

What Does the Mechanism of Spinal Cord Stimulation Tell Us about Complex Regional Pain Syndrome?

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Abstract

Spinal cord stimulation (SCS) can have dramatic effects on painful, vascular, and motor symptoms of complex regional pain syndrome (CRPS), but its precise mechanism of action is unclear. Better understanding of the physiologic effects of SCS may improve understanding not only of this treatment modality but also of CRPS pathophysiology.

Effects of SCS on pain perception are likely to occur through activation of inhibitory GABA-ergic and cholinergic spinal interneurons. Increased release of both neurotransmitters has been demonstrated following SCS in animal models of neuropathic pain, with accompanying reductions in pain behaviors. Effects of SCS on vascular symptoms of CRPS are thought to occur through two main mechanisms: antidromic activation of spinal afferent neurons and inhibition of sympathetic efferents. Cutaneous vasodilation following SCS in animal models has been shown to involve antidromic release of calcitonin gene-related peptide and possibly nitric oxide, from small-diameter sensory neurons expressing the transient receptor potential V1 (TRPV1) receptor. The involvement of sympathetic efferents in the effects of SCS has not been studied in animal models of neuropathic pain, but has been demonstrated in models of angina pectoris.

In conclusion, SCS is of clinical benefit in CRPS, and although its mechanism of action merits further elucidation, what little we do know is informative and

can partially explain some of the pathophysiology of CRPS.

Key Words. Complex Regional Pain Syndrome (CRPS); Spinal Cord Stimulation

Introduction

Spinal cord stimulation (SCS) can have dramatic effects on painful [1], vascular [2,3], and motor symptoms [1] of complex regional pain syndrome (CRPS). The clinical effects of SCS include decreased allodynia, increased blood flow, decreased symptoms of movement disorders, such as tremor and dystonia, decreased edema, increased skin temperature, and decreased hyperhidrosis. These effects have been shown to translate into clinically meaningful results in patients with CRPS. However, the mechanism of action of SCS in CRPS requires further investigation.

Clinical Evidence for SCS in CRPS

In a systematic clinical review that included 25 case series, which involved 500 patients with a mean follow-up of 33 months, among patients with CRPS with implanted SCS systems, 67% (95% confidence interval [CI] 51%, 84%), on average, achieved pain relief of at least 50% [4]. In the studies that assessed pain with a visual analog scale (VAS) the mean score reduction was 4.7 (95% CI 3.4, 6) [4]. SCS also produced significant improvements in health-related quality of life and in functional ability ($P \leq 0.05$) [4]. Complications following SCS were recorded in eight of the studies, and were experienced by 33% (22/66) of the patients, however, none experienced adverse sequelae [4]. The review also included a randomized controlled trial [5] and an economic analysis [6]. The authors commented: "The data from the randomised controlled trial and the economic analysis of this trial support the conclusion that SCS, combined with physical therapy, is both clinically effective and cost effective for the treatment of patients with CRPS type I" [4].

The clinical trial included in the review was conducted by Kemler et al. (2000), in the Netherlands, and compared SCS plus physical therapy (PT) (N = 36) with PT alone (N = 18) [5]. This group of patients has now been followed up at two and five years [7,8]. At 6 and 24 months, there were significantly greater improvements in the VAS pain score with SCS plus PT, than with PT alone ($P < 0.001$) [5,7]. In addition, significant improvements in global

perceived effect scores were reported at 6 months with SCS plus PT compared with PT alone ($P = 0.01$) [5] and were maintained at 24 months ($P = 0.001$) [7]. However, at the 5-year follow-up, the differences between the SCS plus PT and the PT groups were no longer statistically significant [8]. There are a number of methodological limitations to the study that should be considered. Patient numbers were lower at the 5-year analysis and some patients were excluded, so the analysis may not have been powered to achieve a statistically significant result. As the comparison was with pain scores recorded 5 years previously, pain could have increased in the interval due to disease progression, increased activity, or the patients may have reassessed their pain. The intention-to-treat analysis (ITT) excluded patients, and was not therefore a true ITT analysis. The as-treated analysis compared permanently implanted patients (SCS plus PT) with PT only patients and reported a significant difference in global perceived effect ($P = 0.02$), and strong trend to pain relief: the change in VAS was 2.5 with SCS plus PT compared with 1.0 with PT alone ($P = 0.06$) [8]. However, this analysis also excluded patients. In conclusion, although they state that the effects are not durable, the authors note “. . . nevertheless, patient satisfaction at the 5-year follow up remains high” and that 95% of patients with implanted systems would be willing to go through the procedures again for the same result [8]. While the original study demonstrates the effectiveness of SCS in CRPS for up to 2 years, the methodological issues associated with assessing responses at 5 years leave the durability of SCS for CRPS and its longer term benefits awaiting further clarification.

Although the clinical effects of SCS and its effectiveness in managing CRPS have been demonstrated, how neurostimulation achieves these effects has not yet been fully elucidated. The balance of this review looks at the evidence for potential mechanisms of action of SCS in CRPS. Although most of these studies were conducted in neuropathic pain models, the knowledge that SCS works in CRPS suggests that its mechanism of action may be similar to that observed in other pain syndromes. Understanding these mechanisms may provide insights into the underlying pathophysiology of CRPS and how its management could be improved.

Mechanism of Action of SCS

The rationale behind SCS as an analgesic technique originates in the “Gate theory of pain” of Melzack and Wall [9]. This theory proposed that a “gate” exists in the dorsal horn of the spinal cord that governs the transmission of neural signals from sensory afferent neurons to the higher centers where the signals are perceived as pain. Large diameter afferent sensory neurons ($A\beta$ fibers) and small-diameter sensory neurons (C-fibers) form synapses onto spinothalamic tract projection neurons in the dorsal horn of the spinal cord, which convey signals to higher centers. C-fibers are nociceptive, carrying signals from nociceptors (pain receptors), whereas large-diameter $A\beta$ fibers carry input from other types of sensory receptor (non-nociceptive). An intermediate category of afferent neurons,

$A\delta$ fibers, also provides nociceptive input. When input from C-fibers at the synapse with the projection neuron reaches a certain level, the theory states that the “gate” opens and pain signals are transmitted along the projection neurons. If $A\beta$ activity in the same area is increased, it can close the gate, inhibiting transmission of the pain signal between the C-fibers and the projection neuron. Early studies demonstrated that SCS could indeed alleviate pain [10]. However, it is now recognized that stimulation of the $A\beta$ fibers to close the gate cannot completely describe the mechanism by which SCS acts. It remains to be determined what the physiological substrate of the gate is, and why, if the gate is closed, acute nociceptive pain is not blocked while the maladaptive neuropathic pain is attenuated [11]. The antidromic mechanism of SCS has been described but is not yet fully explained.

Various mechanisms of action for SCS have been suggested since the “Gate control theory” was proposed. A simple conduction block is unlikely, as SCS does not directly activate the fibers that inhibit nociceptive pain, the sensations of acute pain are preserved and the effects of SCS persist after stimulation has ceased. Spinal mechanisms involving circuits of afferent spinal and projection neurons have been implicated, and supraspinal mechanisms are also likely to be involved although as yet few data are available [11]. Effects on the sympathetic nervous system are also likely in some cases, particularly underlying the effects on the vascular system [11].

Spinal Neurochemistry

Changes in the neurochemistry of spinal neurons, in particular affecting the neurotransmitters gamma-aminobutyric acid (GABA) and acetylcholine, which act as inhibitory neurotransmitters in the spinal gray matter, have been shown to play a role in neuropathic pain and may therefore also have a role in CRPS. Reduced spinal levels of GABA [12] and acetylcholine [13] have been reported in animal models of neuropathic pain, e.g., spinal nerve ligation models. This suggests that there might also be a reduction in these transmitter levels in CRPS, which could lead to enhanced and inappropriate pain sensations.

Animal models have been used to explore the effects of SCS on spinal neurochemistry. Microdialysis studies in rats have shown that spinal levels of both GABA [12,14] and acetylcholine [13] increase during SCS in the animals that respond to this stimulation with a reduction in allodynic behavior [13]. The anti-allodynic effects of SCS in animals that respond can be blocked by $GABA_B$ antagonists [15], atropine, or other muscarinic acetylcholine receptor antagonists [13], and augmented by agonists [13,16]. For example, in a study by Schechtmann et al. (2008), rats underwent partial nerve ligation (the Seltzer model) and 55% subsequently developed tactile allodynia demonstrated by a lowered withdrawal threshold to von Frey filaments [13]. SCS systems were implanted and stimulation at two-thirds motor threshold provided relief of tactile allodynia in 40% of rats [13]. Among the responders, the mean baseline withdrawal threshold

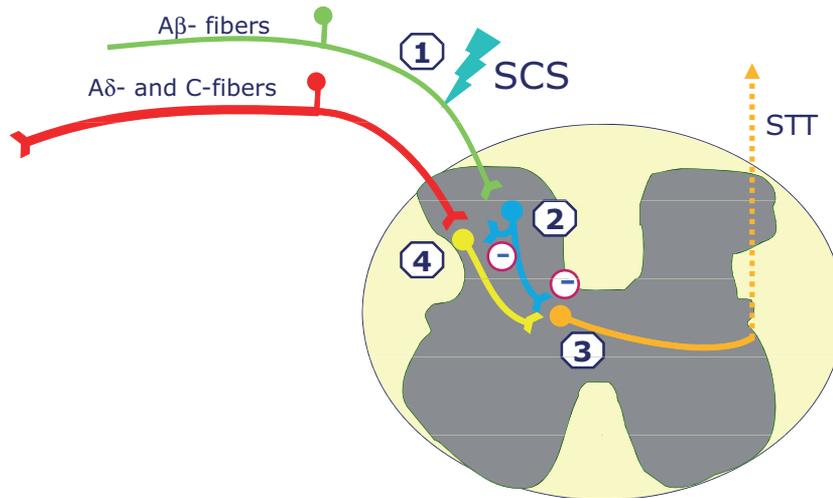


Figure 1 A suggested mechanism for spinal cord stimulation (SCS) pain control, via effects on spinal neurophysiology. (1) SCS activates low-threshold, large diameter A β -fibers, which synapse (2) onto inhibitory (GABA-ergic or cholinergic) interneurons in the dorsal horn. (3) These inhibitory interneurons release transmitter (e.g., GABA, acting via GABA_B receptors) to reduce the excitability of spinal projection neurons, such that subsequent inputs from A δ and C fibers are attenuated. GABA = gamma-aminobutyric acid; STT = spinothalamic tract.

was 1.6 ± 0.4 mg, which increased to a peak of 15.1 ± 1.8 mg after 20 minutes of SCS [13]. The non-selective muscarinic receptor antagonist atropine and an M₄-selective antagonist reversed the effects of SCS, while M₁- and M₂-selective antagonists partially reversed the effect, indicating that all three types of muscarinic acetylcholine receptors were involved [13].

Although effects of SCS on the spinal levels of GABA and acetylcholine have been explored in models of neuropathic pain, they have not been studied in models of CRPS.

These findings suggest that SCS closes the gate by activation of inhibitory interneurons, which may be GABAergic or cholinergic. In theory, SCS could activate low-threshold large-diameter A β fibers, which activate inhibitory interneurons in the dorsal horn to release inhibitory neurotransmitters (GABA, acetylcholine) that reduce the excitability of projection neurons (e.g., in the spinothalamic tract), such that their response to subsequent input from nociceptive A δ - and C-fibers are attenuated (Figure 1).

Vasodilation

Another mechanism by which SCS may provide pain relief is through effects on peripheral vasodilation. This effect that has been extensively studied in animal models, and is thought to involve two mechanisms: antidromic activation of sensory fibers to release vasoactive substances [17];

and, in some cases, inhibition of sympathetic efferent activity (reducing vasoconstriction).

Sensory Afferents

SCS-induced vasodilation via sensory afferents has been extensively studied in anesthetized rats. It has been shown to involve antidromic release of calcitonin gene-related peptide (CGRP) [18,19] and possibly nitric oxide (NO) [20] from primary afferents, and to be blocked by CGRP antagonists. The subset of small-diameter nociceptive afferents that express the transient receptor potential (TRPV1) receptor are thought to be of key importance in the release of these vasoactive substance and are thus essential for the response to SCS [21]. Wu et al. (2008) demonstrated that resiniferatoxin, a high-potency capsaicin analogue that binds to the TRPV1 receptor and desensitizes neurons expressing this receptor, abolished SCS-induced increases in cutaneous blood flow in the anesthetized rat [21]. It seems therefore that CGRP, released after antidromic activation of small diameter sensory afferents that express TRPV1, may produce vasodilation by binding to its receptors on vascular endothelial cells, to induce NO release and also act directly on vascular smooth muscle cells to a less extent [22].

The important question now arises as to *how* sensory afferents are activated by SCS: is this activation direct, or is it mediated via spinal interneurons? A study by Barron

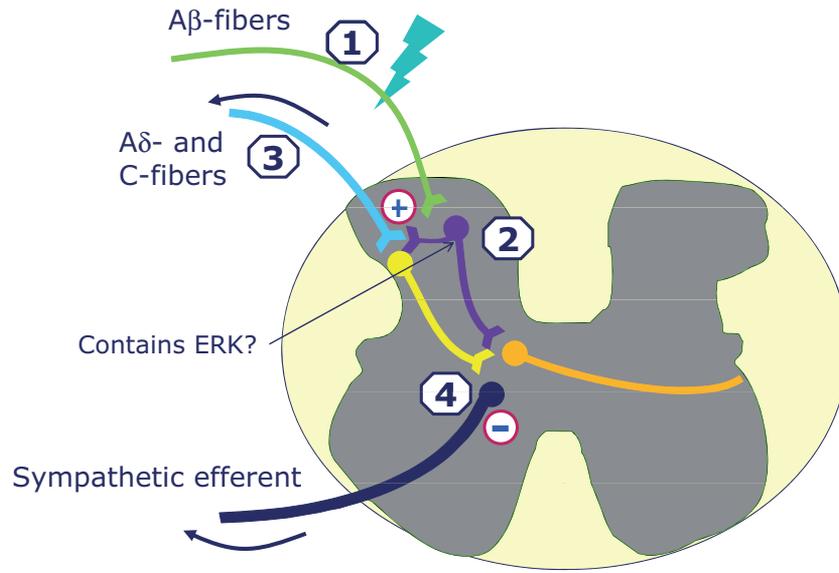


Figure 2 A suggested mechanism for spinal cord stimulation (SCS) effects on vasodilation, via effects on spinal neurophysiology. (1) SCS at dorsal columns activates large-diameter fibers, mainly Aβ-fibers. Branches of these fibers in the superficial laminae connect to spinal interneurons (2), which are activated following SCS and subsequently activate small-diameter, high-threshold sensory afferent fibers (3), activating both the central terminals and antidromic activation of neurotransmitter release from peripheral terminals, and also leading to (4) inhibition of the sympathetic efferent fiber.

et al. (1999) addressed this issue: in anesthetized rats, stimulation of the dorsal surface of the spinal cord resulted in increased blood flow in the ipsilateral hind paw [23]. When muscimol, a GABA_A receptor agonist was applied to the spinal cord to inhibit general synaptic activity, the vasodilatory response to SCS was markedly reduced. This indicates that spinal neuronal integration is essential for SCS-induced vasodilation [23].

Extracellular signal-regulated kinase (ERK) is expressed in neurons of the superficial laminae I and II of the dorsal horn. It is a key participant in intracellular signaling cascades initiated by many neurotransmitters, and is therefore a useful marker of neuronal activity [24]. Activation of ERK in primary afferent neurons has been demonstrated following C-fiber activation and is associated with pain hypersensitivity. Its activation has also been demonstrated in a rat model of neuropathic pain [24]. The key role of ERK signaling in SCS-induced vasodilation was demonstrated in a study in anesthetized rats, where SCS between L2–L3 at 60% and 90% of motor threshold produced large increases in cutaneous blood flow. Application of U0126, an ERK antagonist, produced profound reductions in the SCS-induced increase in blood flow. This indicated that ERK signaling in spinal cord neurons is important in SCS-induced vasodilation [25].

Together the evidence from these studies can be used to construct a possible model of the spinal circuits underlying

SCS-induced vasodilation. SCS activates large-diameter fibers in the dorsal columns, mainly Aβ-fibers. Branches of these fibers in the superficial laminae synapse with spinal interneurons, which are activated following SCS, and subsequently activate small diameter, high threshold sensory afferent fibers, stimulating both neurotransmitter release from the central nerve terminals and antidromic activation of neurotransmitter release from peripheral terminals (Figure 2).

Sympathetic Nervous System

The second mechanism by which SCS may influence vasodilation is via actions on the sympathetic nervous system. No studies have explored this in detail with respect to neuropathic pain or CRPS, but data are available from normal animal models and an animal model of angina pectoris. Both antidromic activation of sensory afferent fibers and inhibition of sympathetic efferents contribute to vasodilation [22]. Studies showed that vasodilation induced by SCS predominately was dependent on antidromic activation of sensory afferents when the temperature of the hindpaw was maintained at moderate temperatures, and relied on both antidromic activation of sensory afferent fibers and inhibition of sympathetic efferent fibers when the hindpaw was cooled [25]. Thus, SCS-induced vasodilation appears to depend on two complementary mechanisms.

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The animal model of angina pectoris further supports a role for the sympathetic nervous system. The intrinsic cardiac nervous system regulates cardiac function via an aggregate of cardiac neurons and neural interconnections function originating in the right atrial ganglion that receives input from spinal neurons [26]. In anesthetized dogs, Foreman et al. (2000) demonstrated that coronary artery occlusion stimulated neuronal activity in the intrinsic cardiac nervous system and that this activity continued after removal of the occlusion [26]. When SCS between T1 and T2 started before the occlusion, and was terminated after the occlusion was released, there was no increase in activity in the intrinsic cardiac nervous system. Indeed, neuronal activity was similarly suppressed by SCS before, during, and after the period of occlusion and only slowly returned to normal after SCS ceased [26]. These findings suggest that both afferent and efferent sympathetic fibers originating in the thoracic spinal cord contributed to intrinsic cardiac nervous activity and that it is these fibers that SCS acts on [26]. It also suggests that the effects of SCS on vasodilation associated with CRPS and neuropathic pain syndrome may be mediated through stimulation of the sympathetic nervous system.

Discussion

In summary, what do the clinical responses to SCS tell us about CRPS? The available clinical studies and case series tell us that SCS can alleviate pain and other CRPS symptoms in a portion of patients with SCS. Whether stimulation achieves this through resolution of the underlying pathology is not yet clear.

There are inherent difficulties in the long-term follow-up of CRPS patients, and the absence of statistically significant benefits of SCS over PT alone at 5 years should perhaps be considered as the absence of evidence, rather than evidence of an absent effect. Over 5 years, SCS provided benefits for patients, the majority of whom would be willing to repeat the procedure. It is important to stress that SCS should always be used as part of an interdisciplinary approach to management of pain and other aspects of CRPS.

Neurophysiologic responses to SCS in animal models suggest that GABA and acetylcholine are important neurotransmitters in mediating the actions of SCS, and also in the pathogenesis of neuropathic pain syndromes. ERK may be an important signaling intermediary in the vasodilatory response to SCS and in animal models of neuropathic pain.

What do we still need to know? The investigations reviewed in this summary have been conducted in models of other neuropathic pain states. Further investigation is needed on the neurophysiologic effects of SCS in models of CRPS and on the specific role of GABA, acetylcholine, and other neurotransmitters, as well as intermediary signaling molecules, such as ERK, in the pathophysiology of

CRPS. Investigations of the supraspinal effects of SCS in animal models of CRPS and in affected subjects are also required.

In conclusion, SCS is of clinical benefit in CRPS, and although its mechanism of action merits further elucidation, what little we know thus far is informative and useful in understanding the pathophysiology of CRPS.

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