Upper Thoracic Respiratory Interneurons Integrate Noxious Somatic and Visceral Information in Rats

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Qin, Chao, Margaret J. Chandler, Robert D. Foreman, and Jay P. Farber. Upper thoracic respiratory interneurons integrate noxious somatic and visceral information in rats. J Neurophysiol 88: 2215–2223, 2002; 10.1152/jn.00120.2002. The aim of this study was to determine if thoracic respiratory interneurons (TRINs) might receive peripheral noxious somatic and visceral inputs. Extracellular potentials of 78 respiration-related T3 neurons were recorded from the intercostal zone in pentobarbital anesthetized, paralyzed, and ventilated male rats. These neurons were identified as interneurons by their locations and by the absence of antidromic activation from the cervical sympathetic trunk and cerebellum. Thoracic esophageal distension (ED) was produced by water inflation of a latex balloon (0.1–0.5 ml, 20 s). A catheter was placed in the pericardial sac to administer 0.2 ml bradykinin (10^{-5} M) for noxious cardiac stimulation. Of 78 TRINs examined for ED, activity of 24 TRINs increased and activity of 8 TRINs decreased. Intrapericardial bradykinin increased activity in 26/65 TRINs tested and decreased activity in 5 TRINs. Seventy-four TRINs were tested for effects of brush, pressure, and pinch of the chest and upper back areas. No TRINs responded to brushing hair. Low-threshold responses to pressure were observed in 27 TRINs. Fourteen TRINs were wide dynamic range and 4 TRINs had high-threshold responses. Peripheral stimuli affected all types of TRINs, including inspiratory, expiratory, and biphasic neurons. Simultaneous phrenic recordings showed that effects of various somatic and visceral stimuli on TRINs were independent of central respiratory drive. Various somatovisceral and viscerovisceral patterns of input were observed in TRINs. The results suggested that TRINs participate in intraspinal processing and integration of noceptive information from somatic fields and visceral organs.

INTRODUCTION

Much effort has been directed at understanding the organization of inputs to spinal interneurons (Edgley 2001; Kirkwood et al. 1987; Lundberg 1979; Zimmermann 1977). For example, spinal dorsal horn interneurons encode noxious and nonnoxious information and are linked to segmental motor and sympathetic outputs. These interneurons also are subject to modulatory influences originating from other spinal segments and the brain (Zimmermann 1977). Because the majority of inputs to spinal motoneurons originate from intrinsic spinal premotor interneurons, the organization of inputs to different subgroups of spinal interneurons is likely to be crucial to outflows of spinal motoneurons (Edgley 2001).

The respiratory drive from the medulla to the phrenic motoneurons is generally accepted as having a strong monosynaptic component, whereas the intercostal motoneurons are generally viewed as receiving much less monosynaptic drive. Thus control of thoracic respiratory motoneurons is suggested to be dependent mainly on respiratory interneurons (Kirkwood 1995; Merrill and Lipski 1987). However, the function of spinal respiratory interneurons probably is not simply to relay respiratory drive from the medulla. For example, thoracic respiratory interneurons (TRINs) of the cat project to the contralateral ventral horn and are hypothesized to coordinate respiratory and/or other motor activities bilaterally (Kirkwood et al. 1988, 1993; Schmid et al. 1993).

In addition to supraspinal respiration-related inputs, spinal respiratory interneurons at various segments receive other information. Upper cervical inspiratory neurons integrate noxious information from cardiorespiratory and abdominal sympathetic afferents (Yuan et al. 2000) and also are excited by vagal stimulation (Dawkins et al. 1992; Duffin et al. 1994; Lipski et al. 1993). Respiratory interneurons within the phrenic motor nucleus respond to stimulation of phrenic afferents (Bellinger and Lipski 1990; Iscoe and Duffin 1996). We recently presented evidence that most TRINs received propriospinal inputs from distant (C1–C2) spinal segments (Qin et al. 2002b). The aim of this study was to examine responses of TRINs to various peripheral somatic and visceral stimuli and to determine the incidence of various inputs onto TRINs. A preliminary report has been published in abstract form (Farber et al. 2001).

METHODS

Experiments were performed on 37 male Sprague-Dawley rats weighing 320–460 g (Charles River, Boston, MA). Anesthesia was initially induced with a bolus injection of pentobarbital sodium (60 mg/kg ip) and maintained by supplementary doses (10–15 mg kg^{-1} h^{-1} intravenous) through a catheter placed in the left jugular vein. The right carotid artery was cannulated to measure arterial blood pressure. Arterial pressure and pupil diameter were monitored to determine the anesthesia level during experiments. Following muscle paralysis with pancuronium bromide (0.4 mg/kg ip), the animals were artificially ventilated with room air administered by a positive-pressure pump (50–60 strokes/min, 3–5 ml stroke volume). Supplemental doses of pancuronium bromide (0.2 mg · kg^{-1} · h^{-1} ip) were administered to maintain muscle relaxation throughout experiments. Rectal temperature was kept between 37 and 38°C by a servo-controlled heating system.
The left phrenic nerve crossing the brachial plexus in the neck was exposed, desheathed, and crushed caudally. A bipolar platinum hook electrode was placed around it to monitor central inspiratory drive. Because continuous infusion of pentobarbital anesthesia over a long experiment could depress ventilation, an adequate phrenic signal was assured by adding CO₂ (≤4%) to the inspired air. A pair of platinum stimulating electrodes was wrapped around the left cervical sympathetic trunk after it was crushed rostrally. Stimulation parameters were 25–33 V, 1 Hz, 0.2 ms. Bipolar stainless steel stimulating electrodes (4–5 mm apart) were placed across the midline of the cerebellum, just below the surface (Edgley and Grant 1991; Hirai et al. 1988). Stimulation parameters were 1–2 mA, 1 Hz, 0.2 ms.

Somatic receptive fields of spinal neurons were examined for responses to innocuous brushing with a camel-hair brush, pressure with a blunt stick, and noxious pinching of skin with a blunt forceps. Neurons were classified as follows: low-threshold (LT) neurons were excited by hair movement and/or pressure; high-threshold (HT) neurons responded only to noxious pinching of the somatic field; wide dynamic range (WDR) neurons were excited by innocuous stimuli and also had greater responses to noxious pinch of somatic fields. Outlines and descriptions of receptive fields were recorded manually for all neurons examined.

A small latex balloon 1.0 cm in length was attached at the end of PE-240 tubing (ID, 1.67 mm; OD, 2.42 mm) and was inserted peripherally into the thoracic esophagus (9–10 cm from the upper front incisors). Graded esophageal distension (ED) was produced by injecting warm water (0.1, 0.2, 0.3, 0.4, 0.5 ml, 20 s) at 0.05–0.1 ml/s (Wei et al. 1997). Esophageal distension (0.3–0.4 ml) was used to identify responsive neurons. A high midline thoracotomy was made to expose the pericardial sac by opening the thymus gland. A silicone tubing (0.020 ID, 0.037 OD, 14–16 cm in length) with 7–10 small holes in the distal 2 cm was inserted into the pericardial sac over the left ventricle (Euchner-Wamser et al. 1994). A solution of bradykinin (10⁻⁵ M, 0.2 ml) was injected into the pericardial sac for chemical activation of afferent endings on the heart. The protocol for administering bradykinin was to inject warm saline (0.2 ml) into the pericardial sac and withdraw after 60 s to determine volume effects, to inject 0.2 ml of the solution of bradykinin and withdraw after 60 s, and to rinse the chemicals within the pericardial sac with two or three saline flushes (0.2 ml each).

After the T₃ spinal segment was exposed for extracellular recording, the rat was mounted in a stereotaxic headholder and stabilized with vertebral clamps at T₂ and T₅–T₆. Dura mater was carefully removed, and the spinal cord was covered with warm agar (3–4% in saline) to improve recording stability. Carbon-filament glass microelectrodes were used for recording extracellular potentials of single T₃ spinal neurons within 0–1.4 mm from the dorsal surface and 0.5–2.0 mm lateral to midline in left side of the spinal cord. To identify thoracic respiratory interneurons (TRINs), the following criteria were used: 1) respiration-related discharges of spinal neurons were not abolished when the ventilator was stopped for 5–10 s. 2) The depth of electrode penetration was limited to 1,400 μm so that recorded cells were generally confined to the deep dorsal horn and intermediate zone (Fig. 1). This was assumed to eliminate recording from motor neurons in most instances. 3) Both preganglionic sympathetic and spinocerebellar neurons are known to receive respiratory drive (Edgley and Grant 1991; Gilbey et al. 1982; Hedger and Webber 1976; Hirai et al. 1997).

**FIG. 1.** Lesion sites of thoracic respiratory interneurons (TRINs) in representative T₃ segment of the rat spinal cord. In all examples, • TRINs responding to somatic and/or visceral stimuli. ○ TRINs not responding to various peripheral stimuli. A: inspiratory TRINs. B: expiratory TRINs. C: biphasic TRINs. D: laminae of T₃ segment based on Molander et al. (1989). I-X, laminae; CC, column of Clarke; IL, intermediolateral nucleus; IM, intermediolateral nucleus; Liss, Lissauer’s tract; LSN, lateral spinal nucleus; Pyr, pyramidal tract.
1988). Cells activated by antidromic stimulation of sympathetic chain or cerebellum were excluded from these studies. All neural signals were documented on-line with the Spike 3 data-acquisition system (CED, Cambridge). An increase or decrease in cell activity > 20% of baseline activity during a stimulus was considered an excitatory or inhibitory response, respectively. Maximal response and duration of response were measured using rate histograms (1 s/bin) after various manipulations. Also, inspiratory and expiratory peaks of respiratory phasic activity were measured using rate histograms (0.1 s/bin) of 10 breaths for control activity or maximal response to a stimulus. For purposes of illustration, rate histograms with 0.04 s/bin for cell activity are presented in all panels showing expanded recordings. After phrenic nerve discharges were filtered and rectified, the signal was averaged over successive 0.04-s bins. This moving average was used to assess any changes in phrenic nerve activity or breathing rate accompanying the various manipulations.

After the study of a spinal neuron was completed, an electrolytic lesion (50 μA DC) was made at most recording sites. The thoracic spinal cord was removed and placed in 10% buffered formalin solution. Frozen sections (55–60 μm) were made using Student files and laminae of lesions were identified (Molander et al. 1989). Statistical comparisons were made using Student’s paired or unpaired t-test and χ² analysis. Bonferroni’s inequality was used for comparisons between control conditions and responses to saline and bradykinin. Statistical significance was established as P < 0.05, and data are presented as means ± SE.

RESULTS

Categories of TRINs

Extracellular recordings from the left side of T₃ spinal segment were made from 78 neurons judged to be TRINs. According to the timing of increasing firing within the respiratory period assessed on phrenic nerve activity, TRINs were divided into three different categories: 51 (65%) inspiratory neurons with maximal discharge during phrenic nerve activity, 15 (19%) expiratory neurons with maximal discharges during phrenic silence, and 12 (16%) biphasic or phase-spanning neurons that did not fit into the preceding categories.

Various convergent patterns of TRINs receiving inputs from somatic fields and visceral organs were observed. A comparison of discharge patterns of TRINs and convergence of inputs are shown in Table 1. Lesions made at recording sites were identified histologically for 38 neurons in the intermediate zone of the spinal cord (Fig. 1).

Responses to somatic inputs

Seventy-four TRINs were tested for their responses to various mechanical stimuli of somatic fields. Of these, 45 (61%) TRINs received somatic inputs from chest wall, axilla, and upper back area. Twenty-seven (36%) TRINs were excited by pressure of somatic fields and were classified as LT neurons. Fourteen (19%) WDR neurons were excited by pressure and had even greater responses to noxious pinching of somatic fields. Four TRINs were excited only by noxious pinching and were identified as HT neurons. Examples are presented in Fig. 2, A–C. No TRIN responded to brushing the hair over the somatic fields. Comparisons of receptive field properties and respiration-related firing patterns of responsive TRINs are presented in Fig. 3A. No expiratory TRIN was classified as a HT neuron.

Responses to esophageal distension

Esophageal distension (0.4 ml) changed respiration-related activity of 32/78 (41%) TRINs (Table 2). Of these, ED increased activity of 24 (31%) TRINs from 13.9 ± 2.3 to 28.8 ± 3.4 imp/s measured on rate histograms (1 s/bin). An example of a TRIN excited by ED and a summary for excitatory responses of TRINs to ED are shown in Fig. 4A and Table 2, respectively. Respiratory firing patterns and excitatory responses of TRINs to ED are compared in Fig. 3B. For eight TRINs examined for graded ED, stimulus-response curves were obtained (Fig. 5A). For TRINs excited by ED, both inspiratory and expiratory phasic activity significantly increased with ED (P < 0.01), whereas phrenic nerve activity did not change during ED (Fig. 5B).

Spontaneous activity of 8/32 responsive TRINs was reduced by ED (0.4 ml) from 8.0 ± 1.2 to 2.7 ± 1.2 imp/s (1 s/bin, 34% of control). Table 2 shows the characteristics of TRINs inhibited by ED. An example of an inhibitory response to ED is shown in Fig. 4B. For three TRINs inhibited by graded ED, stimulus-response relationships are presented in Fig. 5C. Also, ED significantly decreased inspiratory discharge levels of TRINs independent of phrenic nerve activity (Fig. 5D).

Responses to intrapericardial bradykinin

Intrapericardial bradykinin (IB) changed the respiration-related activity of 31/65 (48%) TRINs. Respiratory firing patterns of these TRINs and their responses to IB were compared (Fig. 3C). The discharge rate (1 s/bin) of 26/31 (84%) TRINs increased with IB from 13.0 ± 2.1 to 29.6 ± 3.7 imp/s (Table 3), whereas intrapericardial injection of saline (Fig. 6A) did not change activity of TRINs (13.6 ± 2.2 vs. 13.7 ± 2.3 imp/s). An example of an excitatory response of a TRIN to IB is shown in Fig. 6B, a–c. In contrast to effects of intrapericardial saline on phasic activity of these TRINs (Fig. 6C), both inspiratory and expiratory phasic activity of TRINs significantly increased

<table>
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SI, somatic inputs produced by pressure and/or pinch of somatic fields; ED, esophageal distension (0.4 ml, 20 s); IB, intrapericardial bradykinin (10⁻⁷ M, 0.2 ml); NR, neurons non-responsive or non-tested to somatic and visceral stimuli. All of 78 thoracic respiratory interneurons (TRINs) were examined for esophageal distensions; 74 TRINs were tested for somatic inputs; 65 TRINs were tested for intrapericardial bradykinin.

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with IB (P < 0.01, Fig. 6D), whereas phrenic nerve activity did not change during intrapericardial saline or IB (Fig. 6, C and D).

Intrapercardial bradykinin reduced respiration-related activity of 5/31 TRINs from 10.0 ± 2.6 to 3.6 ± 1.8 imp/s (1 s/bin, 36% of control; Table 3), which was compared with effects of intrapericardial saline (Fig. 7A) on these TRINs (9.7 ± 2.8 vs. 9.6 ± 2.7 imp/s). An inhibitory response to IB is shown in Fig. 7B, a–c. While overall TRIN discharge decreased, the small sample size did not show significant effects in each phase of respiration. Furthermore, phrenic activity was unaffected (Fig. 7, C and D).

**DISCUSSION**

TRINs are driven by supraspinal respiratory activity (Kirkwood et al. 1988, 1993), and data suggested that they are modulated by propriospinal inputs from distant segments (Qin et al. 2002b). TRINs might transmit supraspinal respiratory activity to motoneurons to drive intercostal muscles and are hypothesized to coordinate respiratory and/or other motor activity bilaterally (Schmid et al. 1993). The present study found that almost two-thirds of TRINs were inspiratory and that 51/78 inspiratory, expiratory, and biphasic TRINs received noxious and nonnoxious inputs from somatic structures and/or visceral organs. Almost half of TRINs (15/36) responding to various peripheral stimuli exhibited viscerosomatic or viscerovisceral convergent patterns. The convergence could have been directly onto these cells or on presynaptic neurons to these cells. In either case, these data support the concept that TRINs participate in intraspinal processing and integration of nociceptive and nonnociceptive information from somatic fields and visceral organs. Effects of somatic and visceral inputs on TRINs in the current study are similar to results obtained from other studies of spinal interneurons (Edgley 2001; Kirkwood et al. 1987; Lundberg 1979; Zimmermann 1977). Kirkwood et al. (1988) noted that respiratory interneurons were distributed among motor neuron populations as well as more superficially. Our search criteria purposely avoided interneurons that were deep enough to approximate motor neurons. Our population statistics, then, would not reflect these deep cells. Different electrode types were used in the present study compared with Kirkwood et al. (1988) so this also could have influenced cell populations obtained. Two other points should be considered with respect to the present classification of interneurons. The first is that antidromic stimulation of cerebellum and sympa-

![FIG. 2. Classification of TRINs to mechanical stimuli of somatic fields. In all examples, traces from top to bottom are integrated phrenic nerve activity (0.04 s/bin), discharges of phrenic nerve, activity of a single thoracic spinal neuron, rate histogram of cell activity (1 s/bin, 0.04 s/bin for panels with extended recordings). A: a TRIN with low-threshold (LT) response to pressure stimulus of somatic field on chest (top). B: a wide dynamic range (WDR) TRIN with response to pressure and greater response to noxious pinch of somatic fields on chest (top). C: a TRIN with high-threshold (HT) response to pinch of axilla (top). A, a–c, B, a–c, and C, a–c: expanded recording of phrenic nerve and cell activity.](http://jn.physiology.org/Content/Full/88/6/2218/F002.jpg)
Effects of somatic inputs among thoracic neurons

Somatic inputs from muscle proprioceptors (for example muscle spindles) and cutaneous receptors contribute to a multisensory organization of spinal interneuron populations (Edgley 2001; Zimmermann 1977). Also, afferents from different origins could converge onto common interneurons in segmental reflex pathways (Kirkwood et al. 1987). In rats, the majority of upper thoracic spinal neurons (T2–T4) within dorsal horn and immediate zone of the spinal cord receive somatic inputs from skin, muscle, and joints (Hummel et al. 1997). These data are in general similar to findings of the present study in which 61% of TRINs responded to various mechanical stimuli of somatic fields. However, some functional differences were revealed by further comparison. First, 23% of T2–T4 spinal neurons responded to brushing of the skin (Hummel et al. 1997), whereas none of 78 TRINs had such a response. Second, 41/78 (53%) TRINs responded to pressure on the chest, axilla, and upper back, which were presumed to be proprioceptive inputs from muscle, joints, and deep tissue. Responses to pressure are more frequently encountered in TRINs than in a population of dorsal horn and intermediate zone thoracic spinal neurons that were not tested for respiratory modulation (25%) (Qin et al. 2002a). Third, noxious pinching of the skin produced a response in 23% of TRINs, which is much lower than 60–74% of T2–T4 spinal neurons within dorsal horn and immediate zone that respond to noxious pinch. In particular, only 4/78 (5%) TRINs were identified as HT neurons in the present study, whereas 75/224 (33%) spinal neurons were HT (Qin et al. 2002a).

The significance of modulation of TRINs by peripheral cutaneous and muscular inputs is unknown. Previous studies show that the respiratory movement pattern or phrenic nerve activity are reflexly changed by cutaneous and muscle afferents, which are processed at the spinal level and do not involve supraspinal sites (Decima and Von Euler 1969; Eldridge et al. 1981; Koizumi et al. 1961; Remmers 1970). TRINs receiving peripheral proprioceptive and noxious somatic inputs could play a role in respiratory proprioreceptive reflexes and spinal processing of noxious information.

Effects of esophageal inputs among thoracic neurons

Spinal dorsal horn and intermediate zone neurons in upper thoracic spinal cord have been electrophysiologically examined for responses to esophageal distension in cats (Garrison et al. 1992) and in rats (Euchner-Wamser et al. 1993; Qin et al. 2000). Euchner-Wamser et al. (1993) reported that 16% of T2–T4 spinal neurons responded to ED. Of responsive neurons, 84% were excited by ED, 12% were inhibited, and 4% exhibited a biphasic (excited/inhibited) response. Preliminary results from our laboratory showed that ED excited 27% and inhibited 2% of spinal neurons within T2–T4 segments of spinal cord in noxious inputs and respiratory drive. Previous studies showed that application of capsaicin or bradykinin to epicardial receptors in the left and right ventricle in cats elicited increases in respiration (Waldrop 1986; Waldrop and Mullins 1987). Also, esophageal distension in dogs reduced inspiratory activation of the diaphragm (Cherniack et al. 1984; DeTroyer and Rousso 1982). In the present study, no significant changes of respiratory pattern were obtained by monitoring phrenic nerve activity during noxious cardiac or esophageal inputs. Besides possible species differences, there are two specific issues related to our protocol. 1) In the present study, ≤4% CO2 was added to inspired air to drive respiration in pentobarbital anesthetized animals. This could stabilize phrenic nerve activity. 2) An intact vagal afferent pathway typically synchronizes central respiratory activity to the ventilator, but we wished to maintain vagal inputs for cardiac and esophageal stimuli.
rats (Qin et al. 2000). In contrast, 41% of TRINs responded to ED, which was considerably higher than the overall proportion of spinal neurons responding to ED. Response patterns of TRINs were similar to previous studies (Euchner-Wamser et al. 1993), i.e., 75% of responsive TRINs were excited and 25% were inhibited by ED. We also found that ED excited and inhibited both inspiratory and expiratory phasic activity of TRINs, and no difference was found between respiratory firing pattern and responses to ED. These results suggested that esophageal afferents are a potentially important input to TRINs and could strongly modulate respiration-related activity of TRINs. It is of interest that some ED-responsive neurons in T2–T4 segments of rats receive convergent inputs from airways and respond to various stimuli, such as tracheal distension and hyperinflation as well as smoke and ammonia (Hummel et al. 1997).

FIG. 4. Responses of TRINs to graded ED. A: a TRIN excited by graded ED. B: a TRIN inhibited by graded ED. A, a–c, and B, a–c: expanded recording of phrenic nerve and cell activity. In all examples, traces from top to bottom are integrated phrenic nerve activity (0.04 s/bin), discharges of phrenic nerve, activity of a single thoracic spinal neuron, rate histogram of cell activity (1 s/bin, 0.04 s/bin for panels with expanded recordings).

FIG. 5. Summary for effects of ED on respiration-related activity and phasic discharges levels of TRINs. A: stimulus-response relationship of TRINs excited by graded ED. B: summary for excitatory effects of ED (0.4 ml) on phrenic activity and phasic activity of TRINs (n = 24). C: stimulus-response curve of TRINs inhibited by graded ED. D: summary for inhibitory effects of ED (0.4 ml) on phrenic nerve activity and phasic activity of TRINs (n = 8). Excitation and inhibition of TRINs (imp/s) by ED are presented by a maximal change of cell activity during the stimulus, which is calculated by subtracting the mean of 10 s of control activity from the mean of 10 s of the greatest activity during esophageal distension. B/M, breaths per min. PMA, peak moving average of phrenic activity in arbitrary units. *P < 0.05; **P < 0.01.
Like other viscera, afferent fibers from the esophagus reach the CNS via spinal visceral (sympathetic) afferent fibers to the spinal cord and via vagal parasympathetic afferent fibers to the nucleus of the solitary tract. In rats, the muscular wall of the whole esophagus consists exclusively of striated muscle fiber, which is different from cats, dogs, and humans (Collman et al. 1992; Khurana and Petras 1991; Neuhuber and Clerc 1990). Spinal visceral afferents from the esophagus are in dorsal root ganglia distributed through the cervical and thoracic spinal cord in rats (Dutsch et al. 1998; Uddman et al. 1995). With respect to parasympathetic innervation, the cervical and upper thoracic portions of the esophagus are innervated predominantly by afferent fibers in the recurrent laryngeal nerves. The lower thoracic and abdominal portions of the esophagus are innervated by vagal afferent fibers originating in the myenteric plexus (Fryscak et al. 1984; Mei 1983; Neuhuber 1987). Because spinal transection at lower cervical segments does not abolish the excitatory responses of T3–T4 spinal neurons to thoracic ED (Qin et al. 2000), it is reasonable to suppose that excitatory effects of ED on TRINs resulted from activation of somatic and visceral stimuli (Ammons et al. 1983; Hobbs et al. 1989; Thies and Foreman 1983), the inhibitory effects of ED on TRINs observed in the present study might be mediated by spinal visceral (sympathetic) afferent fibers to the thoracic spinal cord. Because activation of cervical and thoracic vagal afferents reduces responses of thoracic spinohyaltral tract and spinal neurons to noxious somatic and visceral stimuli (Ammons et al. 1983; Hobbs et al. 1989; Thies and Foreman 1983), the inhibitory effects of ED on TRINs observed in the present study might be mediated by vagal-brain stem-spinal pathways. However, spinal visceral afferent pathways cannot be excluded as a cause of inhibitory effects of esophageal distension on TRINs.

### TABLE 3. Responses of TRINs to intrapericardial bradykinin

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<tr>
<td>Inhibition</td>
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<td>3.6 ± 1.8</td>
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Values are means ± SE.

During embryonic development, the esophagus and the lower airways (trachea, bronchi, and lungs) are derived from the same segment of foregut and share a similar nervous innervation and control (Mansfield 2001). Therefore these organs must coordinate their functions through a complex series of reflex and voluntary control. A number of investigations show that esophageal distension reflexively alters the pattern of ventilation and the distribution of motor activity to the respiratory muscles in humans and animals (Cherniack et al. 1984; Monges et al. 1978; Oliven et al. 1989; Pickering et al. 2002). For example, activation of mechanoreceptors in the esophagus reflexively inhibits the muscles surrounding the abdominal cavity and augments the parasternal and expiratory muscles of the chest wall (Oliven et al. 1989). Physiologically, this reflex reduces the thoracoabdominal pressure gradient during both inspiration and expiration and could facilitate the movement of esophageal contents into the stomach. This also may contribute to maintenance of tidal volume and ventilation while eating.

Interaction of esophageal afferents and respiratory motor activity also has been suggested as a pathophysiological mechanism of asthma secondary to gastroesophageal reflux (Harding 2001; Mansfield and Stein 1978). The modulation of thoracic respiratory interneurons by esophageal afferents observed in the present study might provide a spinal mechanism contributing to the physiological and pathophysiological situations mentioned in the preceding text.

### Effects of cardiac inputs among thoracic neurons

Several groups of projecting and nonprojecting neurons in upper thoracic segments of the spinal cord have been examined electrophysiologically for responses to chemical, electrical or mechanical activation of cardiac afferents in monkeys, cats, and rats (Foreman 1999). In rats, activation of cardiac afferent fibers with noxious intrapericardial chemicals changed background activity in 42% of T2–T4 spinal neurons (Euchner-...
Wamser et al. 1994; Qin et al. 2002a). Of responsive spinal neurons, 85% of neurons were excited, 11% were inhibited, and 4% had excitatory-inhibitory responses. In the present study, intrapericardial bradykinin changed the respiration-related activity in 48% of TRINs. Activity increased in 84% of responsive TRINs and decreased in 16% of TRINs during noxious cardiac stimulation. Furthermore, intrapericardial bradykinin changed both inspiratory and expiratory phasic activity in 48% of TRINs. Activity increased in 84% of TRINs during the preceding text.

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REFERENCES


FIG. 7. Inhibitory responses of TRINs to IB. A: effect of intrapericardial saline on activity of a TRIN. B: IB decreased activity of this TRIN. B, a–c, shows expanded recording of phrenic nerve and cell activity. C and D: summary for effects of intrapericardial saline or bradykinin on phrenic nerve activity and phasic activity of TRINs (n = 5).