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Inhalation of a pulmonary irritant modulates activity of lumbosacral spinal neurons receiving colonic input in rats

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Qin C, Foreman RD, Farber JP. Inhalation of a pulmonary irritant modulates activity of lumbosacral spinal neurons receiving colonic input in rats. *Am J Physiol Regul Integr Comp Physiol* 293: R2052–R2058, 2007. First published August 29, 2007; doi:10.1152/ajpregu.00154.2007.—The purpose of the present study was to determine whether an intraspinal nociceptive pathway from the lungs modulated activity of spinal neurons that also received afferent input from the colon. Extracellular potentials of single lumbosacral (L6–S2) spinal neurons were recorded in pentobarbital-anesthetized, paralyzed, and ventilated male rats. The lower airways and lungs were irritated by injecting ammonia vapor over a 30% NH_4OH solution into the inspiratory line of the ventilator (0.5 ml, 20 s). Graded colorectal distension (CRD; 20–60 mmHg, 20 s) was produced by air inflation of a balloon. Inhaled ammonia (IA) altered activity of 31/51 (61%) lumbosacral spinal neurons responding to noxious CRD (60 mmHg, 20 s). In contrast, IA changed activity of 3/30 (10%) spinal neurons with somatic fields that did not respond to colorectal inputs. IA decreased activity of 16/31 (52%) spinal neurons and increased activity of the other 15 neurons with colorectal input. Multiple patterns of viscerovisceral convergent spinal neurons with excitatory and inhibitory responses to CRD and IA were observed; 87% (27/31) of the viscerovisceral convergent neurons also responded to innocuous and/or noxious stimuli of somatic fields. Bilateral cervical vagotomy abolished responses to IA in 2/8 tested neurons, indicating that the remaining 6 neurons had input originating from sympathetic afferent fibers. Rostral C1 spinal transection did not abolish inhibitory responses to IA in 4/4 neurons, but L2 transection eliminated inhibitory responses to IA in 3/3 neurons. These results indicated that irritation of the lower airways modulated activity of lumbosacral spinal neurons with colorectal input. It might contribute to intraspinal cross talk between the colon and lungs.

ammonia; colorectal distension; visceral nociception; vagal afferent; sympathetic afferent

CLINICALLY, AN ASSOCIATION between large bowel diseases and respiratory disorders has been noted in several investigations. The prevalence of impaired lung function, bronchial hyperactivity, and allergy in subjects with inflammatory bowel disease (IBD) or ulcerative colitis is higher compared with abnormalities of pulmonary function in control groups (6, 7, 15, 21, 22). For example, pulmonary function test abnormalities are reported in 27–28% of patients with IBD (7, 15) and 55% of patients with ulcerative colitis (22), whereas this prevalence is 3–8% in the normal population from North America. In addition, chronic bronchial suppuration, localized upper airway obstruction, diffuse obstructive disease, bronchiectasis, granulomatous lung disease, pulmonary vasculitis, and interstitial lung fibrosis also are reported in patients with IBD (6, 15, 22, 38). In patients with irritable bowel syndrome (IBS), symptoms of bronchial hyperresponsiveness, increased airway resistance, and/or asthma are more frequently found than in control groups (2, 3, 19, 37, 39). On the other hand, patients with bronchial asthma have an increased risk of IBS compared with control groups (10, 17, 34, 39). For example, 34% of patients with IBS have respiratory symptoms compared with 5.8% in control groups (39). The IBS prevalence is significantly higher in asthmatics (41%) than in subjects with other pulmonary disorders (22%) and in healthy individuals (21%) (34). Therefore, the previous observations suggest that large bowel diseases and respiratory disorders, such as IBS and asthma, may share a common etiology and pathophysiological mechanism, although some studies do not note such an association (33). Abnormal contractility of smooth muscle, neuromuscular transmission, and inflammation of both gastrointestinal and bronchial smooth muscles have been suggested to cause the clinical symptoms (2, 3, 7, 19, 39).

Viscerovisceral cross-organ interactions in the central and peripheral nervous systems have been recognized as etiological factors in some pathophysiological conditions. For example, patients with IBS often have coexisting urinary bladder dysfunction (26, 35), and viscerovisceral cross-organ sensitization in peripheral afferents, dorsal root ganglia, and spinal cord may play a role in the symptomatic overlap of these pelvic disorders (9, 23, 27, 31). However, most previous studies of spinal neuronal viscerovisceral convergence have been limited to examining visceroreceptive processing in the same or near spinal segments that receive inputs from two visceral organs in either the thoracic or pelvic cavities (1, 4, 8, 14, 29, 30, 32). Only a few studies have focused on intraspinal cross talk between pelvic and thoracic visceral organs innervated by distant spinal segments (5, 8, 12). For example, electrical stimulation of cardiopulmonary sympathetic afferents reduces responses of most sacral spinothalamic tract (STT) neurons to colorectal and/or urinary bladder distensions in monkeys (8, 12). Also, electrical stimulation of phrenic afferent fibers or mechanical stimulation of the diaphragm modulates the activity of lumbosacral STT neurons responding to urinary bladder distension in primates (5). We hypothesized that cross-organ viscerovisceral communication in the spinal cord might be a central nervous system mechanism involved in symptomatic association between large bowel diseases and respiratory disorders. Viscerovisceral convergence in the spinal cord provides a preexisting neuronal substrate for possibly eliciting and maintaining visceral organ cross-sensitization and viscerovisceral hyperalgesia. In the present study, inhaled ammonia was

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used as a natural stimulus of the lungs for examining the effects of activating pulmonary nociceptors on activity of lumbosacral spinal neurons with colorectal input. A preliminary report of this work has been published (11).

MATERIALS AND METHODS

Experiments were performed in 22 male Sprague-Dawley rats (Charles River) weighing between 350 and 460 g. After initial anesthesia with pentobarbital sodium (60 mg/kg ip), catheters were inserted into the right carotid artery to monitor blood pressure throughout the experiments and into the left jugular vein to infuse pentobarbital sodium (15–25 $mg \cdot kg^{-1} \cdot h^{-1}$) to maintain a constant level of anesthesia throughout the experiment. The mean blood pressure was maintained between 80 and 120 mmHg by adjusting the level of anesthesia and administering supplementary physiological saline with a perfusion pump. A tracheotomy was performed for artificial ventilation using a constant-volume pump (55–60 strokes/min, stroke volume 3–5 ml). Animals were paralyzed with pancuronium bromide (0.4 mg/kg ip), and paralysis was maintained with 0.2 mg/kg ip hourly injections during the experiment. A thermostatically controlled heating pad and overhead infrared lamps were used to keep rectal temperature between 36.7 and 37.3°C. Experimental protocols of the present study were approved by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

To irritate the lower airways, inhaled ammonia (IA) was used as the noxious pulmonary stimulus (32). Briefly, ammonia vapor from a 150-ml bottle containing 25–30 ml of ammonium hydroxide solution (28–30%) was drawn into a syringe. Ammonia vapor (volume 0.5 ml) was injected manually through the inspiratory tube of the ventilator over 20 s. This allowed IA to reach lower airways within 7–10 breaths of 3- to 5-ml stroke volume of artificial ventilation. Multiple IA exposures were examined for spinal neuronal responses at interstimulus intervals of >8 min to avoid desensitization (18, 32). Graded colorectal distensions (CRD; 20, 40, and 60 mmHg, 20 s) were produced by air inflation of a 4- to 5-cm-long latex balloon that was inserted into the descending colon and connected to a sphygmomanometer (30). Noxious CRD of 60 mmHg for 20 s was used as a search stimulus, and neurons receiving colonic input were tested with this stimulus two to three times to make sure responses were consistent and repeatable.

Laminectomies were performed to expose lumbosacral (L6–S2) spinal segments for recording spinal neuronal activity. After rats were mounted in a stereotaxic head holder, the dura mater of L6–S2 spinal segments was carefully removed and the spinal cord was covered with warm agar (3–4% in saline) to improve stability for neuronal recording. Carbon-filament glass microelectrodes were used to record extracellular action potentials of single spinal neurons. All recordings were made 0.5–2 mm lateral from the midline and at depths between 0 and 1.2 mm from the dorsal surface of the spinal cord. Neuronal activity was recorded online with the Spike 3 data acquisition system (CED, Cambridge, UK). An excitatory or inhibitory response (imp/s) of spinal neurons to visceral stimulation was calculated as the change between the mean of 10 s of spontaneous activity as well as maximal/minimal activity evoked by colorectal and pulmonary stimuli. A neuron was identified as responsive to various stimuli if the maximal change in activity was at least 20% compared with control activity. For neurons with no spontaneous activity, the minimum threshold of response was ≥2 imp/s. Data are means ± SE. Statistical comparisons were made using Student's paired or unpaired *t*-test and χ^2 test. Differences were considered statistically significant at $P < 0.05$.

Somatic receptive fields of spinal neurons were characterized for responses to innocuous stimulation, using a camel hair brush or a blunt probe, and to noxious pinch of the skin and muscle with blunt forceps. Neurons were categorized as follows: low-threshold (LT) neurons responded primarily to brushing stimuli; high-threshold (HT) neurons responded only to noxious pinching of the somatic field; and wide dynamic range (WDR) neurons responded to brushing the hair and had greater responses to noxious pinching of the somatic field. If a somatic receptive field was not found, movement of the tail (MT) was examined.

To mark the locations of spinal neurons, electrolytic lesions (50 μA direct current, 20 s) were made at two to three recording sites after neurons with visceral inputs had been studied in each animal. At the end of the experiments, animals were euthanized with an overdose of pentobarbital. The lumbosacral spinal cord was removed and placed in 10% buffered formalin solution. After at least 3 days, frozen sections (55–60 μm) of the spinal cord were made and lesion sites in the spinal cord were viewed under a microscope.

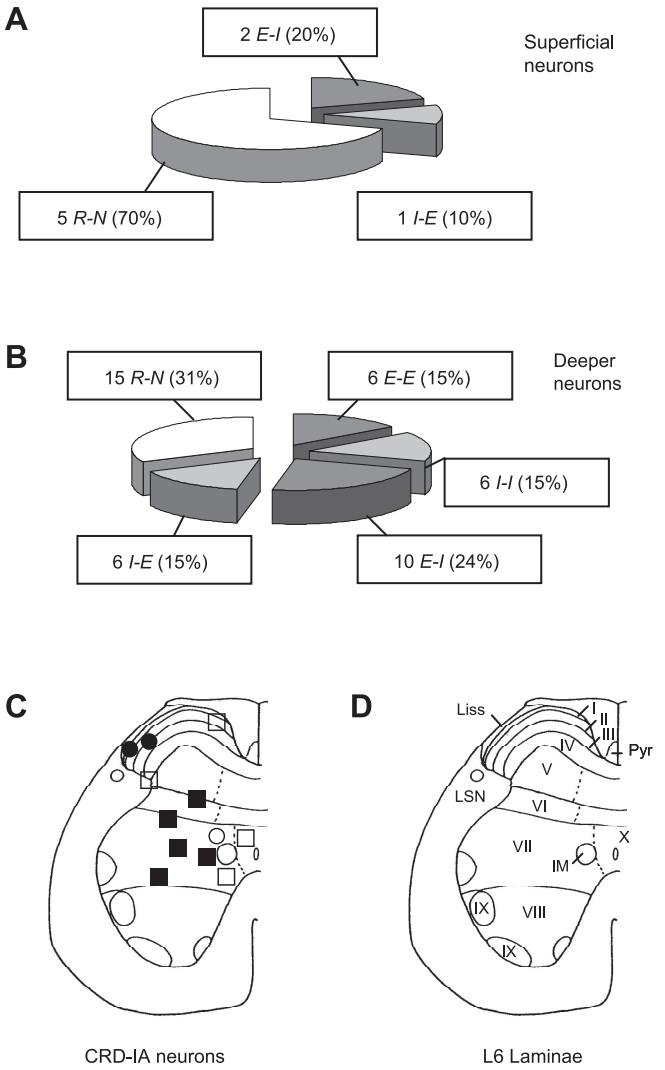

Fig. 1. Response patterns to colorectal distension (CRD) and inhaled ammonia (IA) and recording sites for lumbosacral (L6–S2) spinal neurons. *A* and *B*: comparison of populations of superficial and deeper spinal neurons with colorectal and/or pulmonary inputs. First response is to CRD, and second response is to IA. E-E, neurons with excitatory (E) responses to both CRD and IA. I-I, neurons with inhibitory (I) responses to both CRD and IA. R-N, neurons with response to CRD and no response to IA. *C*: locations of spinal neurons responding to both CRD and IA. ■, Neurons excited by both CRD and IA; □, neurons inhibited by CRD but excited by IA; ●, neurons excited by CRD but inhibited by IA; ○, a neuron inhibited by both CRD and IA. *D*: schematic drawing of the L6 spinal segment (25). I-X indicates laminae; Liss, Liss's tract; LSN, lateral spinal nucleus; Pyr, pyramidal tract; IM, intermediomedial nucleus.

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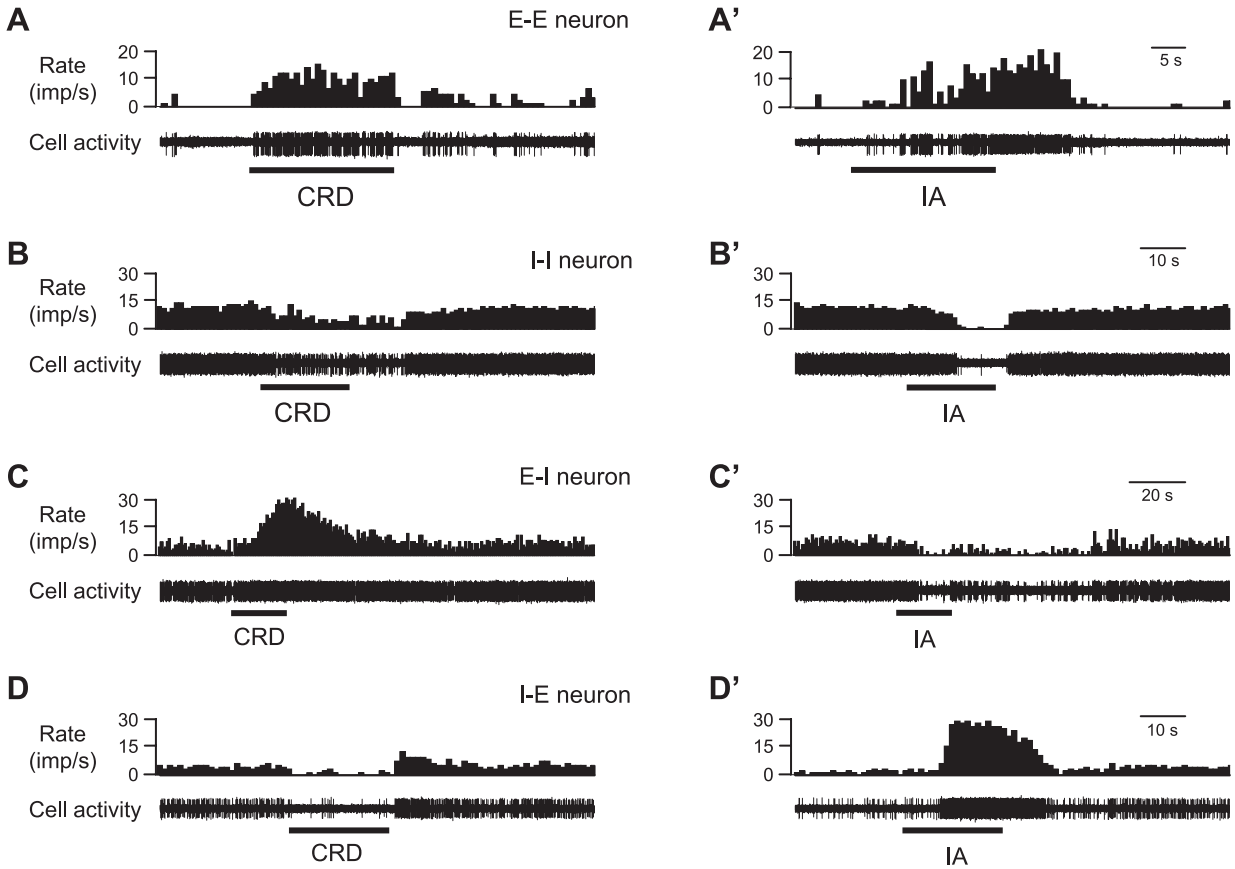

Fig. 2. Convergent patterns of colorectal and pulmonary inputs onto spinal neurons. *A* and *A′*: an E-E neuron, excited by both CRD (60 mmHg, 20 s; *A*) and IA (0.5 ml, 20 s; *A′*). *B* and *B′*: an I-I neuron, inhibited by both CRD (*B*) and IA (*B′*). *C* and *C′*: an E-I neuron, excited by CRD (*C*) but inhibited by IA (*C′*). *D* and *D′*: an I-E neuron, inhibited by CRD (*D*) but excited by IA (*D′*). *Top* traces show moving average rates of neuronal firing (imp/s); *bottom* traces show raw neuronal action potentials.

Laminae of gray matter were identified using the cytoarchitectonic scheme of spinal cord in rats (25).

RESULTS

IA altered activity of 31/51 (61%) lumbosacral (L6–S2) spinal neurons responding to noxious CRD (60 mmHg, 20 s). In contrast, IA changed activity of 3/30 (10%) spinal neurons that had somatic receptive fields but did not respond to CRD. These proportions were significantly different ($P < 0.01$). Inhaled ammonia decreased activity of 16/31 (52%) spinal neurons and increased activity of 15 neurons with colorectal input. Also, inhaled ammonia affected activity of 3/8 (38%) superficial spinal neurons (depth <0.3 mm) responding to CRD, whereas IA altered activity of 28/43 (65%) neurons in deeper laminae of lumbosacral spinal cord (depth 0.3–1.2 mm). A comparison of proportions of superficial and deeper neurons responding to colorectal and pulmonary stimuli is shown in Fig. 1, *A* and *B*. Electrolytic lesions of recording sites for spinal neurons responding to both CRD and IA were verified histologically (Fig. 1, *C* and *D*). Neurons responding to both CRD and IA were primarily located in laminae I, II, III, V, VII, and X of gray matter in the lumbosacral spinal cord.

Multiple patterns of excitatory and inhibitory responses to CRD and IA were observed. Examples of spinal neurons with different response patterns to CRD and IA are shown in Fig. 2, and their proportions are shown in Fig. 1, *A* and *B*. Statistical analyses of the characteristics of neuronal excitatory and inhibitory responses to CRD and IA are summarized in Table 1. Based on the intracolonic pressure that produced a neuronal response, lumbosacral neurons responding to CRD were divided into the following two subgroups: LT neurons, which responded to intracolorectal pressure ≤20 mmHg, and HT

Table 1. *Comparison of all excitatory or inhibitory responses of lumbosacral spinal neurons to CRD and IA*

Stimuli	*n*	Spontaneous Activity, imp/s	Latency, s	Changes in Activity, imp/s	Duration, s
CRD-E	18	6.5±1.4	1.7±0.3	11.4±1.3	33.9±4.9
IA-E	15	6.6±1.2	7.8±0.5*	12.8±1.5	34.4±4.1
CRD-I	13	8.1±0.9	2.5±0.7	6.9±0.7	37.3±5.1
IA-I	16	8.3±1.1	8.5±0.8†	7.8±0.8	35.2±5.4

CRD-E or CRD-I, excitatory or inhibitory responses to colorectal distension (60 mmHg, 20 s); IA-E or IA-I, excitatory or inhibitory responses to inhaled ammonia (0.5 ml, 20 s). *$P < 0.01$ compared with corresponding responses to CRD-E. †$P < 0.01$ compared with corresponding responses to CRD-I.

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Table 2. *Comparison of excitatory and inhibitory CRD response thresholds of lumbosacral spinal neurons and responses to IA*

	CRD-E		CRD-I	
	LT	HT	LT	HT
IA-E	4	4	3	4
IA-I	6	4	2	4
Total	10	8	5	8

LT, low threshold; HT, high threshold.

neurons, which responded to ≥40 mmHg of CRD (30). IA affected activity of spinal neurons with both LT and HT responses to CRD (Table 2). In addition, 42/51 (82%) neurons with colorectal input responded to stimulation of somatic receptive fields or tail rotation. Of 31 spinal neurons receiving both colorectal and pulmonary inputs, 27 (87%) neurons had somatic receptive fields. Somatic receptive fields were generally on the scrotum, perianal region, lower back, hindlimb, and areas around the tail. Figure 3 shows examples and a summary of the response characteristics of viscerosomatic convergent neurons.

To determine afferent pathways for IA effects on lumbosacral spinal neurons with colorectal input, we performed cervical vagotomy and spinal transections at different levels. Bilateral cervical vagotomy abolished responses to IA in two (1 excitatory, 1 inhibitory) of eight tested neurons, indicating that six (2 excitatory, 4 inhibitory) neurons had pulmonary input originating from spinal (sympathetic) afferent fibers. Sequential spinal transection at rostral C1 segment did not abolish IA inhibitory responses in 4/4 neurons, but spinal transection at L2 segment eliminated IA inhibitory responses in 3/3 neurons. An example of the effects of different transections is shown in Fig. 4.

In all animals, IA produced an increase in mean arterial blood pressure (MABP) with an onset that roughly coincided with the changes in neuronal activity of lumbosacral spinal neurons. To examine whether the change in neuronal activity was the result of an indirect effect of a change in MABP, we administered phenylephrine (2 μg/kg iv), a rapidly acting and short-duration α-adrenergic vasoconstrictor, to increase MABP. For six tested neurons excited by IA, IA increased MABP by 16.4 ± 1.9 mmHg and increased neuronal activity from 4.1 ± 1.8 to 10.2 ± 2.1 imp/s ($P < 0.01$). For those same neurons, phenylephrine produced a more significant increase in MABP, by 42.5 ± 4.1 mmHg, than did IA ($P < 0.01$) but did not affect neuronal activity (4.5 ± 1.8 vs. 4.3 ± 1.5 imp/s). A typical example of these responses is shown in Fig. 5, *A* and *A′*. Furthermore, for three neurons inhibited by IA, IA increased MABP by 19.6 ± 1.9 mmHg and decreased neuronal activity from 5.6 ± 1.0 to 0.1 ± 0.1 imp/s ($P < 0.05$), but phenylephrine did not affect activity in those same neurons (5.0 ± 1.7 vs. 4.0 ± 0.8 imp/s) during the increase (51.9 ± 4.4 mmHg) in MABP. Figure 5, *B* and *B′*, shows an example of these responses. Based on these observations, it is very unlikely that neuronal responses to IA were secondary to increases in arterial blood pressure.

DISCUSSION

The results of this study showed that IA altered activity of 31/51 (61%) lumbosacral spinal neurons responding to noxious CRD. Of these IA-responsive neurons, 16/31 (52%) neurons were inhibited and 15/31 (48%) neurons were excited. Multiple patterns of spinal neurons with excitatory and inhibitory response to CRD and IA were observed. IA affected activity of spinal neurons with both LT and HT responses to CRD. Furthermore, observations from vagotomy and spinal transections showed that spinal visceral afferent pathways and, to a lesser extent, vagal afferents contributed to intraspinal cross talk between lungs and colon. Viscerovisceral interaction between afferent information from lower airways and colon to single lumbosacral spinal neurons might provide a pathophysiological basis for symptomatic association between respiratory disorders and large bowel diseases.

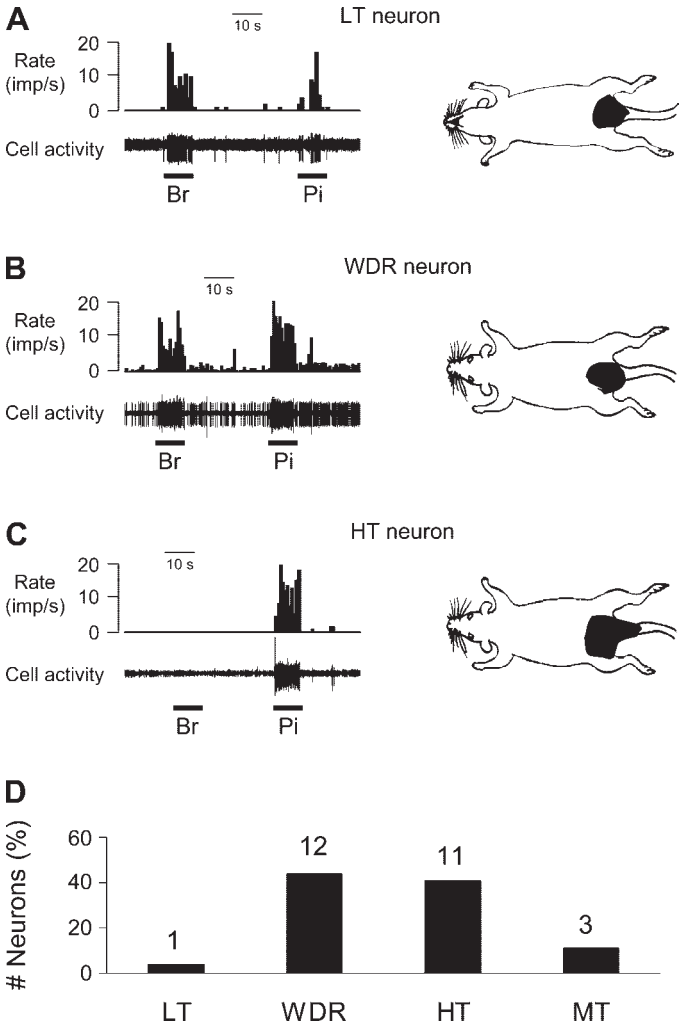

Fig. 3. Somatic field properties and locations of lumbosacral spinal neurons responding to both CRD and IA. *A*: a low-threshold (LT) neuron that responded to brush but less to pinch of the somatic field. *B*: a wide dynamic range (WDR) neuron with responses to both brush and pinch. *C*: a high-threshold (HT) neuron with response to pinch but not to brushing the somatic field. *D*: summary for types of somatic receptive fields of spinal neurons responding to both CRD and IA. Number above each column represents the number of neurons with somatic receptive field. Br, brush of somatic field; Pi, pinch of somatic field; MT, neuron that responded to movement of tail.

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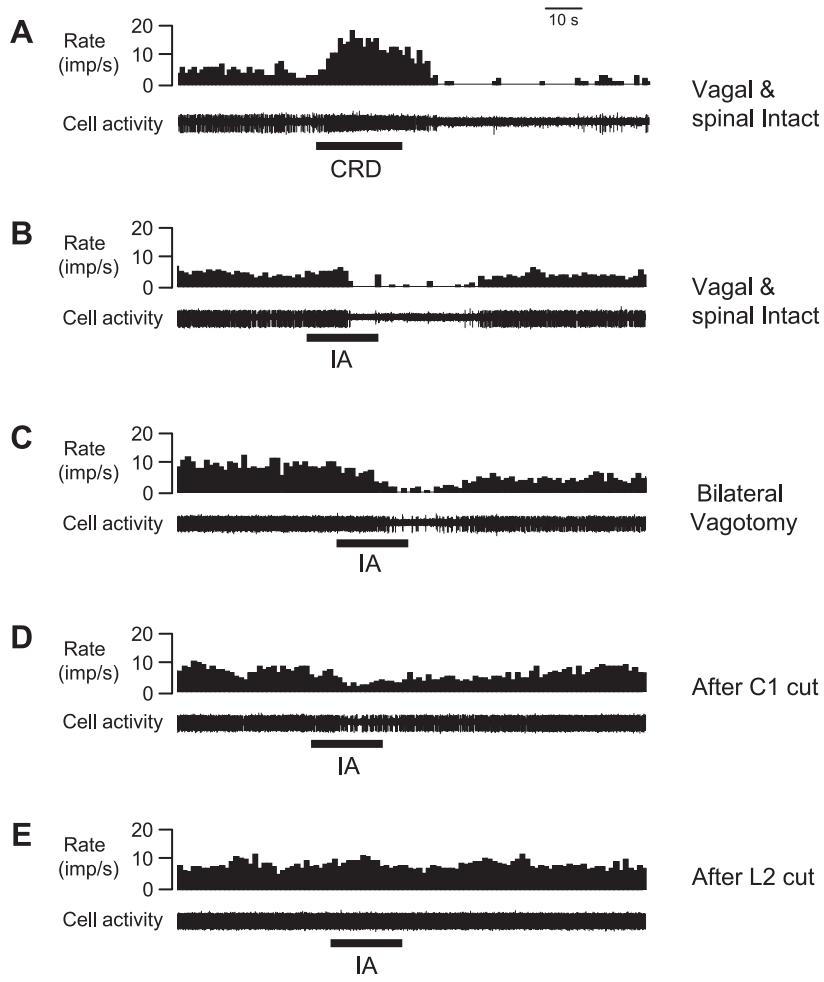

Fig. 4. Effects of cervical vagotomy and spinal transections on IA response of a spinal neuron with colorectal input. *A* and *B*: excitatory responses to CRD (*A*) and inhibitory response to IA (*B*) in an animal with intact vagus nerves and spinal cord. *C*: effects of bilateral cervical vagotomy on inhibitory response to IA. *D*: effect of spinal transection at rostral C1 segment on inhibitory response to IA. *E*: spinal transection at L2 segment eliminated inhibitory response to IA.

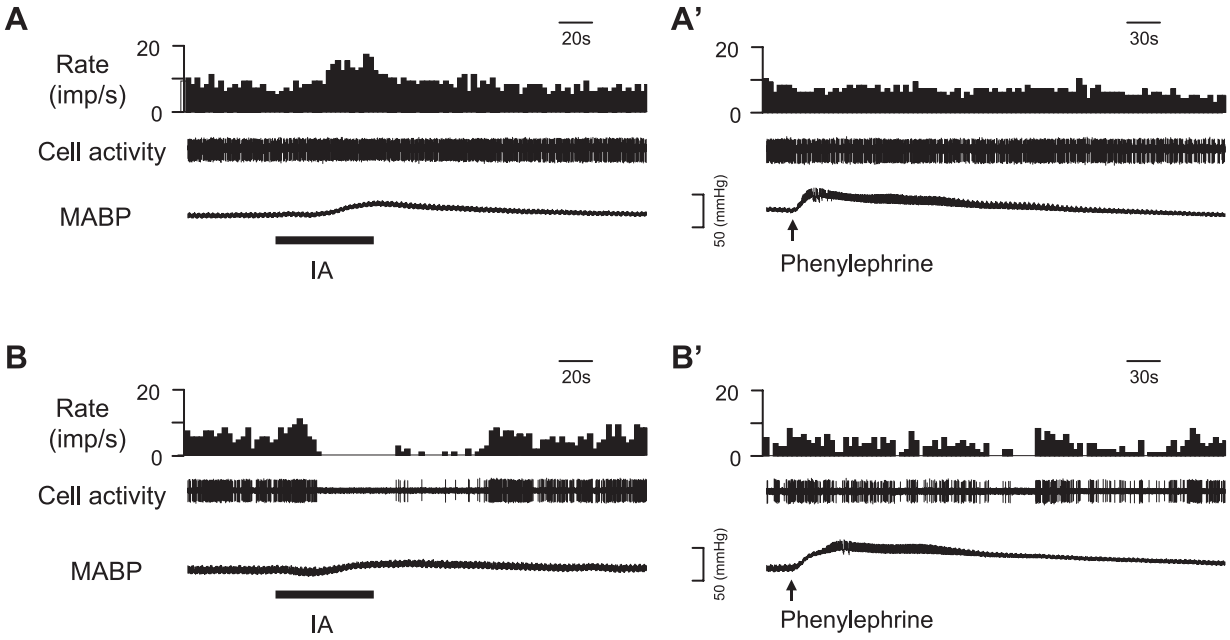

Fig. 5. Effects of phenylephrine on the neuronal activity and mean arterial blood pressure (MABP). *A* and *A′*: a neuron with an excitatory response to IA (*A*) but without neuronal responses to phenylephrine (*A′*), although both IA and phenylephrine increased MABP. *B* and *B′*: a neuron with an inhibitory response to IA (*B*) but without activity change during an increase in MABP by phenylephrine (*B′*).

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Responses to colorectal and pulmonary stimuli. Previous studies have described the effects of thoracic visceral afferent inputs on neurons in lumbosacral spinal segments that receive pelvic visceral inputs. For example, electrical stimulation of cardiopulmonary sympathetic afferents in monkeys reduces responses of 75% (6/8) and 63% (5/8) of sacral STT neurons to CRD and urinary bladder distension, respectively (8). These results are similar to those of an earlier study in which inhibitory effects of electrical stimulation of cardiopulmonary sympathetic afferents were observed on lumbosacral STT neurons with urinary bladder inputs (12). Furthermore, electrical stimulation of phrenic afferent fibers reduced the activity of 65%, did not affect 33%, and excited only one lumbosacral STT neuron responding to urinary bladder distension and/or somatic field stimulation (5). Similar results in lumbosacral STT neurons have been observed with mechanical stimulation of the diaphragm (5). In the present study, IA was used for examining effects of activating thoracic visceral afferents on the activity of lumbosacral spinal neurons with colorectal input. Results showed that IA altered activity of 61% of the lumbosacral spinal neurons responding to noxious CRD. Of these IA-affected neurons, 52% were inhibited and 48% were excited. The increased incidence of excitatory effects from activation of thoracic spinal afferents on lumbosacral neurons with colorectal input compared with previous observations might be due to differences in animal preparations. In previous studies, a homogeneous group of STT neurons with projections to the thalamus were examined in monkeys for effects of electrically stimulating cardiopulmonary sympathetic or phrenic afferent fibers (5, 8, 12). In contrast, the present study examined lumbosacral spinal neurons in rats that generally were located in the dorsal horn and intermedial zone of the gray matter. Furthermore, IA is a more natural noxious pulmonary stimulus than electrical stimulation of visceral afferent nerves. Thus variations between the present and previous findings could be partly explained. In addition, it should be noted that in the present study, IA affected 61% of the lumbosacral spinal neurons responding to CRD, whereas IA changed activity of only 10% of the spinal neurons that had somatic receptive fields but did not respond to CRD. It is suggested that pulmonary afferent inputs are more likely to affect spinal neurons in distant segments that receive visceral input than neurons with somatic input only.

Pathway of pulmonary modulation. Ammonia is an irritant of lower airways that activates vagal pulmonary afferents (20, 24, 36) as well as upper thoracic spinal neurons receiving pulmonary sympathetic afferent input (18, 32). Therefore, it is believed that both vagal and spinal visceral afferent pathways could be involved in respiratory reflex responses to ammonia as well as pulmonary nociception. In the present study, bilateral cervical vagotomy abolished lumbosacral spinal neuronal responses to IA in 25% of tested neurons, indicating that 75% of neurons had pulmonary input originating from spinal visceral afferent fibers. These data are different from a previous study in rats, in which effects of IA were examined in upper thoracic (T3) spinal neurons (32). Cervical vagotomy did not abolish any T3 spinal neuronal responses to IA, although vagal afferent modulation was observed (32). It is suggested that vagal afferent pathways activated by pulmonary irritation modulate thoracic and lumbosacral spinal neurons differently. Furthermore, spinal transection at rostral C1 segment did not abolish inhibitory responses to IA in all tested neurons following vagotomy, but a sequential spinal transection at L2 segment eliminated IA inhibitory responses in all tested neurons in the present study. This finding indicates that IA had no effect on colon afferents via the general blood circulation. It is suggested that inhibitory modulation by IA on lumbosacral spinal neurons has a propriospinal origin. One possible pathway for lumbosacral spinal neuronal inhibition would be via descending propriospinal connections from thoracic segments down to caudal spinal segments (40). Another possible pathway is via propriospinal neurons in upper cervical segments. Stimulation of cardiopulmonary sympathetic afferents still inhibits primate lumbosacral STT cells after C1 spinal transection, whereas a spinal transection between C3 and C7 in monkeys and rats eliminates the inhibitory effect of cardiopulmonary inputs on lumbosacral STT neurons (16). Sequential transections at rostral C1 and C4–C6 segments produce similar findings in lumbar STT and dorsal horn cells in rat spinal cord (41). These results suggest that propriospinal neurons in high cervical segments process inhibitory effects on sensory neurons in lumbosacral segments. Furthermore, electrical and chemical activation of upper cervical (C1–C2) spinal neurons in rats can modulate activity of thoracic spinal neurons responding to IA as well as lumbosacral spinal neurons with colorectal input (28, 32). Therefore, in the present study, it is reasonable to suggest that the descending modulation by IA on lumbosacral spinal neurons responding to CRD involves neuronal connections in high cervical spinal segments. These spinal segments are considered to be an important propriospinal source for integration and regulation of visceral inputs to caudal spinal neurons (13).

Possible implication. An association between symptoms of large bowel diseases, such as IBD and IBS, and bronchopulmonary diseases has been investigated (2, 3, 6, 7, 10, 15, 17, 21, 22, 33, 34, 38). Several mechanisms have been proposed to explain the association of these pathological conditions involving two physiologically distinct systems (2, 3, 7, 19, 39). These include *1*) altered contractility of the gastrointestinal and bronchial smooth muscle to causes similar symptoms, *2*) visceral neuromuscular and transmitter dysfunctions to induce an imbalance in adrenergic and cholinergic modulation of autonomic function, *3*) dysfunction of the immune system to produce a common inflammatory pathogenesis for the respiratory and gastrointestinal symptoms, and *4*) colonic and bronchial epithelium, both originating from the primitive gut, that are similarly sensitized to some irritants. The present study showed that noxious pulmonary inputs modulated spinal neuronal activity in distant lumbosacral spinal neurons receiving input from the colon. This pulmonary-colorectal afferent convergence in the lumbosacral spinal cord provides a cross talk substrate for processing visceral inputs from lower airways and the colon.

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