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Visceral nociceptive input to the area of the medullary lateral reticular nucleus ascends in the lateral spinal cord

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Abstract

In halothane-anesthetized rats, neurons stereotaxically located in the region of the medullary lateral reticular nucleus (LRN) and responsive to urinary bladder distension (UBD) were characterized using extracellular electrodes. Most neurons excited by UBD were also excited by noxious stimuli applied to bilateral receptive fields comprising at least half of the body surface. These bilateral nociceptive specific (bNS) neurons exhibited graded responses to graded intensities of UBD. Neuronal responses to noxious UBD were highly positively correlated with responses to noxious colorectal distension, suggesting a convergence of visceral sensory information in the area of LRN. Bilateral lateral mid-cervical spinal cord lesions virtually abolished activity of bNS neurons evoked by noxious UBD, while dorsal midline lesions had no significant effect. These data support a role for neurons in the region of the LRN in visceral nociception and implicate traditional lateral spinal cord pain pathways in the transmission of visceral information to caudal ventrolateral medullary structures.
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Extensive use has been made of models of visceral pain using gut distension as a stimulus, but less is known about the neurophysiology and pathways involved in other types of visceral sensory processing. The question arises whether the afferent pathways and supraspinal populations of neurons responsible for visceral nociceptive processing differ depending upon the origination of the stimulus (i.e. bladder versus colon). We previously characterized neurons in the area of the medullary lateral reticular nucleus (LRN) responsive to the visceral stimulus, colorectal distension (CRD), [19] and described many characteristics of those neurons. They encoded CRD in an intensity-dependent fashion, and most were also excited by noxious cutaneous stimuli presented to large areas of the body surface. We also found that CRD-evoked medullary activity was significantly attenuated by lateral lesions of the spinal cord [18], which implies that nociceptive information from the colon to the ventrolateral medulla is relayed via lateral, rather than dorsal column, spinal projections.

In order to determine whether the neuronal substrates and pathways related to urinary bladder sensation were similar to those associated with gut sensation, the present study characterized responses of ventrolateral medullary neurons in the area of the LRN to urinary bladder distension (UBD), cutaneous stimulation and CRD. We also examined UBD-evoked responses after sequential cervical spinal cord lesions in order to determine whether nociceptive information from the bladder to these neurons also ascends in the lateral spinal cord.

Studies were performed in female, Sprague–Dawley rats anesthetized with a mixture of halothane and oxygen. The halothane concentration was reduced from 4–5% to 1.5–2% after placement of intratracheal and jugular venous cannulae. Rats were placed in a stereotaxic apparatus with the head tilted downwards 45°. A cervical laminectomy and occipital craniotomy were performed, exposing the mid- to upper cervical spinal cord and caudal medulla at the level of obex. After surgery, the halothane concentration was maintained at 0.75–1.0%, and rats were artificially ventilated. No spontaneous movement, escape behavior or evidence of tonic sympathetic nervous system activation was observed prior to

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paralysis induced by i.v. administration of 0.5 ml pancuronium bromide (Baxter, Deerfield, IL). At the end of the experiment, rats were euthanized with an overdose of halothane followed by decapitation. All studies were approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham in accordance with the guidelines provided by the National Institutes of Health.

A 22-gauge polytetrafluoroethylene angiocatheter was placed into the bladder via the urethra and held in place by a tight suture around the distal urethral orifice. UBD was induced using compressed air and a previously described distension control device [4] and intravesical pressure monitored using an in-line, low volume pressure transducer.

Distension of the descending colon and rectum was produced by air inflation of a 7 cm latex balloon inserted via the anus and kept in position by taping the connecting catheter to the tail. The same pressure control device and pressure monitoring was performed as described above.

Tungsten microelectrodes (Micro Probe, Clarksburg, MD, 1.2–1.8 MΩ) were used for conventional extracellular single-unit recording. The area 1.5–2.5 mm lateral to obex and greater than 2.0 mm below the dorsal surface was searched for units responsive to UBD (60 mmHg). Responsive units were defined as those demonstrating a consistent alteration in spontaneous activity on at least three consecutive presentations of UBD. If a reliable response was obtained, neurons were fully characterized for response to UBD (60 mmHg, 20 s, every 3 min) and for excitatory/inhibitory responses to non-noxious light touch (paintbrush) and noxious pinch (with fine forceps) stimuli applied to cutaneous structures. The depth of electrode penetration at the site of recording and upon subsequent contact with the basilar skull was recorded. Units were displayed on an oscilloscope for continuous monitoring, discriminated conventionally from background, converted into uniform pulses, counted, and saved by computer.

In one group of rats, responses to graded UBD (20, 40, 60 mmHg, 20 s) were measured, and stimulus–response functions (SRFs) of quantified responses (described below) were obtained for each individual neuron. Units were also tested for responses to noxious CRD (80 mmHg, 20 s).

After establishing a reliable and reproducible unit response to UBD, three sequential lesions of the mid-cervical spinal cord were performed using a hand-held, bent, heated wire assembly (Accu-temp, Xomed-Trease, Jacksonville, FL) in a subset of rats. Sites of lesioning were the following: (1) the dorsal midline (DM lesion) generally to a depth of approximately 1 mm and extending 0.5–1.0 mm bilaterally (a wedge-shaped lesion); (2) the lateral spinal cord contralateral to the recording site (cLAT lesion); and (3) the lateral spinal cord ipsilateral to the recording site (iLAT lesion). Lesions were performed at 8 min intervals. In half of the rats, in each group, the order of lesions performed was DM then cLAT then iLAT; in the other half the order was iLAT then cLAT then DM. Responses to UBD were determined 1 and 5 min after each lesion was performed. In four rats, a total transection of the spinal cord was performed.

The total number of unit discharges was counted during a 20 s distending stimulus. 'Evoked activity' was defined as the mean number of unit discharges during this preselected interval minus mean rate of background (spontaneous) activity determined immediately preceding the onset of distension. SRFs of evoked activity to graded UBD were plotted for individual neurons. Because responses of different neurons to the same distending stimulus naturally varied in maximal response and total number of unit discharges, each unit's response was expressed as a percentage of the mean of the baseline UBDs (response to 60 mmHg) for purposes of within and between group comparisons. A Pearson's correlation (two-tailed) was used to assess the correlation between UBD- and CRD-evoked neuronal responses. An absolute correlation coefficient of 0.7–1.0 was considered a high correlation. Treatment effects in the lesion studies were assessed using a repeated measures analysis of variance (ANOVA). Individual treatment steps were compared using a before–after paired *t*-test. For all tests, $p \leq 0.05$ was considered statistically significant.

A total of 51 neurons located in the caudal ventrolateral medulla and responsive to UBD were characterized: 45 units were reliably excited by and six were reliably inhibited by UBD. Inhibitory neurons did not respond to cutaneous inputs ($n = 1$), had excitatory inputs ($n = 1$), had no excitatory inputs but were inhibited by noxious cutaneous stimuli ($n = 3$), or had mixed excitatory/inhibitory responses to cutaneous stimuli based on body site ($n = 1$). Of the neurons excited by UBD, approximately half were located in the ventral medulla within 0.75 mm of the base of the skull and so are in the area of the LRN. Half of the units sampled were located immediately dorsal to this region.

UBD-excited neurons were divided into subgroups based on their cutaneous receptive fields. A majority of these units were excited by noxious stimuli applied to bilateral receptive fields comprising at least half of the body surface ($n = 31$) and were termed 'bilateral nociceptive specific' (bNS) neurons. These bNS neurons were subdivided into dorsal ($n = 19$) and ventral ($n = 12$) according to the above criteria, since this distinction rendered a bimodal distribution of neurons in our previous study of medullary neurons excited by CRD [19].

Other neurons excited by UBD were not excited by cutaneous stimuli ($n = 9$), were excited by noxious stimuli in unilateral receptive fields ($n = 1$), or had mixed excitatory/inhibitory responses to cutaneous stimuli based on body site ($n = 1$). These three types of neurons were mainly located immediately dorsal to the LRN and were treated as a single group called 'medullary reticular formation' (MRF) neurons. A summary of the characteristics of medullary neurons responsive to UBD as stratified by their cutaneous receptive fields and by their relation to the ventral surface of the medulla is shown in Table 1.

The effects of graded UBD on neuronal activity were examined to determine if these neurons encoded for this stimulus. Examples of graded responses of bNS and MRF neurons and grouped characteristics of all these neurons are given in

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