

# Mechanisms of Spinal Cord Stimulation in Neuropathic Pain

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## 1. Introduction

The effects of electrical stimulation of the body or nervous system have been recognized for thousands of years in every culture. It is said that since circa 9000 BC, bracelets and necklaces of magnetite and amber were used to prevent headaches and arthritis (Schechter, 1971). The ancient Egyptians used electrical discharges of the Nile catfish to treat neuralgia, headaches and other painful disorders (Kane & Taub, 1975). The first documented attempt to use electricity for pain treatment appeared in circa 15 AD. A Roman physician, Scribonius Largus, observed torpedo fish shock relieved gout pain and subsequently recommended torpedo fish therapy as a general treatment of pain (Stillings, 1971). The first electrostatic generator was presented by the German engineer Otto von Guericke in 1672, almost a century before the Leyden jar was developed. From then, man was able to generate, store and discharge electricity at any time. It extended its application as physicians were able to provide on-demand electrotherapy in patients for the treatment of pain syndromes.

Since the 18<sup>th</sup> century, electro-analgesia therapy has been embedded in the armamentarium of physicians. Its clinical application in English hospitals was called 'Franklinism', after the American statesman and scientist Benjamin Franklin. He acquired fame after observing that lightening and electrostatic charge on a Leyden jar were identical. Moreover, he was the first to discriminate positive and negative electricity and investigated the effects of muscle contraction after the administration of electrical shocks. The 19<sup>th</sup> century, also called 'the golden age of medical electricity', commenced with the discovery of the electrochemical battery in 1800. Several years later, Michael Faraday exposed the principles of electromagnetic induction which was followed by the introduction of the electric generator in 1848 by Du Bois-Raymond. In those years electrical machines could be found in every doctors consulting room. However, the number of skeptics who depicted electrotherapy as 'medical quackery' grew. Eventually, the Flexner report led to the legally exclusion of electrotherapy from clinical practice in 1910 (Macklis, 1993). The association with 'quackery', growing influence of drug industry and the appearance of radiographic imaging contributed to the loss of interest of science in the phenomenon of electroanalgesia. A reawakened interest in the application of electricity for pain treatment was commenced, as Chaffee and Light presented a method for remote control of electrical stimulation of the

nervous system in the early 1930s (Chaffee & Light, 1934). The contemporary evolution of cardiac pacing techniques contributed to the development of original neural stimulators. In the early years of the 20<sup>th</sup> century, the English neurologist Sir Henry Head postulated the conceptual basics for a theory of central inhibition of pain by non-painful stimuli. This concept was eventually presented as the Gate Control Theory by Melzack and Wall in 1965 (Melzack & Wall, 1965). The gate control theory, which is further explored in paragraph 2.4, states that stimulation of large primary afferent fibers 'close the gate' and inhibit nociceptive processes. After first stimulating their own infra-orbital nerves, Wall and Sweet initiated therapeutic stimulation of peripheral nerves clinically. The initial results were promising, as the first patients experienced partial or complete pain alleviation during stimulation (Wall & Sweet, 1967; Wall 1985). Shealy et al. documented the first clinical application of spinal cord stimulation (SCS) or dorsal column stimulation (DCS) in 1967 (Shealy, 1967a). It was then presented as a novel analgesic method to relieve pain in a variety of chronic pain syndromes. The mechanisms of action of SCS are actually a clinically outgrowth of the Gate Control Theory (Melzack & Wall, 1965). The supposed mechanisms of action of SCS were predominantly described in these 'gating terms'. Initially, evidence for the efficacy of SCS in exerting a significant analgesic effect in a broad spectrum of neuropathic pain syndromes was lacking. In the 70's and 80's several studies appeared with the aim to unravel the mechanisms of action of SCS (Handwerker et al., 1975). Numerous studies investigated the effects of SCS on noxious stimuli in healthy animals. SCS was administrated with current intensities that cannot be used in a clinical setting on patients who are awake. Thus, conclusions obtained from these studies cannot be translated 'from bench to bedside' without question. The development of a reliable animal model of neuropathic pain made it possible to investigate the mechanisms of SCS more thoroughly (Meyerson et al., 1994). As more studies appeared there was more convincing evidence that also supraspinal interactions have an eminent role in explaining mechanisms in which SCS exerts its analgesic-effects. The mechanisms of SCS-induced pain relief became elusive and complex. A significant part of the current knowledge is provided by a few prominent laboratories in this field (B. Linderroth M.D Ph.D. and B.A Meyerson M.D Ph.D., Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden, and Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden. N.Saadé Ph.D., Professor, American University of Beirut, Beirut, Lebanon, and of R. Foreman, Ph.D., Professor and Chair, Department of Physiology, Oklahoma Health Sciences Center, Oklahoma, City, Oklahoma). It was not until recently that a reawakened interest in exploring the mechanisms of action of SCS was presented by Guan et al (Guan et al., 2010). Over the years, much questions has been answered although certain details of the mechanisms of SCS are still controversial and require additional evidence. In the last two decennia, SCS is being increasingly used as a neuromodulation technique in a narrowing spectrum of pain diagnosis. It is estimated that, currently, more than 30,000 SCS systems are implanted every year worldwide (Linderroth & Meyerson, 2010).

## **2. Mechanisms of action**

### **2.1 Physiological anatomy of the spinal cord**

A thorough understanding of the mechanisms of spinal cord stimulation needs a thorough knowledge of the anatomy and neurophysiology of the spinal cord and related structures.

Furthermore, appreciation of the electrical characteristics of intraspinal structures is required. Primary afferent fibers have their cell bodies of the first order located in the dorsal root ganglia. Proximal to the dorsal root ganglion the afferent fibers form a single dorsal nerve root (Light, 1988). Dorsal root fibers have a curve shape and an average diameter of 15  $\mu\text{m}$ . As these axons proceed towards the dorsal column they bifurcate into ascending and descending pathways. A segregation of innocuous and nociceptive afferents occurs as the axons approach the spinal cord. The angle of the fibers varies as they enter the spinal cord, which has major consequences on their excitation thresholds. The dorsal horn of the spinal cord encompasses the grey matter of the spinal cord located dorsal to the central canal. In the 1950s Rexed distinguished six more-or-less different laminae of the spinal grey matter, using cytoarchitectonic criteria (Rexed, 1952). However, based on cytoarchitecture, the spinal gray matter is currently divided into 10 laminae (Whitehouse et al., 1983). Collaterals of large-diameter fibers, which mediate tactile sense and proprioception, enter the dorsal horn and extend mainly to lamina III and IV (Light, 1988). The dorsal column refers to the area of white matter in the dorsomedial side of the spinal cord. Collaterals of large-diameter fibers occupies the largest part, about 85%, of the dorsal columns. Their averaged diameter diminishes from 12 $\mu\text{m}$  at the origin to 8 $\mu\text{m}$  a few segments rostrally (Barolat & Sharan, 2004). The fasciculus gracilis contains neurons of the dorsal column-medial lemniscus system, which carries primary afferents from the lower extremities, and synapse in the nucleus gracilis at the level of the foramen magnum. The fasciculus cuneatus is positioned more lateral in the dorsal column and carries primary afferent signals from the upper extremities (Barolat & Sharan, 2004). As the primary afferent fibers ascend, they gradually shift medially and dorsally. Therefore, the accessibility to dorsal medial-stimulating electrode changes as their location in the spinal cord varies. Posterior located ascending and descending pathways are most accessible at normal stimulation parameters (Oakley & Prager, 2002). Hence, the anatomy and physiology of the spinal cord is complex, but understanding is essential when discussing the issues around mechanisms of spinal cord stimulation.

## 2.2 Electrical stimulation

In spinal cord stimulation, a lead is positioned in the dorsal epidural space and connected to a subcutaneously implantable pulse generator (IPG). The rostrocaudal position of the lead, with multiple contacts, can be altered to enable electrical stimulation at several spinal levels. The cathode is positioned between the dorsal median sulcus and the dorsal root entry zone area. During a stimulation pulse, current flows from a negatively charged active electrode (cathode) to a positively charged electrode (anode). In principle, sufficiently high electrical stimulation can activate every neural structure in close proximity of the cathode (Holsheimer, 2002). However, current flow chooses the path of lowest resistance and is therefore directed through anatomic structures characterized by high electrical conductivity (table 1). Cerebrospinal fluid (CSF) obviously has the lowest electrical resistivity and therefore conduct approximately 90% of injected current, followed by longitudinal white matter. Because its anisotropic characteristics, transverse white matter is proven to be less conductive as is grey matter. Epidural fat and dura mater also demonstrates low conductivity. Vertebral bone is characterized by having the lowest electrical conductivity. Therefore it functions as an insulator and prevents surrounding tissues (e.g the heart and pelvic structures) from being stimulated (Oakley & Prager, 2002; Holsheimer 2002). Initially,

it was thought that dorsomedial electrical stimulation first activated fibers in the dorsal column as the name 'dorsal column stimulation' implies (Shealy, 1967a; Struijk et al., 1993). Coburn introduced the hypothesis that dorsal root fibers may be involved as well, based on a theoretical study which indicated that dorsal root fibers have lower stimulation thresholds than dorsal column fibers (Coburn, 1985). Moreover, the name 'dorsal column stimulation' has been proven physiologically simplistic. Despite the fact that the distance between electrodes and dorsal root fibers is higher compared to the dorsal column fibers, the activation threshold is predicted to be lower. Therefore, a correct position of the lead in the radiological midline is essential to prevent dorsal roots excitation. Several factors have been demonstrated to contribute to lower dorsal root activation threshold, including the curved shape and larger fiber diameter of dorsal root fibers. Dorsal root fibers are activated in the dorsal root entry zone (DREZ), where fibers enter the dorsal horn, because of its lowest activation threshold. Electrical activation of large fiber afferents in the dorsal root or dorsal column by configuration of cathodal and anodal contacts cause a tingling sensation, called paresthesia. Large fiber afferents are activated during stimulation within the usage range and can subsequently 'close the gate'. Excitation of dorsal root afferent fibers produces paresthesias in a few dermatomas, as only rootlets in close proximity of the cathode will be activated. Stimulation of one afferent A $\beta$  fiber may elicit paresthesia in the whole corresponding dermatoma. Lemniscal dorsal column fiber stimulation generates an extensive area of paresthesia coverage, because all dorsal column fibers below the level of the electrode may potentially be activated. A prerequisite for effective pain management is to direct generated paresthesias to cover the whole painful area, which is often difficult to achieve because optimal lead positioning remains difficult. Several empirical and theoretical computer modeling studies were performed in order to obtain a more thorough understanding of factors determining optimal lead positioning (Law & Miller 1982; Coburn 1985). Holsheimer and colleagues investigated whether the geometry of a rostrocaudal array of electrode contacts and contact combination changes the stimulation threshold ratio of dorsal column and dorsal root fibers. Monopolar stimulation with a large cathode favors activation of dorsal root fibers. Preferential activation of dorsal column fibers is effectuated by tripolar stimulation with small contacts and small contact spacings. The problem of optimal lead positioning can be solved by increasing the number of electrode contacts, which increases contact points and anode-cathode combinations and therefore the probability for generating effective paresthesias. The leads are positioned a few segments rostral to the level of where target dorsal roots enter the spinal cord (Barolat et al., 1991). Furthermore, several anatomical and technical factors have been described to determine the topographical area of induced paresthesias, including; pulse width, pulse amplitude, nerve fiber diameter, electrode-spinal cord distance, anode-cathode combination. Empirical studies showed that incomplete paresthesia coverage of the painful area can be compensated by increasing pulse width as the pulse amplitude extends caudally with increasing pulse width (Holsheimer et al., 2011). The therapeutic range of spinal cord stimulation is between the perception threshold (PT) and discomfort threshold (DT) (*figure 1*). The perception threshold is defined as the lowest stimulus amplitude needed to elicit paresthesia. The discomfort threshold is defined as the stimulation amplitude above which paresthesia become unendurable. DT is generally reached at a mean stimulus amplitude of 40-60% above perception threshold. The PT for eliciting paresthesia is related to the activation of dorsal root fibers, indicated by the observation of progressively decreased PT

as the electrode deviates from the midline (Barolat et al., 1991). At cervical and low thoracic level it may occur that some dorsal column fibers are activated when the electrode-to-spinal distance is less than 2 mm. At mid-thoracic level (T4-T7) the electrode-to-spinal distance is largest in most patients. Therefore, it is unlikely that dorsal column fibers are stimulated within the therapeutic range, whereas paresthesiae get a segmentary distribution (Holsheimer & Wesselink, 1997). It is well known that the range of stimulation amplitude between PT and DT is narrow and therefore stimulation results regularly in incomplete paresthesia coverage of the painful area. Only large fiber afferents in the dorsal column and dorsal roots are activated during SCS at voltages within the therapeutic range. In the dorsal column only superficially oriented fibers (0.20-0.25mm depth) with a diameter  $> 9.4 \mu\text{m}$  are activated during SCS (Holzheimer, 2002). The mean diameter of large afferents in the dorsal root is  $15 \mu\text{m}$ . As voltage is increased to approximate DT, smaller fibers ( $\pm 12 \mu\text{m}$ ) are excited as well. These proprioceptive fibers elicit segmental motor effects and uncomfortable sensations, which is a major drawback of dorsal root stimulation. This prevents stimulation amplitude from being increased in order to recruit more dorsal column fibers. To increase SCS efficacy, recruitment of dorsal column fibers is maximized as it generally results in a broad paresthesia coverage of the painful area which is the main goal of SCS. Despite the fact that SCS techniques developed enormously over the past decennia, there are some major drawbacks in the application of SCS that needs to be solved (Holsheimer et al., 1997). Computer modeling provides a considerable contribution in

Compartment	Conductivity ( $\text{S m}^{-1}$ )
Cerebrospinal fluid	1.7
White matter	(longitudinal) (transversal) 0.60 0.083
Grey matter	0.23
Epidural fat	0.04
Vertebral bone	0.04
Dura mater	0.03
Surrounding layer	0.004
Electrode insulation	0.001

Table 1. Conductivity of intraspinal structures. Modified from [Holsheimer et al., 1995]

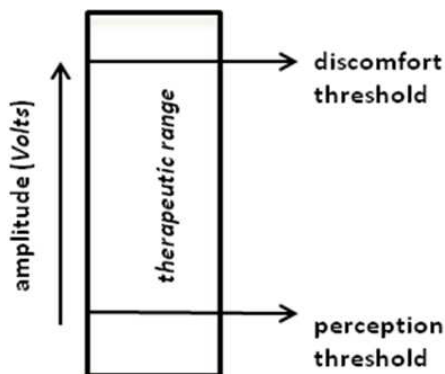


Fig. 1. Therapeutic range in Spinal Cord Stimulation

knowledge of the physiological effects of spinal cord stimulation. Most clinical phenomena observed in spinal cord stimulation are predicted by computer modeling studies, which emphasizes its usefulness. Because of the large intersubject variation in anatomical characteristics, a computer model remains a simplification of reality. Conclusions drawn from these studies needs to be questioned for their clinical relevance (Holsheimer et al., 1997). Close interdisciplinary collaboration is warranted in order to direct future research and provide a better understanding of the effects of electrical stimulation on spinal nerve fibers.

### 2.3 Animal models

At the time of the introduction of spinal cord stimulation in clinical medicine, insights in possible underlying mechanisms of action were sparse. Initially, there seemed to be little interest in the research community to explore the biological basis of the possible modulatory effects of SCS on neuropathic pain. In the beginning of the 1970s some first attempts were made in laboratories to explore the pathophysiological mechanisms of pain in animals. These studies concentrated on the acute behavioral and electrophysiological responses to a short-lived nociceptive (thermal or mechanical) stimulus. Clinical pain syndromes are mostly characterized by spontaneous pain and a hyperesthetic state (e.g. hyperalgesia and allodynia). Therefore, clinical relevancy of behavioral studies of intact animals subjected to acute nociceptive pain is questionable. Simultaneously, the first preclinical studies aimed at the elucidation of the effector mechanism of spinal cord stimulation appeared (Handwerker et al., 1975). The main shortcoming of these studies is that they used healthy anesthetized animals and applied only acute and noxious stimuli. Furthermore, spinal cord stimulation was only shortly applied at high current intensities which cannot be used clinically on conscious patients. Although these experiments are of limited clinical relevance, they gave direction to the design of more appropriate experiments. Of major importance was the recognition of distinct pathophysiological mechanisms elicited by peripheral nerve injury, which differed from that generated by an acute noxious stimulus (Wall & Gutnick, 1974). These findings were followed by numerous attempts to develop a preclinical neuropathic pain model, in which clinical pain states should adequately be mimicked. Since then, many animal models of peripheral nerve injury (trauma, disease, metabolic disorders, and toxins) have been described in literature. Until the chronic constriction model of Bennett was presented in 1988, none of them reported to produce disorders of pain sensations like those that accompany peripheral neuropathies in humans. The inability to produce these sensory disorders in laboratory animals has been a major obstacle to the experimental analysis of the problem (Bennett & Xie, 1988). In addition, the neuroma model, in which a peripheral nerve is transected completely, showed a limited spectrum of somatosensory disorders normally accompanying neuropathies. In particular hyperalgesia and allodynia were not seen after complete deafferentation and neuroma formation. Furthermore, high incidences of autonomy or self-mutilation were reported for rats with complete transections of the sciatic nerve (Wall et al., 1979; Sweet 1981). Bennett developed a model wherein painful peripheral mononeuropathy was produced by placing loosely tied constrictive ligatures around the common sciatic nerve (Bennett, 1988). A few years later, Selzer presented a slightly different behavioral model of neuropathic pain disorders in rats by a tight ligation of a part of the sciatic nerve (Selzer et al., 1990). Kim and Chung ligated an entire spinal segmental nerve in their experimental model for peripheral neuropathy (Kim & Chung, 1992). Decosterd and Woolf presented the 'spared nerve injury model' which comprises a partial lesion of the

sciatic nerve as only the tibial and common peroneal nerves are ligated, leaving the remaining sural nerve intact (Decosterd & Woolf, 2000). This model differs from the previously mentioned preclinical neuropathic pain models as it allows behavioral testing of intact cutaneous areas adjacent to injured denervated regions (Decosterd & Woolf, 2000). In addition to these three extensively used models (the Bennett chronic constriction injury model, the Selzer partial sciatic nerve ligation model and the Chung spinal nerve ligation model), other animal models based on photochemically induced ischaemia in the spinal cord have been described (Watson et al., 1986; Hao et al., 1991; Gazelius et al., 1996). All preclinical pain models have been developed in order to mimic clinical pain states in humans as closely as possible. It was not until 1994 when a research group from the Karolinska Institute concentrated on the effects of spinal cord stimulation on neuropathic pain (Meyerson et al., 1994). They produced experimental models of neuropathic pain as described by Bennett and Selzer, implanted miniaturized electrodes in the awake animals and monitored the effects of stimulation during evoked pain (Bennett & Xie, 1988; Selzer et al., 1991; Meyerson et al., 1994). They applied SCS acutely or chronically with stimulation parameters similar to those used in patients. Since then, only a few experiments focused on the effects of spinal cords stimulation in patients.

**From 'bench to bedside'.** In general, preclinical pain models use a withdrawal response to noxious or innocuous stimulations as behavioral endpoint. In contrary, the numeric rating pain scale (NRS) or visual analog score (VAS) is commonly used in clinical research. This discrepancy makes results from preclinical studies difficult to interpret, as different pain assessment methods focus on different aspects of pain (Mao, 2002). It is important to recognize the restraints of basic research as they can provide in guidelines for the development of clinically relevant studies. Translational pain research comprises a two-way direction. Equitably important as the translation from 'bench to bedside' is the translation from 'bedside to bench'. Guarantying a correct initial translation from 'bedside to bench' makes meaningful translation from 'bench to bedside' possible. Mao described some examples of structural weaknesses in the interpretation of results obtained in preclinical experiments, commonly incorrect generalized to prove their clinical relevancy (Mao, 2002). For example, chronic pain conditions are commonly characterized by the existence of spontaneous pain which is present without obvious stimulation. Prevention of thermal or mechanical stimuli is not sufficient to alleviate this pain. In the clinical setting, thermal stimulation is rarely followed by a persistent pain condition. A persistent pain condition is generally assessed in animal models using stimulus-induced nociception such as thermal hyperalgesia. Clinical significance of these unfiltered results obtained in animal models is doubtful, as thermal hyperalgesia is rarely present in the clinical setting. Furthermore, the understanding of how a chronic pain condition develops after a transient tissue injury is poor. For years clinicians are struggling to explain this phenomenon of central sensitization. In basic research most experiments focused on cellular and molecular changes shortly after nerve injury or inflammation. These observed changes during the early phase are thought to play a key role in explaining pathophysiological mechanisms in persistent pain states. However this is not necessarily true. Moreover, most observed cellular and molecular changes disappear before pain-like behavior does (Mao, 2002). It is important to acknowledge translational pain research as an essential contributor to increase the effectiveness and relevance of both preclinical and clinical research and for determining future research direction. Furthermore, there needs to be more attention for interaction between basic researchers and clinicians.

## 2.4 Neurophysiological mechanisms

The well-known Gate Control Theory (GCT) was proposed by Melzack and Wall in 1965 (*figure 2*). The theory describes in an elegant and concise way, that activation of afferent A $\beta$  fibers attenuates spinal pain transmission (Melzack & Wall, 1965). The GCT hypothesizes that an excess of small fiber activity would 'open' and an excess of large fiber activity would 'close' the 'gate'. Moreover, large fibers have a lower activation threshold than small fibers for depolarization by an electrical field and they may be stimulated selectively. The GCT provided a framework for examining the interactions between local and distant excitatory and inhibitory systems in the dorsal horn (Dickenson, 2002). As formerly mentioned, spinal cord stimulation is actually a clinical outgrowth of the gate control theory. The exact mechanisms of spinal cord stimulation are still largely unknown, but the supposed mechanisms of actions are still predominantly described in these 'gating terms'. One would expect, based on the GCT, that spinal cord stimulation could alleviate nociceptive forms of pain. However, despite a few reports it is still very controversial whether spinal cord stimulation directly attenuates nociceptive pain components. Moreover, spinal cord stimulation is clinically most often administered in specific neuropathic pain conditions. Flexion reflex thresholds of the lower limbs (RIII responses) has been reported to be lowered in neuropathic pain patients, which is in agreement with former experimental findings in rats (Garcia-Larrea et al., 1989). They also showed a close relationship between the threshold of flexor responses (RIII) and the subjective sensation of pain. Spinal cord stimulation induced an increase of these abnormally lowered withdrawal thresholds, which are mediated through alpha and beta fibers. These observations suggests SCS predominantly affects pain related to abnormal A $\beta$  fiber function, as in allodynia ( Handwerker et al., 1975; Carstens & Campbell, 1988; Garcia-Larrea et al., 1989; Meyerson et al., 1995; Oakley & Prager, 2002). Repetitive noxious stimulation of primary afferent fibers after peripheral nerve injury induces long-term changes of the excitability of spinal cord neurons (Rygh et al., 1999). These plastic neural changes involve increased spontaneous and evoked firing rate of wide dynamic range (WDR) neurons in the dorsal horn and contribute to the development of chronic pain. SCS may effectuate a normalization of the hyperexcitability of these wide dynamic range cells in de dorsal horn in response to innocuous stimuli (Yakhnitsa et al., 1999). Therefore, wide dynamic range neurons in the dorsal horn are thought to play a key role in spinal pain transmission and may play the integrative role of the 'transmission' (T) cells as described in the GCT (*figure 2*) (Woolf & Salter, 2000; Guan et al., 2006; Cervero, 2009; Guan et al., 2010). Since the 70's multiple studies suggested that the mechanisms of action of SCS could not solely be explained by interactions of neurons located in the dorsal horn and postulated the existence of supra spinal loops (Nyquist & Greenhoot, 1973; Bantli et al., 1975). In a series of studies Saadé and colleagues demonstrated the contribution of brainstem pain-modulating centres in inhibiting nociceptive processing (Saadé et al., 1985; Saadé et al., 1990; Saadé et al., 1999; El-Khoury et al., 2002). Roberts and Rees have shown that SCS in animals activates the anterior pretectal nucleus, which has descending pain inhibitory influences on lower segments (Roberts & Rees, 1994). Furthermore, SCS produces increased activity in the somatosensory cortex (SI and SII areas) and cingulate gyri. These brain areas activated by spinal cord stimulation correspond to pain pathways involved in processing of somatosensory (SI, SII) and affective components (cingulate gyri) of pain. Hence, during SCS both segmental and supraspinal (spinal-brainstem-spinal loops and thalamocortical systems) pathways are activated and contribute to the inhibition of neuropathic manifestations.



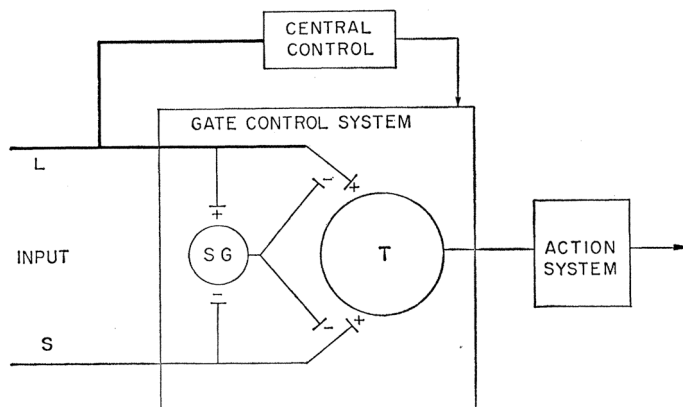


Fig. 2. **The Gate Control Theory.** Central transmission cell (T) cells, located in the dorsal horn of the spinal cord, receive a balanced input of large ( $A\beta$ ) and small ( $A\delta$  and C) fiber activity in peripheral nerves. Inhibitory interneurons, located in the substantia gelatinosa (SG), can be activated by large (L) afferents and can modulate pain transmission via projection to small (S) fibers and central transmission cells. (Melzack & Wall, 1965).

## 2.5 Neurochemistry

Generally, patients use spinal cord stimulation intermittently to alleviate neuropathic pain. It is remarkable that pain-relieving activity continues for several hours after spinal cord stimulation has been switched off. These long-term effects are supposed to result from modulation of neural activity including neurotransmitter systems at the dorsal horn or supra-spinal levels. Little is known about which transmitter systems have a pivotal role in the pain-relieving effects of SCS in neuropathic pain. Only a few human studies have been performed and current knowledge is mainly based on data obtained from animal experiments. As previously mentioned, Meyerson described a suitable animal model comprising sciatic nerve injury and tactile allodynia for evaluating the mechanisms of SCS as treatment modality for neuropathic pain (Meyerson, 1994). Most of these experiments used a microdialysis technique in order to obtain fluid samples during SCS from areas involved. These microsamples have provided some insight into neurochemical mechanisms at the synaps level (Stiller et al., 1996; Oakley & Prager, 2002). There is evidence that substance-P (SP) and serotonin (5-HT) have an inhibitory role in nociceptive transmission in the spinal cord and recently the existence of a descending serotonergic pathways has been suggested (Song et al., 2009). There is evidence that a descending noradrenergic system is involved as well. Analysis of CSF dialysates in decerebrated and intact adult cats showed an elevation of the level of SP and 5-HT during SCS (Linderoth et al., 1992) (table 2). Whether these substances actually participate in the pain modulating effects of SCS in chronic neuropathic pain remains unclear, because most experimental studies investigated intact animals. Several behavioral studies appeared, aimed at elucidating the role of amino acids in exerting pain alleviation during SCS. The main inhibitory neurotransmitter in the central nervous system is gamma amino butyric acid (GABA). Preclinical neuropathic pain studies showed that GABA levels in the dorsal spinal cord of animals with allodynia are significantly lower in animals than GABA levels in nonallodynic nerve-lesioned and intact

animals. It has been suggested that reduced GABA levels might result in hyperexcitability of other neurons involved in processing nociceptive information, in particular 'wide dynamic range' neurons. Experimental studies showed an increased release of GABA during spinal cord stimulation (table 2). Strikingly, increased GABA release was only observed in the so-called 'responders', the rats who showed behavior befitting symptom alleviation during SCS (Stiller et al., 1996). Thus, SCS normalized withdrawal response thresholds in these 'responders' by restoring normal GABA levels. This increased GABA release could be important for the suppression of tactile allodynia in humans. Similar mechanisms could also be involved in the SCS-induced alleviation of pain in patients with peripheral neuropathies (Stiller et al., 1996). In the 'non-responders' group, the rats who did not show behavior indicating symptom alleviation, they did not observe an increased GABA release. In these studies, alleviation of allodynia was defined as a significant increase in withdrawal threshold in response to innocuous stimulation using von Frey filaments administered to the nerve-injured hindpaw. Cui et al. investigated mononeuropathic animals with allodynia, that did not respond to SCS (Cui et al., 1996). They showed that after intrathecal injection of baclofen, a GABA<sub>B</sub> receptor agonist, the animals showed increased withdrawal thresholds and thus potentiated the effect of SCS on allodynia. Actually, 'non-responders' transformed into 'responders' by manipulation of the GABA receptor with subclinical doses of baclofen. Furthermore, the administration of muscimol, a GABA<sub>A</sub> agonist, resulted in a significant but less obvious increase in withdrawal threshold (Cui et al., 1996). The action of GABA<sub>A</sub> and GABA<sub>B</sub> antagonists were also evaluated during the application of SCS. After the administration of a GABA<sub>B</sub> antagonist, 5-aminovaleic acid (5-AVA), a significant reduction of the increased withdrawal threshold was observed during SCS. The intrathecal administration of the GABA<sub>A</sub> antagonist bicuculline had no significant effect. Thus, in particular the GABA<sub>B</sub>-receptor system is likely to be linked to the effects of SCS. Allodynia and hyperalgesia characterizes peripheral hypersensitivity which in fact reflects underlying disturbances in GABA-mediated inhibition and increased levels of excitatory amino acids (Woolf & Doubell et al., 1994). The prime excitatory neurotransmitters, glutamate and aspartate, have a pivotal role in transmission of nociceptive information (table 2). Dorsal horn concentrations of excitatory amino acids have been shown to decrease during SCS, concurrently with antiallodynic effects (Cui et al., 1997). When a GABA<sub>B</sub> antagonist was administered, the SCS-induced reduction of excitatory amino acids was abolished. Thus, SCS might exert its pain reducing effects, at least partially due to activation of GABAergic mechanisms which inhibit the release of excitatory amino acids which are already elevated in neuropathic pain conditions (Cui et al., 1997). Intravenous or intrathecal administration of the central neuromodulator adenosine seems to have potentiating effects comparable with selective GABA<sub>B</sub> agonists (e.g. baclofen). Therefore SCS is thought to exert its analgesic action by both GABA<sub>B</sub> and adenosine dependent systems (adenosine A-1 receptor). Some studies have showed that the cholinergic system is likely to be involved as well (table 2) (Schechtmann et al., 2004; Schechtmann et al., 2008). Subclinical intrathecal doses of clonidine enhanced the effect of SCS on tactile hypersensitivity in an animal model of neuropathic pain, when solitary SCS appeared to be ineffective. A synergistic effect was observed when electrical nerve stimulation and pharmacotherapy were combined. The way in which clonidine exerts its analgesic action is not fully understood. Clonidine, an  $\alpha_2$ -adrenoreceptor agonist, is thought to increase dorsal horn acetylcholine release and nitric oxide synthesis (Xu et al., 2000). Intrathecal administration of a selective muscarinic M<sub>4</sub> receptor antagonist completely abolished the analgesic action of SCS. Endogenous opioids

are not likely to have a significant contribution to the pain alleviating effects of spinal cord stimulation (Linderoth & Foreman, 1999). Most convincing evidence is that effects of SCS are not blocked by the administration of naloxone, which is an opioid receptor antagonist. There are investigators who keep the door open for a potential role of the dynorphin system exerting its effect primarily through the  $\kappa$ -opioid receptor, which has a lower affinity for naloxone (Han et al., 1991). As already mentioned, most knowledge concerning neurochemistry is derived from animal experiments and its clinical significance needs to be explored. However, up to 40% of well selected neuropathic pain patients do not experience significant pain amelioration during SCS. Hence, adjunct pharmacological therapy can provide a major contribution in increasing efficacy of the application of SCS. Lind et al. illustrated the administration of intrathecal baclofen in patients increasing the effects of SCS in neuropathic pain of peripheral origin. These patients initially responded poorly to SCS however they experienced a satisfactory relief during SCS (Lind et al., 2004, Lind et al., 2008). A promising observation was that follow-up obviously demonstrated a sustained pain relieving effect. Most experiments have focused on segmental changes in transmitter systems (e.g. excitatory amino acids, adenosine) to explain the mode of action of SCS. However, 5-HT and noradrenalin might involve supra-spinal circuits and descending inhibitory pathways. The degree of contribution of descending inhibitory pathways compared to segmental mechanisms is currently under debate (Song et al., 2009).

<b>Spinal transmitter</b>	<b>Influence of SCS</b>
<b>GABA</b>	Increased
<b>Serotonin (5-HT)</b>	Increased
<b>Substance-P (SP)</b>	Increased
<b>Norepinephrine</b>	Increased
<b>Acetylcholine (Ach)</b>	Increased
<b>Adenosine</b>	Increased
<b>Glutamate</b>	Decreased
<b>Aspartate</b>	Decreased

Table 2. Spinal transmitters possibly involved in alleviating neuropathic pain during Spinal Cord Stimulation (SCS). SCS may result in a decreased or increased release of a particular transmitter.

### 3. Spinal cord stimulators

#### 3.1 Introduction

Shortly after the gate control theory was proposed by Melzack and Wall, pain research focused attention on the dorsal column as a target for pain management. First reports described they used an anesthetic needle, which was placed in the cerebrospinal fluid at the level of target nerve roots (Melzack & Wall, 1996). An electrode was advanced through the needle and positioned along the dorsal column. Patients experienced significant pain relief during short periods of gentle electrical stimulation (Wall & Sweet, 1967). After realizing electrical stimulation in the close proximity of sensory roots can alleviate chronic pain, more radical procedures were developed in order to allow chronic stimulation of the dorsal column (Shealy et al., 1967a). Shealy and colleagues first investigated the efficacy of dorsal column stimulation in cats in which electrodes were placed by cervical laminectomy. Shortly thereafter they reported the abolition of intractable pain in a patient suffering inoperable

bronchiogenic carcinoma by electrical stimulation of the dorsal columns of the thoracic spinal cord (Shealy et al., 1967b). They placed an intradural electrode dorsal to the spinal cord. The circuit design was based on a modified Medtronic device (Medtronic, Inc, Minneapolis, MN, USA) for the stimulation of the carotid sinus to control angina and hypertension (Govolac, 2010). These procedures comprises major surgical interventions which were often complicated with equipment failure (lead breakage), cerebrospinal fluid leakage or infection. Furthermore, experienced pain relief appeared to be transient. These radicular methods of dorsal column stimulation were replaced in the mid 70's with percutaneously implantable flexible electrodes (Erickson, 1975). A 17G thin-walled Tuohy spinal needle allowed leads to be inserted in the spinal cord and positioned close to the dorsal columns. The development of percutaneous inserted flexible leads allowed a trial of stimulation which mimicks that of the permanent implantable device. During trial stimulation, candidate suitability for permanent implantation is determined. However, the technique of inserting electrodes into the spinal cord seemed inherent to several complications including spinal fluid leaks, postdural puncture headache and infection (bacterial meningitis) (Erickson, 1975). It was realized that permanent implantation of stimulators over the dorsum of the spinal cord under the dura will ultimately fail (Cook, 1976). The technique of epidural electrode placement evolved, as complications like those seen after sub- or intradural electrode implantation, were less likely to occur.

### 3.2 Devices

Spinal cord stimulation systems consist of; trial or permanent (plate) electrodes, implantable pulse generators or radiofrequency (RF)-driven passive drivers. SCS systems have been produced by multiple manufactures; including Medtronic, Cordis, Advanced Neuromodulation Systems, and Boston Scientific. Initially, SCS systems used unipolar electrodes to deliver stimulation. Radiofrequency (RF)-driven passive drivers were nonprogrammable and could not be implanted. Because of the private industry contributions to the development of neuromodulatory systems, equipment improved enormously over the last 40 years. Moreover, progressive advances in cardiac pacemaker technology were utilized in the design and technology of the implantable pulse generators (IPG). Nowadays, systems are composed of complex electrodes arrays, and a implantable pulse generator (IPG) or radiofrequency (RF)-driven radio receiver. The basic goal of these connected components is to provide an isolated electrical pathway to the neural structures being activated. Several electrodes, either percutaneous or plate, with octapolar or even up to 16 electrodes are available. Contact spacing and contact points vary according to the therapeutic goal (e.g quadripolar electrodes for limb pain and octopolar electrodes for axial pain). Furthermore, multi-programmable and even rechargeable power units are available. Plate electrodes are implanted permanently and requires an open procedure and direct visualization for implantation. In the first phase of spinal cord stimulation, laminectomy was required to insert plate electrodes. Over the last years, thinner and more flexible plate electrodes were developed allowing insertion via smaller laminotomy.

### 3.3 Anesthetic management

Anesthetic management of spinal cord implantation comprises general anesthesia or local anesthetic techniques if necessary combined with sedation. When the procedure is performed using general anesthesia, it is difficult for the clinician to achieve optimal lead

positioning. The clinician has to rely on radiographic positioning of the electrodes and/or somatosensory evoked potentials (SSEP). Moreover, it is difficult to assess whether uncomfortable motor effects occur during stimulation. It is well known that dermatomal coverage of paresthesia is a prerequisite for successful treatment, which is impossible to determine when a patient is anesthetized. In order to obtain immediate feedback of patients there are two options remaining; the electrodes are implanted using local anesthetic techniques (in combination with short acting sedatives), or waking up anesthetized patients in between. During the test phase the patient has to be alert and fully cooperative. Local anesthetics are used liberally in order to reduce the need for sedatives (propofol, benzodiazepines) and optimize patient comfort (Barolat & Sharan, 2004).

### **3.4 Spinal cord stimulator implantation**

#### **3.4.1 Percutaneous techniques**

First of all it is important to emphasize the whole procedure of electrode placement is a sterile technique. Infection is potentially hazardous and requires re-operation and/or intravenous antibiotic therapy. Percutaneous placement is performed with the patient in prone position on a X-ray-compatible table with some pillows under the abdomen in order to create a kyphosis which facilitates electrode implantation. Prone position combined with sedation may complicate airway management. Some clinicians prefer the lateral decubitus position as it facilitates subcutaneous implantation of the pulse generator in de buttock or lateral abdominal wall. Moreover, positioning is important as rotation of the spine increases difficulty of electrode placement (Barolat & Sharan, 2004). The electrodes are placed under fluoroscopy guidance to allow anteroposterior and lateral views to ensure midline lead placement and appropriate entry into the epidural space. The insertion point of a 17G Tuohy needle is usually in the midline, although a paramedian approach may also be employed. Several methods have been used to identify the epidural space. Most clinicians use the loss-of-resistance technique. This technique comprises the use of a syringe filled with saline or air. When the needle is advanced through the ligamentum flavum, a sudden absence of resistance to injection is felt. There is no consensus as whether air or a liquid should be used for identifying the epidural space when using the loss-of-resistance technique. It has been hypothesized that the use of liquid expands the epidural space and therefore predisposes to lead migration. Furthermore, liquid flush may attenuate the uniformity of paresthesias (Brook et al., 2009). Alternative approaches to needle placement have been described as in specific circumstances (e.g congenital underdeveloped ligamentum flavum or defects of the ligamentum flavum after spinal surgery) the loss-of-resistance technique seems inappropriate. In these conditions identification of the epidural space using the loss-of-resistance technique is potentially difficult, because the level of resistance is unclear and the risk of false loss is present (Zhu et al., 2011). Zhu and colleagues described an approach for percutaneous lead placement which relies on lateral views of fluoroscopic landmarks to confirm when the needle tip enters the epidural space. When the epidural space is identified, electrodes are advanced rostrally under patient feedback in order to optimize their position. The lead is inserted at least a few centimeters into the epidural space to ascertain its position and prevent migration of the lead. After lead placement it is important to confirm its position in the epidural space as accidental subarachnoidal placement have been described in literature. Implantation of cervical electrodes is advisable below the cervical spine enlargement which extends from about C3 to Th2. For treatment of back and lower limb pain, identification of the epidural space at the level of Th12-L1, L1-2, or L2-3 is

preferred (figure 3). Electrode insertion for upper extremity pain is recommended at the level of Th1-2 or Th2-3 (Barolat & Sharan, 2004; Brook et al., 2009). When optimal lead position is ascertained, for permanent stimulation the leads are anchored and sutured internally. Leads may then be tunneled subcutaneously a few centimeter laterally to the flank, where they may be externalized for trial stimulation or connected to an implanted pulse generator (figure 3) (North et al., 1977). The definite placement of a spinal cord stimulator is preceded by a trial stimulation phase of approximately 7 days. The introduction of a test phase and thorough preoperative screening increased success rates of the procedure. After the trial period, the patient will be asked whether the elicited paresthesias were effective in reducing the pain they experienced before the trial phase. A permanent system is implanted if trial stimulation reduces the patient's pain by more than 50%.

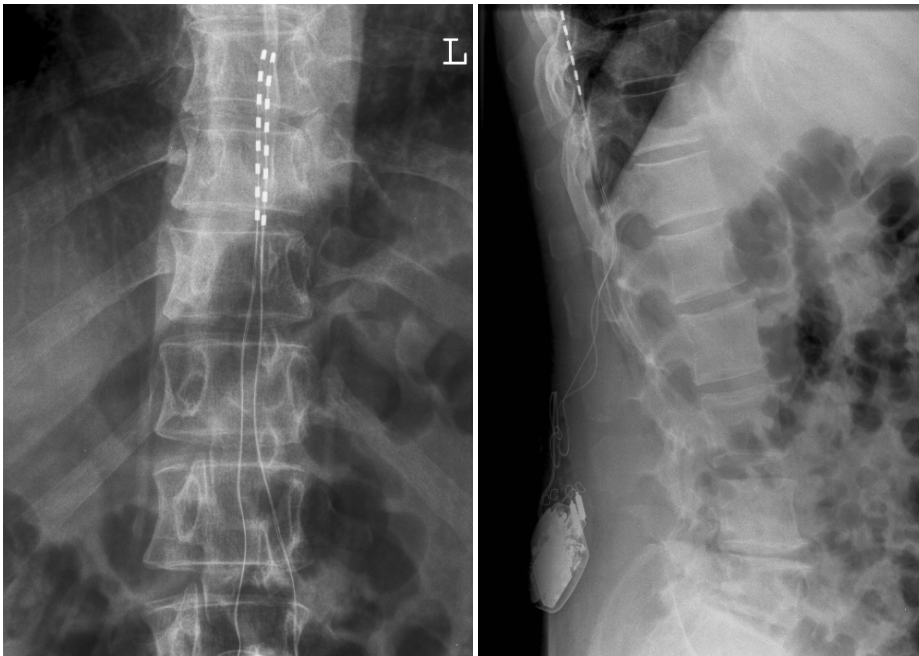


Fig. 3. Percutaneously inserted epidural electrodes including pulse generator

### 3.4.2 Surgical techniques

Most spinal cord leads are inserted percutaneously, as the technique is easier, less-invasive, and less-expensive compared to surgical methods. However, surgical lead placement may become a necessity when patients anatomy prevents leads from being implanted percutaneously; when lead breakage or dislodgement repeatedly requires lead revision; or when trial stimulation of percutaneous leads cannot suffice in adequate paresthesia coverage (Kumar et al., 2009). Surgical techniques comprises electrode positioning under direct vision, after a small laminotomy is performed. Under fluoroscopic guidance the plate electrode is introduced into the epidural space. Laminotomy, up to Th8-Th9, can be performed using spinal anesthesia (Lind et al., 2003). Moreover, during spinal anesthesia not all sensory transmission is blocked which enables intraoperative testing for proper lead

positioning. However, laminotomy is generally performed using general anesthesia whereupon accurate lead positioning relies on radiographic imaging, somatosensory evoked potentials or patients feedback by waking them up in between. After paresthesia is elicited in the anatomic distribution of the patient's pain, a strain relief loop is placed in the epifascial plane and the lead is anchored (Kumar et al., 2009). There are some advantages of surgical leads compared to percutaneous leads; higher success rates (up to 80-90%); less long-term migration rates; and better long term survival have been described (Villavicencio et al., 2000; North et al., 2002). It has been suggested that increased effectiveness of stimulation and therefore higher success rates can be explained by the large sized plate electrodes which causes compression of the cerebrospinal fluid space and bringing electrodes into closer contact to the dorsal column of the spinal cord.

#### **4. Clinical application of SCS in neuropathic pain syndromes**

Neuropathic pain is often underdiagnosed and mistreated. Chronic neuropathic pain is regularly unresponsive to pharmacological and conventional treatment. Therefore, more treatment strategies such as neurostimulation techniques were assessed for efficacy in relieving neuropathic pain. Despite clear evidence for its efficacy was lacking, neurostimulation techniques were increasingly used by clinicians in a variety of neuropathic pain syndromes. The last decennia several studies appeared to provide comprehensive evidence for efficacy of SCS in specific neuropathic pain syndromes. An important development was the introduction of trial stimulation period. During a trial stimulation period the numeric rating pain scale (NRS) or visual analog score (VAS) can be used to document patients pain ratings. A trial period is considered to be successful when patient-reported pain relief was at least 50% at rest and during physical activity. Furthermore, patient satisfaction and potential reduction in analgesic consumption could be assessed. The most common painful neuropathies (Failed Back Surgery Syndrome and CRPS type I and II) for which SCS is clinically used will be discussed.

##### **4.1 SCS for failed back surgery syndrome**

Low back pain patients that fail to improve after (repeated) surgery are most commonly referred to as having 'failed back surgery syndrome'. Studies showed 10-40% of patients who underwent lumbosacral spinal surgery in order to alleviate neuropathic radicular pain experience persistent or recurrent pain. FBSS is thought to be an inaccurate term (Slipman et al., 2002). FBSS comprises a diverse group of disorders in which pain symptoms persists or recurs after lumbar surgery (Slipman et al., 2002). The etiology of FBSS is complex and encompasses multiple possible explanatory etiologies, which can be classified as surgical (e.g internal disc disruption, canal stenosis, epidural fibrosis) or non-surgical (e.g radiculopathy, degenerative disc, Facet syndrome). Pain in FBSS is most commonly considered to be of neuropathic origin. However, several studies showed that neuropathic and nociceptive pain are often concurrently present in FBSS patients and it is difficult to isolate the neuropathic component. The armamentarium of clinicians comprises pharmacological, physical, psychological and interventional techniques. In many FBSS patients pharmacological treatment is insufficient and the efficacy of interventional techniques is only modest. Neuropathic pain in the Failed Back Surgery Syndrome (FBSS) is the most common indication for the administration of SCS. Turner et al were the first to present a systematic literature synthesis to analyze the long-term risks and benefits of spinal cord stimulation for patients with failed back surgery syndrome (Turner et al., 1995). They concluded that approximately 50

to 60% of FBSS experienced a clinically significant pain relief of more than 50% during SCS treatment at long-term (mean, 16 months; range, 1-45 months) follow-up visits. Furthermore, North et al. presented some evidence in favor of SCS in relieving neuropathic pain compared to reoperation for FBSS, although results did not reach significance (North et al., 1994). SCS provides significant increased pain alleviation compared to conventional treatment when administered in carefully selected FBSS patients suffering neuropathic pain. Furthermore, SCS provides improved functional status and quality of life (Kumar et al., 2007). It appears that SCS diminishes continuous and evoked pain (in particular tactile/thermal allodynia), while acute nociceptive pain is unaffected (Mailis-Gagnon et al., 2007). According to EFNS (European Federation of Neurological Societies) guidelines there is evidence that SCS is efficacious for failed back surgery syndrome (FBSS) (grade B recommendation) (Cruccu et al., 2007). The indicated evidence is Level II-1 or II-2 for long-term relief in managing patients with failed back surgery syndrome (Frey et al., 2009). However, a Cochrane review published in 2004 concluded there is limited evidence for the effectiveness of SCS in FBSS (and CRPS type I) and stated that more randomized clinical trial are needed to determine the effectiveness of SCS in specific neuropathic pain syndromes (Mailis-Gagnon et al., 2004).

#### 4.2 SCS for complex regional pain syndrome

Evan introduced the name reflex sympathetic dystrophy (RSD) in 1946, formerly known as causalgia in the 19<sup>th</sup> century. Synonyms for RSD include; Sudeck's atrophy, posttraumatic pain syndrome, painful posttraumatic dystrophy, algodystrophia and algoneurodystrophia (Albazaz et al., 2008). RSD did not correctly reflected the symptoms the syndrome comprises and it assumes involvement of a sympathetically maintained reflex arc, which is controversial. Therefore, it was replaced with the name Complex Regional Pain Syndrome (CRPS) by the International Association for the Study of Pain (IASP). Symptoms and signs includes sensory, motor, autonomic dysfunction and trophic changes. CRPS can be divided into two categories: Type 1 (RSD), in which there is no evident nerve trunk injury but all the clinical features are present. Type 2 (causalgia), in which nerve trunk injury can be demonstrated. Additional differentiation is the distinction of 'sympathetically maintained pain syndrome' (SMPS) and 'sympathetically independent pain syndromes' (SIPS), based on the role of the sympathetic nerve system. SMPS is characterized by an augmented activity of the sympathetic nerve system which maintains neuropathic pain. SMPS can be differentiated from SIPS by the observation of pain alleviation following blockage of the sympathetic outflow tract. Several other factors, psychological, viral infections, peripheral nerve injury and systemic neuropathic processes, are important in maintaining neuropathic pain in SIPS. In 10% of the patients, possible maintaining factors remain unclear. CRPS is characterized by a minor injury (trauma of surgery) followed by severe pains which are disproportionate compared to the inciting event. The IASP developed explicit criteria to facilitate and demarcate the complex diagnosis of CRPS. However, the clinical diagnosis of CRPS remains difficult and is mainly based on the combination of a suggestive history and thorough physical examination. The pathophysiology of CRPS is largely unknown. Increased regional sympathetic tone was initially suggested to be of major importance in clarifying pathophysiological mechanisms. However, several alternative hypotheses have been presented based on current evidence. There is growing evidence that pathophysiological mechanisms of CRPS I are sited in central pathways, which is probably illustrated best by the presence of myoclonic activity (Sandroni et al., 1998). One hypothesis suggests the existence of a vicious circle, which is initiated by peripheral tissue injury



leading to augmented afferent input to the dorsal horn. This increased activity is subsequently followed by increased sympathetic activity, which is thought to maintain augmented input of afferent signals to the dorsal horn. Another hypothesis suggests that activation of peripheral A $\delta$  and C-fibers following tissue injury excites wide dynamic range (WDR) neurons, which subsequently become sensitized to afferent input (Roberts, 1986). Currently, there is no curative treatment for CRPS available. Numerous studies investigated the efficacy of pharmacological treatment (e.g. opioids, nonsteroidal inflammatory drugs, NMDA antagonists, antidepressants, antiepileptics, free radical scavengers and corticosteroids) in CRPS patients. Most pharmacological therapies are used to provide some analgesia during physical therapy, which is generally recommended as first-line treatment. Physical therapy can be helpful for reducing pain and improving active mobility in patients with CRPS I compared to occupational therapy (Oerlemans et al., 1999). Furthermore, several regional anesthesia techniques (e.g. sympathetic blockade, sympathectomy) have been investigated. Patients who experience pain reduction after a diagnostic sympathetic blockade may be candidates for regional anesthetic blockade. Although evidence for its effectiveness is lacking, sympathetic blockade (e.g. epidural infusion of anesthetics) is an important element in the armamentarium of clinicians. Invasive sympathectomy (chemical, surgical or radiofrequent) can provide long-term sympathetic blockage and long-term pain reduction in significant number of CRPS patients (Bandyk et al., 2002). However, recurrence of pain symptoms, possible due to regeneration of sympathetic chains, have also been described (Bandyk et al., 2002). However, because of its irreversibility and relative high complication rate (e.g. Horner syndrome, compensatory hyperhidrosis) it is generally considered as final therapeutic option. SCS can modulate neuropathic pain pathways and has therefore extensively been investigated for its efficacy in relieving pain in CRPS patients. Several attempts were made trying to elucidate the mechanisms by which SCS provides pain alleviation in CRPS patients. These possible mechanisms have been extensively described in preceding paragraphs. Several studies showed SCS to be effective in alleviating pain in CRPS patients in up to 80% and is a generally accepted treatment modality for CRPS (Bennet & Cameron, 2003; North et al., 2007). Kemler showed SCS in combination with physiotherapy provides a significant alleviation of neuropathic pain in CRPS patients at 6 months and 2 years compared to physiotherapy alone (Kemler et al., 2006). Ongoing research demonstrated SCS is also effective in the treatment of CRPS I in the medium-term. There is some recent evidence it also provides long-term efficacy, high percentages of patient satisfaction and the ability to improve functional status (Kumar et al., 2011). The first years of SCS treatment are more expensive compared to conventional therapies, mainly because of one-time purchasing the costly equipment and conducting a screening period. In life-time analysis showed favorable cost-effectiveness of SCS compared to conventional treatment modalities (Kemler et al., 2002). SCS is a safe, minimally invasive and reversible procedure. A major advantage is the possibility of patient selection during a trial stimulation period, before definite implantation is commenced. The majority of complications that occur are minor and correctable in which infection, lead breakage, battery failure and electrode migration were most common (Bennet & Cameron, 2003; Cameron, 2004). Its advantages compared to invasive sympathectomy are obvious. However, most studies have been retrospective or comprises small-cohorts with a limited follow-up period. There is some evidence in favor of SCS in CRPS type II patients. No firm recommendation can be made because literature comprises only class IV studies (Bennet & Cameron, 2003). Therefore, no clear-cut conclusion can be drawn at present and its application in CRPS I and II patients is still under debate.

### 4.3 Conclusion

In conclusion, most systematic reviews focused on the efficacy of SCS in failed back surgery syndrome and CRPS I. SCS has a grade B recommendation for administration in FBSS and CRPS I. However, the value of these systematic review is limited because of the heterogeneity of the literature. Several other specific neuropathic syndrome have not been extensively studied and more randomized clinical trials are urgently needed, before the use of SCS can be recommended without question in specific neuropathic pain syndromes. At present it is unclear at which point in treatment SCS must be considered, which patient factors can predict treatment successful and optimal stimulation parameter needs to be explored (Frey et al., 2009).

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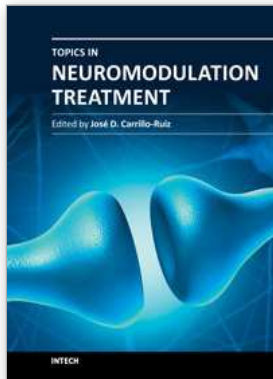
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"Topics in Neuromodulation Treatment" is a book that invites to the reader to make an update in this important and well-defined area involved in the Neuroscience world. The book pays attention in some aspects of the electrical therapy and also in the drug delivery management of several neurological illnesses including the classic ones like epilepsy, Parkinson's disease, pain, and other indications more recently incorporated to this important tool like bladder incontinency, heart ischemia and stroke. The manuscript is dedicated not only to the expert, but also to the scientist that begins in this amazing field. The authors are physicians of different specialties and they guarantee the clinical expertise to provide to the reader the best guide to treat the patient.

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