

## Mechanisms, Actions and New Paradigms: Spinal Cord Stimulation for Pain Management

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### Abstract

Ever since the discovery of Spinal cord stimulation (SCS) in the late 1960s, it has been widely used as a treatment option for chronic neuropathic pain management. SCS has succeeded clinically in a subset of managing chronic neuropathic pain syndromic conditions. It has several limitations as well such as insufficient pain relief or control, uncomfortable sensation called paresthesia etc. These limitations pushed the conventional methods to the need of developing new targets or paradigms for Spinal Cord Stimulation like the dorsal root ganglion stimulation, burst waveform stimulation and high frequency Spinal cord Stimulation. The aim of this review is to provide a brief and concrete detail on the mechanisms and actions of SCS.

**Keywords:** SCS (Spinal Cord Stimulation), DRG (Dorsal Root Ganglion), HF Stimulation (High Frequency Stimulation)

### Introduction

Spinal cord stimulation is indicated as an FDA approved treatment option for multiple chronic neuropathic pain syndromes, including failed back syndrome, complex regional pain syndrome, diabetic poly-neuropathy and post spinal cord injury pain. Spinal cord stimulation (SCS) procedure requires one or two electronic chips which are also called as SCS leads and these leads get placed in the epidural space. Probe Electrodes are usually placed on top of the dorsal column of the spine. The reason for this is, the nerve roots associated with the painful dermatomes are considered that they enter the spinal cord from the dorsal column. Shealy, *et al.* first introduced SCS in 1967. Since then it has evolved as a treatment option for chronic neuropathic pain management [1].

### Conventional-SCS

Conventional spinal cord stimulation was first demonstrated by Shealy, *et al.* Conventional stimulation is usually applied with frequency ranging from 40 to 80 HZ and pulse width varying between 120 to 450 to look for intensities which can induce tingling sensation or paresthesia [2]. Melzack and wall, in their study, first elucidated that conventional SCS therapy is based on the gate control theory. In SCS, the electrical pulses are delivered to activate A-Beta fibers in the dorsal column. These impulses directly affect on antidromic transmission which activate inhibitory interneurons in the spinal dorsal horn. These interneurons modulate incoming nociceptive input from A-Delta and C fibers and release the inhibitory neurotransmitter Gama aminodromic acid (GABA), thereby closing the gate. The closed gate prevents transmission of nociceptive signals to the brain which directly inhibits the pain sensation [3]. Preclinical studies have established the involvement of the neurotransmitter GABA and the inhibitory GABA-ergic interneurons in the mechanism of underlying conventional SCS mediated analgesia. A few animal studies demonstrated that spinal column stimulations increased the GABA concentration in the dorsal horn region in the neuropathic rat's model [4]. Furthermore, Janssen, *et al.* showed in their study that there was reduced intracellular GABA immune-reactivity in the dorsal horn of rats with Partial Sciatic Nerve Ligation (PSNL) after few minutes of conventional spinal cord stimulation [5]. From above all studies, it was concluded that conventional SCS increased GABA concentration into the extracellular area

in the dorsal horn region. These studies hence forth concluded that pivotal mechanism was the underlying mechanism of the conventional SCS for pain control [6-8]. Early evidence for the SCS mechanism was based on a study by Saadé, *et al.* and in that study they demonstrated that conventional SCS inhibited dorsal horn neurons [9,10]. Hence, conventional spinal segment stimulation results in the activation of supra-spinal areas which modulate incoming nociceptive signals at the spinal levels through their descending projections. Earlier studies also showed that those rostral ventromedial medullas (RVM) were involved in the modulation of pain via serotonergic input to the dorsal horn [11]. Like serotonin, nor-epinephrine is also involved in mediating conventional spinal segment stimulation induced anti-nociception as well and this showed increase in the nor-epinephrine synthesis in the locus coeruleus by SCS [12,13]. In addition, orthodromic activation of A-beta-fibers causes the sensation of paresthesia.

### Dorsal root ganglion (DRG) stimulation

As technology improves, the stimulation pattern also needs to improve, so accordingly new medical technological advancements have opened new ways for us to design new targets areas for Spinal cord stimulation systems, such as the dorsal root ganglion (DRG) stimulation. Few studies showed that dorsal root neurons transmitted sensory inputs to the central nervous system from the periphery. In DRG neurons, pathological changes are observed after nerve injury, which contribute to acute chronic neuropathic pain [14-16]. DRG somas modulate the pain transmission at their connection to the axon and to the T-junction. This T-junction can (1) Stop signals of action potentials (APs), (2) It can actively assist in the production of APs, and (3) It can act as a low pass filter, (4) It can selectively allow the multiplications of APs to the dorsal horn region [17-20]. Previously many clinical studies have shown that DRG stimulation is an effective stimulation in the terms of relieving pain [21,22]. Despite of all the successful clinical trials, the main mechanisms of DRG stimulation are still largely unknown. Preclinical trials have shown that the dorsal horn is not involved for GABA release [23] but an adjustment role has been hypothesized in the DRG via GABA [24]. Furthermore, clinical studies showed changes in bold response of brain areas associated with pain [25] and also reduction of neuronal excitability due to DRG stimulation [26].

### Novel SCS pattern and their mechanisms

As clinical trials increase with DRG SCS system, at the same time there is a need to design new targets for covering more areas with SCS treatment, and keeping this in mind, new SCS paradigms have been developed and implemented like Burst and High Frequency (HF) stimulations. According to previous studies, conventional SCS develops paresthesia whereas HF and burst SCS stimulation are paresthesia-free. Previous clinical studies have shown similar high efficacy using burst or HF-spinal segment stimulation as with conventional stimulation. Though these novel SCS patterns gain more attractions in current SCS therapy, there are still needs for more randomized clinical trials for these novel SCS patterns to find out its superiority over conventional SCS pattern. According to these, two new SCS patterns and their clinical trials gained more interests to find out exact mechanism of actions of these two paradigms regarding their charge delivery actions and how these affect on the nervous systems. So far, focuses are on the single programming for spinal segment stimulation which needs to change and area of interest should be on amplitude and pulse width because those two parameters regulate the charge delivery and the amount of charge delivery determine the pain gateway to control the pain [27-30].

### High-frequency (HF) SCS

The hypothesis behind the high-frequency stimulation is it mainly distributes tonic energies on the implanted area of the spinal segment and the frequencies vary from 1 to 10 kHz, depending on the delivery of more charge per second as contrast to the conventional way of spinal segment stimulation. Both conventional and high frequency stimulation deliver stream of pulses in a consistent way but the main contrast is in the frequency and amplitude distribution between the two patterns which give the impressions of different neural activations mechanism. It is suggested that high frequency stimulation on the spinal segments do not activate A-beta axons in the dorsal column, which may explain the absence of paresthesia. In spite of different clinical trials, the main hypothesis for high frequency stimulation is still unclear and implemented methods of actions need to be elucidated more deeper way.

Currently, there are three main hypotheses [27,30]:

- (1) High frequency stimulation produces depolarization blocks, stopping the proliferations of action potentials;
- (2) High frequency stimulation produces disorganized pulses which may be involved in false responses on the neuronal activity in the spinal 'gate'.
- (3) High frequency stimulation may produce temporal combined responses, where multiple impulses on their own are not sufficient and produce neuronal activation within a certain time frame.

### Burst SCS

Burst stimulation diverge from conventional and high frequency stimulation as pulses are delivered to the thoracic segment of the spine in a group, of high frequency, separated by long period of time frame which is known as inter-pulse interval also. Compared to conventional spinal stimulation, burst has a lower charge per pulse, whereas in conventional methods the charge per second is considerably very high [31]. The amplitude per burst session has shown to be important for stopping the activation of the pain spreading neurons in the dorsal horn of rats [32]. Interestingly, the way of actions of Burst stimulation and conventional stimulation are both shown to involve the GABA-ergic interneuron's activation in the spinal dorsal horn [33]. In clinical studies, it has been demonstrated that pharmacological therapies and intrathecal way of delivery of GABA-A and GABA-B antagonists were shown to compensate the pain-controlling effect of both conventional and burst stimulation [33]. Considering this fact, it is highly recommended that GABA signaling has to be part of the main actions in burst stimulation. Later on, delayed fade-away effects are also demonstrated in various preclinical trials on the effect of Burst stimulation as compared to conventional way of stimulations in chronic neuropathic animals [34]. Thereby, it is elucidated that the detained fade-away effects with Burst stimulation is because of activation and involvement of supraspinal areas. To support this hypothesis, both electroencephalography and imaging studies have been done which showed that burst stimulation activates supraspinal areas [35,36]. It is also concluded that burst stimulation activates both the medial and lateral spinothalamic tract whereas conventional stimulation only activates the lateral [37].

### Closed-loop SCS

The burst or high frequency or conventional way of stimulation, described in above spinal cord stimulation paradigms, deliver current to the dorsal column of the spinal segments by fixed input, which means all the stimulation parameters (i.e. frequency, pulse width, inter-pulse interval, and amplitude) are unchanged during stimulation time. This way of stimulation usually refers to as open-loop system stimulation. Conventional stimulation of the dorsal column segments generates Evoked Compound Action Potentials (EC-APs), which is usually used to measure A-beta fiber recruitment [38]. A study by Parker and colleagues demonstrated EC-APs in chronic pain patients undergoing spinal stimulation, who later on discovered that EC-AP amplitude increases with increasing spinal stimulation current. In addition to this study, the distinction between comfortable and uncomfortable stimulation intensity could be analyzed based on EC- AP shape [38]. These findings helped to design new patterns of stimulation which are now called as closed-loop spinal cord stimulation system, where the potency of conventional stimulation patterns modify themselves without any interruptions by measuring EC-APs which adjust them to a proper point of pleasant stimulation and provide maximum pain control, with the help of changing input energy (i.e. amplitude) of a feedback mechanism [39]. Post one year follow-up, clinical study shows a prospective and multicenter single-arm study (Avalon trail) [40] and a double-blind RCT (Evoke trail) [41] on EC-AP-controlled closed-loop spinal cord stimulation showed sustained significant pain relief [40,41] and also showed superiority over open-loop spinal cord stimulation system [42]. However, proper clinical investigations require finding out exact mechanisms of underlying EC-AP-controlled closed-loop SCS which still needs to be designed and categorized.

## Conclusion

Above this review, it is demonstrated that conventional way of spinal cord stimulation is a valuable treatment option for neuropathic pain managements. This therapy mainly acts over implanted area of spinal cord and stimulate that spinal region via induced actions on GABA release from stopping interneurons in the spinal dorsal horn. At the same time, it is demonstrated that conventional spinal stimulation also modulates neuropathic pain through a supraspinal-spinal feedback loop with the help of serotonergic descending fibers. Considering this and to overcome limitations of conventional spinal stimulation, not all patients were treated with conventional methods of spinal cord stimulation as they experienced insufficient pain relief and also the presence of uncomfortable paresthesia. On the contrary, conventional stimulation has been evolving and expanding to a new paradigm and includes additional targets, the dorsal root ganglion stimulation, multiple novel stimulation patterns, such as high frequency stimulation and burst stimulation and in new way of an EC-AP-controlled closed-loop spinal stimulation system. The actions of stimulation at the dorsal root ganglion as well as the new spinal segment stimulation patterns still require more clinical trials for clearly elucidating its mode of actions. On the other hand, it looks that Burst stimulation not only stimulates sensory but also stimulates on specific regions of dorsal horn for emotional, affective and motivational aspects of pain to relief. Analysis of reflex-based sensory pain in addition to affective, emotional and motivational aspects of pain is also important to analyze the exact mode of actions of new spinal segmental stimulation patterns in the treatment of neuropathic pain management.

## Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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