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Intra-spinal microstimulation may alleviate chronic pain after spinal cord injury

Bin Shu, MD^{a,b}, Fei Yang, PhD^a, and Yun Guan, MD, PhD^{a,†}

^aDepartment of Anesthesiology and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, Maryland, 21205, USA

^bDepartment of Anesthesiology and Pain Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Abstract

Chronic pain after spinal cord injury (SCI) is a form of central neuropathic pain that is debilitating and often refractory to current pharmacological treatments. Neurostimulation pain therapies, such as epidural spinal cord stimulation, have only moderate success in reducing SCI pain. The pathogenesis of SCI pain may involve a state of central neuronal hyperexcitability, especially in the spinal cord dorsal horn, that develops after injury. We hypothesize that the neuronal structures near the spinal cord injury site may be an important pain generator, and intraspinal microstimulation (ISMS) may normalize dorsal horn neuronal hyperexcitability and hence alleviate SCI pain. Specifically, ISMS may induce frequency-dependent conduction block on axons of afferent sensory neurons, in the spinothalamic tract and Lissauer's tract. ISMS may also facilitate primary afferent depolarization that elicits presynaptic inhibition of incoming afferent inputs. Together, these actions will reduce abnormal afferent inputs and ascending pain signals before they can reach the brain. Furthermore, ISMS may directly induce inhibitory postsynaptic potentials in dorsal horn neurons, and trigger the release of endogenous inhibitory neurotransmitters, opioids and serotonin to inhibit postsynaptic neurons and restore the compromised segmental pain inhibition after SCI. Finally, ISMS may alter the frequency and pattern of discharge such that the rostrally conducted impulses no longer code pain or activate brain areas concerned with pain signaling. Based on recent progress in understanding spinal learning and plasticity, we also postulate that repetitive or long-term ISMS may help the dorsal horn "reset" neuronal excitability and regain normal pain processing for a prolonged period. By finely tuning the stimulation parameters (e.g., intensity, pulse width, frequency), position, and geometry of ISMS electrode, multiple spinal structures (e.g., dorsal horn, dorsal column, spinothalamic tract) may be modulated to induce synergistic pain inhibition. Our hypothesis can be readily tested in preclinical models of SCI pain by using a combination of *in vivo*

[†]Correspondence to: Yun Guan, MD, PhD, Division of Pain Medicine, Department of Anesthesiology/CCM, the Johns Hopkins University, 720 Rutland Ave., Ross 350, Baltimore, MD 21205. Phone: 410-502-5510; Fax: 410-614-2109; yguan1@jhmi.edu.

conflict of interest statement:

The authors declare no conflict of interest.

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electrophysiological (neuronal activity) and animal behavioral (pain response) approaches. Since ISMS electrodes stimulate the spinal structures directly, we expect that the effective stimulus intensity and energy consumption can be lower than that for epidural spinal cord stimulation. The proposed hypothesis may provide insights and rationales for developing a novel neurostimulation pain therapy by directly inhibiting the pain generators in the spinal cord, and ISMS may be an alternative strategy to treat SCI pain.

Keywords

spinal cord injury; neuropathic pain; dorsal horn; spinal cord stimulation

INTRODUCTION

Chronic disabling pain often develops after spinal cord injury

Chronic pain is a frequent consequence of spinal cord injury (SCI) that results from trauma, tumor, infection, or other diseases [1,2]. More than two-thirds of patients with SCI may experience chronic pain and nearly one-third report severe pain [3,4]. SCI pain often has devastating effects on a patient's quality of life and can lead to depression and even suicide. The International Association for the Study of Pain introduced a three-tiered system to define the affected structure and pathology responsible for SCI pain [5,6]. The first tier divides SCI pain into two broad categories known as nociceptive and neuropathic pain. Nociceptive pain manifests as dull aching and cramping in regions of sensory preservation. Neuropathic pain is manifest as sharp, shooting, electric, or burning symptoms and occurs in a region of sensory disturbance [7]. In tier two, the neuropathic pain is further divided into above-level, at-level, and below-level with respect to the location of the injury [8]. At-level pain, which occurs in dermatomes near the spinal injury, is often characterized as either stabbing or spontaneous pain that is accompanied by mechanical and thermal hypersensitivity. Below-level pain is localized to dermatomes distal to the injury site and is often described as a stimulus-independent burning pain that develops more gradually than at-level pain. The incidence of pain is much higher in the lower extremities than in the upper limbs [9], and more than half of patients with SCI suffer severe at-level pain [10].

Dorsal horn neuronal hyperexcitability is an important mechanism of SCI pain

Several preclinical animal models have been developed to mimic the clinical manifestation of SCI pain and to examine the etiologies of motor and sensory dysfunctions that follow SCI [11–14]. Although the mechanisms that underlie SCI pain are not yet completely understood, studies in patients and experimental animal models have generated some critical insights. The pathogenesis of SCI pain may involve both peripheral neuronal dysfunction and a state of central neuronal hyperexcitability [15–18]. In particular, dorsal horn neurons near the injury become abnormally active, showing increased spontaneous firing and enhanced responses and post-discharges to peripheral stimulation [19–21]. The development of dorsal horn neuronal hyperexcitability, which correlates well with SCI pain behavior, may involve multiple mechanisms, including a loss of spinal segmental inhibition (e.g., GABAergic), increased gene expression and function modulation of glutamate receptors and

NK-1 receptors in postsynaptic neurons, changes in voltage-gated sodium channel expression, and glial activation in spinal cord [22–25]. It can also result from changes in dorsal root ganglion (DRG) neuronal properties after SCI, such as chronic spontaneous activity and increased excitability [26,27]. Supraspinal mechanisms may contribute to spinal hyperexcitability and SCI pain through enhanced net descending pain facilitation [28–31]. Whether pain signals arise in the brain itself after SCI remains debatable. Although SCI increases neuronal excitability in the thalamus, clinical observation argues against the possibility that pain signals arise in supraspinal sites independent of the injured spinal cord. For example, application of spinal anesthesia and intrathecal lidocaine often induce significant SCI pain relief [32].

Current treatment of SCI pain remains unsatisfactory

Treatment of central neuropathic pain after SCI remains a significant unmet medical need [1]. For example, SCI pain is often refractory to current pharmacological treatments, including high doses of opioids [33], antidepressants, and anticonvulsant medications [1,34,35]. Spinal cord ablative procedures, such as thermal destruction of the dorsal horn or dorsal root entry zone near the region of spinal injury, may correct pain in some SCI patients. However, most SCI patients respond poorly to neurodestructive procedures, and this unsavory approach also causes additional damage to spinal cord tissue and permanent loss of its function. In some patients who undergo the ablative procedure, pain may occur or even become worse in the long term [36,37]. Functional electrical stimulation has been used for cardiac and diaphragmatic pacing to improve bone and muscle health, as well as to restore or prevent the loss of function after SCI [38]. However, neuromodulatory techniques, such as transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS), often show little or no ability to alleviate SCI pain, particularly with below-level pain [6,39–41]. Other techniques, such as deep-brain stimulation, are very invasive and have limited evidence of efficacy [42].

TENS and SCS are clinically proven to be effective for managing a variety of pathological pain conditions, including peripheral neurogenic pain and muscle pain [43–46]. It is unclear why they are often ineffective for treating SCI pain. We postulate that TENS and SCS might simply miss the essential targets for inhibiting SCI pain. Alternatively, the critical substrate and essential machinery through which TENS and SCS attenuate pain may not be present under SCI pain conditions. It has been suggested that the gate-control theory underlies the mechanism of TENS- and SCS-induced analgesia [47]. This theory suggests that closing the “gate” in spinal cord by activating large afferent fibers in peripheral tissue or in the dorsal column can prevent the ascending pain signal from reaching the brain, thus blocking recognition of pain [45,48–50]. TENS electrodes are placed over the affected peripheral tissue, and epidural SCS electrodes are often placed overlaying the dorsal column structure a few levels rostral to the affected spinal segment. Thus, TENS- and SCS-induced analgesia requires the dorsal column structure and afferent pathway that conducts signals from the painful region to be intact. Interestingly, SCS was shown to induce better pain relief in patients with incomplete cord lesion than in those with complete cord transection. Importantly, SCI pain likely involves etiologies and mechanisms that differ from those of other pathological pain states. In particular, direct spinal tissue damage and the subsequent

anatomical and pathological changes in the surrounding uninjured region after SCI may interrupt this anatomical and functional connection [51,52]. Therefore, a radically different neuromodulatory approach to preventing the pain signal from reaching brain is needed to treat SCI pain.

THE HYPOTHESIS

Intraspinal microstimulation near the spinal cord injury site may alleviate SCI pain

The dorsal horn is an important site for integration and modulation of nociceptive information. When SCI involves a complete cord transection, the dorsal horn region just above the SCI still has connections with peripheral nerve inputs and can transmit ascending pain signals to supraspinal structures. We hypothesize that the hyperexcitability that occurs in dorsal horn cells rostral to the injury site may be a central cellular mechanism that underlies ongoing pain. This hyperexcitability would account for at-level and above-level hyperalgesia and allodynia, because the signals below the level of injury cannot reach the brain. In patients who have incomplete cord transection, the neuronal structure responsible for spinal pain signaling could also involve regions at or below the injury. Pain may also develop in distal body regions (below-level pain) because of abnormal spontaneous activity in pain-generating neurons in the dorsal horn of the spinal cord at the level of injury. Below-level pain may also arise because these cells have acquired the capacity to activate neurons in the brainstem/thalamus/cortex that signal sensation in the body regions that have lost input to the brain as a result of the SCI. In either case, spinal structures near the injury site may be a key mechanistic substrate of SCI pain. They not only serve as a critical relay station of the exaggerated spontaneous activity and peripheral noxious inputs from afferent sensory neurons, but also develop the capacity to generate pain. This notion is supported by clinical evidence that thermal destruction of spinal cord or the dorsal root entry zone near the region of spinal injury may temporarily alleviate pain [53].

We hypothesize that spinal structures near the injury site may represent an important target through which neuromodulation can inhibit SCI pain. Specifically, we postulate that intraspinal microstimulation (ISMS) of spinal structures at or below the injury level can inhibit spinal pain transmission and alleviate SCI pain. By finely tuning the position (e.g., depth, level) of an electrode placed directly into the spinal cord, the geometry of the electrode (e.g., multipolar), and stimulation parameters (e.g., intensity, pulse width, frequency), multiple spinal structures (e.g., dorsal horn, dorsal column, spinothalamic tract) can be activated together to induce synergistic pain inhibition, or individually to achieve selective analgesia coverage, depending on the source and features of pain. Thus, ISMS has the potential to induce stronger and more selective pain relief from SCI than do other neuromodulatory techniques. Modulating plasticity within spinal circuits by direct ventral horn stimulation has been shown to help the spinal cord “relearn” lost function and facilitate the recovery of locomotor capabilities. Based on recent progress in understanding spinal learning and plasticity, we also postulate that repetitive or long-term ISMS may help the dorsal horn “reset” neuronal excitability and regain normal pain processing for a prolonged period.

The hypothetical mode of action for ISMS to inhibit SCI pain

Current treatment for SCI pain is unsatisfactory, likely because of our limited knowledge of the underlying mechanisms and a lack of treatment targets. The future therapeutic modality based on our hypothesis may provide a means to directly target the SCI pain generator/mechanism within the spinal cord, block abnormal input from the periphery (e.g., ectopic discharge from DRG), and activate descending pain inhibition. Stimulation applied to the focalized spinal area may prevent nonselective activation of other structures (e.g., ventral horn, dorsal root) and limit untoward side effects. The effect of ISMS is likely critically dependent on the position of the electrode and the stimulation parameters. High stimulus intensities carry a risk of inducing pain and sensitization. Therefore, ISMS is expected to work at an intensity that selectively activates A-beta fibers (non-noxious), especially for at-level stimulation and in incomplete cord transection. However, a greater stimulus intensity may be tested for below-level stimulation in patients with complete cord transection. Since ISMS electrodes stimulate the spinal structures directly, we expect that the effective stimulus intensity and energy consumption can be lower than for electrodes placed in the epidural space (e.g., SCS).

We postulate that synchronized electrical pulses applied directly to spinal cord structures, including dorsal horn neurons, glia cells, spinal tracts, and afferent fibers, may activate multiple mechanisms to inhibit pain. Specifically, ISMS may: 1) Cause frequency-dependent conduction block or a compromised conductive capacity along axons of afferent sensory neurons, in the spinothalamic tract, and in Lissauer's tract, especially if ISMS is applied at high frequency. Thus, the abnormal afferent inputs and spontaneous activity from the dysfunctional DRG neurons and ascending pain signals from postsynaptic dorsal horn neurons would be jammed or prevented from reaching the brain [54]. The conduction block may involve a blockage of voltage-gated sodium channels [55–57]; 2) Facilitate primary afferent depolarization that elicits presynaptic inhibition of incoming afferent inputs [58]; 3) Directly induce inhibitory postsynaptic potentials in dorsal horn neurons (presumable excitatory interneuron or projection neurons) [59,60]. 4) Induce release of endogenous inhibitory neurotransmitters in spinal dorsal horn, such as by activation of the inhibitory interneurons that express gamma-aminobutyric acid (GABA) in superficial laminae dorsal horn, which can be activated by SCS to inhibit postsynaptic neurons [61,62]; 5) Alter the frequency and pattern of discharge such that the rostrally conducted impulses no longer code pain or activate brain areas concerned with pain signaling; 6) Induce other segmental neurochemical changes, including release of endogenous opioids and serotonin to restore the segmental pain inhibition.

CRITICAL EVALUATION OF THE HYPOTHESIS

Validation of the hypothesis with experimental animal studies

Our hypothesis may be tested in preclinical models of SCI pain by using a combination of *in vivo* electrophysiological (neuronal activity) and animal behavioral (pain response) approaches. Because attenuation of dorsal horn neuronal hyperexcitability is closely related to pain inhibition, such as that after SCS and TENS [46,46,63,64], the first step toward validation of our hypothesis will be to examine whether ISMS also attenuates the dorsal

horn hyperexcitability in SCI rats. Like any other neuromodulatory technique, the stimulation parameters (e.g., intensity and frequency) can be vital to the outcomes of ISMS. If the stimulation parameters used in treatment are not selected carefully, the intended treatment may actually engage sensitization processes and decrease the therapeutic value of ISMS. Recently, we established an *in vivo* electrophysiological approach to study the cellular mechanisms of SCS-induced analgesia in neuropathic rats and to identify the optimal parameters[48,64,65]. A similar setup can be used to examine whether ISMS of the spinal segment at or below the injury level attenuates dorsal horn neuronal hyperexcitability in SCI rats.

We postulate that ISMS may attenuate spinal pain transmission at intensities that are non-noxious and selectively activate large-diameter A-beta afferents fibers. To standardize the stimulation intensities, antidromic compound action potentials evoked by graded ISMS can be recorded at the sciatic nerve or dorsal root. Different compound action potential waveforms corresponding to A-beta and A-delta fiber activation can be distinguished on the basis of the activation threshold and the conduction velocity as described previously[46,48,64]. The readout in the electrophysiological study may include spontaneous activity, evoked responses to natural mechanical/heat stimuli, and wind-up response (a model of short-term neuronal sensitization) to repetitive electrical stimulation of the receptive field of wide-dynamic-range (WDR) neurons that are located above the injury level. The *in vivo* electrophysiological study will identify the important parameters and characterize the features (e.g., time course, peak effect) of neuronal inhibition from ISMS. The information gathered will be useful for the subsequent animal behavioral testing. The second step is to carry out behavioral experiments to demonstrate that ISMS attenuates mechanical and heat hypersensitivity and spontaneous pain in SCI rats. This study requires the development and validation of a miniature bipolar electrode that can be surgically implanted in the spinal cord. The electrodes can be placed through an open surgical procedure in which the surgeon opens the dura to gain direct access to the spinal cord for implantation of the leads. As an initial attempt, electrodes may be implanted in the spinal cord at or slightly below the injury level so as not to introduce additional damage to the uninjured rostral segment.

Potential limitations of this hypothesis

The severity and prolongation of central neuropathic pain after SCI may be related not only to the pathologic condition (e.g., trauma, cancer) and the site and magnitude of tissue damage, but also to other factors (e.g., genetic polymorphisms, gender, age, reorganization of the central nervous system, and intervening variables) [66–71]. Owing to the inherent variability and the evolving nature of anatomical and functional changes in the nervous system associated with the progress of SCI pain, no single mechanism or animal model may represent all categories (e.g., at-level, below-level pain) or symptomatology (e.g., spontaneous pain, mechanical allodynia) of pain observed in clinic. Our hypothesis is based on the assumption that the development of spinal neuronal hyperexcitability represents the fundamental cellular mechanism for SCI pain. However, it is possible that other important but unidentified mechanisms of SCI pain are not targeted by ISMS. For example, SCI pain

may gradually shift its dependence from peripheral and spinal hyperexcitability to a supraspinally located mechanism and become a “central pain” in the chronic phase.

Chronic neuropathic pain often is associated with a host of negative emotional, psychological, and cognitive outcomes in patients. Experimental animals with neuropathic pain often exhibit impaired learning, augmented escape behaviors, and a tonic aversive state [72–75]. Since pain is multidimensional, the treatment should also be multidimensional. Therefore, the overall value of ISMS in treating SCI pain may also depend on whether it has a beneficial effect on the affective component of chronic pain.

One challenge in implementation of ISMS is in the design and manufacture of the miniature electrode. Additionally, implanting electrodes into the body always carries the risk of infection and migration. However, recent progress in microelectrode engineering and the knowledge gained from using implantable electrodes as a therapeutic approach to improving limb movement and bladder control after SCI can be applied to limit these potential drawbacks to a chronically implanted ISMS device [76,77].

Clinical implications of the hypothesis

Peripheral stimulation techniques such as TENS, acupuncture, and SCS have enjoyed only moderate success in reducing SCI pain. Central stimulation techniques such as deep brain stimulation and epidural motor cortex stimulation are highly invasive and associated with relatively poor long-term outcomes. The proposed hypothesis may provide critical insights and rationales for developing a novel neuromodulatory approach that may be particularly useful for alleviating pain in patients with SCI. The valuable information generated from studies in experimental animals can be subsequently tested in humans to establish the clinical use of this treatment approach. By directly targeting the pain generators in spinal cord, ISMS may potentially be used as an alternative strategy to treat SCI pain, especially for at-level and below-level pain, when other approaches are ineffective.

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