Nucleus Prepositus Hypoglossi
A Medullary Pressor Region
William T. Talman and Scott C. Robertson

Electrical stimulation of fibers of passage through the fastigial nucleus increases arterial pressure. To identify nuclei that may project through the pressor region of the fastigial nucleus, we injected the retrograde tracer fast blue unilaterally at confirmed pressor sites in the nucleus. In seven rats, we found dense fluorescent labeling bilaterally in the external cuneate, lateral reticular, medial vestibular, and caudal prepositus hypoglossi nuclei, and contralaterally in the inferior olivary nucleus. There had been no reports of a cardiovascular role for the nucleus prepositus hypoglossi; thus, we sought to determine if electrical or chemical stimulation of that nucleus or the adjacent medial vestibular nucleus altered arterial pressure or heart rate in 24 anesthetized rats. Both types of stimuli to the caudal, but not the rostral, pole of the nucleus prepositus hypoglossi or to the medial vestibular nucleus elicited an increase in arterial pressure; bradycardia accompanied the former and tachycardia the latter. Both the nucleus prepositus hypoglossi and medial vestibular nucleus may participate in central cardiovascular regulation. (Hypertension 1991;17:1173–1176)

Electrical stimulation of the rostral fastigial nucleus of the cerebellum causes a prominent increase in arterial pressure and heart rate. This “fastigial pressor response” is now thought to result from activation of fibers of passage instead of local fastigial neurons, because activation of fastigial neurons by excitatory amino acid analogues causes a depressor response. Furthermore, transection of the inferior cerebellar peduncle and thus projections to fastigial nucleus has been shown to abolish the fastigial pressor response.

Previous reports have indicated that the nucleus prepositus hypoglossi project to the fastigial (or median) nucleus of the cerebellum. Although the latter nuclear region may serve an important role in stabilizing blood pressure during postural changes, no cardiovascular role has been ascribed previously to the nucleus prepositus hypoglossi. In fact, the predominantly recognized role for that nucleus is in the integration of extraocular movements in humans and experimental animals. Other nuclei projecting to the fastigial nucleus have been studied with respect to their role in cardiovascular regulation, but neither the other nuclei projecting to the fastigial nucleus nor the nucleus prepositus hypoglossi projections to the fastigial nucleus have been studied with respect both to their point of termination in the fastigial nucleus and to the functional role of that point of termination.

In this study, therefore, we sought to determine the source of fibers passing through (or terminating in) the pressor region of the fastigial nucleus, to determine if it is that functionally defined region to which the nucleus prepositus hypoglossi projects, and to determine if stimulation of nucleus prepositus hypoglossi causes changes in arterial pressure and heart rate.

Methods

General

In adult (350–400 g) male Sprague-Dawley rats anesthetized with halothane (1.5%), a cannula was passed into a femoral artery and vein for recording arterial pressure and for delivering drugs, respectively. Heart rate was derived from the arterial pulse wave and was recorded with arterial pressure by a polygraph. Adequate oxygenation was assured by the delivery of 100% oxygen via a nasal mask, and temperature was maintained between 36.5°C and 37.5°C by a temperature controller (Yellow Springs Instrument Co., Yellow Springs, Ohio) connected to a rectal thermistor.

The animals were placed in a stereotaxic frame, and a burrhole was made in the occipital bone for passage of electrodes and micropipettes into the brain. At the completion of these preparations, halothane was stopped; anesthesia was maintained with chloralose (60 mg/kg i.v. with 20 mg/kg/hr maintenance doses subsequently). In the following
studies, electrical stimuli were delivered through a monopolar electrode with 100–200 μm of the tip exposed. The electrode was connected to the cathode of a constant current stimulus isolation unit, and stimulus parameters were set by a Digitimer (model D4030, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). The electrode was cemented to a single-barrel or multibarrel pipette whose tip was positioned 50 μm from the electrode tip.

Identification of Sites Projecting Into the Fastigial Pressor Region

In seven rats, the electrode/pipette array was passed into the rostral fastigial nucleus. Stimuli (0.5-msec pulse duration, 200 μA, 100 Hz) were delivered as the tip was advanced in 200-μm steps until a fastigial pressor response of greater than 10 mm Hg was elicited. In some rats, at the site in the pipette tract from which a maximum response was elicited, a 100-nl injection of kainic acid (5 nmol) was made to confirm the presence of a fastigial depressor response deriving from the same region (Figure 1). At that site, fast blue (2% solution) was injected (200 nl) over a 10-minute period. The electrode/pipette was left in place for 5 minutes after the injection to minimize diffusion from the tract. With removal of the instrument, the femoral cannulas also were removed, the vessels were ligated, and all wounds were locally anesthetized with 2% procaine and closed. The animals were carefully observed and supported until fully awake and ambulatory.

Seven days later, the animals were again anesthetized and were killed by exsanguination. Tissues were fixed by intracardiac perfusion of 500 ml cold 4% paraformaldehyde. After perfusion fixation, the brain was removed and stored in cacodylic acid/30% sucrose solution (pH 7.2) overnight or until the brains could be sectioned. Transverse sections (40 μm) were made through the brain stem and cerebellum. Sections were mounted on Gatenby coated slides and air-dried on a slide warmer for 1 hour. Neurons labeled by the retrograde transport of the fluorescent tracer fast blue were identified by standard fluorescent microscopic techniques.

Stimulation of the Nucleus Prepositus Hypoglossi

This series of studies was performed in 24 rats fixed in a stereotaxic frame with the incisor bar set at zero. The electrode/pipette array, held at a 20° angle from the vertical with the tip aimed rostrally, was passed into the nucleus prepositus hypoglossi using the calamus scriptorius as the anterior, posterior, and lateral zero. Sites of stimulation in the nucleus prepositus hypoglossi were 2.5–3.0 mm rostral to the calamus scriptorius, 0.5–0.8 mm lateral to the midline, and 0.1–0.5 mm dorsal to the calamus scriptorius. The nucleus prepositus hypoglossi or adjacent sites were stimulated with a constant current delivered in pulses of 0.5 msec at a frequency of 50 Hz. A stimulus amplitude of 50 μA was used to identify positive sites as the electrode was passed, and stimuli of 100 and 200 μA were delivered at the responsive sites. At those sites, sodium L-glutamate (10 mM) was microinjected (100 nl), and the site of injection was marked with a concentrated solution of methylene blue. Glutamate was used in these experiments to stimulate local neurons and to compare and contrast responses elicited by the chemical and the electrical stimulus that would activate both fibers and cells. In some animals, sites of electrical and chemical stimulation were marked by an electrolytic lesion made by passage of a 2-mA DC current for 2 minutes. All stimulus sites were confirmed by direct visualization of transverse sections through the brain stem at postmortem examination.

Results

Studies of those nuclei that project into the pressor region of the fastigial nucleus revealed dense labeling (>5 cells per high power field) bilaterally in the external cuneate nuclei, the lateral reticular nuclei, the medial vestibular nuclei, and the caudal poles of the nuclei prepositus hypoglossi. Similar labeling also was found in the contralateral inferior olivary nucleus. Less densely labeled areas included the area postrema, the nucleus tractus solitarii, the nucleus of Roller, the nucleus raphe obscurus, the nucleus reticularis gigantocellularis, the nucleus locus coeruleus, the Kölliker-Fuse nucleus, and the parabrachial nucleus. Scattered cells were labeled in these nuclei, as were a large number of fibers. Labeled fibers also could be found in the dorsal spinocerebellar/olivo-cerebellar tract, the inferior cerebellar peduncle, the ventral spinocerebellar tract, the trapezoid body leading to the medial lemniscus, the raphe magnus nucleus, the raphe pontis nucleus, and rarely in the caudal pontine reticular nucleus. Labeled fibers were
Arterial Pressure (mmHg)  
Mean Arterial Pressure (mmHg)  
Heart Rate (bpm)  

![Figure 2](image-url)  
**Figure 2.** Prominent pressor and bradycardiac responses elicited by electrical (left traces) or chemical (right traces) stimulation of nucleus prepositus hypoglossi. Glu, L-glutamate.

seen extending from the injection site in the fastigial nucleus to the contralateral fastigial nucleus and from that nucleus to the inferior cerebellar peduncle.

The following studies were performed to determine the cardiovascular responses to stimulation of one of the densely labeled nuclei, the nucleus prepositus hypoglossi. Electrical stimulation (50, 100, or 200 µA) of the caudal pole of that nucleus produced a prominent pressor response that was greatest with the 200-µA stimulus (Figure 2) and least with the 50-µA stimulus. Excitation of local neurons at the same site by microinjection of L-glutamate (10 mM in 100 nl) increased arterial pressure by 81.8 ± 2.8 mm Hg (mean ± SEM). The pressor response to stimulation of nucleus prepositus hypoglossi, regardless of stimulus intensity or stimulus type, usually was accompanied by a decrease in heart rate, although at times heart rate increased.

The same range of electrical stimuli or glutamate delivered to the adjacent medial vestibular nucleus also increased arterial pressure, but heart rate tended to increase with this stimulus. Stimuli delivered ventral to the nucleus prepositus hypoglossi or medial vestibular nucleus, but lying outside other nuclei involved in cardiovascular regulation, such as the nuclei raphe magnus, had no effect on arterial pressure or heart rate (Figure 3). Similarly, the responses to stimulation of the nucleus prepositus hypoglossi were seen when stimuli were confined to the caudal pole of that nucleus and were not evident with stimuli rostrally in the same nucleus or caudally in the hypoglossal nucleus itself.

**Discussion**

This study has demonstrated that fibers project from the caudal pole of the nucleus prepositus hypoglossi into the region of the fastigial nucleus from which electrical stimulation produces pressor responses. Fast blue, used in this study, is transported by fibers of passage as well as anterogradely and retrogradely from an injection site. Thus, it cannot be determined whether fibers from the nucleus prepositus hypoglossi terminate in the fastigial nucleus, pass through it, or lie in a subfastigial fiber bundle that may be the site of origin of the fastigial pressor response.12 Nuclei projecting to the fastigial nucleus have been identified previously by others4,5 in detailed anatomic studies. However, the functional relevance of the sites of termination in the fastigial nucleus was not determined. The current study has confirmed those earlier studies and shown that the site to or through which the afferents project may modulate arterial pressure.

Of the nuclei found to be densely labeled in this study, all but the nucleus prepositus hypoglossi have recognized potential roles in cardiovascular regulation. The nucleus prepositus hypoglossi, on the other hand, had been considered to be involved only in integration of extraocular movements.9,10 There had been clues that this nucleus may be involved in some way in cardiovascular control. A clinical paper8 and an experimental study9 both described effects of lesions of the nucleus prepositus hypoglossi. In the human subject, in whom the nucleus appeared to be particularly susceptible to lithium toxicity, the abnormalities of extraocular movement associated with destruction of the nucleus were followed by death secondary to unexplained cardiopulmonary compro-

**Figure 3.** Diagrammatic representation of a transverse section of the medulla at the level of the caudal nucleus prepositus hypoglossi and approximately 100 µm rostral to the nucleus hypoglossi and nucleus intercalatus. Circles represent sites at which stimuli elicited increases in arterial pressure and decreases in heart rate; triangles, sites at which stimuli elicited increases in arterial pressure and heart rate; squares, sites at which stimuli produced biphasic changes in arterial pressure and variable changes in heart rate; and asterisks, sites at which no response occurred. Each symbol represents one stimulus. MVN, medial vestibular nucleus; NPH, nucleus prepositus hypoglossi; I.O., inferior olivary nucleus.
misse. Death also occurred in the monkey after bilateral injection of neurotoxic doses of kainic acid into the nucleus. In neither the human nor the experimental animal study was there any apparent cause of death.

The role the nucleus prepositus hypoglossi plays in cardiovascular regulation in the intact animal is unclear. The current study does not address whether the nucleus is the source of the fastigial pressor response. Further studies will be needed to clarify its relation to that response. However, others have reported\textsuperscript{13,14} that a region in the dorsal medial medulla is responsible for the fastigial pressor response. Stimuli delivered to the putatively responsible region are depicted close to the nucleus prepositus hypoglossi, but no stimuli were delivered specifically to that nucleus. Likewise, no stimuli were delivered to the medial vestibular nucleus, which in the current study also produced pressor responses.

The fastigial pressor response is associated with a tachycardiac response in contrast to the bradycardiac response that usually followed stimulation of the nucleus prepositus hypoglossi. The tachycardiac response associated with stimuli to the medial vestibular nucleus is, in fact, more typical of the fastigial pressor response.

This study was designed to determine if the region of the nucleus prepositus hypoglossi, from which fibers projected to the fastigial nucleus, was itself capable of modulating arterial pressure and heart rate. The 100-nl volumes injected in this study can identify active versus inactive sites that lie as little as 200 \( \mu \text{m} \) apart.\textsuperscript{15} As a number of the injection stimuli within the nucleus prepositus hypoglossi lay 200 \( \mu \text{m} \) or more from the border of the nucleus, this study indicates that the stimuli were producing responses by an action within the nucleus rather than by diffusion to other sites. It is not surprising that stimulation of the adjacent medial vestibular nucleus, which also projects to the fastigial nucleus, likewise increases arterial pressure, because the vestibular nerve itself has been shown to be involved in control of arterial pressure during postural changes.\textsuperscript{16} The difference in responses of heart rate with stimuli at the two sites further supports the ability of the method to detect regional functional differences.

The chemical stimulus used in this study was L-glutamate, which has been shown to activate local neurons rather than fibers of passage.\textsuperscript{11} Thus, neurons within the nucleus prepositus hypoglossi may play a role in central cardiovascular control. The pressor response to stimulation of the nucleus may be mediated by axonal projections passing through the fastigial nucleus, but direct projections from the nucleus to the spinal cord\textsuperscript{17} or other sites also could contribute to the responses seen.

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