Spinal Inhibitory Effects of Cardiopulmonary Afferent Inputs in Monkeys: Neuronal Processing in High Cervical Segments

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Chandler, Margaret J., Jianhua Zhang, Chao Qin, and Robert D. Foreman. Spinal inhibitory effects of cardiopulmonary afferent inputs in monkeys: neuronal processing in high cervical segments. J Neurophysiol 87: 1290–1302, 2002; 10.1152/jn.00079.2001. Noxious stimulation of spinal afferents inhibits primate spinothalamic tract (STT) neurons in segments distant from the region of afferent entry. Inhibitory effects of cardiopulmonary sympathetic afferent (CPSA) stimulation remain after C1 transection but disappear with spinal transection between C1 and C2. We hypothesized that spinal inhibitory effects produced by CPSA stimulation are processed by neurons in C1–C3 segments. One purpose of this study in anesthetized monkeys was to determine whether chemical activation of high cervical neurons reduced sacral STT cell responses to colorectal distension (CRD) and urinary bladder distension (UBD). First, effects and interactions of pelvic and cardiopulmonary visceral afferent inputs were determined in 10 monkeys on extracellular activity of sacral STT neurons recorded in deep dorsal horn. CRD and UBD increased activity in 95 and 91% of sacral STT neurons, respectively. CPSA and cardiopulmonary vagal stimulation decreased activity in 84 and 56% of STT neurons, respectively. CPSA stimulation decreased CRD-evoked activity in six of eight sacral STT neurons and decreased UBD-evoked activity in five of eight STT neurons tested. Excitatory amino acid application at C2 segment decreased CRD-evoked responses in 7 of 10 sacral STT neurons and decreased UBD-evoked responses in 9 of 12 STT neurons. The second purpose of this study was to examine responses of C1–C3 descending propriospinal neurons to stimulation of cardiopulmonary afferent fibers. If C1–C3 neurons process CPSA input to suppress STT transmission, then CPSA stimulation should excite C1–C3 neurons with descending projections. Effects of thoracic vagus nerve stimulation also were examined. Vagal stimulation inhibits STT neurons in segments below C1 but excites C1–C3 STT neurons; we theorized that vagal inhibition of sensory transmission might relay in high cervical segments and, therefore, excite C1–C3 descending propriospinal neurons. Extracellular discharge rate was recorded for C1–C3 neurons antidromically activated from thoracic or lumbar spinal cord in 24 monkeys. CPSA stimulation increased activity of 16 of 45 neurons and inhibited one cell. Thoracic vagus stimulation increased activity of 20 of 43 neurons and inhibited one cell; stimulation of abdominal vagus fibers did not affect activity of six of six cells that were excited by thoracic vagal input. Mechanical stimulation of somatic fields excited 30 of 41 neurons tested. All neurons activated by visceral input received convergent somatic input from noxious pinch of somatic receptive fields that generally included the neck and upper body; 11 C1–C3 propriospinal neurons did not respond to any afferent input examined. Results of these studies were consistent with the idea that modulation of spinal nociceptive transmission might involve neuronal connections in high cervical segments.

INTRODUCTION

Stimulation of Aδ and C-fiber cardiopulmonary sympathetic afferents (CPSA) that pass through the stellate ganglion primarily excites thoracic and cervical spinothalamic tract (STT) neurons in monkeys (Blair et al. 1981; Chandler et al. 1996, Hobbs et al. 1992a). In contrast, STT neurons located in lumbosacral segments are inhibited by noxious stimulation of visceral and somatic afferent fibers that enter thoracic segments (Foreman et al. 1988; Hobbs et al. 1992b). We initially expected that STT inhibition produced by nociceptive spinal inputs would depend on descending pathways that arise in supraspinal nuclei (Bashbaum and Fields 1984; Jones 1992; Willis 1988). Contrary to this assumption, we found that stimulation of CPSA or proximal upper body somatic fields still inhibits primate lumbosacral STT cells after C1 spinal transection (Hobbs et al. 1992b). Another possible pathway for lumbosacral STT inhibition would be via descending propriospinal connections from thoracic segments. This idea also was refuted because spinal transection between C3 and C2 in other monkeys eliminates the inhibitory effects of thoracic inputs in lumbosacral STT neurons (Hobbs et al. 1992b). Sequential transections in rat spinal cord produce similar effects (Zhang et al. 1996). These results suggest that propriospinal neurons in high cervical segments could process inhibitory effects on sensory neurons in lumbosacral segments.

If propriospinal neurons in C1–C3 segments are involved in inhibitory effects on spinal sensory neurons, then activation of high cervical cell bodies should inhibit evoked activity of STT neurons in distant segments. A recent study in rats shows that excitatory responses to colorectal distension (CRD) in unidentified lumbosacral spinal neurons often are reduced by glutamate activation of cervical cell bodies (Qin et al. 1999). In the present study in primates, effects of chemically stimulating cervical cell bodies were examined in identified STT neurons. Glutamate or DL-homocysteic acid (DLH) was applied to high cervical segments, and effects on activity evoked by noxious CRD or urinary bladder distension (UBD) were determined in sacral STT neurons. Additionally, responses to stimulating...
somatic and visceral afferent inputs were determined in sacral STT neurons. In some STT neurons, the effects of CPSA inputs were examined on activity evoked by CRD or UBD.

Electrophysiological techniques also were used to examine responses of C1–C3 propriospinal neurons to cardiopulmonary inputs. If C1–C3 neurons process nociceptive visceral inputs to suppress STT transmission, then stimulation of cardiopulmonary afferents should excite C1–C3 neurons with descending projections. Because myocardiial ischemia activates both sympathetic and vagal afferent fibers (Brown 1967; Thörén 1976), we examined effects of stimulating vagal afferents as well as CPSA. Vagal stimulation generally inhibits primate STT neurons below C3 segment (Ammons et al. 1983; Chandler et al. 1991; Hobbs et al. 1989) but excites STT neurons in high cervical segments (Chandler et al. 1996). We theorized that, in addition to synaptic connections in nucleus tractus solitarius (NTS) and other central nuclei (Randich and Gebhart 1992), vagal afferent input might excite C1–C3 propriospinal neurons to provide another processing level for vagal inhibitory effects. Thus we determined responses of C1–C3 descending propriospinal neurons to stimulation of both CPSA and vagal afferents and to stimulation of somatic receptive fields. Preliminary data of some parts of this study have been presented in an abstract (Chandler et al. 1994).

METHODS

Experiments were performed on 34 male monkeys (Macaca fascicularis) weighing between 3.9 and 7.8 kg. Animals used in this study also were used to examine hypotheses not addressed in this report. Protocols were approved by the Institutional Animal Care and Use Committee and followed guidelines of the American Physiological Society and the International Association for the Study of Pain. Monkeys were tranquilized with ketamine (10–20 mg/kg im), and catheters were placed in the right femoral vein and artery to infuse drugs and to measure blood pressure, respectively. Anesthesia was induced with α-chloralose (40–60 mg/kg iv). Animals were artificially ventilated and paralyzed with pancuronium bromide (0.08–0.1 mg/kg iv). Anesthesia and muscle paralysis were maintained with constant infusion of pentobarbital sodium (2 mg/kg iv). Anesthesia and muscle paralysis were maintained with pancuronium (0.15 mg/kg iv) and other central nuclei (Randich and Gebhart 1992), cervical segments (Chandler et al. 1996). We theorized that, in order to provide another processing level for vagal inhibitory effects.

CO2 was maintained at 4 °C. Diameters were monitored to regulate anesthesia level. End-expiratory pressure was maintained between 36 and 38 mmHg. Activity evoked by CRD or UBD was examined on activity evoked by CRD or UBD. Animals were artifically ventilated and paralyzed with pancuronium bromide (0.08–0.1 mg/kg iv). Anesthesia and muscle paralysis were maintained with constant infusion of pentobarbital sodium (2–4 mg·kg⁻¹·h⁻¹) and pancuronium (0.15–0.2 mg·kg⁻¹·h⁻¹). Blood pressure and pupil diameters were monitored to regulate anesthesia level. End-expiratory CO2 was maintained at 4–5%, and core body temperature was maintained between 36 and 38 °C.

To stimulate CPSA fibers passing through the stellate ganglion, one hook of a bipolar platinum hook electrode was placed around the left ansa subclavia, and the other hook was placed around the sympathetic chain between T2 and T3 rami communicantes. Both hooks of a second bipolar electrode were placed around the left thoracic vagus nerve superior to the aortic arch to stimulate ipsilateral vagal fibers. In seven monkeys, an electrode also was placed on the left vagus nerve just rostral to the diaphragm to stimulate vagal fibers arising from abdominal organs. Standard nociceptive stimulus parameters were 20 Hz, 33 V, 0.1 ms duration. These stimuli are sufficient to activate both A-δ and C fibers traveling in CPSA and vagal nerves (Blair et al. 1981; Chandler et al. 1996). Effects of graded intensities (2–33 V) or graded frequencies (1–20 Hz) of CPSA and thoracic vagal stimulations were measured in some C1–C3 propriospinal neurons. Hook electrodes were surrounded with dental impression material to hold electrodes in place, to prevent nerves from drying out, and to isolate the stimulus. The right cervical vagus nerve was crushed in 24 animals used to determine effects of afferent inputs in C1–C3 propriospinal neurons

In 10 monkeys used to determine effects of afferent inputs and high cervical chemical stimulation in lumbosacral STT neurons, latex balloons were placed in the urinary bladder and the descending colon for distension of these visceral organs. The urinary bladder was exposed with a midline incision, a small opening was made in the dome wall, and a latex balloon attached to double lumen plastic tubing was inserted and tied in place with suture. The outer tubing was attached to a water reservoir and a pressure transducer was attached to the inner tubing. The urinary bladder was distended by increasing the height of the reservoir. Colorectal distension was produced using a modification of the method developed in the rat (Ness and Gebhart 1988). A latex balloon attached to plastic tubing was inserted intranally into the descending colon and rectum. The tubing was connected to a sphygmomanometer for inflating the balloon with air, and intracolonic pressure was monitored via a pressure transducer. For both UBD and CRD, rapid (1–2 s) distensions to 80 mmHg were used as standard noxious stimuli. Additionally, effects of CRD were measured in some STT cells at graded pressures (20–80 mmHg). Great care was taken to differentiate responses to UBD and CRD from mechanical movement of the excitatory somatic fields and receptive endings on abdominal tissues.

Monkeys were placed in a stereotaxic frame and the head was flexed about 45 °C. A concentric bipolar stimulating electrode was placed in the right ventroposterolateral (VPL) thalamus of 10 monkeys to activate axons of lumbosacral STT neurons antidromically. To guide placement, the electrode was used to record multunit thalamic activity evoked by tapping the left hip; activity was fed into an audio amplifier and the electrode was placed where a brisk response was heard. The electrode then was attached to a stimulator. To activate axons of descending C1–C3 propriospinal neurons antidromically in 24 monkeys, a concentric bipolar stimulating electrode was placed in the left lateral white matter of thoracic (T5–T8) segments approximately 2–3 mm below the dorsal surface; a stimulating electrode also was placed at lumbar (L1–L4) segments in 10 of 24 animals. The search stimulus for locating antidromically activated neurons was 2 mA, 5–10 Hz, 0.1 ms; threshold stimulus was the intensity that produced an evoked discharge for 50% of stimulus repetitions. Extracellular potentials of lumbosacral STT neurons and C1–C3 propriospinal neurons in the left dorsal gray matter were recorded with carbon-filament glass microelectrodes. All neurons met the following criteria for antidromic activation (Lipski 1981): constant latency of the antidromic spike; ability to follow a high-frequency (250–500 Hz) train of antidromic stimuli; collision of the antidromic spike with an orthodromic spike, except for some descending propriospinal cells without detectable sensory input. Visceral and somatic afferent inputs were stimulated to determine effects on antidromically activated neurons. A neuron was considered excited or inhibited by a stimulus if discharge rate (imp/s) changed ±2 imp/s and/or ±20% from control activity in a rate histogram (1-s bins) (Hobbs et al. 1992a). Changes in activity were calculated by subtracting the mean of 10 s of control activity from the mean of 10 s of activity recorded during a stimulus. Peristimulus histograms (50 bins, 1-ms bins) were generated at 1 Hz (1–3 stimulus pulses, 3 ms apart) for some propriospinal neurons that were excited by electrical stimulation of visceral nerves. To calculate evoked impulses, control activity was measured for the same number of bins that comprised the peak of evoked activity and was subtracted from total impulses of the histogram peak. Evoked impulses were divided by 50 to determine impulses/stimulus. Excitatory somatic receptive fields were mapped using mechanical stimuli. Neurons were classified high threshold (HT) if activity increased only during noxious pinch of skin or skin and underlying muscle with blunt forceps. Low-threshold (LT) neurons were excited maximally by innocuous brushing of hair and skin. Activity of wide dynamic range (WDR) neurons increased during innocuous brushing but increased maximally during noxious pinch. Glutamic acid (1 M) was absorbed on filter paper pledges (approximately 5 × 5 mm) for bilateral application to the dorsal surface of high cervical spinal segments; DLH (0.1 M) was used in some
cases. Pledgets were placed at the entry point of C2 dorsal roots for 2–3 min. Cervical spinal segments were rinsed with saline after the pledget was removed. Effects of chemically stimulating high cervical cell bodies were determined on CRD- or UBD-evoked activity in sacral STT neurons. Effects on changes in STT cell activity evoked by visceral stimulation were calculated as the difference between the control activity change to CRD or UBD and the change in activity elicited by CRD or UBD during chemical activation of high cervical cell bodies.

Recording and stimulating sites were lesioned with DC (50 μA, 20 s). The brain and spinal cord segments containing lesions were removed and placed in 10% buffered formalin. Frozen sections (60 μM) were mounted on slides, and camera lucida drawings were made of lesion sites. Laminae of recording sites were identified histologically in dorsal gray matter of S1 and S2 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in nine animals and were located in the lateral portion of the right ventroposterolateral thalamic nucleus. Threshold stimulus intensity was determined in 17 of 22 STT neurons; mean threshold stimulus was 0.39 ± 0.09 mA, range: 0.07–1.4 mA. An example of antidromic activation is shown in Fig. 1, B and C.

RESULTS

Lumbosacral STT neurons

Extracellular unit recordings were made from 22 STT neurons in the sacral spinal cord of 10 monkeys. Average recording depth was 1.37 ± 0.09 mm (range, 0.5–1.94 mm; n = 22). Lesions made at recording sites were located histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray matter of S1–S3 spinal segments for 14 neurons (Fig. 1A); average recording depth (1.25 ± 0.12 mm, n = 14) was not different compared with the total population of STT neurons. The majority of lesions were found in laminae IV and V. Antidromic activation sites were identified histologically in dorsal gray

FIG. 1. Locations of recording sites of spinothalamic tract (STT) neurons and an example of antidromic activation of a left S3 STT neuron from right ventroposterolateral (VPL)-thalamic nucleus. A: ● lesions of S1–S3 recording sites that were located histologically (n = 14). Drawings are based on Apkarian and Hodge (1989). B: antidromic impulses followed a high-frequency train (333 Hz). ↑, 1st of 4 stimulus artifacts; *, 1st of 4 antidromic impulses. C, top: stimulus artifact followed by antidromic impulse (5 stimuli). Constant latency of antidromic activation was 4.8 ms. Bottom: antidromic impulse collided with an orthodromic impulse produced by a somatic stimulus within the critical interval. Open arrow, orthodromic impulse.
Responses to distending the urinary bladder (80 mmHg) were determined in 22 neurons. Activity of 20 neurons increased from 9.2 ± 1.5 to 27.0 ± 2.2 imp/s, activity of 1 neuron decreased from 3.3 to 0 imp/s, and activity of 1 neuron increased and then decreased during UBD. Activity changes were compared for 18 neurons that were excited by inputs from both pelvic viscera; at 80 mmHg distension pressures, UBD were compared for 18 neurons that were excited by inputs from visceral and somatic stimuli. Activity changes in activity evoked by CRD and UBD in the same S2 neuron (lamina V) are shown in Fig. 2C.

Somatic fields were located primarily on the ipsilateral gluteal and perineal regions, proximal hindlimb or tail. Four of 22 neurons were excited only by noxious pinching of the receptive field (HT), 2 neurons received only innocuous somatic input (LT), 15 neurons were excited maximally by noxious stimulation (WDR), and 1 neuron was not examined for somatic field characteristics. An example of a WDR somatic receptive field is shown in Fig. 2, D and E, for a S2 cell located in lamina IV of S3 segment. Table 1 shows the patterns of convergent visceral-somatic inputs observed in 16 neurons that were examined with each visceral and somatic stimulus. In general, STT neurons in the caudal spinal cord were excited by noxious inputs from pelvic organs and proximal lower-body somatic fields and were inhibited by CPSA and vagal inputs.

EFFECTS OF CPSA INPUT ON EVOKED STT CELL ACTIVITY. Inhibitory effects of stimulating the left stellate ganglion were examined on activity evoked by noxious CRD (80 mmHg) in eight sacral STT neurons. Figure 3A shows an example of an excitatory CRD-evoked change in activity that was suppressed during the background activity produced by stimulating the stellate ganglion. The somatic field and recording location of this cell are shown in Fig. 2E. Activity changes evoked by CRD were reduced in six cells during CPSA stimulation and were not affected in two cells (Fig. 3B). Average CRD-evoked activity was reduced from the control change in activity of 16.2 ± 3.5 imp/s (9.6 ± 2.1 imp/s increased to 25.8 ± 5.5 imp/s) to 8.9 ± 4.4 imp/s (5.5 ± 2.0 imp/s increased to 14.4 ± 6.1 imp/s) during stimulation of CPSA input (n = 8, P < 0.05). Mean changes in activity to CRD returned to 16.5 ± 4.1 imp/s after removal of input from stimulating the stellate ganglion.

Eight sacral STT neurons were examined for the effects of CPSA input on activity evoked by noxious UBD; changes in activity to UBD were reduced in five cells and were not affected in three cells (Fig. 3C). Average UBD-evoked activity was reduced from the control change in activity of 15.1 ± 2.0 imp/s (10.7 ± 2.2 imp/s increased to 25.8 ± 3.0 imp/s) to 11.0 ± 1.8 imp/s (5.4 ± 1.6 imp/s increased to 16.4 ± 2.9

TABLE 1. Convergent inputs to S1-S3 STT neurons

<table>
<thead>
<tr>
<th>No. of Neurons</th>
<th>CPSA</th>
<th>VAG</th>
<th>CRD</th>
<th>UBD</th>
<th>SOM</th>
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<tbody>
<tr>
<td>8</td>
<td>I</td>
<td>I</td>
<td>E</td>
<td>7E, 1EI</td>
<td>2HT, 6WDR</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>NR</td>
<td>E</td>
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<td>1</td>
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<td>I</td>
<td>E</td>
<td>E</td>
<td>HT</td>
</tr>
<tr>
<td>2</td>
<td>NR</td>
<td>1E, 1NR</td>
<td>E</td>
<td>E</td>
<td>1HT, 1WDR</td>
</tr>
</tbody>
</table>

CPSA, cardiopulmonary sympathetic afferent input; VAG, vagal afferent input; CRD, colorectal distension; UBD, urinary bladder distension; SOM, somatic afferent input; E, excitatory; I, inhibitory; NR, no response; HT, high threshold; WDR, wide dynamic range; LT, low threshold.
imp/s) during stimulation of CPSA input \((n = 8, P < 0.05)\). Mean changes in activity to UBD recovered to 15.5 ± 2.3 imp/s after CPSA stimulation was removed.

CHEMICAL ACTIVATION OF CERVICAL CELL BODIES. Ten sacral STT neurons were examined for effects of chemically activating high cervical cell bodies on activity evoked by CRD. Figure 4A shows a S2 STT neuron in which CRD-evoked activity was reduced by 10.2% from control CRD response during application of glutamate at C2 spinal segment. In 7 of 10 STT neurons, the excitatory change in activity to CRD was sup-

![Diagram](image)

**FIG. 3.** Effects of CPSA input on responses of sacral STT neurons to pelvic visceral inputs. A, left: control response of a S3 STT neuron to CRD. Middle: attenuated response to CRD during CPSA stimulation (15 min after control response). Right: response to CRD 5 min after removal of CPSA stimulation. B: CRD-evoked changes in activity of individual sacral STT cells before, during, and after CPSA stimulation \((n = 8)\). C: UBD-evoked changes in activity of individual sacral STT cells before, during, and after CPSA stimulation \((n = 10)\).

![Diagram](image)

**FIG. 4.** Effects of chemical activation of high cervical cell bodies on evoked activity in sacral STT neurons. A, left: control response of a S2 STT neuron to CRD. Middle: attenuated response to CRD (5 min after control response) during application of glutamate to C2 dorsal spinal cord. Right: response to CRD 4 min after removal of glutamate pledget (7 min after CRD-evoked response in middle histogram). B, left: control response of a S3 STT neuron to UBD. Middle: attenuated response to UBD (5 min after control response) during application of glutamate to C2 dorsal spinal cord. Right: response to UBD 5 min after removal of glutamate pledget (7 min after UBD-evoked response in middle histogram). C: CRD-evoked changes in activity of individual sacral STT cells before, during, and after chemical activation of high cervical cell bodies \((n = 10)\). EAA, excitatory amino acid. — glutamate application; ——, DL-homocysteic acid (DLH) application. D: UBD-evoked changes in activity of individual sacral STT cells before, during, and after chemical activation of high cervical cell bodies \((n = 12)\).
pressed during application of glutamate \((n = 6)\) or DLH \((n = 1)\) on the dorsal surface of C\(_2\) segment. High cervical application of glutamate \((n = 2)\) or DLH \((n = 1)\) did not affect CRD-evoked changes in activity in 3 of 10 cells examined. Mean CRD-evoked changes in activity to high cervical application of glutamate or DLH were reduced from 17.9 ± 3.6 imp/s \((10.2 ± 1.9 \text{ imp/s increased to } 28.0 ± 5.4 \text{ imp/s})\) to 12.5 ± 3.2 imp/s \((6.9 ± 1.8 \text{ imp/s increased to } 19.4 ± 4.6 \text{ imp/s}; n = 10, P < 0.01)\). In 8 of 10 neurons, responses to CRD were measured after chemicals were removed; CRD-evoked changes in activity returned to 15.5 ± 3.1 imp/s, which was not different from control CRD responses in these neurons \((15.7 ± 4.0 \text{ imp/s}; n = 8)\). Figure 4C is a graph of CRD-evoked changes in activity in individual sacral STT cells before, during, and after chemical activation of high cervical cell bodies.

Twelve sacral STT neurons were examined for effects of chemically activating high cervical cell bodies on activity evoked by UBD. Figure 4B shows a S\(_3\) STT neuron in which UBD-evoked activity was reduced during application of glutamate at C\(_2\) spinal segment. In 9 of 12 STT neurons, the excitatory change in activity to UBD was suppressed during application of glutamate \((n = 8)\) or DLH \((n = 1)\) at the C\(_2\) spinal segment. Additionally, C\(_2\) application of glutamate \((n = 1)\) or DLH \((n = 1)\) increased UBD-evoked activity changes in two cells, and glutamate application did not change the response to UBD in one STT cell. The average UBD-evoked change in activity was reduced from 17.7 ± 2.3 imp/s \((9.6 ± 2.0 \text{ imp/s increased to } 27.4 ± 3.1 \text{ imp/s})\) to 10.9 ± 2.3 imp/s \((6.6 ± 2.3 \text{ imp/s increased to } 17.5 ± 3.9 \text{ imp/s})\) during high cervical application of glutamate or DLH \((n = 12, P < 0.01)\). Responses to UBD were measured in 10 of 12 neurons after high cervical chemicals were removed. The mean UBD-evoked change in activity recovered to 15.2 ± 1.3 imp/s and was not different from average control responses in these cells \((17.3 ± 2.1 \text{ imp/s}; n = 10)\). Figure 4D shows a graph of individual UBD-evoked changes in activity before, during, and after application of glutamate or DLH to C\(_2\) spinal segment.

Responses of C\(_1\)–C\(_3\) propriospinal neurons to cardiopulmonary inputs

Forty-five descending propriospinal neurons were recorded in left C\(_1\)–C\(_3\) spinal segments of 24 monkeys. The locations of the recording sites are shown in Fig. 5A \((n = 30)\). Axons of

![Diagram](http://jn.physiology.org/)

**FIG. 5.** Locations of recording sites of descending propriospinal neurons and an example of antidromic activation of a left C\(_1\) neuron from an electrode in left T\(_4\) segment. A: lesion sites of C\(_1\)–C\(_3\) descending propriospinal neurons that were located histologically \((n = 30)\). Symbols indicate effects of stimulating cardiopulmonary sympathetic afferents (CPSA), thoracic vagus afferents (VAG) and excitatory somatic fields (SOM). ●, CPSA, VAG, SOM excitatory; ■, CPSA, SOM excitatory, VAG no response; ▲, VAG, SOM excitatory, CPSA no response; □, CPSA, VAG, SOM no response; △, SOM excitatory, CPSA, VAG no response; ○, CPSA inhibitory, VAG no response, SOM excitatory; ○, CPSA, SOM excitatory, VAG not tested. Drawings are based on Apkarian and Hodge (1989). B: antidromic impulses followed a high-frequency train (333 Hz). †, 1st of 4 stimulus artifacts; ‡, 1st of 4 antidromic impulses. C: top: stimulus artifact followed by antidromic impulse. Constant latency of antidromic activation was 3.7 ms. Bottom: antidromic impulse collided with an orthodromic impulse produced by stimulating thestellate ganglion. Open arrow, orthodromic impulse; ●, stimulus artifact from CPSA stimulation.
descending propriospinal neurons were antidromically activated from the ventral white matter of left thoracic segments for 36 neurons (mean conduction velocity, 18.7 ± 1.7 m/s), from thoracic cord gray matter for 5 neurons (mean conduction velocity, 21.1 ± 5.1 m/s), and from ventral white matter of lumbar segments for 4 neurons (mean conduction velocity, 26.4 ± 5.2 m/s). Threshold stimulus intensity for antidromic activation was determined for 35 neurons; average threshold intensity was 0.82 ± 0.07 mA, range: 0.02–1.5 mA. There were no significant differences in threshold stimulus intensity between neurons activated from electrodes placed in the thoracic ventral white matter (0.87 ± 0.07 mA, n = 27), thoracic gray matter (0.99 ± 0.20 mA, n = 4), or lumbar white matter (0.33 ± 0.21 mA, n = 4). An example of antidromic activation is shown in Fig. 5, B and C.

RESPONSES TO STIMULATING THE STELLATE GANGLION. Stimulation of the left stellate ganglion increased activity of 16 of 45 (36%) descending propriospinal neurons in C1–C3 segments. Activity of one neuron decreased from 9.1 to 2.5 imp/s with 20 Hz, 33 V stimulus, and activity of 28 cells was not affected at any stimulus parameter tested. Figure 6A shows peristimulus histograms of responses at 25, 17, and 2 V for a single C2 propriospinal cell, and Fig. 6B shows increased responses to increased stimulus frequencies for the same C2 cell. Lesion sites for locations of the recording electrode (lamina VI) and the antidromic stimulating electrode (T6) are shown in Fig. 6C. Mean excitatory responses at varying stimulus intensities (2–33 V, 1 Hz, 0.1 ms) are shown in Fig. 7A (n = 4), and mean responses to different stimulus frequencies (1–20 Hz, 33 V, 0.1 ms) are shown in Fig. 7B (n = 5). In all, peristimulus histograms (1 Hz, 33 V, 0.1–0.5 ms, 1–3 pulses) were generated for excitatory responses of 10 neurons. Average evoked activity was 2.0 ± 0.4 imp/stimulus; mean threshold stimulus intensity was 16.2 ± 4.7 V (n = 8). Separate long latency peaks of evoked impulses were not observed in these neurons. Excitatory effects of CPSA input were recorded as rate histograms (20 Hz, 33 V, 0.1–0.5 ms, single stimulus pulse) for 13 neurons. Mean activity increased from 1.7 ± 0.8 to 17.5 ± 3.2 imp/s.

RESPONSES TO VAGAL AFFERENT INPUTS. Stimulation of the left thoracic vagus nerve increased activity for 20 of 43 (47%) C1–C3 propriospinal neurons examined for effects of ipsilateral vagal input. Activity of one neuron decreased from 7.9 to 5.3 imp/s with 20-Hz, 33-V stimulus, and activity of 22 cells was not affected by vagal stimulation. Mean responses to varying stimulus intensities (n = 6) and stimulus frequencies (n = 8) are shown in Fig. 7, C and D, respectively. In all, responses of 15 neurons excited by vagal input were recorded as peristimulus histograms (1 Hz, 33 V, 0.1–1.0 ms, 1–3 pulses). Average evoked activity of the first peak of impulses was 4.4 ± 0.7 imp/stimulus; mean threshold stimulus intensity was 6.4 ± 1.5 V (n = 12). Separate long-latency peaks of activity were observed in 2 of 15 neurons. Excitatory effects of vagal input were recorded as rate histograms (20 Hz, 33 V, 0.1–0.5 ms, single stimulus pulse) for 16 neurons; mean activity increased from 0.5 ± 0.2 to 30.5 ± 8.4 imp/s.

Effects of abdominal vagal input were compared with effects of thoracic vagal input for 10 C1–C3 descending propriospinal neurons recorded in six animals. Six of 10 cells were excited by stimulating left thoracic vagal fibers rostral to the heart but did not respond to stimulating the left vagus nerve just above the diaphragm. Four cells did not respond to either vagal stimulus. Figure 8 shows responses of a single C3 descending propriospinal neuron. Single-trace recordings and peristimulus histograms of re-

![Fig. 6. Effects on a C2 propriospinal neuron of stimulating across the left stellate ganglion. A: 3 peristimulus histograms (50 sweeps, 1 Hz, 0.1 ms) recorded at 25, 9, and 2 V, † artifacts for 2-pulse stimulus train. B: increased responses to increased stimulus frequencies (1–20 Hz, 33 V, 0.1 ms). C: lesion sites of the recording electrode (C2) and the antidromic stimulation electrode (T6).](http://jn.physiology.org/organism/10.220332)
Responses to stimulating the left vagus nerve rostral and caudal to the heart are shown in Fig. 8, A and B, respectively. Figure 8C shows responses to stimulating the somatic receptive field and the location of the somatic field. Locations of the lesion sites for the recording electrode (lamina VI) and the antidromic stimulation electrode (T4) are drawn in Fig. 8D.

Responses to Somatic Stimulation. Eleven of 41 C1–C3 descending propriospinal neurons examined for somatic fields did not respond to either somatic or visceral afferent stimuli. Most (26 of 30) neurons with somatic receptive fields were excited only by noxious pinch (HT), three cells were WDR, and one cell was LT. Input from deep structures was found for 16 of 19 cells tested for effects of pinching muscle or muscle plus skin compared with pinching skin only. Most neurons with somatic receptive fields (25 of 30) responded to electrical stimulation of visceral afferent nerve fibers; one LT and four HT cells did not respond to visceral nerve stimulation. Thus neurons that were excited by inputs from visceral nerves received convergent input from noxious mechanical stimulation of somatic fields (22 HT, 3 WDR).
Size and locations of excitatory receptive fields were variable. Most somatic fields included the ipsilateral neck and/or inferior jaw region, although three cells had small somatic fields on the ipsilateral head that excluded neck and jaw areas. Bilateral upper body fields were found for two cells (see Fig. 8C). Excitatory ipsilateral and/or contralateral somatic fields were found on proximal lower body areas for 11 cells. Seven of 11 cells responded also to noxious input from proximal upper body areas, and 4 cells responded only to stimulation of hindlimbs, hips and/or tail; 2 of these cells were activated from the lumbar spinal cord.

CONVERGENCE OF AFFERENT INPUTS. A total of 43 C<sub>1</sub>–C<sub>3</sub> descending propriospinal neurons were examined for responses to electrical stimulation of both vagal and CPSA fibers. Twenty-six of 43 neurons received afferent input from stimulating one or both visceral nerves; 10 of 26 neurons received convergent input from both vagal and sympathetic nerve fibers. Additionally, two cells that were not tested for vagal effects were excited by stimulating the stellate ganglion. A comparison of excitatory responses to stimulation of CPSA and vagal afferents at 1 and 20 Hz (33 V), and stimulus threshold currents measured at 1 Hz are given in Table 2. Seventeen neurons did not receive inputs from electrical stimulation of either visceral nerve. As described in the preceding text, 16 of these cells were examined for somatic receptive fields and 11 of 16 cells also did not respond to somatic stimuli. In contrast, all neurons that responded to visceral input and were examined with somatic stimuli received input from noxious stimulation of receptive fields.

Responses to visceral and somatic stimuli are summarized in Table 3. The symbols in Fig. 5 indicate responses of neurons in various laminae to visceral and somatic afferent inputs. No differences in cell laminae were observed for the different patterns of responses to afferent stimulations. Recording depths of neurons in the various categories were not significantly different (Table 3); additionally, the mean recording depth of neurons that did not respond to visceral or somatic stimuli (2.62 ± 0.17 mm, n = 12) was not significantly different from the recording depth of neurons that did not respond to visceral or somatic stimuli (2.30 ± 0.09 mm, n = 32).

**DISCUSSION**

**Sacral STT neurons**

The first portion of this study in monkeys described the effects and interactions in sacral STT neurons of visceral afferent inputs that enter different segments of the spinal cord. Stimulation of urinary bladder and colorectal afferents, which enter lumbosacral segments (Bahns et al. 1986, 1987), increased spontaneous activity of deep dorsal horn STT neurons with convergent somatic input from lumbosacral dermatomes. Previous reports have shown that UBD and CRD excite primary STT neurons (Al-Chaer et al. 1999; Milne et al. 1981) and postsynaptic dorsal column (PSDC) neurons in sacral segments (Al-Chaer et al. 1999). In contrast, electrical stimulation of the stellate ganglion to activate CPSA, which enter high thoracic spinal segments (Kuo et al. 1984), decreased spontaneous activity of sacral STT neurons recorded in this study. These results agreed with previous findings in primates (Brennan et al. 1989; Hobbs et al. 1992a). The current examination of interactions between spinal visceral afferent inputs in deep dorsal horn neurons showed that sacral STT activity evoked by UBD or CRD was significantly decreased by CPSA. An earlier brief presentation also has described CPSA inhibition of UBD-evoked activity as well as somatic-evoked activity in L<sub>6</sub>–S<sub>2</sub> primate STT neurons (Foreman et al. 1988).

Additionally, stimulation of thoracic vagus fibers primarily inhibited sacral STT neurons in the present study. Previous reports in monkeys and rats have described vagal inhibition of STT cell activity in segments below C<sub>3</sub> (Ammons et al. 1983; Chandler et al. 1991; Hobbs et al. 1989; Ren et al. 1991) and vagal excitation of STT neurons in C<sub>1</sub>–C<sub>3</sub> segments (Chandler et al. 1996). Studies in primate C<sub>2</sub>–T<sub>5</sub> and T<sub>5</sub>–S<sub>1</sub> STT neurons, which used stimulation of specific vagal branches to differentiate the origin of vagal afferent input, suggest that cardiopulmonary, but not abdominal, vagal fibers are primarily responsible for inhibitory vagal effects on STT neurons (Ammons et al. 1983; Hobbs et al. 1989). However, excitatory responses to vagal stimulation observed in C<sub>1</sub>–C<sub>3</sub> STT neurons can include inputs from abdominal as well as thoracic vagal fibers (Chandler et al. 1996).

Previous experiments in primates produced the unexpected finding that inhibitory effects of visceral spinal afferents on distant STT neurons can occur via inputs to high cervical segments (Hobbs et al. 1992b). That study utilized spinal cord transections at either rostral C<sub>1</sub> or caudal to C<sub>3</sub> to demonstrate that inhibitory effects of CPSA or splanchic inputs in lumbosacral STT neurons do not require supraspinal nuclei and do not travel directly from thoracic to lumbosacral segments. Sequential transections of the same cervical segments in rat
spinal cord also suggest that CPSA inhibition of lumbar STT or dorsal horn neurons involves cervical spinal segments (Zhang et al. 1996).

These earlier studies did not examine the likelihood that inhibitory effects from high cervical segments involve cell bodies in these segments. Excitatory amino acids (EAA), such as glutamate, do not affect axons of passage but activate cell bodies (Fries and Ziegglansberger 1974). Glutamate pledges therefore have been applied to cervical spinal segments in other studies to activate cell bodies (Poree and Schramm 1992; Qin et al. 1999; Sandkuhler et al. 1993). In the current study, C2 application of a pledget soaked in either glutamate or DLH significantly reduced activity evoked in sacral STT neurons by inputs from pelvic viscera. This finding is consistent with a c-fos study in rats that shows that high cervical glutamate microinjections significantly reduce the number of lumbar spinal neurons demonstrating heat-evoked Fos-like immunoreactivity (Jones 1998). It was not possible to determine the axonal projections of chemically activated neurons with our protocol. Either ascending or descending high cervical neurons, as well as interneurons, could have been stimulated. Thus inhibitory effects observed in sacral STT neurons could have resulted from high cervical projections to well-established supraspinal inhibitory centers (Jones 1992) or via descending propriospinal projections. However, results in rats suggest that inhibitory effects from high cervical segments do not require supraspinal nuclei. Glutamate activation of cervical neurons in spinal rats inhibits spontaneous and splanchic nerve-evoked activity in thoracic spinal neurons (Poree and Schramm 1992). Furthermore a study from our laboratory provides evidence that descending projections from cervical neurons are involved in inhibition of rat lumbarosacral neurons (Qin et al. 1999); average decreases in CRD-evoked activity observed in L6–S2 spinal neurons during cervical glutamate application were not significantly different before or after C1 spinal transection. Based on the previous results obtained after cervical spinal transections in primates and rats (Hobbs et al. 1992b; Zhang et al. 1996) and to cervical application of glutamate in spinal rats (Poree and Schramm 1992; Qin et al. 1999) as well as present responses to cervical EAA observed in sacral STT neurons, we reasoned that high cervical propriospinal neurons can be excited by visceral afferent inputs to process descending inhibitory effects on STT neurons.

**Descending propriospinal C1–C3 neurons**

Results of the second part of this study showed that C1–C3 descending propriospinal neurons usually were excited or did not respond to the visceral inputs examined; inhibition rarely was observed. Most neurons were antidromically activated from thoracic spinal cord. Four cells were antidromically activated from lumbar spinal cord, but it is possible that other C1–C3 neurons projected to lumbar segments; axonal terminations were not determined in this study. Projections and locations of C1–C3 descending propriospinal neurons have been described in some anatomical studies. In monkeys, horseradish peroxidase (HRP) injected in thoracic spinal cord labeled C1–C2 cells in lateral cervical nucleus, central gray region, lamina I, and lateral regions of laminae V-VIII (Burton and Loewy 1976). In rats, fluorogold or horseradish peroxidase (HRP) injected in lumbarosacral segments labeled C1–C2 cells primarily in laminae V and X, lateral cervical nucleus and ventral horn (Miller et al. 1998). Similar distributions of C1–C3 neurons were found in cats after HRP injections in upper lumbar segments (Matsushita et al. 1979; Yezierski et al. 1980). Some lesions of recording sites in the current study were located in the laminae that were labeled in various anatomical studies; however, lesions also were found in lamina IV. No significant differences were found in the responses of descending propriospinal neurons recorded in the various laminae.

Various patterns of afferent nerve convergence were found in C1–C3 descending propriospinal neurons. Nine of 26 neurons that were tested for effects of stimulating both vagal and CPSA fibers and that responded to at least one visceral stimulus were excited by input from both pathways. However, the majority of cells (16 of 26, 62%) were affected only by one visceral input; an additional cell was excited by vagal stimulation but inhibited by stellate stimulation. Thus electrical stimulation of vagal and sympathetic nerve fibers did not uniformly activate C1–C3 neurons. Myocardial ischemia has been shown to activate afferent fibers that travel in vagal and sympathetic nerves (Brown 1967; Thoren 1976), but it appears that vagal or sympathetic inputs stimulated by cardiac ischemia often would activate different C1–C3 descending propriospinal neurons. This divergence might be related to the different pathways used by each afferent input. Anatomic studies show that cardiac sympathetic afferents enter T5–T6 spinal segments (Hopkins and Armour 1989; Kuo et al. 1984). Because primary visceral afferents can travel in the zone of Lissauer for at least five segments (Kuo et al. 1984; Sugiuara et al. 1989), it is possible that some primary CPSA input projected to upper cervical segments. It also is possible that CPSA inputs synapsed in gray matter of thoracic or lower cervical segments and ascended to C1–C3 via short propriospinal pathways. In rats, results after spinal transections suggest that CPSA information ascends bilaterally in ventrolateral pathways to activate C1–C3 spinal neurons (Zhang et al. 1997). Vagal afferents project to nucleus solitarius (NTS) (Beckstead and Norgren 1979). Some vagal fibers reach C1 segment in monkeys, but most fibers synapse in NTS and then project to other brain stem nuclei before descending to the spinal cord (Beckstead and Norgren 1979; Beckstead et al. 1980; Rhoton et al. 1966). No obvious differences in neuronal distribution were observed for the various combinations of convergent afferent inputs.

Propriospinal neurons activated by CPSA or vagal afferents received convergent inputs from mechanical stimulation of somatic receptive fields. Neurons frequently were activated more vigorously when underlying muscle was included in a noxious pinch compared with pinch of skin alone. Spinothalamic tract and dorsal horn neurons that receive visceral inputs also are more likely to receive somatic input from proximal deep fields than from distal cutaneous fields (Giamberadino et al. 1996; Hobbs et al. 1992a). Somatic receptive field locations and sizes were variable, but excitatory fields usually included regions innervated from high cervical segments. Most (87%) C1–C3 propriospinal neurons that responded to mechanical stimuli were activated only by noxious pinch and 10% were WDR neurons. This contrasts with somatic field characteristics of STT neurons in C1–C3 segments; 32% of STT neurons that responded to somatic stimuli were HT neurons and 59% were WDR (Chandler et al. 1996). The large number of HT propri-
spinal neurons supports our hypothesis that noxious somatic and visceral inputs can be processed in high cervical segments to produce descending inhibitory effects in distant spinal segments. About 25% of propriospinal neurons, however, were not excited or inhibited by any somatic or visceral stimulus tested. This percentage might be underestimated because some “silent” cells that were observed during searches for antidromically activated neurons were not isolated and documented. Perhaps these neurons respond to thermal stimulation of somatic fields or to inputs arising from brain nuclei.

Potential functional implications

Abdominal vagal fibers did not contribute to excitation of C1–C3 propriospinal neurons examined in this study. This contrasts with results in C1–C3 STT neurons, which received input from abdominal vagal fibers in 50% of cells tested. However, the finding that C1–C3 propriospinal neurons did not receive inputs from abdominal vagal fibers correlates with previous studies in primate thoracic and lumbar sacral STT cells that show the importance of cardiopulmonary vagal afferent input in producing inhibition of spinal sensory neurons (Ammons et al. 1983; Hobbs et al. 1989). Some investigators provide evidence that cytokine-induced hyperalgesia is mediated by subdiaphragmatic vagal fibers (Goehler et al. 2000). Sectioning the abdominal vagus nerve inhibits acute phase responses such as fever (Watkins et al. 1995), and vagal afferents are activated by immune stimuli (Goehler et al. 1998). Thus these experiments imply that stimulation of vagal afferents generates thermal hyperalgesia. On the other hand, Coelho et al. (2000) show that vagotomy amplifies the responses to peritoneal inflammation produced by lipopolysaccharide in conscious rats. Furthermore, Jäning and co-workers (2000) report that vagotomy enhances mechanical hyperalgesic behavior; paw-withdrawal threshold to hyperalgesia induced by intradermal bradykinin is decreased following vagotomy.

Electrophysiological studies in primates show that stimulation of vagal fibers primarily inhibits STT neurons in all segments below C3 (Ammons et al. 1983; Chandler et al. 1991; Hobbs et al. 1989). Facilitatory effects of vagal stimulation on lumbar STT neurons in rats occur only with low-intensity vagal stimulation; stimulation at intensities comparable with the current study inhibits most facilitated lumbar neurons (Ren et al. 1991). Widespread spinal inhibition produced by cardiopulmonary vagal input would seem to suppress transmission of cardiac nociceptive information. Generally it is assumed that this effect is not beneficial and puts patients at risk (Cohn 1989). However, nociceptive suppression might interrupt positive feedback that increases work demands on the heart; noxious stimuli can increase motor activity and blood pressure (Ranich and Maixner 1984). Stimulation of vagal afferents also decreases activity in sympathetic preganglionic fibers that are directed to the heart (Schwartz et al. 1973). Thus vagal stimulation might in fact protect a compromised cardiopulmonary system from reflex demands (Hobbs et al. 1989). Some upper cervical neurons project to the intermediolateral cell column (Craig 1993; Jansen and Loewy 1997) and therefore could affect autonomic responses to noxious stimuli.

In contrast to the widespread inhibitory effects of vagal stimulation on spinal sensory neurons below C3, effects of stimulating the stellate ganglion are dependent on the spinal segments examined. Neurons in T1–T6 segments are excited by CPSA stimulation (Blair et al. 1981; Hobbs et al. 1992a), whereas CPSA input can be processed in high cervical segments to produce inhibition of lumbar sacral STT neurons (Hobbs et al. 1992b). Previous studies in rats also show the importance of high cervical segments in processing lumbar sacral inhibitory effects originating from thoracic visceral inputs (Qin et al. 1999; Zhang et al. 1996).

Propriospinal inhibition of sensory inputs from pelvic regions to STT neurons, such as CPSA inhibition of CRD- and UBD-evoked responses in the present study, could modulate transmission and processing of nociceptive information. Inhibition of sacral STT cells should result in amplification of excitatory effects in thoracic sensory neurons by reducing the effects of afferent inputs to lumbar sacral segments (Hobbs et al. 1992b; LeBars et al. 1986; Qin et al. 1999). This modulation of sensory inputs might exacerbate pain sensations that accompany disordered myocardial function (Hobbs et al. 1992b; Qin et al. 1999; White 1957). We do not know from current results whether the inhibitory effects described in the current study are specific for sacral STT neurons or would affect other sensory neurons, such as PSDC neurons. Observations made in rats and primates by Al-Chaer et al. (1996, 1998) and in rats by Ness (2000) show that pelvic visceral input to VPL thalamic neurons travels primarily in dorsal pathways, even though both PSDC and STT neurons are activated by CRD (Al-Chaer et al. 1999).

In addition to changes in sensory processing, motor reflexes to nociceptive stimuli could be altered via descending inhibition from C1–C3 segments. Descending projections from high cervical neurons to hindlimb motoneurons have been found with the horseradish peroxidase technique (Matsushita et al. 1979).

Results from this study do not discount the importance of descending inhibition from supraspinal nuclei (Babasa and Fields 1984; Jones 1992). In fact, it is intriguing to speculate that C1–C3 propriospinal neurons might be involved in modulating descending inhibition arising from supraspinal nuclei. In support of this idea, a preliminary study in rats showed that fibers containing either tyrosine hydroxylase or serotonin immunoreactivity were apposed to C1–C3 propriospinal neurons (Miller et al. 1996); descending inhibitory neurons arising from brain stem nuclei primarily contain either norepinephrine or serotonin (Jones 1992). Our data have shown, however, that intraspinal processing of nociceptive transmission in high cervical segments also has the capability of adjusting the impact of noxious stimuli on brain centers. Processing of thoracic nociceptive information in high cervical segments might filter and modify sensory signals from widespread segments of the spinal cord before these inputs ascend to supraspinal sites.

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