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Neuromodulation of thoracic intraspinal visceroreceptive transmission by electrical stimulation of spinal dorsal column and somatic afferents in rats

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Abstract

Clinical studies have shown that neuromodulation therapies, such as spinal cord stimulation (SCS) and transcutaneous electrical nerve stimulation (TENS), reduce symptoms of chronic neuropathic and visceral pain. The neural mechanisms underlying SCS and TENS therapy are poorly understood. The present study was designed to compare the effects of SCS and TENS on spinal neuronal responses to noxious stimuli applied to the heart and esophagus. Direct stimulation of an intercostal nerve (ICNS) was used to simulate the effects of TENS. Extracellular potentials of left thoracic (T3) spinal neurons were recorded in pentobarbital anesthetized, paralyzed and ventilated male rats. SCS (50 Hz, 0.2 ms, 3–5 min) at a clinical relevant intensity (90% of motor threshold) was applied on the C1–C2 or C8–T1 ipsilateral spinal segments. Intercostal nerve stimulation (ICNS) at T3 spinal level was performed using the same parameters as SCS. Intrapericardial injection of bradykinin (IB, 10 µg/ml, 0.2 ml, 1 min) was employed as the noxious cardiac stimulus. Noxious thoracic esophageal distension (ED, 0.4 ml, 20 s) was produced by water inflation of a latex balloon. C1–C2 SCS suppressed excitatory responses of 16/22 T3 spinal neurons to IB and 25/30 neurons to ED. C8–T1 SCS suppressed excitatory responses of 10/15 spinal neurons to IB and 17/23 neurons to ED. ICNS suppressed excitatory responses of 9/12 spinal neurons to IB and 17/22 neurons to ED. These data showed that SCS and ICNS modulated excitatory responses of T3 spinal neurons to noxious stimulation of the heart and esophagus.

Perspective: Neuromodulation of noxious cardiac and esophageal inputs onto thoracic spinal neurons by spinal cord and intercostal nerves stimulation observed in the present study may help account for therapeutic effects on thoracic visceral pain by activating the spinal dorsal column or somatic afferents.

Keywords

Visceral pain; angina pectoris; esophageal pain; spinal cord stimulation; spinal neuron

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Introduction

Spinal cord stimulation (SCS) has been widely used to treat certain chronic pains, such as neuropathic pain and angina pectoris.^{4, 5, 28, 29} Based on the gate control theory,³¹ it is believed that electrical stimulation of large diameter afferent fibers in the dorsal column can inhibit intrasegmental transmission of nociceptive information, although activation of supraspinal circuits may also be involved.^{10, 28, 29, 44, 47} SCS can suppresses excitatory responses of spinothalamic tract neurons (STT) and spinal neurons to noxious somatic stimuli in monkeys¹² and cats,²⁷ and SCS also inhibits hyperexcitability or long-term potentiation of dorsal horn neurons responding to stimulation of noxious somatic afferents in rats.^{50, 52} These studies describe effects of SCS on spinal neuronal activity associated with noxious somatic afferent inputs. Clinical reports also indicate the efficacy of SCS applied to the upper thoracic dorsal columns in relieving visceral pain, such as cardiac pain in patients with severe angina pectoris.^{4, 5, 9} An interesting observation is that SCS of the upper cervical dorsal columns also relieves the symptoms of myocardial ischemia.¹⁷ Recent clinical case observations have reported efficacy of SCS in other visceral diseases, such as persistent esophageal pain²² and refractory abdominal pain due to various pathological conditions.^{23, 24, 26, 49} With respect to spinal mechanisms, Chandler et al.⁶ reported that SCS suppresses excitatory responses of thoracic STT neurons to electrical stimulation of cardiopulmonary sympathetic afferents and to intracardiac injection of bradykinin in primates. SCS at upper cervical and lumbar segments also suppress responses of lumbosacral spinal neurons to noxious colonic distension and attenuate a nociceptive visceromotor reflex produced by colorectal distension in rats with or without colonic hypersensitivity.^{18, 19, 43}

Various manipulations that activate peripheral somatic afferents, e.g. transcutaneous electrical nerve stimulation (TENS), manual acupuncture or electroacupuncture, direct or percutaneous peripheral nerve stimulation, and massage therapy, have been commonly used for treatment and relief of some visceral pains. Acupuncture and TENS have beneficial effects for patients with cardiac arrhythmias, angina pectoris, syndrome X, myocardial infarction and hypertension,^{2, 3, 8, 30, 32, 45, 48} and for painful esophageal peristalsis and gastroesophageal reflux diseases.^{3, 20, 53} Percutaneous or subcutaneous peripheral nerve stimulation can successfully treat chronic abdominal pain and intractable pain syndromes.^{37, 51} A common physiological feature of these therapies is activation of somatic myelinated and even non-myelinated afferent fibers, which then modulate noxious visceral transmission and processing at almost all levels of the central nervous system.^{21, 51} In the spinal cord, analgesic effects of somatic afferents on noxious visceral afferent information may involve activation of a segmental dorsal horn pain-modulating system according to the gate-control theory. It has been shown that manual or electrical acupuncture suppresses nociceptive responses of spinal dorsal horn neurons to activation of afferent C-fibers in cats³⁸ and nociceptive spinal cell responses to colorectal over-distension in rats.⁴⁶ TENS decreases spontaneous activity and responses to noxious somatic stimuli in spinal dorsal horn neurons,^{16, 16} and to noxious renal stimulation in cats.³⁷ Studies also show that noxious conditioning pinch or hot water applied to skin at distant areas significantly reduces nociceptive responses of spinal neurons during noxious colorectal distension or occlusion of the ureter and renal artery.^{35, 36, 46} The purpose of the present study was to compare effects of SCS at C8-T1 or C1-C2 spinal segments and peripheral somatic nerve stimulation on excitatory responses of T3 spinal neurons to nociceptive cardiac and esophageal stimuli. A preliminary report has been published as an abstract.⁴²

Methods

Experiments were performed on 26 male Sprague-Dawley rats weighing 320–460 g (Charles River, Boston, MA). The Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center approved the protocols performed in this study. Rats were

initially anesthetized with a bolus injection of sodium pentobarbital (60 mg/kg, i.p.) and maintained by supplementary infusion (15–25 mg/kg/hr, i.v.). The right carotid artery and left jugular vein were cannulated to monitor arterial blood pressure and inject saline and drugs, respectively. Rats were initially paralyzed with pancuronium bromide (0.4 mg/kg i.p.) and given supplemental doses (0.2 mg/kg i.p.) hourly to maintain muscle relaxation throughout the experiments. The trachea was cannulated to administer artificial ventilation with a consistent-volume pump (55–60 strokes/min, 3–5 ml stroke volume). The mean arterial blood pressure was maintained between 80–100 mmHg by adjusting the level of anesthesia and administering supplementary physiological saline with a perfusion pump. Rectal temperature was kept between 37–38°C by using a servo-controlled heating blanket and overhead infrared lamps.

Laminectomies were performed to expose the T₃ spinal segment for recording neurons and to expose C1–C2 and C8–T1 segments for electrical spinal cord stimulation (SCS). Rats were mounted in a stereotaxic headholder and stabilized with vertebral clamps. After the dura mater was carefully cut, the T₃ spinal cord was covered with warm agar (3–4% in saline) to stabilize neuronal recordings. Carbon-filament glass microelectrodes were used for recording extracellular potentials of single T₃ spinal neurons at 0.5–2.0 mm lateral to midline of the left spinal cord. Extracellular potentials were fed into a window discriminator, displayed on an oscilloscope, and stored in a computer with Spike 3 data acquisition system (CED, Cambridge) for off-line analysis. Neuronal activity during various manipulations was measured using rate histograms (1 s per bin). Only spinal neurons with excitatory responses to visceral stimuli were selected for this study. Spontaneous activity (imp/s) of spinal neurons was determined by averaging 10 s of background activity. The response of a spinal neuron to a visceral stimulus was calculated as total counts of a change in neuronal activity from the onset of increased activity until the evoked activity returned to control. A maximal increase in baseline neuronal activity >20% during a stimulus was considered an excitatory response. For neurons with a firing rate less than 5 Hz, activity needed to increase by 1 Hz to be counted. Data are presented as means ± S.E. Statistical comparisons were made using Student's paired or unpaired t-test and Chi-square test. Statistical significance was established as $P < 0.05$.

The technique for SCS in rats was performed as described in previous studies from this laboratory.^{41, 43} Briefly, a spring-loaded unipolar silver ball electrode 0.5–1.0 mm in diameter was placed on the dorsal column at C1–C2 and C8–T1 spinal segments (0.5 mm rostral to the C2 or T1 dorsal root entry zones). A reference plate electrode was inserted into the cervical or thoracic paraspinal muscles. To simulate TENS, somatic afferents were stimulated directly. A dorsal approach was used to expose the left T₃ intercostal nerve. A bipolar platinum hook electrode was placed around the intercostal nerve, which was crushed peripherally. Stimulus parameters for SCS and ICNS were 50 Hz, 0.2 ms duration, and the stimulus intensity was 90% of motor threshold; these stimulus parameters are clinically relevant.^{28, 29} Motor threshold was determined by slowly increasing electrical stimulus current from zero until a weak spasm of the paraspinal muscle was observed. Average motor thresholds of C1–C2 SCS, C8–T1 SCS and ICNS were 0.34 ± 0.5 mA, 0.47 ± 0.8 mA and 0.41 ± 0.8 mA, respectively. Stimuli were applied for 3–5 min to allow for examination of the effects of SCS and ICNS on excitatory responses of spinal neurons to visceral afferent inputs.

Visceral stimuli were produced using intrapericardial bradykinin (IB) and esophageal distension (ED). For IB, the thoracic thymus gland was exposed and opened on the midline and a small hole was made in the pericardial sac. A silicone tubing (0.020 ID, 0.037 OD, 14–16 cm in length) with 5–8 small holes at the distal ending was inserted into the pericardial sac over the left ventricle.⁴¹ The catheter was fixed in place by suturing together the thymus lobes and the layers of the chest wall. Bradykinin (10 µg/ml, 0.2 ml) was injected into the pericardial sac using a 1 ml syringe. After one min, bradykinin was removed and 2–3 saline flushes (0.2 ml each) of the intrapericardial sac followed. To distend the thoracic esophagus, a tubing

(PE-240) with a small latex balloon (1.0 cm in length) at the end was inserted perorally 9–10 cm from the front incisors.⁴¹ Esophageal distension was produced by manually injecting warm water (0.2, 0.4 ml, 20s) at the rate of 0.1–0.2 ml/s. The search volume used to examine responses of spinal neurons to ED was 0.3–0.4 ml, because this volume of ED is considered a noxious esophageal stimulus.^{11, 41}

Results

Effects of C1–C2 SCS

SCS applied to the dorsal surface of C1–C2 segments suppressed excitatory responses of 16/22 (73%) upper thoracic (T3) spinal neurons to IB; SCS enhanced IB-evoked activity of 3 neurons and had no effect on 3 neurons. An example of the reduction of IB-evoked spinal neuronal activity during C1–C2 SCS is shown in Fig. 1A. For all 22 neurons tested for the effects of C1–C2 SCS, mean excitatory responses to IB (1388.0 ± 297.6 imp) was significantly reduced to 584.4 ± 158.5 imp during C1–C2 SCS ($P < 0.01$, Fig. 2A). At 17.7 ± 1.1 min (range 15.0–25.7 min) after the end of C1–C2 SCS, mean excitatory responses to IB recovered to 1362.8 ± 335.0 imp. Mean spontaneous activity of these neurons before (11.1 ± 1.6 imp/s), during (9.4 ± 1.8 imp/s) and after (7.0 ± 1.7 imp/s) C1–C2 SCS was not significantly different.

Excitatory responses of 25/30 (83%) spinal neurons to noxious ED (0.4 ml, 20s) were suppressed by C1–C2 SCS; responses were augmented in 2 neurons, and 3 neurons were not affected. Fig. 3A shows an example of suppression of an excitatory response to ED by C1–C2 SCS. For all 30 neurons tested for effects of C1–C2 SCS, mean responses to ED significantly decreased from 390.1 ± 35.2 imp to 170.2 ± 40.8 imp after the end of C1–C2 SCS ($P < 0.01$). At 7.2 ± 0.6 min (range 4.7–14.7 min) after offset of C1–C2 SCS, mean excitatory responses to ED recovered to 356.7 ± 41.6 imp (Fig. 2B). There were no significant differences in mean spontaneous activity of tested neurons before (9.7 ± 1.5 imp/s), during (7.5 ± 1.3) and after (8.4 ± 1.6 imp/s) C1–C2 SCS.

Effects of C8–T1 SCS

Of 15 T3 spinal neurons tested for effects of C8–T1 SCS, excitatory responses to IB were reduced in 10 (67%) neurons; responses of 2 neurons were enhanced and 3 neurons were unaffected. Fig. 1B shows an example of an excitatory response of a spinal neuron to IB that was inhibited by C8–T1 SCS. Mean excitatory responses to IB for all 15 neurons were reduced by SCS from 1129.6 ± 302.1 imp to 542.7 ± 252.4 imp ($P < 0.05$, Fig. 2A). At 16.9 ± 2.1 min (range 14.5–23.7 min) after the end of C8–T1 SCS, excitatory responses recovered to 1437.1 ± 418.1 imp. Mean spontaneous activity of the neurons before (10.0 ± 2.2 imp/s), during (10.2 ± 1.8 imp/s) and after (7.6 ± 1.8 imp/s) C8–T1 SCS was not significantly different.

Of 23 spinal neurons responding to noxious ED (0.4 ml, 20 s) examined for effects of C8–T1 SCS, excitatory responses of 17 (74%) neurons were decreased; ED-evoked activity of 3 neurons was increased, and 3 neurons were unaffected. An example of the suppression of ED-evoked activity by C8–T1 SCS is shown in Fig. 3B. For all 23 of these neurons, C8–T1 SCS suppressed mean excitatory responses to ED from 395.4 ± 50.1 imp to 173.9 ± 48.0 imp ($n=23$, $P < 0.01$). At 7.9 ± 1.2 min (range 3.3–17.7 min) after the end of C8–T1 SCS, average excitatory responses recovered to 379.4 ± 53.5 imp (Fig. 2B). Mean spontaneous activity before (8.5 ± 1.5 imp/s), during (9.5 ± 1.6 imp/s) and after (7.8 ± 1.6 imp/s) C8–T1 SCS was not significantly altered.

Effects of ICNS

A total of 12 neurons with excitatory responses to IB were examined for effects of intercostal nerve stimulation (ICNS). Of these neurons, ICNS suppressed responses of 9/12 (75%) neurons

to IB, enhanced the response in one neuron, and had no effect on 2 neurons. Fig. 1C shows an example of an excitatory response to IB that was inhibited by ICNS. Mean excitatory responses to IB during ICNS were significantly less than those before ICNS (1641.5 ± 561.6 vs 665.8 ± 227.2 , $P < 0.05$, $n = 12$). Excitatory responses to IB of these neurons recovered at 19.4 ± 1.9 min (range 11.2–23.7 min) after the end of ICNS to 1787.9 ± 522.4 imp. A summary for effects of ICNS on spinal neuronal responses to IB are shown in Fig. 2A. Mean spontaneous activity of the examined neurons before (11.1 ± 2.5 imp/s), during (11.4 ± 2.3 imp/s) and after (8.2 ± 2.0 imp/s) ICNS was not significantly different.

Effects of ICNS on excitatory responses to ED were tested in 22 neurons. Of these neurons, ICNS decreased ED-induced activity of 17 neurons, increased activity of 3 neurons and did not affect 2 neurons. Fig. 3C shows the suppression of an excitatory response to ED by ICNS. For all neurons examined for effects of ICNS, mean excitatory responses to ED were significantly less during ICNS than those before ICNS (435.4 ± 62.2 imp vs 176.6 ± 41.8 imp, $n = 22$, $P < 0.01$). At 6.0 ± 0.9 min (range 3.2–13.0 min) after the end of ICNS, mean excitatory responses to ED were 395.7 ± 48.4 imp. A summary for effects of ICNS is shown in Fig. 2B. No significant differences in mean spontaneous activity of the tested neurons before (8.6 ± 1.8 imp/s), during (9.4 ± 1.6) and after (7.6 ± 1.8 imp/s) ICNS were found.

Discussion

Effects of C1-C2 SCS

The upper cervical spinal cord (C1–C2) was selected as a site to perform SCS because a clinical study has indicated that SCS on upper cervical spinal segments reduces pain symptoms and significantly increases the quality of life of patients with unstable angina.¹⁷ Results of the present study in rats indicated that C1–C2 SCS suppressed excitatory responses of 73% and 83% upper thoracic spinal neurons to IB and ED, respectively. These results clearly demonstrate that SCS in these distant segments can modulate the processing of noxious cardiac information in T3–T4 spinal neurons. Information from the upper cervical segments to the thoracic segments could be transmitted in the dorsal columns, propriospinal pathways, and/or spinosupraspinal loops. The dorsal column pathway is likely candidate because transection of the dorsal column at the C7–C8, but not transection of the spinal cord at the spinomedullary junction, significantly reduces the ability of C1–C2 SCS to suppress neuronal activity in lumbosacral spinal neurons to noxious colorectal distension.⁴³ The most likely mechanism is SCS activation of action potentials in large primary afferent fibers that are transmitted antidromically to the collaterals in the gray matter of the T3–T4 segments.^{28, 29} The collaterals then release transmitters that directly and/or indirectly suppress the activity of spinal neurons receiving cardiac and esophageal nociceptive input. It should also be noted that the C1–C2 segments are also considered a source of important propriospinal regulation of visceral sensory processing in more caudal spinal segments.^{7, 13, 34, 39, 40, 41, 43} However, this pathway does not appear to play a key role because transection of the C7–C8 dorsal columns, but not application of ibotenic acid to the C1–C2 segments markedly attenuated the effects of SCS on lumbosacral spinal neurons.⁴³ Thus, it is suggested that the stimulation of the dorsal columns rather than spinal neurons at C1–C2 segments modulated the activity of T3 spinal neurons receiving cardiac and esophageal inputs.

Effects of C8-T1 SCS

In patients, low intensity SCS often is performed at or near spinal segments that receive afferent inputs from the origin of somatic or visceral pain.^{4, 5} To mimic the clinical SCS setting in this study, C8-T1 segments were selected for SCS because cardiac and esophageal inputs enter the spinal cord at T3–T4 segments in rats.⁴¹ Results showed that C8-T1 SCS suppressed excitatory responses of 67% and 74% of spinal neurons to IB and ED, respectively. These data

are similar to a previous observation in lumbosacral spinal cord in rats, in which L2–L3 SCS inhibits 67% L6–S2 spinal neurons responding to noxious colorectal distension.⁴³ However, C3–C5 SCS reduces excitatory responses of 86% of upper thoracic STT neurons to intracardiac injection of bradykinin and of all STT neurons excited by electrical stimulation of cardiopulmonary sympathetic afferent fibers in monkeys.⁶ The different species, neuronal classifications and visceral stimuli tested might contribute to the differences in these investigations. In particular, it should be noted that SCS with relatively long duration (3–5 min) and low intensity (90% MT) was performed in the present study and produced post-stimulus effects of SCS on spinal neuronal responses to IB (14.5–23.7 min) and ED (3.3–17.7 min). The SCS parameters applied in the present study have been used in patients^{5, 28, 29} and also in other animal studies with longer periods to induce inhibition of intraspinal nociceptive transmission for thermal and mechanical stimulation of somatic fields or electrical stimulation of somatic nerve fibers,^{27, 44, 50, 52} as well as visceral input from colon.⁴³ In contrast, single or short trains of pulses used in previous studies usually results in short-lasting inhibition of nociceptive responses in STT neurons.^{6, 12} Furthermore, in the present study, mean spontaneous activity for the entire group of tested neurons was not different before and after C8–T1 SCS. The present results are generally similar to previous reports of the effects of SCS on thoracic STT and spinal neurons with cardiac input in monkeys as well as on lumbosacral neurons with somatic and colorectal inputs in rats.^{6, 43, 50, 52}

Comparison of effects of C1–C2 and C8–T1 SCS

In the present study, C1–C2 or C8–T1 SCS suppressed excitatory responses of 73% and 67% of T3 spinal neurons to IB, respectively. Similar populations of spinal neurons with noxious esophageal inputs also were suppressed by C1–C2 or C8–T1 SCS (83% and 74%). For all of tested neurons, C1–C2 SCS reduced neuronal responses to IB and ED to approximately 42% and 44% of control, and C8–T1 SCS reduced these responses to approximately 48% and 44% of control, respectively. The delayed recovery time of C1–C2 SCS (17.7 ± 1.1 min) on neuronal responses to IB was similar to that of C8–T1 SCS (16.9 ± 2.1 min). The delayed recovery times of SCS at different sites on ED-responses were also similar (7.2 ± 0.6 min vs 6.0 ± 0.9 min). These differences were most likely due to the different types of stimuli, i.e. chemical or mechanical and the length of time that the stimulus was applied to the organs. The chemical stimulus was applied for a longer period of time (1 min) than the mechanical stimulus (20 s). In previous studies, there was a relationship between stimulus period and the length of the post-stimulus recovery time.^{1, 14} For example SCS of the T1 dorsal column for four minutes suppressed the activity of the intrinsic cardiac nervous system for approximately one minute;¹⁴ stimulation for 15 minutes suppressed the activity for approximately 35 minutes.¹ To the best of our knowledge no studies have been addressed to determine the mechanisms, neurotransmitters and neuromodulators underlying the long recovery time following termination of SCS effects on visceral spinal inputs.

Besides effects on pain SCS is known to produce vasodilation in certain vascular beds.²⁹ For ischemic tissue, vasodilation is probably responsible for at least some of the effects of SCS on pain through reduction of nociceptive input to spinal cord.³³ Furthermore, the antinociceptive effect of SCS on ischemic heart tissue does not include an increase in blood flow.²⁵ In the present study, tissues were not ischemic and vasodilation that would have been unlikely to account for the reduced nociceptive effects on spinal neurons. Nevertheless, blood flow was not measured for heart or esophagus in the present study so a component of antinociception due to vasodilation cannot be entirely dismissed.

Effects of ICNS

Since clinically there is often secondary hyperalgesia in the dermatomes supplied by the same spinal segments that receive inputs from the involved viscera, therapeutic stimulation of

somatic afferents using TENS and acupuncture, are commonly performed in corresponding dermatomal areas. Thus, the T3 intercostal nerve was selected on the basis that several therapies such as TENS, acupuncture, and massage stimulate peripheral afferents from corresponding dermatomes. In addition this nerve was also selected for electrical stimulation because this spinal segment also receives visceral inputs from the heart and esophagus in rats.⁴¹ The stimulus parameters (90% of MT, 50 Hz, 0.2 ms) were selected for C1–C2 and T1–T2 SCS because the large myelinated primary afferent fibers (A-beta) were mainly activated without producing muscle contractions in animals and paresthesias in patients.^{9, 28, 43} Since the selection of same parameters for SCS or ICNS, the results of all three stimulation sites were comparable.

With this SCS parameter, the present results showed that effects of T3 ICNS suppressed excitatory responses to noxious cardiac and esophageal stimuli in 75% and 77% thoracic spinal neurons, respectively. Nociceptive responses of spinal neurons to IB or ED were reduced to 40.5 % and 40.4 % after ICNS, respectively. Inhibitory effects of ICNS on excitatory neuronal responses to IB and ED lasted 11.2–23.7 min and 3.2–13.0 min after ICNS, respectively. These results are similar to the previous observations on the interaction of somatic and visceral afferent inputs in spinal dorsal horn neurons. During TENS in cats, spinal cell responses evoked by acute occlusion of the ureter or renal artery were reduced to 37.5% and 46.3% of the control value, respectively.³⁵ This analgesic effect lasted 10 min after TENS. In rats, manual acupuncture at hindlimb acupoint St-36 (Zusanli, located below the capitulum fibulae and lateral to the tibia) produces a maximal inhibition (68.6%) of nociceptive responses in spinal dorsal horn neuron with noxious mechanical colorectal input.⁴⁶ Furthermore, in comparison to inhibitory effects of SCS at either C1–C2 or C8–T1, ICNS on neuronal nociceptive responses to IB or ED was not significantly different. Similarity between actions of ICNS and SCS on thoracic spinal neurons excited by noxious visceral inputs might suggest that the mechanism underlying low-intensity ICNS neuromodulation on activity of spinal neurons was mainly to activate large somatic afferent fibers. According to the gate control theory, innocuous impulses transmitted to spinal dorsal horn would block noxious visceral inputs that travel in smaller afferent fibers.³¹ However, descending modulatory activity originating from supraspinal sites also might be involved in neuromodulation by stimulation of somatic afferents during procedures such as TENS, acupuncture and percutaneous or subcutaneous peripheral nerve direct or field stimulation.^{4, 21, 37, 46, 51}

Summary

The main finding of this study was that SCS at either near or distant spinal segments as well as activation of somatic afferents (ICNS) applied at clinically relevant stimulus parameters had equal inhibitory effects on spinal neurons receiving noxious visceral inputs from the heart and esophagus in rats. These results are consistent with stimulation-induced suppression of noxious somatic inputs to the spinal cord, which has been observed in previous animal studies.^{12, 27, 47, 50, 52} Therefore, the results of the present study provide evidence for a neural mechanism supporting the therapeutic use of spinal dorsal column stimulation or peripheral somatic nerve stimulation for the management of patients with angina pectoris and esophageal hypersensitivity or pain.

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Fig. 1.

Inhibitory effects of spinal cord stimulation (SCS) and intercostal nerve stimulation (ICNS) on excitatory responses of upper thoracic (T3) spinal neurons to intrapericardial bradykinin (IB, 10 μ g/ml, 0.2 ml). *A*: excitatory response of a spinal neuron to IB that was suppressed by C1-C2 SCS. *B*: excitatory response of a spinal neuron to IB that was suppressed by C8-T1 SCS. *C*: excitatory response of a spinal neuron to IB that was suppressed by ICNS. Left panels are control responses; middle panels are responses during SCS; and right panels are responses recovery.

Fig. 2.

A summary for effects of SCS and ICNS on excitatory responses of upper thoracic (T3) spinal neurons to noxious cardiac and esophageal stimuli. *A*: effects on responses to intrapericardial bradykinin (IB). * $P < 0.05$, ** $P < 0.01$ compared to corresponding neuronal responses to IB before and after SCS or ICNS. *B*: effects on responses to noxious esophageal distension (ED). * $P < 0.01$ compared to corresponding neuronal responses to ED before and after SCS or ICNS.

Fig. 3. Inhibitory effects of spinal cord stimulation (SCS) and intercostal nerve stimulation (ICNS) on excitatory responses of upper thoracic (T3) spinal neurons to noxious esophageal distension (ED, 0.4 ml, 20 s). *A*: excitatory response of a spinal neuron to ED that was suppressed by C1–C2 SCS. *B*: excitatory response of a neuron to ED that was suppressed by C8–T1 SCS. *C*: excitatory response of a neuron to ED that was suppressed by ICNS. Panels are arranged as in Fig. 1.