Mechanisms of Spinal Cord Stimulation in Painful Syndromes: Role of Animal Models

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Abstract

Spinal cord stimulation (SCS) came into clinical practice as a direct spin-off from the “gate control theory.” This therapy has been used to treat neuropathic pain of peripheral origin as well as ischemic pain states, vasospastic conditions, and therapy-resistant angina pectoris. The physiological mechanisms of action for SCS are slowly emerging but still are only fragmentarily understood.

This chapter will describe the research methods and basic studies used to explore these mechanisms in normal healthy animals, as well as the use of animal models exhibiting different neuropathic, vasculopathic, and other pathological conditions. Brief discussions will address human experimental and clinical studies. The results show that SCS is effective in some pain syndromes otherwise resistant to treatment.

The mechanisms of SCS differ between the pathologies treated; in neuropathic pain, stimulation-induced suppression of central hyperexcitability seems pivotal, while in ischemic pain, inhibition of sympathetic outflow and in particular antidromic vasodilation are important mechanisms. Depending on where along the neuro-axis SCS is applied, stimulation can be used to control autonomic and viscerosomatic reflex activity involved in a certain syndrome, thereby alleviating the disease symptoms. Additionally, SCS may have its primary effect on improving organ function and could also reduce pain associated with the disease. SCS is a therapy that is safe, minimally invasive, reversible, and has few side effects compared with chronic pharmacotherapy. We firmly believe that SCS at present is an underused treatment modality. Furthermore, our society demands “evidence-based” and “mechanism-based” therapies. This demand amplifies the need to expand our knowledge through research projects aimed at further exploration of physiological mechanisms that are activated using neurostimulation. The results of these studies will lead to improvement and expansion of future neuromodulation therapies that will be of benefit to patients.

Key Words. Spinal Cord Stimulation; Animal; Neuropathic Pain; Ischemic Pain; Visceral Dysfunction; Angina Pectoris

Background

Spinal cord stimulation (SCS) emerged as a direct clinical spin-off from the “gate control theory” [1]. The clinical use of SCS increases steadily. It has been estimated that more than 14,000 new systems for SCS are implanted every year worldwide. SCS has since long been utilized in neuropathic pain of peripheral origin, in ischemic pain states, for example, peripheral arterial occlusive disease (PAOD), in vasospastic conditions, and in therapy-resistant angina pectoris. The exact mechanisms of action for SCS are still poorly understood, but in recent years more solid evidence for the underlying physiological mechanisms has emerged [2,3]. Presently, conceptual mechanisms concerning the pain relief with SCS
differ fundamentally between the use of this therapy in neuropathic and in ischemic pain conditions [4,5].

This chapter will describe the methods used in research aimed at the exploration of these mechanisms in neuromodulation. Knowledge of the physiological mechanisms is a fundamental requirement of the medical profession as it strives to move toward evidence-based therapies. The detailed mapping of mechanisms has also proven necessary for the further development of the techniques used in neuromodulation. In the chapter, we will describe basic studies in normal healthy animals as well as the use of animal models exhibiting neuropathic, vasculopathic, and other pathological conditions. These models will be used to discuss some of the mechanisms that are activated during SCS to provide pain relief and improve organ function. We will also briefly touch on human experimental and clinical studies to elucidate mechanisms.

Animal Models: Assets and Drawbacks

Most of the data used to explain physiological mechanisms are actually, hitherto, based on experimental studies performed on normal animals, isolated organs, isolated tissues, or cell cultures. Such simple systems are necessary to establish the basic mechanisms within a field of study. However, great caution must be exercised in the clinical interpretation of the data generated from such studies because the results may not bear relevance to the clinical situation and may actually be misleading. One example requiring careful interpretation is the dynamics of the neurotransmitters found in the spinal dorsal root ganglion and dorsal horn (DH) following peripheral nerve lesions. The concentration of neurotransmitters change markedly, and furthermore their functions may be transformed after an injury [6,7]. Nevertheless, studies conducted in normal animals have provided the background data to interpret the results gleaned from animal models of disease. Only recently (during the last two decades), more systematic studies have been initiated using animal model systems. Now it seems self-evident that a model of the condition under study should be developed, but are the models used presently relevant clinically? There is a constant debate between clinicians and basic researchers about the clinical relevance [8], but for many reasons, a clear difference still exists between most models and the clinical conditions they are tailored to resemble. One reason is the limited repertoire of responses that can be obtained from the most common lab animals like the rat and mouse. Studies in larger animals and, especially, primates are costly and raise ethical concerns. Another reason is the use of knockout mice to study the importance of specific receptor molecules. These studies now seem fruitful but may produce results that could be misinterpreted, because these mice suffer from multiple defects that may not reflect the relevant problem. Even though these animals may appear “normal,” they may have compensated for the deficiencies and masked defects that may affect the interpretation of the data. Another reason for the debate is the paucity of direct cooperation and collaboration between basic scientists and clinicians to develop models, design experiments, and discuss results that would facilitate the translation of the studies between the bench and the bedside.

Animal Models of Pain in Neuropathy

Animal models of neuropathic pain will be used as examples to amplify the problem of the fundamental differences that exist between the clinical conditions and the results obtained from the animal models. Many models of nerve injury-induced “pain-like behavior” have been described [9–14]. After the nerve lesion (sciatic nerve; spinal roots; or peripheral branches), the animals rapidly develop a change in posture. The origin of this postural abnormality has been much discussed; in the earlier reports it was often referred to as keeping the lesioned paw in “protected position.” However, later authors have questioned this interpretation and instead hypothesized motor interference behind the behavioral change. The major reaction quantified in such studies is usually a facilitated withdrawal reaction to innocuous stimuli (e.g., prodding on the lesioned hind paw with a series of von Frey filaments). Normal rats may tolerate a stiff filament (i.e., ≥30 g) without withdrawal, but some nerve-lesioned animals develop severe hypersensitivity (similar to clinical static mechanical allodynia) and may withdraw readily with the application of a filament calibrated to 2–7 g bending force. The quantified “symptom” is thus a “stimulus-evoked pain-like reaction,” which could be interpreted as equivalent to the “allodynia” observed in patients with neuropathic syndromes.

A major problem in this context is that not more than 20–40% at most of neuropathic pain patients present with mechanical allodynia [8], and
The major complaint of the neuropathic pain patient is thus usually the continuous pain. Only in a few clinical studies have the effects of SCS on the continuous pain and on the stimulus evoked component been reported separately. However, recently Harke et al. [15], in a group of complex regional pain syndromes (CRPS)-I patients, reported a higher frequency of tactile allodynia as 22/29 cases (76%) complained of this symptom. In these cases, SCS therapy afforded equal alleviation of the allodynic component as compared with the effect on the continuous pain.

Thus, generalization of conclusions based on data from animal models of neuropathy with stimulus-evoked “pain reactions” (tactile or temperature hypersensitivity) to humans with neuropathic ongoing spontaneous pain should be made with caution. The mechanisms that seem to underlie the animal symptomatology may not be the same as those generating the symptoms in the patients. Even when it comes to discerning the mechanisms behind dynamic mechanical allodynia per se, we are at present not able to propose one single mechanism. Some candidates proposed are: 1) peripheral sensitization of A-delta/C-fibers; 2) awakening of silent nociceptors; 3) phenotype switch of A-beta fibers; 4) loss of A-beta mediated inhibition in the DH; 5) central sensitization; 6) sprouting of mechanoreceptive fibers in the DH—contact with nociceptive neurons; and 7) tonic activation of descending facilitation of spinal circuitry from the brain stem [8,16]. In fact, if we are unable to outline the pathophysiological mechanisms behind the neuropathic painful conditions, it should be obvious that the mapping of mechanisms behind the beneficial effects of SCS on such symptoms poses an extremely difficult task to the researcher and, furthermore, to the interested clinician who is trying to bridge the knowledge from the animal data to the patients.

The list above provides only a few examples of the difficulties facing the clinician when trying to generalize observations from animal models to the clinical symptomatology. The only conclusions that can be drawn from these illustrations are that we have to be extremely careful and restrictive in transferring data from animal models to the human situation. Any observation made in an animal experiment in one species has to be repeated in other species and ultimately has to be confirmed by human observations, clinical or experimental [17,18]. However, the search for better and more relevant animal models goes on [11,19,20].

None of these critical comments should, however, deter anyone from pursuing animal models related to clinical conditions. Furthermore, the comments should be used to encourage the clinician and the basic scientist to establish collaborations that will reduce the number of irrelevant animal models, support development of more adequate models, and improve the interpretation of the results as they relate to the symptoms observed in patients.

**Neurogenic Pain**

The major part of the data on effects of SCS in animal models of neuropathic pain have been carried out using Sprague-Dawley (or similar strains) rats submitted to one of the lesion procedures listed above, producing mononeuropathy in one hind limb. The most commonly used has been the Bennett and Seltzer procedures [10,14]. Only a few laboratories have generated experimental data related to effects of SCS [21–28]. A selection of data from such studies will be used below to illustrate different proposed mechanisms of action.

At the Karolinska Institutet [21], SCS has been performed in both acute and chronic studies during the last decade using “clinical current parameters” (50 Hz; 0.2 ms and amplitude about 60–90% of motor threshold). In the acute experiments, a spring-loaded silver ball cathode (OD 1 mm) has been lightly applied to one dorsal column; in the chronic studies, a simple implantable miniature monopolar system has been used [29]. Figure 1 illustrates the simple monopolar system used for the rat and compares it with a human quadripolar plate lead.

In order to briefly and simply summarize the wealth of animal studies performed up to the present, one may conclude that in the neuropathic pain, animal studies show that the hyperexcitability demonstrated by multimodal wide-dynamic range (WDR) cells in the DHs after a symptom-generating nerve injury [31] is related to increased basal release of excitatory amino acids, for example, glutamate [25], and a dysfunction of the local spinal gamma-aminobutyric acid (GABA) system. SCS has, in experiments on animal models of neuropathy, been demonstrated to inhibit DH WDR hyperexcitability [31] and to induce release of GABA in the DHs [25,32], with a subsequent decrease of the interstitial glutamate concentration [25]. The GABA release was solely observed
in animals responding to SCS with markedly decreased hypersensitivity ("allodynia") [32]. Activation of the GABA-B receptor seems to play a pivotal role for the suppression of glutamate release. Available evidence indicates that stimulation-induced release of adenosine [33], serotonin [34], and norepinephrine (the two latter presumably involved in descending inhibition) in the DH also may contribute to the improvements observed with SCS. However, a cascade release of neuroactive substances is probably induced by SCS and multiple, as yet unknown, mechanisms activated.

It is the impression of the Karolinska research group that the major part of the SCS effect is exerted segmentally [35] only requiring the participation of a few spinal segments. A minor additive inhibitory influence may be mediated via the brain stem. However, other groups, for example, the group at the American University of Beirut [22], propose instead that the major mechanism utilizes a supra-spinal loop exerting SCS-induced inhibition of the DH neurons via a descending antinociceptive pathway [27]. Presently, most data favor "the segmental hypothesis." The pathways and transmitters discussed above are schematically outlined in Figure 2.

It is evident during intraoperative test stimulation as well as during the clinical use of SCS that even slight movement/dislocation of the lead may alter the area covered by paresthesiae and also induce other sensory-motor signs. In order to obtain adequate effect on a painful body part, paresthesia should ideally cover this area to 100% and inadequate dispersion of paresthesiae must be corrected by reprogramming or surgical revision of the lead. The stimulation site is thus essential to obtain the desired effect on pain.

Furthermore, it has been demonstrated in a wealth of studies that not only neuropathic pain and other painful syndromes, but also autonomic and viscero-somatic reflexes at various levels may be affected by the stimulation, depending on the site of stimulation along the neuro-axis. These effects may sometimes be looked upon as side effects (as indicated above) but can actually also be used for treatment. An overview of effects depending on the selected stimulation level is given in Figure 3; the effects of SCS applied at different spinal levels on the functions of various organ systems are discussed below.

Ischemic Pain

Ischemic pain is primarily described as a nociceptive pain. The evidence from several studies suggests that SCS does not alleviate acute nociceptive pain [37]. However, in ischemic extremity pain, which is mainly nociceptive, relief of tissue ischemia seems to be the primary event that occurs either by increasing/redistributing blood flow to the ischemic area or by decreasing tissue oxygen...
demand. Animal models have been used to explore the mechanisms that might explain how SCS improves the symptoms of PAOD.

Anesthetized rats have been used as animal models to study changes in peripheral blood flow during SCS [21,26,28,38–42]. Laminectomies were performed to expose the dorsal surface of the lower thoracic and upper lumbar segments of the spinal cord. A spring-loaded unipolar ball electrode was lightly placed on the left or right subdural surface at the L2–L3 spinal segment. Experimental SCS (50 Hz; 0.2 ms, monophasic rectangular pulses), similar to clinical settings, was maintained for 2 minutes at 30%, 60%, or 90% of

![Figure 2](https://academic.oup.com/painmedicine/article-abstract/7/suppl_1/S14/1816865/Mechanisms-of-Spinal-Cord-Stimulation-in-Painful/118665)

**Figure 2** Schematic model illustrating the various mechanisms and transmitter substances discussed in the text. Spinal cord stimulation (SCS) activates the dorsal columns (DC) orthodromically and antidromically (green lightning bolt). The antidromic activity is transmitted into the dorsal horns (DHs) via DC collaterals. In the DHs, it activates inhibitory circuits (GABAergic, etc.), which acts on the hyperexcitable DH neurons both pre- and postsynaptically to decrease the pathologically high level of basal release of the excitatory amino acids, for example, glutamate. Furthermore, activity ascending from the SCS may activate a supraspinal neuronal loop that induces inhibition from descending pathways possibly utilizing 5-HT and norepinephrine as transmitters (modified from Wallin [30]). WDR, wide-dynamic range; GABA, gamma-aminobutyric acid.

![Figure 3](https://academic.oup.com/painmedicine/article-abstract/7/suppl_1/S14/1816865/Mechanisms-of-Spinal-Cord-Stimulation-in-Painful/118666)

**Figure 3** Schematic picture illustrating how spinal cord stimulation (SCS) applied at various levels of the neuroaxis may, besides the effects on neuropathic pain, induce changes in different target organs mediated via stimulation-induced changes in local autonomic activity, dorsal root reflexes, or on viscero-somatic reflexes. The numbers next to the red lightning bolts correspond with the numbers listed under the Organ Response. Some of these changes in target organ function may be beneficial for the individual and SCS at a certain site may thus be utilized therapeutically. (The spinal cord figure is adapted from Bear et al. [36].) ICNS, intrinsic cardiac nervous system.
motor threshold (MT) in random order of stimulus intensities. At least 5 minutes were allowed to elapse between applications of SCS. Cutaneous blood flow was recorded with laser Doppler flow perfusion monitors placed on the glabrous surfaces of the ipsilateral and contralateral hindpaws. The values of blood flow were presented as the percentage of the basal blood flow. Skin temperature was measured with a thermistor probe placed on the plantar aspect of the foot, distal to the footpad and next to the laser Doppler probe. The protocols that were used to determine underlying mechanisms included hexamathionium, calcitonin gene-related peptide (CGRP) antagonist (CGRP 8–37), adrenergic agonists and antagonists, nitric oxide synthase inhibitors (L-NAME, L-NMMA), sympathetic denervation, dorsal rhizotomies, and local paw cooling. These experimental studies support the notion that SCS suppresses efferent sympathetic activity resulting in diminished peripheral vasoconstriction and secondary relief of pain. In addition, evidence also indicates that antidromic mechanisms are activated by SCS intensities far below the motor threshold and that this may result in release of peripheral CGRP with subsequent peripheral vasodilatation. An interesting observation is that SCS suppresses efferent sympathetic activity resulting in diminished peripheral vasoconstriction and secondary relief of pain.

Another model to demonstrate the effects of SCS on vasospasm and ischemia is the island skin flap model in the rat [44,45]. The latter study was designed to explore if preemptive SCS could increase the survival of a long-term skin flap and identify possible neuromediators. In animals implanted with chronic SCS systems, a neurovascular groin skin flap based on epigastric blood vessels was made. The superficial epigastric artery was identified and a detachable microvascular clip was used to occlude the single feeding branch to the flap. The clip was removed after 12 hours. In two groups, SCS was applied for 30 minutes prior to the occlusion and they were compared with control animals. In addition, one group received the CGRP-antagonist CGRP 8–37. After 7 days, the flaps of the control groups were necrotized. However, the majority flaps of animals receiving preemptive SCS survived the 12-hour occlusion. In addition, decreased survival was observed in a group of animals receiving CGRP 8–37. These results provide another manifestation that preemptive SCS improves ischemic conditions and that CGRP is involved in the effect. The hypothetical mechanisms behind SCS-induced peripheral vasodilatation are outlined in Figure 4.

Angina Pectoris

For coronary ischemia, often manifested as angina pectoris, the mechanisms producing pain relief and improved heart function are also unclear. Although early animal data demonstrated direct inhibitory effects of SCS on cardiac nociception, it has later been clearly proven in clinical studies that SCS does not merely relieve pain but improves the function of the heart; resolution of cardiac ischemia remains the primary factor. Some investigators have proposed a stimulation-induced flow increase or redistribution of blood supply, while others interpret the reduction of coronary ischemia (reversal of lactate production) as mainly

Figure 4 A diagram illustrating effects of spinal cord stimulation (SCS) of the L1–L2 dorsal columns on mechanisms that produce vasodilatation of peripheral blood vessels. SCS activates interneurons that may 1) reduce the activity of spinothalamic tract (STT) cells; 2) decrease the activity of sympathetic preganglionic neurons; 3) reduce the release of norepinephrine from sympathetic postganglionic neurons; 4) activate antidromically the dorsal root afferent fibers; and 5) release calcitonin gene-related peptide (CGRP) and nitric oxide (NO).
due to decreased cardiomyocyte oxygen demand [46,47].

A human experimental study to determine changes in blood flow in the coronary arteries during SCS was performed using dipyramidole provocation with and without SCS and utilizing positron emission tomography to measure perfusion changes [48]. The outcome provided some (but weak) evidence for flow redistribution with SCS. An animal study directed to the same problem instead utilized the distribution of isotope-labeled microspheres in the hearts of anesthetized and artificially ventilated adult mongrel dogs [49]. After the animal was placed in the prone position, a Touhy needle was used to enter the epidural space via a small skin incision above the lower thoracic segments. A four-pole electrode was advanced rostrally in the epidural space to the upper thoracic level under anterior-posterior fluoroscopy with the most rostral pole positioned at the T1 level and slightly to the left of the midline according to current clinical practice [50]. Electrical current was delivered via the rostral (cathode) at an intensity of 90% of motor threshold (MT) (50 Hz and 0.2-ms duration) [51,52]. A conductance catheter was placed in the left ventricle to generate total left ventricular pressure–volume loops that were interpreted by using a computer analysis system [53]. Fluoroscopy was used to position a balloon catheter in the left anterior descending coronary artery (LAD) about 2 cm from its origin. Regional blood flow distribution was determined with the radioactive microsphere technique that required six different radiolabeled microspheres [54], and a dye was used to identify the ischemic zone. The results of the experimental protocol did not demonstrate a local flow increase in the myocardium or show any changes in the pressure–volume relationships during SCS. However, the study was performed in normal hearts submitted to acute complete occlusion of the LAD. As patients have long-term coronary ischemic disease, it will be important to conduct such studies also in hearts with previous infarctions and long-term ischemic episodes.

In patients whose coronary arterial blood supply was compromised, SCS at comparable workloads reduced the magnitude of ST segment changes of the electrocardiogram that was induced during exercise and rapid cardiac pacing [45,55]. These results suggested that the heart improves its function during SCS. To resemble the patient development of chronic ischemic heart disease, an ameroid constrictor was implanted around the proximal left circumflex coronary artery of a canine model [56]. The material of the constrictor slowly swells as it absorbs fluid over a period of 3 to 4 weeks and causes slow obliteration of blood flow through the artery and development of collaterals [57,58]. This process creates a collateral-dependent myocardial substrate [59].

Six weeks later, experiments were performed on anesthetized, open-chest animals that were paced at a basal rate of 150 beats/min. A plaque containing unipolar contacts was used to record electrograms from 191 sites on the left ventricle distal to the site of the occlusion of the left coronary artery by the ameroid constrictor. Transient bouts of angiotensin II were administered to right atrial intrinsic cardiac neurons via their coronary artery blood supply, and rapid ventricular pacing was used to stress the heart. ST segment responses to intracoronary angiotensin II were recorded as elevated ST segments; however, SCS attenuated these ST segment changes. In contrast, ST segment responses were unchanged when rapid ventricular pacing (240 beats/min during 60 s) was applied during SCS. These data indicate that SCS may attenuate the deleterious effects that stressors associated with chemical activation of the intrinsic cardiac nervous system exert on the myocardium with reduced coronary reserve. The conclusion one can draw from this observation is that SCS appears to produce anti-ischemic effects that contribute to improved cardiac function. However, the exact mechanism that improves the electrical activity of the heart still needs to be elucidated.

Further evidence to support the anti-ischemic effects of SCS on the heart is the observation that preemptive SCS seems to induce protective changes in the myocardium, which makes it more resistant to critical ischemia—reducing infarct size. Recent studies indicate that SCS-induced local catecholamine release in the myocardium could trigger protective changes related to mechanisms behind “ischemic pre-conditioning” [60].

In ischemia, the intrinsic cardiac nervous system is profoundly activated [50,61]. If this activity persists, it may result in spreading dysrhythmias that lead to more generalized ischemia. SCS stabilizes activity of these intrinsic cardiac neurons, especially during the ischemic challenge. As in the patients, SCS can reduce the activity of the intrinsic cardiac neurons for long periods after the termination of stimulation. The modulation of the intrinsic cardiac nervous system may be at least one mechanism that protects the heart from more
Severe ischemic threats due to generalized arrhythmias (De Jongste unpublished data; [62]).

Pathways and putative mechanisms behind effects of SCS on cardiac function are briefly summarized in Figure 5.

Irritable Bowel Syndrome

Functional bowel disorders, including the irritable bowel syndrome (IBS), are common abnormalities of the gastrointestinal tract that are associated with crampy abdominal pain, abnormal bowel habits, and somatic hypersensitivity [63–67]. The chronic visceral symptoms of IBS are poorly understood and, at present, an effective therapy has not been identified to effectively relieve these symptoms. As SCS is beneficial in reducing some types of visceral pain and effectively suppresses hyperexcitable somatosensory and viscero-somatic (bladder) reflexes in patients experiencing spasticity, our research team [68] decided to study the effects of SCS as a potential therapy for visceral pain originating from the gastrointestinal tract.

A rat model for quantifying the level of visceral pain in rats was developed by Ness and Gebhart [69]. They measured abdominal muscle contractions that represent a noiceptive reflex induced by colorectal distention. To resemble the patient condition of IBS, the model has been modified to produce visceral hypersensitivity by infusing a low concentration of acetic acid into the colon, which causes hypersensitivity in the absence of mucosal damage [70–72]. In this model, a spinal cord electrode was implanted chronically as described earlier. After 1 week, animals were anesthetized briefly with isoflurane (0.7–1.5%) to suture a strain gauge force transducer to the right external oblique abdominal muscle. The signal from the strain gauge was amplified and recorded on a Grass Polygraph (Grass Instruments, Quincy, MA). A colorectal balloon was then used to distend normal colons and colons irrigated with acetic acid; the number of abdominal contractions was recorded both with and without SCS. The results showed that SCS significantly suppressed the visceromotor responses that were produced with colorectal distention in both normal rats and those with sensitized colons. In a more recent study, SCS significantly reduced abdominal contractions during innocuous distension of the colon in a rat model of post-inflammatory colonic hypersensitivity (30 days after inflammation; colon histology normalized) [73]. Thus, the suppressive effect of SCS on colonic sensitivity provides evidence that SCS may have therapeutic potential for the treatment of visceral pain of gastrointestinal origin associated with abdominal cramping and painful abdominal spasms (cf. Figure 3).

The use of SCS in a patient suffering from IBS was an exciting outcome of this animal study, showing that SCS reduced hypersensitivity of the gastrointestinal tract. Krames and Mousad [74] showed that SCS reverses the diarrhea and pain in a patient who had suffered from IBS for several years. Khan et al. [75] in a retrospective study have also shown that SCS can be used effectively to treat a variety of visceral pain syndromes including generalized abdominal pain, chronic nonalcoholic pancreatitis, and pain following posttraumatic splenectomy. The human studies support the observations made in the animal studies and provide further evidence to support the notion that SCS might be used to treat a variety of diseases that originate in the visceral organs. Randomized control trials of SCS in IBS are underway.

Other Organ Dysfunctional Syndromes

Bronchial Tree

Up to the present, only one group has published an abstract describing the effects of SCS for bronchospasm [76]. They used a sheep model submitted to bronchospasm by inhalation of an *Ascaris suum* extract. High cervical SCS (C1–C2) markedly decreased bronchomotor tone.
Urinary Bladder
Several years ago, SCS was often used for spasticity in multiple sclerosis, but with the introduction of intrathecal baclofen therapy, this treatment vanished. However, the most marked effect of SCS was exerted on urinary bladder spasticity by decreasing the urgency of voiding [77–79]. There are also several case reports on beneficial effects of using neuromodulation on other syndromes such as interstitial cystitis, and mixed low midline pain syndromes using a retrograde approach with low sacral, conus, or root stimulation [for reviews see 80,81].

The obvious conclusion from this section is that SCS may influence beneficially various autonomic functions and improve organ function as we move the stimulating electrode up and down the neuroaxis (for review, see Figure 3).

Pain with Dysautonomia
During the past few years, SCS has demonstrated efficacy in CRPS [e.g., 15,82,83]. In pain conditions associated with signs of sympathetic dysfunction (skin discoloration, temperature changes, sweating, change in dermal hairing, atrophy, etc.), which may be the case in CRPS of both types (reflex sympathetic dystrophy, as well as in causalgia), a sympatholytic action of SCS may be part of the mode of action behind the pain-relieving effect [cf., e.g., 82,84,85]. However, these effects are only partially understood and still a matter of controversy [e.g., 86–88]. As already mentioned above, it has also been shown that antidromic activation of large diameter afferents may result in the release of vasoactive substances, and interest has been focused on the possible role of stimulation-induced peripheral release of CGRP [38].

Thus, to summarize, in pain syndromes coupled to signs of autonomic disturbance, SCS might act on the variety of symptoms in several ways: 1) by a direct inhibitory action onto central hyperexcitable neurons (as indicated above); 2) by decreasing sympathetic efferent output acting on the activated adrenoreceptors on the damaged sensory neurons; and 3) by reducing peripheral ischemia by both the anti-sympathetic action and, for example, antidromic mechanisms (see above). This third action is related to the “indirect-coupling hypothesis” for dysautonomic pain conditions where the damaged afferent neurons are supposed to develop hypersensitivity to even mild hypoxia [cf., e.g., 89]. However, there are as yet no firm data to substantiate these hypotheses. It has been pointed out by several researchers that peripheral vasodilatation is not a prerequisite to obtain relief from neuropathic pain [e.g., 88].

Conclusions
Thus, SCS induces effects in multiple systems and the benefit for a certain condition may depend on: 1) the site on the spinal cord activated; and 2) a selection out of this cascade of biological changes which may be relevant and valuable in a certain syndrome.

Knowledge about physiological mechanisms behind the beneficial effects provides a cornerstone for further development of neurostimulation and as well as strategies to support the technique with receptor-active pharmaceuticals in cases with inadequate response to stimulation per se [90]. In order to further explore the physiological mechanisms of SCS in various painful (and other) conditions, a tight dialogue between clinicians and basic researchers is essential. Questions asked by the clinician should furnish concrete research problems for the basic scientist who has the possibility of testing the ideas in simplified systems. The clinician and experimentalist should design and evaluate the animal models and their data outputs together in order to ascertain a maximal relevance of each model for the therapeutic problem.

Spinal cord stimulation is a therapy, effective in some pain syndromes otherwise resistant to treatment, which is lenient to patients, minimally invasive, reversible, and with few side effects compared with chronic pharmacotherapy. Furthermore, in some syndromes, SCS may have its primary effect on improving organ function, which results in reduction of the pain associated with the disease. Recent research also demonstrates that the method is cost-beneficial, and although more expensive initially, in several studies proves to be less expensive than traditional treatment after an average 2.5–3 years [83,91–93].

We firmly believe that SCS at present is an underused treatment modality. Furthermore, our society demands “evidence-based” and “mechanism-based” therapies. This demand amplifies the need to expand our knowledge through research projects aimed at further exploration of physiological mechanisms that are activated using neurostimulation. The results of such studies will lead to improvement and expansion of future neuromodulation therapies that will be of benefit to patients.
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