138 Mechanisms of Action of Spinal Cord Stimulation

B. Linderoth · R. D. Foreman · B. A. Meyerson

Background

Spinal cord stimulation (SCS) has since long been an effective mode of therapy for treating neuropathic pain of peripheral origin, peripheral ischemic pain states, vasospastic conditions and therapy resistant angina pectoris. Estimates indicate that presently more than 18,000 new systems for SCS are implanted annually worldwide. However, the mode of action for SCS is still poorly understood although in recent years some data on the underlying physiological mechanisms have emerged [1–4]. For the implementation of evidence-based and mechanism-directed therapies, which is to-date requested by the medical profession and health care providers, a thorough knowledge about the mode of action is required [5]. This is also a necessary condition for the further development of the techniques used in neuromodulation.

Depending on the level of the neuro-axis where SCS is applied, the stimulation may also affect viscero-somatic reflexes that can modify a multitude of physiological functions. Possible effects of SCS on different organ systems when applied at various sites are illustrated in ❯ *Figure 138-1* [6]. The mechanisms involved in the SCS effects may be quite different depending on the targeted organ; for example, the mode of action for producing pain relief differs fundamentally when SCS is applied in neuropathic and in ischemic pain conditions [3,4,7,8].

In this chapter, firstly, the physiological bases for the use of SCS in neuropathic pain and in ischemic extremity pain will be elucidated. Secondly, the putative mechanisms behind the use of SCS in therapy resistant angina pectoris will be discussed; the possible application of SCS in various visceral pain conditions will also be briefly addressed.

Numerous possibilities for explaining the modes of action of electric neuromodulation have been generated from clinical studies, but animal experiments are required for exploration of the underlying mechanisms [cf. 9]. Such investigations were extensively conducted in the 1970s and 1980s but the use of normal, intact and anesthetized animals, the application of only noxious and phasic peripheral stimuli and the application of SCS for short periods of time only (<1 min) and using parameters different from those applied clinically limited the clinical relevance of these studies. Even with these limitations studies conducted in normal animals have provided background data that are of value for interpretation of the results gathered from animal models of disease (e.g., [10]). There is an on-going discussion between clinicians and basic scientists about the clinical relevance of animal data (e.g., [11]), particularly when a model is designed to mimic a condition like pain that cannot be evaluated objectively but only indirectly by employing behavioral measures. One way of circumventing this problem is a translational approach to pain research, which necessitates a reciprocal transfer of bench-to-bedside data for promoting the further advancement and refinement of treatments [12,13]. This approach, however, will require the development of better animal models that more adequately mimic specific pain conditions as well as investigations to confirm animal findings in human experimental and clinical studies.

■ **Figure 138-1**
Schematic picture illustrating how SCS applied to different spinal cord segments, besides the effects on neuropathic pain, may 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 (redrawn after [3]). ICNS = intrinsic cardiac nervous system
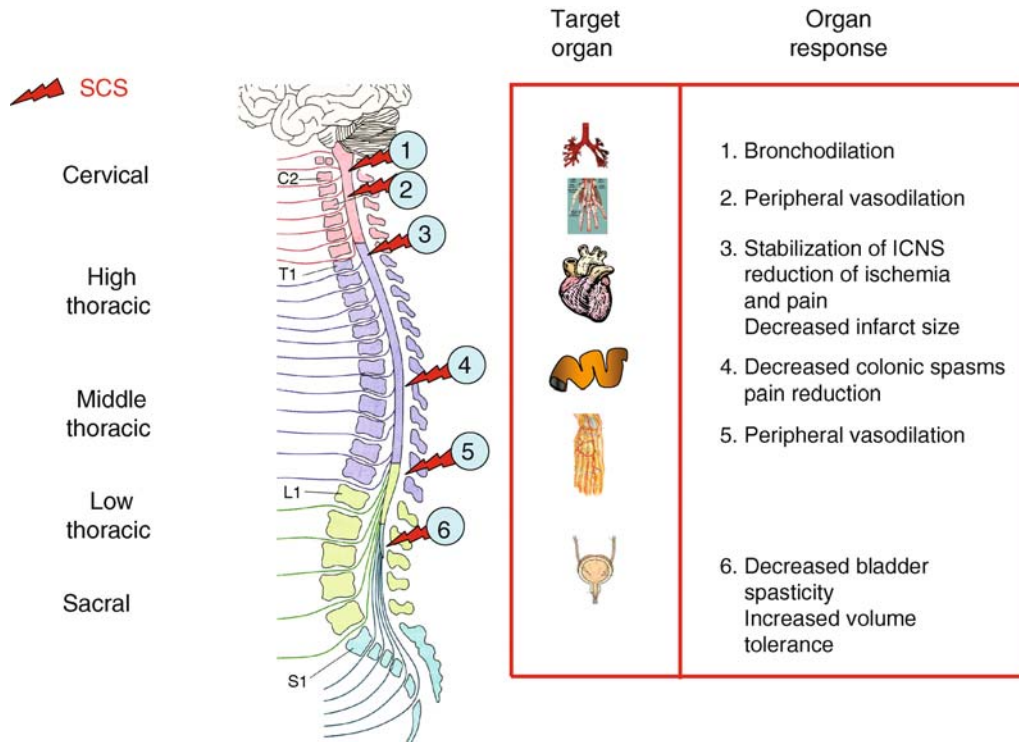
SCS in Neuropathic Pain

Several models of nerve injury-induced "pain-like behavior" have been described (e.g., [14–19]). After a nerve lesion (sciatic nerve or its peripheral branches; spinal roots) the animals soon develop a change in the posture of the nerve-injured extremity as well as increased sensitivity to normally innocuous mechanical and thermal stimuli.

In fact, such hypersensitivity, similar to the clinically observed "allodynia," is the most common behavioral sign that serves to monitor "pain" in animal models of neuropathy. However, the pathophysiological mechanisms behind this phenomenon are still not fully identified [20,21]. The most common method of evaluating the tactile hypersensitivity is to determine the threshold that induces a withdrawal response to innocuous stimuli produced by probing the nerve injured hind paw with von Frey filaments. Normal rats generally tolerate a stiff filament (i.e., ≥ 30 g) without withdrawal while most nerve-lesioned animals develop severe hypersensitivity that may lead to a brisk withdrawal in response to the application of soft filaments calibrated to below 2–7 g of bending force. This quantifiable "symptom" thus mimics a "stimulus-evoked pain-like reaction,"

that can be interpreted as being equivalent to the "allodynia" observed in patients with painful neuropathic conditions (e.g., [22]).

A major concern in this context is that not more than 20–40% of neuropathic pain patients present with mechanical allodynia (e.g., [11]) whereas tactile hypersensitivity occurs in a much larger proportion of nerve injured rats. An important aspect regarding the clinical relevance of animal models of "neuropathic pain" is that these animals almost never display behavioral signs indicating the presence of ongoing, spontaneous pain. These characteristics of animal models assumed to mimic neuropathic pain should therefore be taken into account when findings in studies using such animals subjected to neuromodulation, e.g., SCS, are interpreted in terms of clinical signs and symptoms – i.e., when data are translated from bench to bedside (❯ *Figure 138-2*).

Dorsal Horn and Spinal Circuitry

The presence of paresthesiae, indicating the activation of the dorsal columns (DC), is a prerequisite for pain relief, but it has also been suggested that the tingling and vibratory sensations could be merely epiphenomena. If so, the therapeutic effects could instead be exerted via the activation of other pathways than the DC, notably the dorsolateral funiculus (DLF) containing descending, pain-controlling pathways. However, this tract is located at a distance from an SCS lead overlying the DCs and electric stimuli would therefore most likely first activate the interpositioned dorsal root fibers that enter horizontally and have a low threshold [23]. These roots would then generate segmental paresthesiae at the level of the active electrodes [24]. Thus, it is most likely that activation of the DCs proper evokes mechanisms that provide the pain relief. The pivotal role of the DCs in the SCS effect is further supported by the observation that preservation of somatosensory responses evoked from the painful region is, as a rule, a prerequisite for a positive effect. This is also indicated by the observation that pain associated with extensive deafferentation or direct injury of the DC fibers (where it is not possible to obtain paresthesiae at the painful site) fails to respond to SCS. Most clinicians consider

■ **Figure 138-2**
Radiographic appearance of a quadripolar SCS lead in a human (a) and a monopolar extradural electrode in a rat (b) (lateral projections). Arrows indicate active cathodes
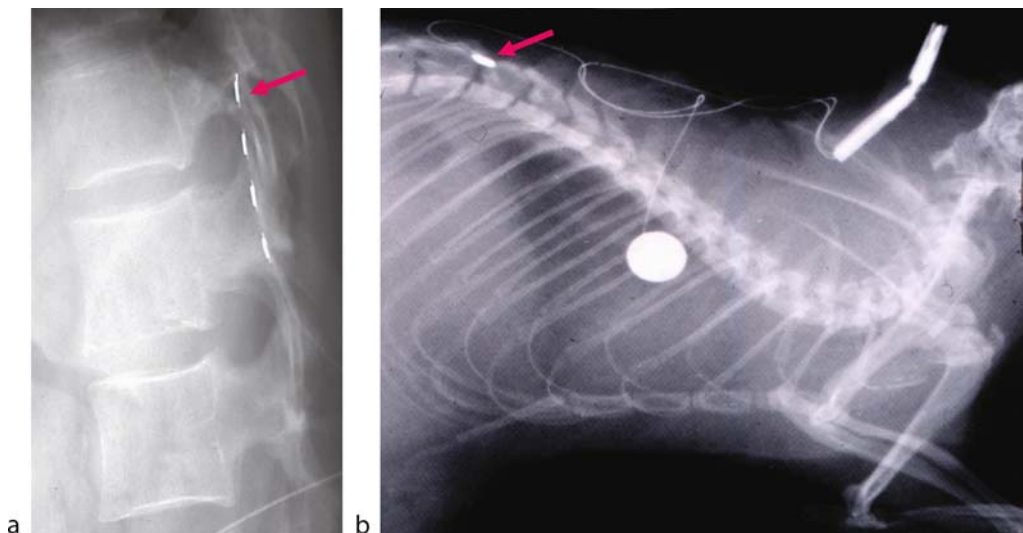
paresthesia-coverage of the painful area as a requirement for a beneficial effect in neuropathic pain.

There is some experimental evidence that SCS may also inhibit nociceptive input at a segmental spinal level [10,25] and this has gained some support by the finding that the stimulation may depress a nociceptive flexor reflex in patients [26] – as well as in animals. Electrical stimuli applied to the sural nerve territory induce a contraction of the biceps femoris when the intensity of the stimulation is perceived as a "pricking" pain sensation. This flexor response conceivably represents the activation of Aδ afferent fibers that may be attenuated by SCS. This effect seems to be related to the clinical pain relieving effect and has been proposed as an objective correlate to the pain relieving effect of SCS. This is, however, difficult to explain in view of the fact that SCS does not otherwise influence either novel acute pain or evoked, experimental pain resulting from Aδ-fiber activation [67,68].

Studies have been performed at the Karolinska Institutet using "models of mononeuropathy," i.e., rats with injury of the sciatic nerve or its branches resulting in hind paw hypersensitivity, in order to explore the mechanisms behind the SCS effects in neuropathic pain [4,8,27]. These animals have been implanted with a miniaturized SCS system so that the effect of stimulation on evoked pain can be monitored in the awake, freely moving animal. It has been demonstrated that in some of the rats SCS may effectively suppress the hypersensitivity, comparable to the effect on allodynia observed in patients. Thus, SCS applied for 20–30 min with stimulus parameters similar to those employed clinically may lead to a significant elevation of the abnormally low withdrawal threshold to innocuous mechanical and thermal (von Frey filaments) stimuli and this effect may outlast the SCS for up to 1 h.

There is much evidence that the phenomenon of tactile allodynia is mediated mainly via low threshold Aβ fibers and that it represents a central state of hyperexcitability [e.g., 28]. The plasticity changes in the spinal cord following peripheral nerve injury are manifested by persistently augmented responsiveness and a high degree of spontaneous discharge of primarily wide-dynamic range dorsal horn neurons. In acute experiments we have demonstrated that SCS may induce a significant and long-lasting inhibition of both the after-discharges and the exaggerated principal response in such neurons in nerve-lesioned rats [29]. In the clinical setting, this suppression of dorsal horn neuronal activity may correspond to the beneficial effect of SCS not only on the allodynia but also on the spontaneous neuropathic pain. These observations suggest that SCS may preferentially influence Aβ-fiber related functions. This notion is further supported by the finding that the threshold of the early component of the flexor reflex, which is Aβ-fiber mediated, is elevated whereas the late C-fiber dependent late phase is unaffected ([27]; see also [30]). However, it has also been reported that the C-fiber flexor reflex can be significantly attenuated, but this observation was made in normal, intact animals [31]. It has further been shown that SCS significantly decreased the duration of long-term-potentiation (LTP) response to C-fiber activation from about 6 h to about 30 min [32]. It should be noted that in these experiments only the sensitized C-fiber response was influenced while neither the normal C- nor Aβ- functions were affected.

The mechanisms involved in the phenomenon of cutaneous hypersensitivity and on-going pain as a result of nerve injury are incompletely understood, and the emphasis on large, low-threshold fiber related functions as pivotal for explaining the effect of SCS is necessarily an oversimplification. It might well be that the mode of action of SCS instead relates to a generalized state of peripheral and central sensitization (involving sensitized or awakened nociceptors), descending spinal facilitation, etc.

The original conceptual basis for SCS presupposes antidromic activation of ascending

dorsal column fibers and this implies that the region of action is primarily segmental. Our experimental data support this interpretation but a research group in Beirut has provided some evidence that instead the effect is predominantly exerted via a supraspinal loop [33,34].

Possible Transmitter Mechanisms Involved in SCS

For obvious reasons, electric current applied to the dorsal aspect of the spinal cord activates multiple transmitter/receptor systems, but little is known about systems that are critically involved in the attenuation of chronic, neuropathic pain by SCS. Human data from analyses of lumbar CSF in conjunction with SCS are sparse and inconclusive. However, it appears that opioid mechanisms conceivably are not involved. There is some evidence that SCS tends to increase substance P (SP) content in human CSF and spinal release of SP and serotonin in cats [35,36]. However, it might well be that the SCS-induced changes of SP are not necessarily related to its pain relieving effect.

In a series of acute experiments using microdialysis in the dorsal horn of nerve lesioned rats we have demonstrated that SCS reduces the release of excitatory amino acids (glutamate, aspartate) and at the same time augments the GABA release [37]. It is of special interest that this effect on the GABA system occurred only in rats that in preceding experiments had been found to respond to SCS with significant suppression of hind paw hypersensitivity [38]. These results confirm earlier observations that the state of central hyperexcitability manifested in the development of allodynia after peripheral nerve injury relates to dysfunction of the spinal GABA systems (e.g., [39]), and it appears that SCS may act by restoring normal GABA levels in the dorsal horn. These findings were supplemented by behavioral experiments where we showed that that the allodynia-suppressive effect of SCS could be counteracted by

intrathecal injection of a GABA$_B$ antagonist whereas the GABA$_A$ antagonist bicuculline was less effective. Conversely, intrathecal administration of GABA or a GABA$_B$ agonist, baclofen, markedly enhanced the effect of SCS [40]. In subsequent studies it was found that rats that were non-responders to SCS, i.e., their hind paw mechanical hypersensitivity was not attenuated, could be converted to responders with intrathecal administration of low, by themselves ineffective, doses of baclofen. The same potentiating effect was found with adenosine and it can thus be concluded that both the GABA- and adenosine related systems are directly involved in the pain relieving effect of SCS [40,41].

These results initiated a clinical study where it was demonstrated that the SCS effect can be enhanced by simultaneously administering intrathecal baclofen in low doses [42,43]. This appears to be a good example of translational research enabling direct transfer of results "from the bench to bedside."

Later studies also demonstrated that gabapentin, pregabalin and clonidine may have similar potentiating effects in non-responding rats [44,45]. In particular, the results obtained with clonidine are of interest since it is known that the antinociceptive effect of this substance is related to activation of the spinal cholinergic system [46]. If so, the effect of SCS might act also via involvement of these mechanisms, and recent studies in the rat have provided evidence supporting this notion [47]. A spinal microdialysis study showed that the release of acetylcholine (Ach) in the dorsal horn was augmented in nerve-injured rats responding to SCS while the Ach levels in the non-responders did not change during SCS treatment. Further behavioral studies using Ach receptor (muscarinic and nicotinic) antagonists administered intrathecally indicate the pivotal importance of activation of the muscarinic M4 and M2 receptors for the SCS effect. A recent immunohistochemical study appears to confirm the crucial role of the M4 muscarinic receptor in the response to SCS after

peripheral nerve injury [48]. Moreover, intrathecal administration of a muscarinic receptor agonist may potentiate the SCS hypersensitivity suppressive effect (Song et al., Submitted).

In conclusion, a cascade of transmitters is probably released by SCS and recent publications point to the complex interactions among the different neuronal circuits that may relate to the SCS effect (e.g., [49–51]).

❯ *Figure 138-3* depicts a tentative scheme of some essential features of the mode of action of SCS when applied for neuropathic pain.

This conceptualization of SCS is necessarily incomplete, in particular with regard to the possible involvement of transmitter/receptor mechanisms. Further, it is primarily based on experiments performed on animal models of mononeuropathy with no definite signs of ongoing, spontaneous pain. Thus, such data should be interpreted with caution.

Clinical Pain States Associated with Dysautonomia

Recent evidence strongly supports the notion that SCS may be efficacious in complex regional pain syndromes (CRPS) e.g., [22,52–55].

◼ **Figure 138-3**

Schematic representation of the possible mode of action of SCS in neuropathic pain based on present knowledge derived predominantly from experiments performed on animal (rat) models of mononeuropathy. Both segmental and supraspinal mechanisms are represented. Possible supraspinal relays are not included because of insufficient knowledge about the organization of a proposed supraspinal loop. Broken arrow lines represent antidromic, and full line arrows ortodromic activation in the dorsal columns, their collaterals and in primary A-afferents. The diagram does not depict a possible SCS activation of the dorsolateral funiculus (DLF). It is conceivable that numerous transmitters and modulators are involved in the modulation exerted by interneurons (represented by ''X''). Descending control of second order neurons is here represented both as inhibitory (black arrows) and facilitatory (white arrows) influences from supraspinal centers. (SP – substance P; EAA – excitatory amino acids (glutatmate, aspartate); Ach- acetylcholine)) (redrawn after [4])
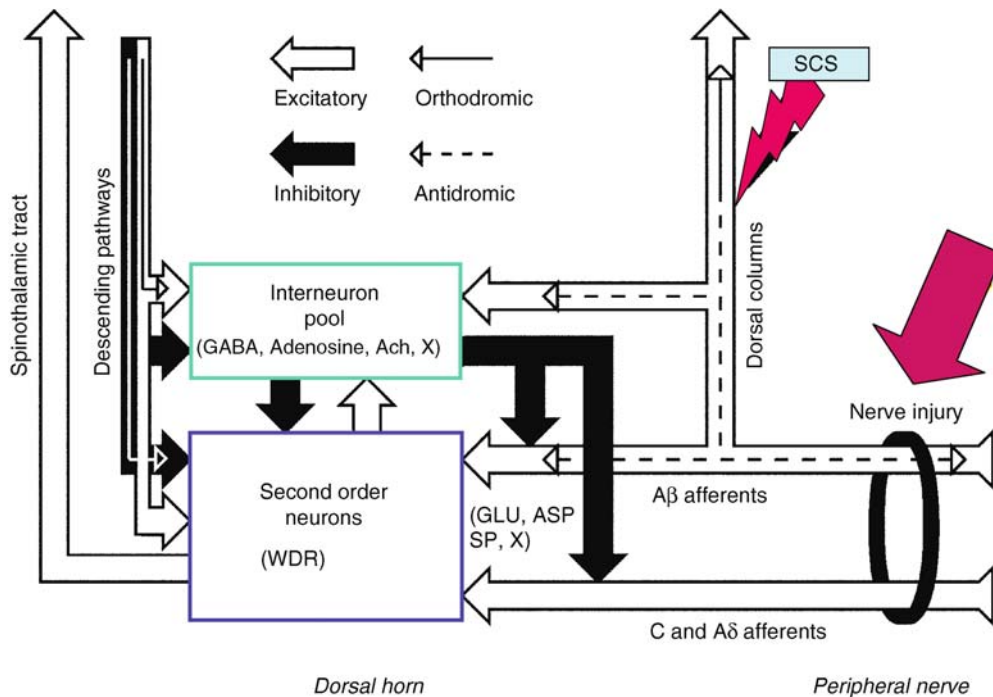
A sympatholytic action of SCS may be part of the mode of action behind the pain relieving effect in conditions associated with signs of sympathetic dysfunction (skin discoloration, temperature changes, sweating, change in dermal hairing, atrophy, etc.) that may be present in CRPS of both types (reflex sympathetic dystrophy – RSD, as well as in causalgia) [56–59]. However, these effects are only partially understood and are still a matter of controversy [57,60,61]. SCS may positively influence CRPS type I that has not been responsive to sympathetic blocks (e.g., [55]) although the probability of positive effects seems more likely in patients responding to diagnostic sympathetic blocks [22].

The effects of SCS in ischemic states (to be further discussed below) have in animal studies been found to depend also on antidromic activation of small diameter afferents that may result in a peripheral release of vasoactive substances. This type of mechanism could conceivably also be involved in the effects of SCS in CRPS. However, it has been argued that SCS induced peripheral vasodilatation is not a prerequisite for pain relief in CRPS I [57,60].

In pain syndromes associated with signs of autonomic disturbance SCS may hypothetically act on the symptoms in several ways: (1) by direct inhibitory actions 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 both by a sympathicolytic action and via e.g., antidromic mechanisms. This proposed 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 [62].

Some animal models of CRPS have been developed ([63,64] type I; [65] type II) but their clinical significance has been questioned [66] and there are as yet no data from such models where SCS has been used.

SCS in Ischemic Pain

Ischemic pain is generally characterized as essentially nociceptive. Several studies have indicated that SCS does not alleviate acute nociceptive pain (e.g., [2,3,67,68]). The pain relief induced by SCS is presumably secondary to attenuation of tissue ischemia that occurs as a result of either increasing/redistributing blood flow to the ischemic area or decreasing tissue oxygen demand (reviews, [69,70]). Further support for the notion that relief of ischemic pain in vascular disease is the result of activation of other mechanisms than those involved in neuropathic pain is the observation that stimulation may be effective also when applied below the threshold for paresthesiae [70,71].

No established animal models of peripheral arterial occlusive disease (PAOD) that gives rise to ischemic pain have yet been developed. Therefore, anesthetized animal models under normal physiological conditions have been used to investigate mechanisms of SCS-induced changes in peripheral blood flow during SCS [70,72–78]. Cutaneous blood flow and calculated vascular resistance in the glabrous surfaces of the ipsilateral and contralateral hind paws have been recorded using laser Doppler flowmetry. In some of the studies also perfusion in muscle tissue has been investigated [35,75]. Skin temperature was measured with a thermistor probe placed on the plantar aspect of the foot, next to the laser Doppler probe. This technique has made it possible to explore underlying mechanisms of peripheral microcirculation by using various interventions such as hexamethonium, CGRP antagonists (e.g., (CGRP 8–37)), adrenergic agonists and antagonists, nitric oxide synthetase inhibitors, sympathetic denervation, dorsal rhizotomies, and local paw cooling. Experimental studies using these interventions have provided evidence that SCS suppresses efferent sympathetic activity causing attenuation of peripheral vasoconstriction, which secondarily could

lead to relief of pain [74,75]. In addition to vasodilatory effects obtained with suppression of sympathetic nervous activity, more recent data have demonstrated that SCS also depends on antidromic mechanisms involving the sensory afferent fibers of the dorsal roots that release peripheral CGRP with subsequent peripheral vasodilatation [72]. A salient observation is that SCS induced-vasodilatation of a cooled hind paw ($<25°C$) evoked an early phase of vasodilatation via the sensory afferent fibers and a late phase via suppression of the sympathetic efferent activity [79]. Thus, the control of each of these mechanisms most likely is related to the activity level of the sympathetic system. Later studies have confirmed that sensory afferent fibers are important mediators of SCS-induced vasodilatation, and that at higher, but not painful, SCS intensities C-fibers may also participate in the effect [78–80]. Thus, SCS at the spinal L2–L5 segments activates interneurons, which subsequently stimulate spinal terminals of Transient Receptor Potential V1 (TRPV1) containing sensory fibers, which are mainly of the C-type [81,82]. These fibers transmit action potentials antidromically from the site of stimulation in the spinal segments to the nerve endings in the peripheral tissues. The action potentials cause the production and release of vasodilators, including CGRP that binds to receptors in endothelial cells in vascular smooth muscle. The activation of endothelial cells leads to the production and subsequent release of nitric oxide (NO) that results in relaxation of vascular smooth muscle cells (review, [80]). The overall result is that vascular smooth muscle cell relaxation decreases vascular resistance and increases peripheral blood flow.

In rats with experimental diabetes the TRPV1 containing sensory fibers appear to be among the first to degenerate and this may be one reason why in such rats SCS is less likely to produce peripheral vasodilatation at higher stimulation intensities [83]. However, SCS at lower intensities was still effective in producing this effect in these animals.

The skin flap model in rat is another way to demonstrate the effects of SCS on vasospasm and ischemia [84,85]. The important aspect of these studies is that they were designed to explore if pre-emptive SCS could increase the length of survival of a long-term groin skin flap and to identify possible neuromediators. The superficial epigastric artery was exposed and a detachable microvascular clip used to occlude this single feeding branch to the flap. The clip was removed after 12 h. SCS was applied for 30 min prior to the occlusion. In addition, one group received the CGRP-antagonist CGRP 8–37. After 7 days, the flaps of the control group were necrotized, but the majority of flaps in animals receiving pre-emptive SCS survived the 12-h occlusion. In addition, decreased survival was observed in a group of animals receiving CGRP 8–37. These results provide evidence that pre-emptive SCS may counteract the consequences of tissue ischemia and that CGRP is involved in this effect.

The hypothetical mechanisms behind SCS-induced peripheral vasodilatation discussed above are schematically outlined in ❯ *Figure 138-4.*

SCS in Angina Pectoris

Angina pectoris is often present in ischemic heart disease, and is characterized clinically by intense pain and discomfort in the chest, jaw, shoulder, back, or arm. The development of angina pectoris most commonly occurs when there is an imbalance between the supply and the demand of oxygen in the heart. The common mechanisms that decrease blood supply to the heart are vasospasm and occlusion of the coronary vessels. A large population of patients with chronic angina pectoris is unresponsive to conventional treatments [86]. However, SCS has been used to treat such

◘ Figure 138-4

A diagram illustrating effects of spinal cord stimulation (SCS) applied to the low thoracic-lumbar dorsal columns on mechanisms that produce vasodilation of peripheral vasculature. SCS activates interneurons that may (A) reduce the activity of spinothalamic tract (STT) cells (less probable in the clinical setting); (B) decrease the activity of sympathetic preganglionic neurons (2); (C) reduce the release of norepinephrine from sympathetic postganglionic neurons; (D) activate antidromically the dorsal root afferent fibers (1) with (E) release of calcitonin gene related peptide (CGRP) and nitric oxide (NO). In addition (not illustrated) intra- and extracellular changes increasing survival probability tissue in severe ischemia may be induced by the electrical activation
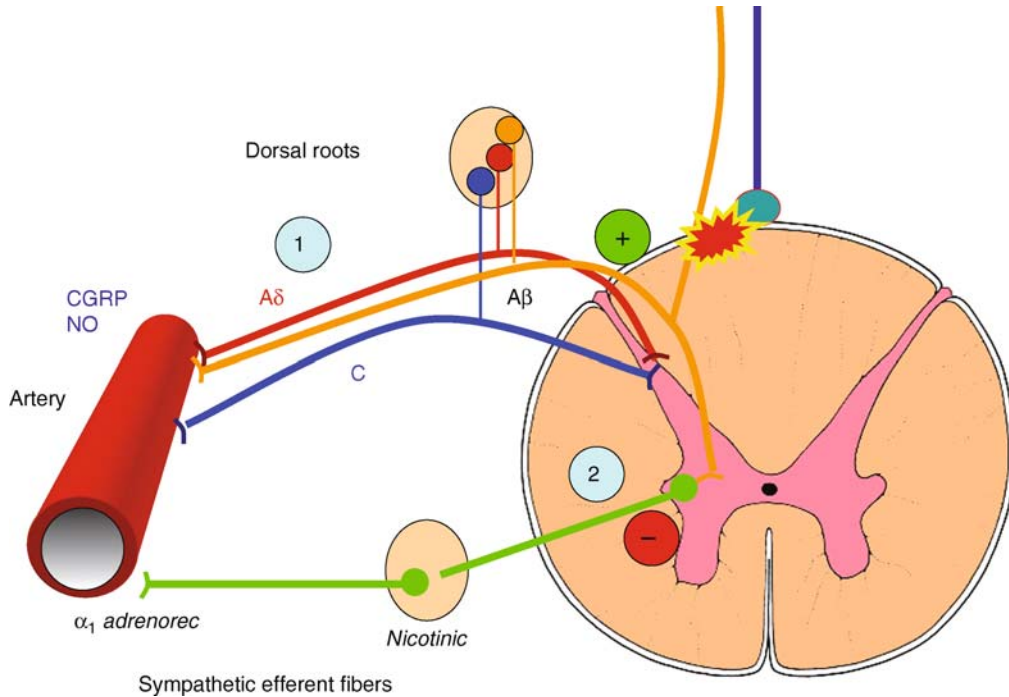
therapy-resistant angina pectoris since the 1980s [87,88] and has proven to very efficacious – but the mechanisms producing pain relief and improved heart function still remain unclear. Although early animal data demonstrated direct inhibitory effects of SCS on cardiac nociception, subsequent clinical studies have clearly proven that SCS does not merely relieve pain but it also improves the function of the heart. Infact, it appears that resolution of cardiac ischemia is 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 (decreased ST changes; reversal of lactate production) as being mainly due to decreased cardiomyocyte oxygen demand (e.g., [89,90]).

Studies have been performed to determine the role of blood flow changes in relieving angina pectoris with SCS. In a human experimental study, PET was utilized to provide some, though weak evidence for flow redistribution with SCS [91]. The same problem was addressed in an animal study by utilizing the distribution of isotope-labeled micro spheres in the hearts of anesthetized and artificially ventilated adult mongrel dogs [92]. The results of this experimental study failed to confirm the existence of a local flow increase in the myocardium or to show any changes in the pressure-volume relationships during SCS. However, a limitation of this study was that occlusions of the left anterior descending coronary arteries were performed in normal hearts. Considering that patients have

long-term coronary ischemic disease, it would be appropriate to conduct such studies in canine hearts with previous infarctions and long-term ischemic episodes.

In patients with compromised coronary arterial blood supply, SCS applied during standardized workloads, comparable to exercise and rapid cardiac pacing, markedly reduced the magnitude of ST segment changes of the electrocardiogram [90,93]. These results support the supposition that SCS may improve the working capacity of the heart. To mimic the development of chronic ischemic heart disease in an animal model of myocardial ischemia, an ameroid constrictor was implanted around the proximal left circumflex coronary artery of a group of canines [94]. The material of the constrictor ring slowly swells and progressively reduces blood flow through the artery and induces development of collaterals [95,96]. This process creates a collateral-dependent myocardial ischemia substrate. In subsequent experiments the chest was opened and the exposed heart was paced at a basal rate of 150 beats/min. An ECG plaque containing unipolar contacts was used to record from 191 sites on the left ventricle distal to the left coronary artery occluded by the ameroid constrictor. In order to stress the heart either angiotensin II was administered via the coronary artery blood supply to the right atrial ganglionated plexus or rapid ventricular pacing was applied via a standard pacemaker.

Both stressors produced an elevation of the ST segments that, however, was markedly attenuated during SCS. In a similar way, ST segment responses were largely 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 a myocardium with reduced coronary reserve. It could be concluded that SCS appears to produce anti-ischemic effects that contribute to improved cardiac function.

Further evidence to support the anti-ischemic effects of SCS on the heart is the observation that pre-emptive SCS seems to have a protective effect on the myocardium. This was illustrated by the finding that the infarct size after controlled coronary artery occlusion is reduced. However, the protective effects of SCS therapy are lost if it is initiated after ischemia induction. Recent studies indicate that SCS-induced release of local catecholamines in the myocardium may trigger protective changes related to mechanisms behind "ischemic pre-conditioning" [97,98] – but without any signs of other ischemic changes. There are also other signs indicating that SCS may induce a state similar to that following a short ischemic period, e.g., the activation of protein-kinase C (for discussion, see e.g., [98]).

In ischemia, the intrinsic cardiac nervous system is profoundly activated [99,100]. If this activity persists it may result in spreading dysrhythmias that lead to more generalized ischemia. An exciting observation is that SCS appears to stabilize the activity of these intrinsic cardiac neurons especially during the ischemic challenge of coronary artery occlusions. As in patients with angina, SCS can reduce the symptoms and signs of ischemia for long periods after the stimulation is terminated. 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 (DeJongste et al., unpublished data; [101].

Some of the pathways and putative mechanisms behind effects of SCS on cardiac function discussed above are briefly summarized in ❯ *Figure 138-5*.

As noted in the introduction a variety of organ functions may be affected by SCS applied at various levels of the spinal cord (❯ *Figure 138-1*). In the concluding paragraphs some further examples of SCS applications are described.

■ **Figure 138-5**

A diagram illustrating effects of SCS applied to the T1-T2 dorsal columns (DC) on neuronal mechanisms that reduce pain and improve cardiac function resulting from ischemic heart disease. SCS activates interneurons that may (1) reduce the activity short-term of spinothalamic tract (STT) cells; (2) modulate the activity of sympathetic preganglionic neurons and (3) stabilize the intrinsic cardiac nervous system (ICN), reduce ischemia and decrease infarct size. In addition a protective effect on ischemic cardiomyocytes related to local release of catecholamines has recently been demonstrated (see text)
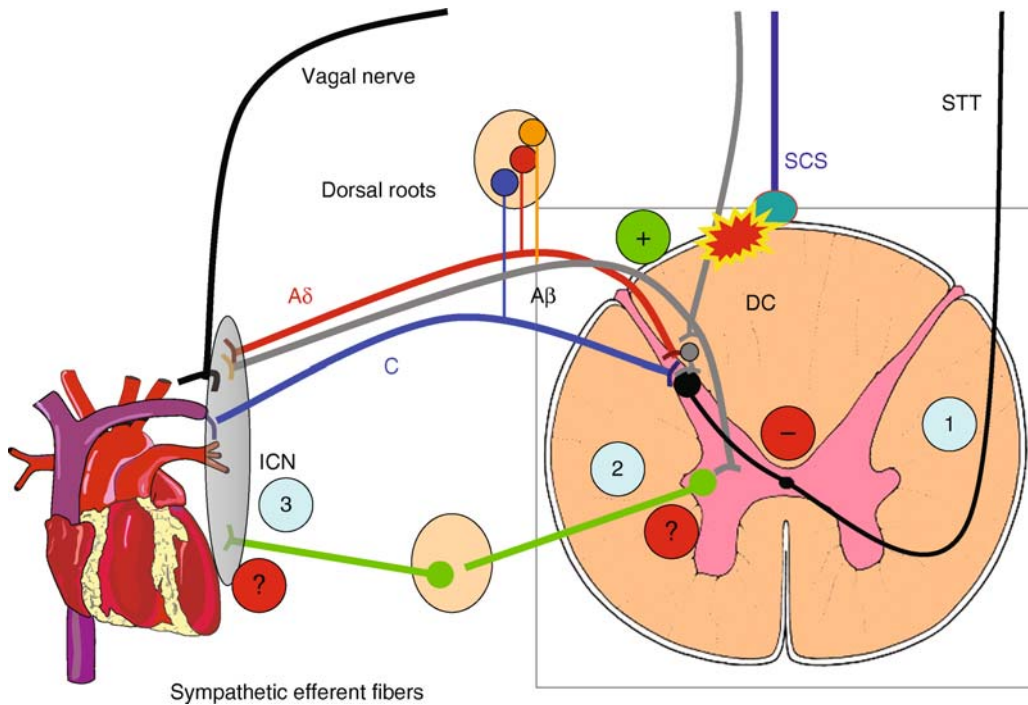
Irritable Bowel Syndrome

Functional bowel disorders, including irritable bowel syndrome (IBS), are common abnormalities of the gastrointestinal tract that are associated with crampy abdominal pain, abnormal bowel habits, and somatic hypersensitivity [102–104]. The mechanisms underlying chronic visceral symptoms of IBS are not well understood, and presently, no effective therapy is available.

Since SCS is beneficial in reducing some types of visceral pain and effectively suppresses hyperexcitable somatosensory and viscerosomatic (bladder) reflexes in patients experiencing spasticity (e.g., [105]), our research team decided to study the effects of SCS as a potential therapy

for visceral pain originating from the gastrointestinal tract [106].

We used a rat model developed by Ness & Gebhart [107] to quantify the level of visceral pain. In this model abdominal muscle contractions are recorded during colorectal distension employed to induce a nociceptive reflex. To resemble the clinical condition of IBS, the model was 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 [108–110]. In this model, a miniature SCS electrode system was chronically implanted with the technique used in our studies on neuropathic pain. After 1 week, animals were anesthetized briefly with

isoflurane to suture a strain gauge force transducer on the right external oblique abdominal muscle. A colorectal balloon was then used to distend normal colons as well as colons irrigated with acetic acid; the number of abdominal contractions both with and without SCS was recorded from the strain gauge. The results showed that SCS significantly suppressed the visceromotor responses that were produced with colorectal distension in both normal rats and in those with sensitized colons. In a subsequent study, a rat model of post-inflammatory colonic hypersensitivity was used and also in this condition SCS significantly reduced abdominal contractions during innocuous distension [111].

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. In fact, there is a case report of a patient suffering from severe IBS who with SCS experienced reduced hypersensitivity and relief of diarrhea [112]. Furthermore, Khan et al. [113] in a retrospective study have shown that SCS can be used effectively to treat a variety of visceral pain syndromes including generalized abdominal pain, chronic non-alcoholic pancreatitis and pain following post traumatic splenectomy. These clinical observations are in agreement with the animal studies and support the notion that SCS might be used to treat various functional bowel as well as other visceral disorders. As a direct consequence of our experiments a randomized controlled trial of SCS therapy in IBS is presently underway.

Other Organ Dysfunctional Syndromes

Bronchial tree. Only one group so far has explored the possible effects of SCS for bronchospasm [114]. They used a sheep model in which bronchospasm was produced by inhalation of an *Ascaris suum* extract. High cervical SCS (C1–C2) markedly decreased bronchomotor tone. If such effects can be demonstrated with more common allergens applied in humans, SCS could develop into a therapy to treat conditions where bronchial constriction is involved.

Urinary bladder. In the 1980s, SCS was commonly used to treat spasticity in multiple sclerosis but with the introduction of intrathecal baclofen this indication was given up. However, decreasing the urgency of voiding was the most marked effect of SCS on urinary bladder spasticity [115,116]. There are also several case reports that discuss the beneficial effects of using neuromodulation on other syndromes such as interstitial cystitis, and mixed low mid-line pain syndromes using a retrograde approach with low sacral, conus or root stimulation (reviews, see [117,118]).

These two examples illustrate that SCS may provide benefits for various autonomic functions and improve organ function as we move the stimulating electrode along the neuro-axis.

Conclusions

SCS induces effects in multiple systems and the benefit for a certain condition may depend on (1) the site on the spinal cord activated (2) selection of a certain biological effect that may be selectively relevant and of benefit in a certain pain syndrome.

Knowledge about physiological mechanisms behind the beneficial effects provides a corner stone for further development of neurostimulation as well as for strategies to support the technique with receptor-active pharmaceuticals in cases with unsatisfactory response to the stimulation per se [42,43]. 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 initiate applied research projects for the basic scientist who has the possibility of testing the ideas in experimental 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.

SCS is a therapy that may be effective in some pain syndromes otherwise resistant to treatment; it is well tolerated for patients, minimally invasive, reversible and with few side effects as compared to chronic pharmacotherapy. Furthermore, in some syndromes, SCS may have its primary effect by improving an organ function, which secondarily can result in attenuation of the pain generating mechanisms associated with the disease.

We firmly believe that SCS at present is an under-used treatment modality. Furthermore, our health care system demands "evidence based" and "mechanism based" therapies, and this amplifies the need to expand our knowledge through research projects aimed at further exploration of physiological mechanisms that are activated by neuromodulation.

Acknowledgments

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