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Modulation of neuronal activity in dorsal column nuclei by upper cervical spinal cord stimulation in rats

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Abstract

Clinical human and animal studies show that upper cervical spinal cord stimulation (cSCS) has beneficial effects in treatment of some cerebral disorders, including those due to deficient cerebral circulation. However, the underlying mechanisms and neural pathways activated by cSCS using clinical parameters remain unclear. We have shown that a cSCS-induced increase in cerebral blood flow is mediated via rostral spinal dorsal column fibers implying that the dorsal column nuclei (DCNs) are involved. The aim of this study was to examine how cSCS modulated neuronal activity of DCNs. A spring-loaded unipolar ball electrode was placed on the left dorsal column at cervical (C2) spinal cord in pentobarbital anesthetized, ventilated and paralyzed male rats. Stimulation with frequencies of 1, 10, 20, 50 Hz (0.2 ms, 10 s) and an intensity of 90% of motor threshold was applied. Extracellular potentials of single neurons in DCNs were recorded and examined for effects of cSCS. In total, 109 neurons in DCNs were isolated and tested for effects of cSCS. Out of these, 56 neurons were recorded from the cuneate nucleus and 53 from the gracile nucleus. Mechanical somatic stimuli altered activity of 87/109 (83.2%) examined neurons. Of the neurons receiving somatic input, 62 were classified as low-threshold and 25 as wide dynamic range. The cSCS at 1 Hz changed the activity of 96/109 (88.1%) of the neurons. Neuronal responses to cSCS exhibited multiple patterns of excitation and/or inhibition: excitation (E, n=21), inhibition (I, n=19), E-I (n=37), I-E (n=8) and E-I-E (n=11). Furthermore, cSCS with high-frequency (50 Hz) altered the activity of 92.7% (51/55) of tested neurons, including 30 E, 24 I, and 2 I-E responses to cSCS. These data suggested that cSCS significantly modulates neuronal activity in dorsal column nuclei. These nuclei might serve as a neural relay for cSCS-induced effects on cerebral dysfunction and diseases.

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Keywords

Neuromodulation; sensory neurons; electrical stimulation; primary afferent fibers

INTRODUCTION

Spinal cord stimulation (SCS), as a therapeutic method, has been applied for a variety of clinical indications, including refractory neuropathic pain, angina pectoris, peripheral vascular ischemic disease, phantom limb pain, multiple sclerosis, and complex regional pain syndromes (Linderth and Meyerson 2009; Linderth and Foreman 1999; Cameron, 2004; Wu et al. 2008). In order to obtain successful clinical treatments, the active electrodes of SCS should be placed at spinal levels where SCS-induced paresthesias cover the pain area corresponding to the segmental innervation of dermatomes. For example, SCS is applied on cervical segments for ischemic pain in the hand, on upper thoracic levels for treatment of angina pectoris; and on low thoracic or upper lumbar levels for treatment of vascular ischemic pain in the foot. In addition to these spinal segmental and caudal effects of SCS, the rostral or cerebral beneficial effects of SCS and underlying mechanisms have also been investigated. A number of clinical and basic studies have indicated that cervical spinal cord stimulation (cSCS) decreases cerebral vascular resistance and increases blood flow velocity, leading to an enhancement of the local-regional delivery of oxygen (Hosobuchi 1985; Visocchi 2006; 2008). Robaina and Clavo 2007a; Wu et al. 2008). Therefore, cSCS has been used for treatment of various cerebral disorders, including cerebral ischemia and stroke (Robaina and Clavo 2007a), postapoplectic spastic hemiplegia (Nakamura and Tsubokawa, 1985), prolonged coma (Fujii et al., 1998), brain tumors (Robaina and Clavo 2007b), persistent vegetative state (Morita et al. 2007), migraine and post-traumatic headache (Dario et al., 2005). Recently, since SCS has been shown to restore locomotion in an animal model of Parkinson's disease, SCS is suggested as a potential treatment for Parkinsonian rigidity (Fuentes et al. 2009). Possible central and peripheral mechanisms of SCS-induced increases in cerebral blood flow have been explored in humans as well as dogs, cats and rats models (Robaina and Clavo 2007a; Wu et al. 2008). A recent study from our laboratory shows that a cSCS-induced increase in cerebral blood flow is mediated via rostral spinal dorsal column fibers implying that the dorsal column nuclei are involved, but does not depend upon activation of upper cervical spinal neurons or of the anterolateral column (Yang et al., 2008). Furthermore, it was presumed that the dorsal column nuclei, rostral ventrolateral medulla, sphenopalatine ganglion, and cortical vascular beds could be potential pathways for cerebral vasodilation by cSCS (Yang et al. 2008).

The dorsal column nuclei (DCN), an early relay station of sensory processing in the somatosensory pathways, receive inputs from somatotopically arranged primary afferent fibers from the trunk and limbs and gives rise to the medial lemniscus pathway that provides the fastest and most precisely organized somatosensory input to the thalamus. Since SCS is directly applied to the dorsal columns, cerebral effects of cSCS should result from activation of fibers with rostral projections to DCN in medulla. Early studies have shown that stimulation of the dorsal columns evokes field potentials from DCN in monkeys and cats, which is comprised of a short latency negative (N)-wave followed by a positive (P)-wave (Andres-Trelles et al. 1976; Møller et al. 1989). These two waves represent the synchronous depolarization of DCN neurons and the depolarization of primary afferent terminals during presynaptic inhibition, respectively (Andres-Trelles et al. 1976; Newberry and Simmonds 1984a). However, there is insufficient information in the literature about alterations of DCN neuronal activity during SCS. One rat study *in vitro* shows that unitary spike potentials recorded from the gracile nucleus following electrical stimulation of the ipsilateral dorsal column are post-synaptic in origin (Newberry and Simmonds 1984b). Another study in decerebrate-decerebellated cats indicates that single electrical stimuli delivered to the dorsal funiculi activate about 40% of the cuneate

neurons (Saadé and Jabbur 1984). In the present study, SCS with different parameter settings was applied at cervical spinal cord to examine the effect on the neuronal activity in DCN in rats. Since the stimulating electrode for clinical and experimental application of cSCS has been placed at various sites from the C1 to C6 segments, and the optimal placement is on the C1-C3 segments (Dario et al. 2005; Goellner and Slavin 2009; Hosobuchi, 1985; Isono et al., 1995; Sagher et al., 2000; Visocchi 2006; 2008; Yang et al. 2008), the upper cervical (C2) spinal segment was selected as a place to apply cSCS in the present study. Results from this study showed that cSCS significantly altered activity in the DCN neurons. These responses might mediate the effect of SCS on brain functions. A preliminary report of the present study has been published in abstract form (Farber et al. 2008).

EXPERIMENTAL PROCEDURES

All experiments were performed on adult male Sprague-Dawley rats (Charles River Inc., n=19) weighing between 350-480 g. Animals initially were anesthetized with sodium pentobarbital (60 mg/kg ip). Supplemental doses of pentobarbital were given through infusion of the left jugular vein (15-25 mg/kg/h) during the experiment. After tracheal cannulation, a constant volume pump was used to provide artificial ventilation (55-60 strokes/min, 3.0-5.0 ml stroke volume). Paralysis of animals was established intravenously with pancuronium bromide (0.2 mg/kg/h). The right carotid artery was cannulated to monitor blood pressure that was kept in a range of 80-120 mmHg during the experiments. Body temperature was kept at $37\pm0.3^{\circ}\text{C}$ using a thermostatically controlled heating blanket and overhead infrared lamps. The experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

Laminectomies were performed to expose C1-C2 spinal segments for the placement of SCS. The occipital bone of the skull was also removed to expose the caudal medulla for recording cells from dorsal column nuclei (DCN). Animals were mounted in a stereotaxic headholder and the upper thoracic vertebrae (T1-T2) were stabilized with spinal clamps attached to a metal frame. The head was flexed and fixed at approximately 30° to allow easy access to the DCN. The dura mater of the exposed caudal medulla and C1-C2 spinal segments were carefully removed. The exposed areas were filled with agar (3-4% in saline) to improve recording stability. Carbon-filament glass microelectrodes were used to record extracellular action potentials of single neurons in a region from the midline to 1-3 mm laterally, 0-1 mm rostral and 0-1 mm caudal to obex (Paxinos and Watson 1986); the searching depth was <0.6 mm from the dorsal surface of medulla (Bermejo et al. 2003; Miki et al. 1998). Spike amplitude and shape were continuously monitored on-line with an oscilloscope and an audio display. Signals of neuronal recordings were filtered (0.3-3 kHz) and amplified with an extracellular preamplifier (DAGAN, 2400 A, MN, USA). Raw traces of neuronal activity were stored in a computer with Spike-3 software (Cambridge Electronic Design, Cambridge, UK) for off-line analysis.

A silver spring-loaded unipolar ball electrode (cathode) with a tip diameter of approximately 1 mm was placed on the left dorsal column 0.5 mm rostral to the C2 dorsal root entry zone to perform cSCS (Qin et al. 2007). The motor threshold (MT) stimulus intensity was determined in each animal at 50 Hz, 0.2 ms duration (monophasic rectangular pulses) by slowly increasing the cSCS current from zero until a clear retraction of the left neck muscles was observed (Qin et al. 2007). The level of stimulation at 90% of MT was used for this study because it approximates the highest parameters used in clinical applications of SCS (Linderorth and Foreman 1999). The average motor threshold of cSCS (50 Hz, 0.2 ms) was 0.35 ± 0.8 mA (n=19). Effects of cSCS with different frequencies (1, 10, 20, 50 Hz, 10 s) were determined on activity of the DCN in some neurons.

Somatic receptive fields of DCN neurons were characterized. For innocuous stimulation of cutaneous receptive fields of spinal neurons, a camel-hair brush or light pressure from a blunt probe was used, whereas for noxious stimulation pinching the skin and muscles with blunt forceps was applied. Neurons were classified as follows: wide dynamic range (WDR) neurons responded to innocuous stimulation of skin and had increased responses to noxious pinching of the somatic fields; high-threshold (HT) neurons responded only to noxious pinching of the somatic fields; and low-threshold (LT) neurons responded primarily to innocuous stimuli. Neuronal responses to movement of the joints (forepaw, arm, leg and toes) were also tested in some cases.

Neuronal activity was measured and evaluated on histograms of discharge frequency using the Spike-3 data acquisition software. Peristimulus histograms (50 sweeps, 1 Hz, 2-ms bin) were used to measure the latency and duration of excitatory or inhibitory responses to cSCS. When rate histograms (1-s bin) were used, neuronal responses (impulses/second; imp/s) were defined as increases or decreases of >20% in maximal evoked activity by cSCS (50 Hz) compared to spontaneous activity. Spontaneous activity of neurons was determined by counting activity for 10 s before cSCS to obtain imp/s. Responses were calculated by subtracting the mean of 10 s of spontaneous activity from the mean of 10 s of activity recorded during stimulation. To obtain correct rate histograms, all raw tracings of neuronal responses to cSCS were processed by a Spike-3 digital filter to eliminate cSCS artifacts. Descriptive data are reported as means $\pm$ SE. Statistical comparisons were made using Student's paired *t*-test and Chi-square analysis. Comparisons of data were considered statistically different if $P < 0.05$.

RESULTS

In total, 109 neurons in the DCN were isolated and examined for responses to somatic stimuli as well as to cSCS. Mechanical somatic stimuli altered the activity of 87/109 (83.2%) tested neurons, including 62 LT neurons and 25 WDR neurons; however, no neuron was classified as HT. Of 65 neurons tested, 28 neurons also responded to movement of joints. Somatic receptive fields were located on the ipsilateral forepaw, arms, shoulder, chest, upper and lower back, the groin, hip or thigh and hindpaw. Based on the locations of neurons recorded and/or somatic fields, 56 neurons were obtained from the cuneate nuclei and 53 from the gracile nuclei. Since the major purpose of this study was to determine the effects of cSCS on neuronal activity in DCN, cuneate and gracile neurons were combined in the following results for further analysis.

Application of cSCS (90% MT, 0.2 ms, 1 Hz) changed activity of 96/109 (88.1%) of the DCN neurons. Neuronal responses to cSCS exhibited different patterns: excitation (E, $n=21$), inhibition (I, $n=19$), E-I ($n=37$), I-E ($n=8$) and E-I-E ($n=11$). For E neurons excited by a single cSCS pulse, 1-7 evoked impulses (average values for number of impulses per stimulus was 3.0 ± 0.3 impulses) with a latency 4.0 ± 0.4 ms. to the first bin of evoked impulses. These evoked impulses lasted 18.6 ± 4.4 ms (range 4-90 ms in peristimulus histogram of 50 sweeps). Examples of these neuronal activities are shown in Fig. 1A. For neurons inhibited by cSCS, the I responses to cSCS lasted 137.4 ± 16.3 ms. An example is shown in Fig. 1B. For E-I neurons, 1-6 evoked impulses (average 2.5 ± 0.2 impulses per stimulus) was followed by inhibition of 163.2 ± 12.1 ms. Fig. 1C and C' shows an example of E-I neurons. For I-E neurons, the inhibitory responses to cSCS (39.3 ± 7.3 ms) were followed by excitatory responses that lasted for 58.1 ± 10.8 ms. An example of I-E neurons is shown in Fig. 2A. For E-I-E neurons ($n=11$), the mean latency to first E responses to cSCS was 2.7 ± 0.5 ms (range of 1-3 evoked impulses per stimulus) was followed by 89.1 ± 21.5 ms inhibition, and second E responses to cSCS lasted 106.4 ± 16.4 ms. Fig. 2C and C' shows an example of E-I-E neurons.

Out of 55 neurons responding to cSCS (1 Hz), continuous cSCS with high-frequency (50 Hz, 10 s) altered the activity of 51 (92.7%) tested neurons, including 30 E, 24 I, and 2 I-E responses to cSCS in rate histograms. Examples and response characteristics of E and I neurons are shown in Fig. 3A, B and Table, respectively. A neuron exhibiting inhibitory-excitatory response to 50 Hz cSCS is shown in Fig. 3C. Out of the 30 neurons excited by 50 Hz cSCS, 16 neurons exhibited E responses; 12 neurons exhibited E-I responses and 2 neurons exhibited E-I-E responses to a single cSCS discharge (1 Hz). Of 24 neurons inhibited by 50 Hz cSCS, 8 neurons had E-I response; 7 neurons had I response; 3 neurons exhibited I-E response and 6 neurons had E-I-E response to a single cSCS pulse (1 Hz). Furthermore, for 25 E neurons examined for 1, 10, 20, and 50 Hz cSCS, the mean excitatory responses to cSCS linearly increased as cSCS frequency increased. An example of these neuronal activities and a stimulus-response curve are shown in Fig. 4A and B, respectively. For 15 I neurons examined for 1, 10, 20 and 50 Hz cSCS, inhibitory effects of cSCS with different frequencies also increased linearly by different frequencies of cSCS. An example of these neurons and a stimulus-response curve are shown in Fig. 4C and D, respectively.

DISCUSSION

The DCN are the principle sites of termination of primary afferent fibers from the trunk and limbs and they play a complex role in the processing of somatic tactile and proprioceptive information. In this study, mechanical somatic stimuli altered the activity for a majority of neurons in the DCN in rats. Of the neurons examined, 56.8% of neurons were classified as LT, and 22.9% of neurons were WDR. No receptive fields, including HT receptive fields were detected in the remainder of the neurons. The proportions of various types of neurons in DCN did not differ from a previous study, in which 58.1% of the LT and 22.6% of the WDR neurons were identified in rat gracile nucleus (Miki et al. 1998). In the present study, 1 Hz and 50 Hz cSCS (90% MT, 0.2 ms) changed the activity of 88.1% and 92.7% of the DCN neurons, respectively. Responses of DCN neurons to cSCS exhibited multiple patterns: excitation (E), inhibition (I), E-I, I-E and E-I-E. These results differ from the observation made in cats (Saadé and Jabbur 1984). In their study, electrical stimuli (0.5-1 Hz, 0.05-0.1 ms duration, 0.5-2.5 mA) were delivered to the dorsal funiculi with stainless-steel bipolar electrodes that activated 41.5% (17/41) of the cuneate neurons; no other response patterns were reported. In addition to different species of animal, it should be noted that their study was performed in decerebrate-decerebellated preparation, while the animals were intact in our experiments. Thus, interrupted pathways between the cortex and the DCN might change the response characteristics of neurons in these nuclei. It has long been known that direct and indirect corticofugal projections from the motor and somatosensory cortex to the DCN exist in several species including rats, cats and monkeys. Stimulation of such cortical areas can modulate afferent transmission in the DCN. For example, microstimulation in the forelimb area of the motor cortex changes the activity of 61% of the neurons in rostral, 11% of the neurons in middle and 28% of the neurons in caudal regions of the DCN in rats (Shin and Chapin 1989). Regarding corticofugal effects, cortical microstimulation primarily produced excitatory neuronal responses in the DCN. In cats, motor cortical stimulation suppresses activity of 61% and facilitates 30% cuneate neurons, whereas the same stimulation inhibits 27% and excites 67% gracile neurons (Towe and Jabbur 1961). Based on intracellular recordings from neurons of DCN *in vitro* or *in vivo*, complex synaptic excitatory and inhibitory interactions occur in the same neuron as was activated by stimulation of dorsal column and corticofugal fibers (Nuñez and Buño 2001; Sánchez et al. 2006). Apparently, corticofugal modulation secondarily evoked by cSCS on DCN neurons could not be excluded from forming multiple response patterns to cSCS in the present study with cerebral intact preparation. It could be presumed that neuronal excitation in the DCN induced by cSCS could be relayed to the somatosensory cortex via a relay in the thalamus corticofugal impulses were transmitted in axons projecting down to DCN and modulated neuronal activity in the DCN. For example, the inhibitory component following the excitatory

response to cSCS of E-I neurons could result from descending modulation from cortex secondary that was evoked by cSCS. However, this hypothesis needs to be demonstrated in animals with decerebration.

Another possible mechanism underlying the multiple response patterns of DCN neurons to cSCS may be due to the activation of different types of neurons. It is well known that the DCNs are not homogeneous, but contain several morphological and functional afferent types of neurons that project to different sites in brain, and also include intrinsic neurons such as local interneurons. Most significant projections from DCN neurons go to the contralateral thalamus via the medial lemniscus; other targets are the spinal cord, the cerebellum, and various brainstem nuclei. For example, in rats, approximately 80% of DCN neurons project to the thalamus, while the remainder project to the spinal cord and cerebellum (Bermejo et al. 2003). In slice preparations from the gracile nucleus, stimulation of the ipsilateral dorsal column evoked post-synaptic excitation of DCN neurons that were classified mainly into two main classes of response pattern; these were analogous to the response patterns of the relay cells and interneurons recorded *in vivo* (Newberry and Simmonds 1984b). In addition, the spontaneous activities of 13% of the DCN neurons were suppressed following stimulation of the dorsal column (Newberry and Simmonds 1984b). The primary afferent inputs to second order DCN neurons mainly utilize glutamate as the main neurotransmitter, whereas about 10% of the interneurons could be GABAergic and/or glycinergic and might mediate both post- and presynaptic inhibition (Galindo et al. 1967; Davidson and Southwick 1971). The DCN field potentials evoked by stimulating the ipsilateral dorsal column are composed of a postsynaptic component that is primarily of short duration, and a presynaptic component that may be important in the more prolonged inhibition (Andres-Trelles et al. 1976; Newberry and Simmonds 1984a; Lue et al. 1996). Therefore, functionally, the DCN are not only just simple pre-thalamic relays for somatosensory processing but also serve complex roles related to sensorimotor integration. In the present study, cSCS at 90% MT was applied and this induced clear modulatory effects on activity of the DCN. Such SCS intensities most likely activated low-threshold myelinated large fibers in the dorsal column (Yang et al. 2008), although a considerable proportion (23%) of unmyelinated afferent fibers has been found in rat dorsal column (Chung et al. 1987). Orthodromic impulses evoked by cSCS arriving at and making synaptic contacts onto different projecting neurons and interneurons could be one way to explain why various response patterns to cSCS were observed in the present study. In addition, the stimulation parameters of cSCS used in this study (90% MT, 50 Hz, 0.2 ms) were clinically relevant; however, it should be noted that limited short trains (10 s) of cSCS used in this study are not routinely utilized in the clinical setting. Effects of applying cSCS for 30 min or longer, which are the durations that are often applied in patients (Linderöth and Foreman 1999), have to be determined in future basic studies.

In summary, cSCS significantly modulated the activity of a majority of neurons in the DCN. Since excitatory as well as excitatory followed by inhibitory effects were often observed among the multiple response patterns of DCN neurons to cSCS, these neurons might play an important role in the beneficial effects of cSCS on some cerebral dysfunctions and disorders including diseases affecting cerebral circulation.

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ABBREVIATIONS

cSCS or SCS, cervical spinal cord stimulation; DCN or DCNs, dorsal column nuclei; MT, motor threshold; WDR, wide dynamic range; LT, low threshold; HT, high threshold; E, excitation; I, inhibition.

REFERENCES

- Andres-Trelles F, Cowan CM, Simmonds MA. The negative potential wave evoked in cuneate nucleus by stimulation of afferent pathways: its origins and susceptibility to inhibition. *J Physiol* 1976;258:173–86. [PubMed: 940053]
- Bermejo PE, Jiménez CE, Torres CV, Avendaño C. Quantitative stereological evaluation of the gracile and cuneate nuclei and their projection neurons in the rat. *J Comp Neurol* 2003;463:419–33. [PubMed: 12836177]
- Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg* 2004;100:254–267. [PubMed: 15029914]
- Chung K, Langford LA, Coggeshall RE. Primary afferent and propriospinal fibers in the rat dorsal and dorsolateral funiculi. *J Comp Neurol* 1987;263:68–75. [PubMed: 3667972]
- Dario A, Scamoni C, Peron S, Tomei G. A case of post-traumatic cervicogenic headache treated by cervical cord stimulation. *J Headache Pain* 2005;6:473. [PubMed: 16388345]
- Davidson N, Southwick CA. Amino acids and presynaptic inhibition in the rat cuneate nucleus. *J Physiol* 1971;219:689–708. [PubMed: 4333671]
- Farber, JP.; Yang, X.; Foreman, RD.; Qin, C. Modulation of neuronal activity in dorsal column nuclei by upper cervical spinal cord stimulation in rats; 2008 Neuroscience Meeting Planner; Washington, DC: Society for Neuroscience. 2008; Program No. 580.1.Online
- Fuentes R, Petersson P, Siesser WB, Caron MG, Nicolelis MA. Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. *Science* 2009;323:1578–82. [PubMed: 19299613]
- Fujii M, Sadamitsu D, Maekawa T, Uesugi S, Ozaki S, Koizumi H, Uetsuka S, Sakamoto K, Yamashita T, Ito H. Spinal cord stimulation therapy at an early stage for unresponsive patients with hypoxic encephalopathy. *No Shinkei Geka* 1998;26:315–321. [PubMed: 9592812]
- Galindo A, Krnjević K, Schwartz S. Micro-iontophoretic studies on neurones in the cuneate nucleus. *J Physiol* 1967;192:359–77. [PubMed: 4292909]
- Goellner E, Slavin KV. Cervical spinal cord stimulation may prevent cerebral vasospasm by modulating sympathetic activity of the superior cervical ganglion at lower cervical spinal level. *Med Hypotheses* 2009;73:410–413. [PubMed: 19409714]
- Hosobuchi Y. Electrical stimulation of the cervical spinal cord increases cerebral blood flow in humans. *Appl Neurophysiol* 1985;48:372–376. [PubMed: 3879799]
- Isono M, Kaga A, Fujiki M, Mori T, Hori S. Effect of spinal cord stimulation on cerebral blood flow in cats. *Stereotact Funct Neurosurg* 1995;64:40–46. [PubMed: 8751313]
- Linderorth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation* 1999;2:150–164.
- Linderorth, B.; Meyerson, BA. Spinal cord stimulation: Techniques, indications and outcome. In: Lozano, AM.; Gildenberg, PL.; Tasker, RR., editors. *Textbook of Stereotactic and Functional Neurosurgery*. Vol. 2 nd ed.. McGraw Hill/Springer Verlag; Berlin-Heidelberg: 2009. p. 3288Chpt. 151
- Linderorth, B.; Foreman, RD.; Meyerson, BA. Mechanisms of spinal cord stimulation in neuropathic and ischemic pain syndromes. In: Krames, E.; Peckham, PH.; Rezai, A., editors. *Neuromodulation*. Academic Press/Elsevier; London: 2009. Chpt 25
- Lue JH, Jiang-Shieh YF, Shieh JY, Wen CY. The synaptic interrelationships between primary afferent terminals, cuneothalamic relay neurons and GABA-immunoreactive boutons in the rat cuneate nucleus. *Neurosci Res* 1996;24:363–71. [PubMed: 8861106]
- Miki K, Iwata K, Tsuboi Y, Sumino R, Fukuoka T, Tachibana T, Tokunaga A, Noguchi K. Responses of dorsal column nuclei neurons in rats with experimental mononeuropathy. *Pain* 1998;76:407–15. [PubMed: 9718259]

- Morita I, Keith MW, Kanno T. Dorsal column stimulation for persistent vegetative state. *Acta Neurochir Suppl* 2007;97:455–459. [PubMed: 17691409]
- Møller AR, Sekiya T, Sen CN. Responses from dorsal column nuclei (DCN) in the monkey to stimulation of upper and lower limbs and spinal cord. *Electroencephalogr Clin Neurophysiol* 1989;73:353–61. [PubMed: 2477221]
- Nakamura S, Tsubokawa T. Evaluation of spinal cord stimulation for postapoplectic spastic hemiplegia. *Neurosurgery* 1985;17:253–9. [PubMed: 3875802]
- Newberry NR, Simmonds MA. The rat gracile nucleus in vitro: I. Evidence for a GABA-mediated depolarisation of the dorsal column afferents. *Brain Res* 1984a;303:41–9. [PubMed: 6329471]
- Newberry NR, Simmonds MA. The rat gracile nucleus in vitro: II. Field potentials and their conditioned depression. *Brain Res* 1984b;303:51–7. [PubMed: 6329472]
- Núñez A, Buño W. Properties and plasticity of synaptic inputs to rat dorsal column neurones recorded in vitro. *J Physiol* 2001;535:483–95. [PubMed: 11533138]
- Paxinos, G.; Watson, C. *The rat brain in stereotaxic coordinates*. Academic Press; Centrecourt, Australia: 1986.
- Qin C, Lehwew RT, Khan KA, Wienecke GM, Foreman RD. Spinal cord stimulation modulates intraspinal colorectal visceroreceptive transmission in rats. *Neurosci Res* 2007;58:58–66. [PubMed: 17324482]
- Robaina F, Clavo B. Spinal cord stimulation in the treatment of post-stroke patients: current state and future directions. *Acta Neurochir Suppl* 2007a;97:277–82. [PubMed: 17691387]
- Robaina F, Clavo B. The role of spinal cord stimulation in the management of patients with brain tumors. *Acta Neurochir Suppl* 2007b;97:445–53. [PubMed: 17691408]
- Sagher O, Huang DL. Effects of cervical spinal cord stimulation on cerebral blood flow in the rat. *J Neurosurg* 2000;93:71–76. [PubMed: 10879761]
- Saadé NE, Jabbur SJ. Interactions of ventral tract and dorsal column inputs into the cat cuneate nucleus. *Brain Res* 1984;299:178–81. [PubMed: 6326961]
- Sánchez E, Barro S, Mariño J, Canedo A. Cortical modulation of dorsal column nuclei: a computational study. *J Comput Neurosci* 2006;21:21–33. [PubMed: 16633940]
- Shin HC, Chapin JK. Mapping the effects of motor cortex stimulation on single neurons in the dorsal column nuclei in the rat: direct responses and afferent modulation. *Brain Res Bull* 1989;22:245–52. [PubMed: 2706535]
- Towe AL, Jabbur SJ. Cortical inhibition of neurons in dorsal column nuclei of cat. *J Neurophysiol* 1961;24:488–98. [PubMed: 13777766]
- Visocchi M. Spinal cord stimulation and cerebral haemodynamics. *Acta Neurochir Suppl* 2006;99:111–116. [PubMed: 17370775]
- Visocchi M. Neuromodulation of cerebral blood flow by spinal cord electrical stimulation: the role of the Italian school and state of art. *J Neurosurg Sci* 2008;52:41–47. [PubMed: 18500217]
- Wu M, Linderorth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a review of experimental studies. *Auton Neurosci* 2008;138:9–23. [PubMed: 18083639]
- Yang X, Farber JP, Wu M, Foreman RD, Qin C. Roles of dorsal column pathway and transient receptor potential vanilloid type 1 in augmentation of cerebral blood flow by upper cervical spinal cord stimulation in rats. *Neuroscience* 2008;152:950–8. [PubMed: 18321652]

Fig. 1.

Excitatory (E), inhibitory (I) and E-I response patterns of DCN neurons to cervical SCS (cSCS or SCS, 1 Hz). *A*: excitatory response of a neuron to cSCS. Upper panel shows a single raw trace of an E responsive neuron evoked by cSCS. Lower panel shows a peristimulus histogram (a sum of 50 sweeps, 2-ms bins) of a neuron with an E response to cSCS. *B*: Upper panel shows a single raw trace of I responsive neurons to cSCS. Lower panel shows a peristimulus histogram of this neuron. *C*: raw traces using different time scales of an E-I neuron responding to cSCS. *C'*: A peristimulus histogram obtained from same E-I neuron as *C*.

Fig. 2.

Inhibitory-excitatory (I-E) and excitatory-inhibitory-excitatory (E-I-E) response patterns of DCN neurons to cervical SCS (cSCS or SCS, 1 Hz). *A*: I-E response of a neuron to cSCS. Upper panel shows a single trace of the impulses in I-E neuron evoked by cSCS. Lower panel shows a peristimulus histogram (a sum of 50 sweeps, 2-ms bins) of a neuron with an I-E response to cSCS. *B*: Upper panel shows a single trace of a neuron that had no response to cSCS. Lower panel shows a peristimulus histogram of this neuron. *C*: the single sweeps with different time scales in an E-I-E neuron responding to cSCS. *C'*: A peristimulus histogram of same E-I-E neuron as *C*.

Fig. 3.

Responses of DCN neurons to cervical SCS (cSCS or SCS) with high frequency (50 Hz). *A*: a neuron with excitatory responses to cSCS. *B*: a neuron with inhibitory responses to cSCS. *C*: A neurons with inhibitory-excitatory responses to cSCS. *D*: a neuron that did not respond to cSCS.

Fig. 4.

Responses of DCN neurons to cervical SCS (cSCS or SCS) with different frequencies (1, 10, 20, 50 Hz, 0.2 ms). *A*: a neuron with excitatory responses to cSCS. *B*: the stimulus-response curve of excitatory responses to cSCS with different frequencies. *C*: a neuron with inhibitory responses to cSCS. *D*: the stimulus-response curve of inhibitory response to cSCS with different frequencies (n=15). *E*: a neuron that showed no response to cSCS.

Table
Response characteristics of neurons in dorsal column nuclei to high frequency of SCS (90% MT, 50 Hz, 0.2 ms, 10 s)

Responses to SCS	n	Spontaneous activity (imp/s)	Latency (s)	Excitatory responses (imp/s)	Inhibitory responses (imp/s)	Duration of responses (s)
Excitatory	30	9.1±1.7	0.5±0.1	53.1±7.6	N/A	17.3±1.3
Inhibitory	24	16.5±1.9 *	0.5±0.2	N/A	10.3±1.1	17.5±2.0

* P<0.01 compared to corresponding activity of neurons with excitatory responses to SCS