return to the control. This enabled us to perform several bradykinin application protocols without repeated microinjections. We found that muscimol microinjection significantly attenuated the sympathetic response to stimulation of cardiac afferents with bradykinin. In our experiments, muscimol microinjection into the PVN significantly lowered basal RSNA and blood pressure, which is consistent with other studies (1, 37). Because inactivation of the PVN reduced basal blood pressure, we restored blood pressure to the control level with norepinephrine or phenylephrine in these animals. However, even when the blood pressure was restored, the reflex response to epicardial bradykinin remained significantly attenuated. These findings suggest that the attenuated cardiogenic reflex after microinjection of muscimol into the PVN is not simply due to lowered basal blood pressure. Thus the tonic PVN activity is likely responsible for maintaining sympathetic tone, which is essential for the full manifestation of the cardiogenic reflex response. It has been shown that the PVN is also required for full manifestation of the chemoreflex. In this regard, bilateral electrolytic lesion of the PVN attenuates the pressor response to intravenous potassium cyanide in conscious rats (22).

Although inactivation of the PVN significantly attenuated the reflex response, it is not clear if the PVN functions as a modulator for sympathetic outflow or acts as a processing center to integrate the input signal from the heart. Cardiac spinal afferents project to the dorsal horn of the upper thoracic spinal cord (14) and synapse on dorsal horn neurons that ascend in the spinoreticular and spinothalamic tracts (4). Also, afferent signals from visceral organs are conveyed through dorsal horn neurons that ascend through the spinothalamic tract to synapse in hypothalamic nuclei, including the PVN (5, 8, 20). Glutamate is the primary excitatory neurotransmitter in the CNS, and it may convey cardiac sensory information to PVN neurons (9, 12, 16, 19). Contrary to our second hypothesis, we did not observe any significant attenuation of the RSNA and blood pressure responses to epicardial bradykinin after microinjection of kynurenic acid into the PVN. Since microinjection of a high concentration of kynurenic acid also failed to alter significantly the RSNA and blood pressure response, it is unlikely that lack of an effect of kynurenic acid on the reflex response is due to an inadequate blockade of ionotropic glutamate receptors in the PVN. Furthermore, microinjection of muscimol into the same coordinate within the PVN in these animals significantly attenuated the reflex response. Hence, the injection site and limited spread of injectants within the PVN cannot explain the negative result from the kynurenic acid protocol.

These data suggest that ionotropic glutamate receptors in the PVN are not essential for the sympathetic response to stimulation of cardiac afferents. We cannot exclude the possibility that this reflex response is mediated by other unidentified neurotransmitters in the PVN. It has been shown that microinjection of ANG II into the PVN augments the sympathoexcitatory response to epicardial bradykinin in rats (38). However, ANG II probably is not a critical neurotransmitter in the PVN mediating this reflex because microinjection of losartan alone into the PVN has no significant effect on the sympathoexcitatory response to bradykinin (38). Nevertheless, it is possible that in heart failure state, ANG II in the PVN may play a role in the sympathetic response to stimulation of cardiac afferents. The reduced excitatory input to the RVLM and spinal IML by inhibition of the PVN appears to account for the attenuated reflex response to epidural bradykinin.

Therefore, although anatomic studies suggest that the PVN receives inputs indirectly from visceral afferents (5, 8, 20), these projections to the PVN appear to be not essential for this cardiogenic sympathetic reflex. A more likely scenario for the role of the PVN in this reflex is that it serves as an important source for tonic excitatory inputs to the RVLM and spinal IML, and this tonic PVN activity is required for the full manifestation of this reflex response. It has been shown that midcollicular decerebration does not attenuate the RSNA and blood pressure response to epicardial application of bradykinin in rats (33). However, this does not exclude the possibility that the supraspinal sites are also involved in this reflex response. This is because decerebration could have removed supramedullary excitatory and inhibitory descending controls for sympathetic outflow. In this regard, previous studies have shown that both the ventrolateral periaqueductal gray and ventral medial prefrontal cortex are important descending inhibitory pathways that modulate the RVLM neurons and sympathetic vasomotor drive (2, 11, 32). Data from the present study strongly suggest that the PVN autonomic neurons not only play an important role in the maintenance of basal sympathetic tone but also are required for increased sympathetic drive in response to stimulation of cardiac afferent nerves.
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