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Spinal Cord Stimulation: Clinical Efficacy and Potential Mechanisms

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INTRODUCTION

The field of spinal cord stimulation (SCS) owes its inception to the concept of gate control theory (GCT), put forth by Wall and Melzack in their landmark 1965 paper, which proposed that "control of pain may be achieved by selectively activating the large, rapidly conducting fibers".[1] The first reported clinical application of dorsal column stimulation came 2 years later, and the field has gradually expanded ever since. Today, an estimated 50,000 spinal cord neurostimulators are implanted annually.[4, 5] The growth of neurostimulation has been fueled in part by the increasing prevalence of neuropathic pain,[6] in particular the upsurge of patients with failed back surgery syndrome (FBSS),[78] and the attempts to use strategies other than chronic opioid therapy to treat chronic neuropathic pain.

Although SCS technology has developed greatly in the past decades,[9] the last few years have witnessed the introduction of several novel devices and stimulation modalities, including high- frequency technology,[10, 11] dorsal root ganglion (DRG) stimulation,[12] burst stimulation,[13] and other paradigms.[14–16] Some of the new waveforms, such has high-frequency stimulation, have challenged our ability to elucidate their mechanisms of action within the framework of the GCT. Fundamentally, SCS, regardless of type, involves the generation of electric fields between metal contacts residing in the epidural space. The applied fields change the electrical potential across membranes based on the properties of tissues near the electrode, such as the dura, layer of cerebrospinal fluid, and white matter. In the case of excitable membranes, such as those found in nearby dorsal column axons, the electric field can trigger one or more action potentials, depending on the bioelectrical properties of the axon (diameter, myelination status, and electrical threshold). As electrodes are typically placed near the physiological midline of the dorsal columns (except in the case of DRG stimulation), electrical stimulation causes activation of dorsal column axons, resulting in orthodromic and antidromic transmission of action potentials that generate segmental and supraspinal effects[2, 14, 17–20] (Figure 1). Large diameter axons have low thresholds for firing action potentials, and thus are preferentially activated over smaller fibers. The bioelectrical properties of the spinal cord have received signficant attention, and

a number of reviews have been published on this topic.[14, 21, 22] Conventional SCS preferentially activates large Ap dorsal column axons. This activation can be measured as action potentials propagated antidromically in peripheral nerves,[23, 24] as epidural action potentials,[25, 26] as somatosensory evoked potentials recorded on the scalp,[25] and as muscle twitches in limb and trunk muscles,[27, 28] and felt by patients as paresthesias.[29] In addition to provoking action potentials, electrical stimulation alters the membrane potential of neurons and other cell types exposed to electric fields, thereby altering electrochemical properties of the segments affected.[17, 30]

Electrical charge can be delievered via various waveforms, and net effects depend on waveform characteristics. The waveforms generated can be characterized in relation to the pulse amplitude, width, and frequency, which combine to deliver a specific amount of charge to tissues. The amount of charge delievered is believed to be fundamental to the electrical fields generated and subsequent recruitment of nerves.[14, 21, 31] As device electronics have improved, the ability to deliver electrical impulses precisely with specific waveforms and various cathode/anode combinations has grown exponentially. Conventional, burst, and high-frequency stimulation differ based on frequencies, waveform patterns, and how charge transfer is balanced (Figure 2), and thus produce different patterns of activation of axons and adjacent neural tissues. Burst is unique in how charge balance is handled: the burst of five individual constant current pulses is charge balanced at the end of burst, instead of for each spike (Figure 2, panel B).[13] Signficant debate exists regarding what fibers are activated by SCS, and how fiber activation varies for the different waveform patterns and intesities.[21, 22, 32–34] Furthermore, it is unclear which specific fibers need to be activated to achieve optimal pain relief, and how activation patterns change in chronic SCS.

CONVENTIONAL WAVEFORMS

Clinical Efficacy

FBSS, defined as peristent or recurring pain despite surgical treatment, is a common condition, present in 10 to 40% of patients after lumbar spine surgery.[7] The condition is believed to be caused by neuropathic back and leg pain, and is associated with high levels of suffering, decreased function, high unemployment rates, and escalating medical costs.[35–37] This poorly understood clincal entity lacks good treatment options, and a number of published reports have described studies of SCS in this population (Table 1).[38, 39]

Numerous early case series and prospective studies showed SCS to be beneficial in this patient population.[37] North et al.[40] conducted the first radomized controlled trial (RCT) comparing conventional SCS to repeat lumbar spine surgery. Among 60 patients randomized to either SCS or reoperation, signficantly more patients in the SCS group than in the reoperation group had 50% or greater pain relief and patient satisfaction. This report clearly established that for FBSS, SCS is superior to reoperation for patients meeting criteria for surgical intervention. In another classic RCT, the PROCESS trial, Kumar et al.[36, 41] compared conservative medical management (CMM) to SCS in this patient population (48 CMM, 52 SCS patients) and measured outcomes at 6, 12, and 24 months. SCS proved superior to CMM at all time points for leg pain (≥50% reduction), function, and health-related quality of life. In one of the largest RCTs to date, optimal medical management

(OMM) was compared to OMM + SCS in 218 patients.[42] This study is completed, and, although the full report is not yet published, preliminary reports suggest that a significantly higher proprotion of patients in the SCS group than in the OMM-only group reached the primary outcome, defined as ≥50% reduction in low back pain intensity at 6 months.[43] In contrast, a study that included only patients with FBSS on worker's compensation, found no differences in the composite primary outcome (≥50% improvement in pain, function, and opioid use) between a group receiving SCS, a usual care group, and a group receiving specialty care through a pain clinic.[44]

Conventional SCS was shown to be superior to physical therapy in patients with complex regional pain syndrome (CRPS) in a study by Kemler et al.[45] The authors reported a mean reduction of 2.4 cm on the visual analog scale (VAS) for pain at 6 months in the intention-to-treat analysis, and 3.6 cm for those actually treated with SCS. The pain scores for the control group increased by 0.2 cm at 6 months. Follow-up at 5 years revealed that pain relief gradually decreased for patients receiving SCS, as mean VAS score showed a 2.5 cm decrease from baseline (compared with a 3.6 cm decrease at 6 months). In contrast, the control group that recieved physical therapy exhibed a 1 cm decrease at 5 years (p=0.06).[46] Conventional SCS was compared to medical management in patients with painful diabetic peripheral neuropathy in two prospective RCTs. These studies demonstrated the superiority of SCS over best medical management, as approximately 60% of patients in the SCS group, but only 5–7% of patients in the control arm, met success criteria at 6 months.[47, 48] Results in the SCS group were sustained over time, with 80% of patients using their devices and 55% of patients achieving treatment success at 5 years.[49, 50]

Despite technologic advances, pain relief outcomes from conventional SCS have remained stagnant.Only 32% of patients in the recently published SUNBURST trial could be described as having treatment success (defined as a ≥50% reduction in pain) after 12 weeks of conventional stimulation (78.7% of patients had FBSS or radiculopathy), although all patients experienced a >50% pain reduction during the trial stimulation before implantation.[51] In the conventional SCS arm of the SENZA RCT, 55.5% of patients were found to have a successful outcome, a value similar to that seen in older studies (for example, ~50% of patients in the PROCESS and North et al. studies had a comparable successful outcome at 6 months).[10] The notion that therapeutic benefit has failed to improve despite technologic advances is supported by data from systemtic reviews, and points to the need for a better understanding of the mechanism of action of conventional SCS.[37, 52]

Mechanistic Studies in Humans

Does dorsal column fiber activation lead to changes in objective measurements of sensory and pain thresholds? Because patients experience paresthesias with conventional SCS, suggesting that afferent pathways are tonically activated, changes in sensory thresholds could be anticipated. One of the first reports of dorsal column stimulation for the treatment of pain noted no changes in touch and vibration sensation, but an increase in pain thresholds to skin stimulation (Table 2).[53] Some studies detected changes in touch[54] and vibration[54, 55] thresholds with SCS, whereas others did not.[56, 57] Similary, mechanical pain thresholds were noted to be altered by SCS in one study[58] but not in others.[54, 57, 59, 60] Temperature

detection thresholds did not differ between patients with SCS and controls in a larger study of patients with CRPS, and only a mild effect on mechanical hyperalgesia was detected.[61] Some have observed changes in temperature discrimination,[59, 62, 63] temporal summation to a painful tonic thermal stimulus,[64] and thermal pain,[62] whereas others have not. [55, 57] Detection and pain thresholds to electrical stimulation were increased in patients implanted chronically compared with those receiving short-term stimulation.[65] SCS was shown to increase pain tolerance thresholds to electrical stimulation in trial patients who ultimately went on to implantation, but not in trial non-responders.[66] Interestingly, chronically implanted patients experienced an increase in current perception thresholds while the device was on, compared to when it was off, highlighting the importance of when the testing is performed.[67] A recent small, but carefully conducted study followed patients longitudinally before a trial of SCS and up to 3 months after implantation for those with a successful trial, and examined a battery of laboratory pain measures, including central sensitization and descending modulation of pain. The authors detected no differences over time, except for a decrease in thermal temporal summation in patients receiving SCS.[60] It is difficult to draw clear conclusions from the accumulating evidence described above, likely reflecting heterogeneous experimental paradigms such as low subject numbers, diverse pain etiologies (and associated nerve damage), different SCS lead locations (epidural vs. subdural) and stimulation frequencies, and acute vs. chronic stimulation state, among many others. As a whole, it can be assumed that, despite tonic activation of dorsal columns, conventional SCS does not impact sensory and pain thresholds to a large extent, and plays a minimal role in controlling acute pain.

SCS has effects on higher order processing of nociceptive information, both at segmental and cortical levels. Segmental effects are challenging to determine directly in humans; however effects on spinal reflexes can be inferred from neurophysiologic tests (Table 3). For example, SCS was found to inhibit sensorimotor reflexes such as the H-reflex in patients with lower limb pain caused by FBSS.[68] This inhibition is thought to occur at least in part via direct effects on motor neurons,[23] although more complex modulation of spinal cord sensorimotor circuits are likely.[69] The effects of SCS on motor systems are robust and reliable, and SCS has been used to treat spasticity and improve motor function in patients with spinal cord injury and other movement disorders such as multiple sclerosis and Parkinson’s disease.[69, 70] The nociceptive sensorimotor reflex (RIII) is a polysynaptic spinal reflex considered to be an objective physiologic measure of nociception, and has been shown to correlate positively with perceived pain.[71, 72] SCS was shown to inhibit the RIII and correlate with efficacy of stimulation in two studies of patients with neuropathic pain.[68, 73] The RIII reflex stands out as a promising test that may be used to establish optimal stimulation parameters, and as an objective evaluation of the treatment efficacy.[74]

In addition to its segmental effects, SCS modulates cortical processing of somatosensory information, as reviewed recently.[75] SCS has been shown to decrease cortical excitability, as measured via sensory evoked potentials (SEP),[68, 76–80] and can normalize pathologic cortical activity.[81] These measures may be useful to predict pain relief.[82] As with other measures, SEP changes do not always correlate with clinical success, meaning that patients with significant suppression of SEP sometimes report minimal pain relief. Thus, larger studies are needed to determine if SEPs can be used to predict outcomes.[75]

Brain activity is pathologically altered in chronic pain states,[83] and considerable evidence supports the notion that abnormal activity in corticolimbic structures serves as the basis for chronic pain.[84] It is enticing to hypothesize that SCS mediates analgesia by inhibiting and normalizing pathologic cortical connectivity and decreasing corticolimbic activation. Numerous studies have examined how SCS alters cortical processing by using imaging approaches such as fMRI, PET, SPECT, and 133-Xe inhalation.[75] Cortical changes during SCS may represent direct effects from dorsal column stimulation or inhibition of nociceptive signals arising from the periphery, or they may reflect complex modulatory effects on somatosensory and affective processing. The earliest study to show the feasibility of using fMRI in patients with stimulators found increased activation of sensory and cingulate cortices in three patients with temporary electrodes.[85] Others found that SCS decreased thalamic-to-cingulate connectivity, [86] diminished activation of primary motor and somatosensory cortex,[87] and modulated resting state connectivity.[88] SCS can increase regional cerebral blood flow (CBF), especially when administered at the cervical level, suggesting a direct effect on CBF regulatory centers.[89–91] Studies using PET and SPECT imaging of CBF had similar findings, with normalization of activity in multiple brain regions, including thalamus, postcentral gyrus, orbitofrontal cortex, and anterior cingulate cortex in one study. [81] Others found regional CBF changes in thalamus, anterior cingulate cortex, prefrontal, and bilateral parietal association areas.[92, 93] As most current SCS systems are MRI-compatible and can deliver paresthesia-free stimulation, allowing for placebo control, it is now possible to design relevant studies to delineate the cortical structures subserving SCS analgesia.[75] Future research efforts should address fundamental questions such as whether long-term SCS success can be predicted from a patient's baseline imaging, for example using resting-state fMRI. Other studies may address whether imaging can be used to adjust stimulation parameters in patients with suboptimal pain relief.

Preclinical Mechanistic Studies

Many outstanding reviews have been written about the mechanisms of action of SCS based on animal studies.[17, 19, 94–98] Convincing evidence indicates that conventional SCS mediates pain relief through a combination of segmental and supraspinal mechanisms, by reversing neuronal hyperactivity and maladaptive changes found in chronic pain states (Table 4).[99–101] Early reports showed that SCS-mediated analgesia could be blocked by blocking inhibition, [102] and that SCS causes an increase in release of inhibitory neurotransmitters, as postulated by the GCT.[96, 102–105] Intrathecal administration of baclofen, a GABA B receptor agonist, augmented SCS analgesia in rats and rescued non-responders, and, when translated clinically, increased the efficacy of SCS in patients with neuropathic pain who were poor responders.[96, 103, 106, 107]

SCS modulates other neurotransmitters, including cholinergic, serotonergic, and opioidergic systems. Acetylcholine levels are increased by SCS in responder rats, but not in non-responder animals, and activation of M4 muscarinic receptors can potentiate SCS-mediated analgesia.[108] Similar to baclofen, clonidine—an alpha-2 adrenoreceptor agonist that augments acetylcholine release in dorsal horn—potentiated inadequate SCS analgesia when delivered intrathecally in rats[109] and offered sustained long-term benefit to patients in one small clinical trial.[106] In addition to acetylcholine, SCS induces release of serotonin in the

dorsal horn of cats and rats.[110, 111] Antagonists to serotonin receptors 5-HT(2A) and 5HT(4) blocked the analgesic effects of SCS, whereas intrathecal injection of a 5-HT(3) agonist enhanced SCS analgesia. This effect was blocked by inhibition of GABA B receptors in a rat model of neuropathic pain.[111, 112] A recent study using prolonged SCS at low (4 Hz) and typical (60 Hz) frequencies found differential modulation by opioid receptor subtype, such that μ opioid receptor blockade with naloxone prevented the SCS-mediated analgesia at low frequencies, whereas δ opioid receptor blockade with naltrindole blocked effects of 60 Hz stimulation.[113] Interestingly, the same group published a study in which proglumide, a drug that enhances the analgesic properties of opioids, had no effect on SCS analgesia or physical activity levels in rats.[114] Another group found that opioid antagonism with naloxone blocked early SCS (administered 3 days after nerve injury), but had no effect on late SCS.[115]

SCS depresses the activity of wide dynamic range (WDR) neurons, a class of output neurons located in deep dorsal horn lamina.[116, 117] This fact is relevant, as WDR neurons are candidates for the transmission cells in GCT and are critical for spinal pain processing and development of neuropathic pain.[99, 118, 119] SCS-mediated suppression of WDR neurons may be achieved through modulation of the neurotransmitter systems detailed above, although circuit-level understanding is lacking. Recently, SCS (applied as stimulation of Aβ fibers) was shown to cause long-term depression of excitatory synaptic transmission in the superficial dorsal horn (lamina II).[120] This synaptic depression was observed in both excitatory and inhibitory neurons; however the network-level effects remain unknown. The synaptic depression was blocked by antagonists of cannabinoid receptor type 1 (CB1), which links the mechanisms of SCS analgesia to a well-established pain control system.[121] Two recent studies showed that intrathecal infusion of AM251, a CB1 receptor antagonist, blocked SCS-mediated reversal of mechanical hyperalgesia in rats with neuropathic pain.[115, 122]

The aforementioned investigations of WDR neurons did not verify that the neurons studied were projection neurons. A recent study addressed this concern by specifically recording from projection neurons—nociceptive-specific and WDR subtypes. The authors observed heterogeneous responses to 20-second-long trains of SCS of various frequencies, supporting the notion that the effects of SCS might be better explained by complex microcircuit interactions than by a gating mechanism.[123]

Because SCS causes activation of supraspinal regions via orthodromic dorsal column action potential transmission, recent studies have tried to tease out the proportion of analgesia attributable to supraspinal circuits, as well as the neurotransmitter involved.[124, 125] In rats with chronic dorsal column lesions, SCS was equally effective at relieving pain when applied at levels rostral or caudal to the lesion, with each site producing about 50% of the pain relief obtained in intact rats. Intraperitoneal administration of antagonists to GABA (A and B), serotonin, beta and alpha adrenergic, and dopaminergic receptors differentially inhibited measures of tactile and thermal hypersensitivity, suggesting that segmental and supraspinal activation involves different circuits and neurotransmitters.[126] The supraspinal effects of SCS are likely mediated by the rostroventral medulla, a key brain region critical for descending modulation of nociception, as shown recently by Song et al.,[127] who reported that SCS in responder rats caused an increase in spontaneous activities of anti-nociceptive

OFF and serotonergic-like neurons. Other supraspinal loops may include adrenergic neurons,[128] although the exact mechanisms are unknown.

HIGH-FREQUENCY STIMULATION

Clinical Efficacy

High-frequency SCS is a broad term meant to imply frequencies higher than that commonly used in conventional SCS (60–200 Hz), although conventional devices generate frequencies up to 1200 Hz. Among the high-frequency rates, 10,000 Hz (10 kHz, or HF10) has been studied the most, and it is available from only one device manufacturer, Nevro (Redwood City, CA, USA). In a feasibility study published in 2013, Tiede and colleagues examined 24 patients with FBSS who were eligible for SCS.[129] After a trial of conventional SCS, patients received a 4-day trial of HF10. Remarkably, average overall VAS pain scores decreased significantly from a baseline of 8.68 ± 0.5, to 3.92 ± 0.9 with conventional SCS and to 2.03 ± 0.75 with HF10. Patients did not experience paresthesias with HF10, and the majority preferred it. Low back pain, which is typically most refractory to treatment, particularly to SCS, improved as much as leg pain. A European prospective study reported a high trial-to-implant ratio (88%) with HF10 and outstanding pain reduction, with 77% of patients reporting ≥50% pain relief at 6 months, again without paresthesias.[130] At the 2-year follow-up, 60% of patients had ≥50% relief of back pain and 71% had ≥50% relief of leg pain; patients also reported significant improvement in function and decreases in opioid medication usage. The vast majority (>80%) were satisfied or better on subjective reports and would recommend it to others.[131]

In one of the largest studies in the field of neuromodulation, Kapural et al.[10] randomized 198 patients 1:1 to HF10 or conventional SCS. Of those enrolled, 93% who trialed HF10 and 88% of those who trialed conventional therapy proceeded to permanent implant. The rates of response, defined as having ≥50% pain decrease, averaged approximately 80% for back and leg pain in the HF10 group but only 50% in the conventional SCS group. Opioid consumption, disability, and satisfaction rates improved at 12 months, but more so in the HF10 group. Complication rates were comparable between the two groups, suggesting that HF10 is a safe therapy. At the 24-month follow-up, the pain relief was sustained for both back and leg pain in more than 70% of patients who received HF10.[11] Importantly, there were no reports of neurologic deficits or injury in either group of patients, supporting the safety of SCS.

Other reports, including small, short-term prospective[132] and long-term retrospective studies,[133–135] have shown consistent and sustained pain relief. A recent non-industry-sponsored clinical trial comparing conventional SCS and HF10 in 60 subjects with FBSS found that both groups had improved from baseline at 12 months; however the pain reduction was less than previously reported, and there were no differences in pain or functional scores between the two groups.[136] Additional retrospective studies in patients with headaches[137, 138] and primarily neuropathic pain[139] have been encouraging, supporting the use of HF10 for segmental pain pathologies.[140–142]

Mechanistic Studies in Humans

To the best of our knowledge no studies have systematically examined the effects of HF10 SCS on sensations using quantitative sensory testing. Youn and colleagues measured thermal and mechanical detection and pain thresholds in 20 patients implanted with SCS devices (4 weeks to 4 months postoperatively), and compared OFF, traditional SCS, and high-frequency (200–1200 Hz) protocols.[143] The body area selected for testing had coverage of pain and paresthesias with traditional SCS. The authors found that higher frequencies were associated with higher detection and pain thresholds for mechanical stimuli, but they noted no differences in thermal testing for threshold or pain detection. In a case report describing the measurement of SEPs in a patient with FBSS and thoracic epidural leads, the authors found that SEPs were inhibited at all frequencies tested (60 Hz, 200 Hz, 500 Hz, and 10 kHz).[144]

Preclinical Mechanistic Studies

A few recent outstanding reviews discuss potential mechanisms of action for pain relief with high-frequency stimulation, including axonal conduction block, desynchronization of axonal activity, and glial-neuronal interactions.[17, 145] It was initially believed that HF10 mediates pain relief by blocking or desynchronizing axonal transmission, as shown in peripheral nerves.[146] However, this is an unlikely mechanism, as a computational study demonstrated that the stimulation amplitudes required for activation and conduction block of dorsal column fibers are outside the range used clinically, and patients do not experience paresthesias.[147] Song et al.[148] found that whereas conventional SCS caused profound activation of dorsal column projection nuclei (gracile), 10 kHz dorsal column stimulation at subparesthesia levels (~40–50% of motor threshold) had no effect, despite attenuating mechanical hyperalgesia. In a carefully designed rat study, Crosby et al.[149] showed that few axons fired action potentials with high-frequency (1 to 20 kHz) dorsal column stimulation, particularly at amplitudes below 50% of motor threshold, and similarly, conduction block rarely occurred at those amplitudes. These studies complement prior work showing that whereas 4 and 60 Hz SCS drove expression of c-fos (an immediate early gene used as a marker to indicated neuronal activity) in supraspinal regions, stimulation at higher frequencies (100 Hz) elicited no such increase.[150]

High-frequency SCS has been shown to attenuate pain in animal models. Using a rat L5 nerve ligation model, Schechter et al.[151] showed that high-frequency SCS (1 and 10 kHz) attenuated hyperalgesia with an earlier time-course and to a greater extent than stimulation at 50 Hz. In addition, high-frequency stimulation decreased Aαβ compound action potential amplitude more than did 50 Hz stimulation. However, 50 Hz stimulation significantly decreased wind up, whereas high-frequency did not. In a recent study, Li et al.[152] measured peripherally evoked activity of WDR and high-threshold (HT) neurons in naïve rats that received SCS with frequencies ranging from 50 Hz to 10 kHz, and determined that 20 minutes of SCS, regardless of frequency, inhibited responses to pinch in all neurons recorded. Furthermore, only 1 kHz stimulation attenuated responses to a second pinch, delivered 4 minutes after the first. This finding was surprising, as the greatest charge transfer occurred at 10 kHz.

When HF10 SCS is implemented with settings similar to those used clinically, it has the intriguing ability to provide pain relief equal or superior to that of conventional SCS, without activating or blocking dorsal column fibers. Preliminary studies, published in abstract form, revealed that HF10 stimulation decreases wind-up and hyperpolarizes superficial dorsal horn neurons, suggesting segmental mechanisms that diverge from gate control mechanisms.[17] These findings indicate that for optimal stimulation, the active electrodes should be placed adjacent to the segments processing painful information, although relation to midline might not be as critical.[153]

BURST STIMULATION

Clinical Efficacy

Despite its recent introduction, burst stimulation has been rapidly adopted by the neuromodulation community, particularly as it has become clear that most patients prefer paresthesia-free stimulation.[3] Multiple studies, although limited by small size and short duration, have consistently shown that burst stimulation suppresses neuropathic pain as well as or better than conventional SCS, and that most patients choose it over paresthesia stimulation.[154] These early proof-of-concept studies are challenging to interpret because they generally consisted of patients with FBSS already receiving conventional SCS, and the duration of stimulation was brief, only 1–2 weeks.[155] In the SUNBURST trial, 100 patients, predominantly with FBSS or radiculopathy, were randomized to tonic (conventional) or burst stimulation for 12 weeks each.[51] Burst met non-inferiority and superiority criteria compared to tonic stimulation for the primary end point, mean daily overall VAS, and the safety profiles were similar. Most patients (68%) preferred burst stimulation, and the majority who received burst SCS did not feel paresthesias, consistent with previous reports. There were no differences between burst and tonic stimulation for function and psychosocial assessments, which was surprising given that burst is hypothesized to mediate pain relief by activating medial pathways and normalizing affective/attentional components of pain.[156] These results replicated findings of previous smaller studies, although the observed difference in pain scores was somewhat less than what others reported.[3, 13, 157] It may be that burst stimulation works best in certain clinical scenarios, as shown in a recent crossover study of patients with CRPS that compared standard (conventional 40 Hz), non-standard (500 Hz, 1200 Hz, and burst), and placebo stimulation for 2 weeks.[158] The authors found that most patients preferred standard SCS, and that pain relief was comparable for standard and non-standard settings. Additional large, high-quality studies are needed to determine how pain relief mediated by burst compares with HF10 and other novel waveforms.[159]

Mechanistic Studies in Humans

To the best of our knowledge no studies have examined the effects of burst stimulation on sensory testing. EEG has been used to compare burst with conventional SCS in five patients. The two modes were found to activate and depress brain activity in different regions, with burst preferentially activating medial pathways thought to be related to descending modulatory systems.[13, 160] Additional studies that use other imaging techniques such as fMRI are needed to determine how burst differs from conventional SCS in chronic pain states.

Preclinical Mechanistic Studies

A few preclinical studies have begun addressing the mechanisms of burst SCS-mediated analgesia. Tang et al.,[161] using a rat model, showed that burst SCS suppressed visceromotor reflexes (increases in external oblique muscle activity in response to colorectal distention) as well as noxious stimulus-induced activity of dorsal horn neurons to a greater degree than tonic stimulation. They also examined the activity of dorsal column nuclei and, surprisingly, found that burst SCS had no effect on the spontaneous activity of gracile nucleus neurons, whereas tonic stimulation activated these neurons. The results suggested that burst SCS does not activate dorsal column-medial lemniscal pathways. As burst and tonic stimulation were delivered at high intensities (90% of motor threshold), it is unlikely that the lower thresholds typically used in subparesthesia SCS (~40% of motor threshold) activate dorsal column pathways. Thus, despite being developed as an ideal, physiological stimulation paradigm, it appears that burst does not activate adjacent dorsal column axons and instead may be similar to HF10 SCS in modulating pain via segmental mechanisms.

Burst SCS significantly suppressed pinch-evoked activity of WDR neurons in a cervical root compression rat model, and increasing individual pulse parameters (width, amplitude, and number) increased the attenuation of neuronal responses; however, augmenting frequency parameters had no effect.[162] This study also found that greater charge per burst correlated to a larger reduction of WDR neuronal firing, and to a higher percentage of neurons responding to burst SCS. In a follow-up study by the same group using the same cervical root compression rat model, burst SCS and tonic SCS attenuated evoked WDR activity to noxious stimuli (heavy von Frey filament and pinch) to a comparable degree; however inhibition of GABA B receptors abolished tonic SCS-mediated, but not burst SCS-mediated, attenuation of WDR neurons.[163] Interestingly, cervical root compression caused a decrease in serum GABA concentrations that was rescued by tonic stimulation, whereas burst stimulation had no effect on serum GABA concentrations. These results strongly suggest that burst SCS suppresses dorsal horn excitability through non-GABAergic mechanisms.

Meuwissen and colleagues also found that increasing pulse amplitude (while maintaining all other waveform parameters constant) suppressed mechanical hypersensitivity in a neuropathic rat model. However they observed a nonlinear effect, such that burst SCS at an amplitude 50% of motor threshold was superior to amplitudes of 33% and 66% of motor threshold.[164] Optimal burst SCS (at 50% of motor threshold) was comparable to conventional SCS at the high intensity (66% of motor threshold) for attenuating hyperalgesia, and interestingly, the charge delivered per second was much greater for burst SCS than for conventional SCS at comparable behavioral outcomes. These findings diverge from those of Crosby et al.,[162] who found that increasing stimulation amplitudes improved suppression of neuronal firing, although the experimental models were different. Thus, the data support a complex, non-linear interplay between charge delivery, activation of neuronal elements, and pain relief.

DRG STIMULATION

Clinical Evidence

Dorsal column SCS has multiple shortcomings, including limited ability to directly target specific dermatomes and vulnerability to positional changes and variation in the thickness of the cerebral spinal fluid layer immediately adjacent to the leads. DRG stimulation was introduced to specifically address these limitations, by delivering stimulation directly to affected nerve root(s) within the enclosed bony structures surrounding the DRG.[165] Technical barriers relating to placing the leads adjacent to the DRG were overcome though development of a specifically designed lead delivery system. Initial studies, which have been encouraging, showed sustained pain relief in patients with focal neuropathic pain, such as CRPS and groin pain, which are traditionally difficult to treat with conventional SCS.[166–170] In a recent prospective RCT, which led to FDA approval in the US, Deer et al.[12] demonstrated that in patients with CRPS, DRG stimulation was superior to conventional SCS for the primary composite outcome (≥50% reduction in VAS score from baseline for the trial and at 3 months after implantation; lack of neurologic deficits) and for secondary end points, including positional effects on paresthesia, quality of life, emotional scales, satisfaction, stimulation specificity, and percent change. The study is remarkable in that 81.2% of patients randomized to DRG SCS achieved success at 3 months, compared with 55.7% in those who received conventional stimulation, and these results were stable at 12 months. The safety profile favored conventional SCS because the DRG arm had a higher rate of procedural events.

Preclinical Mechanistic Studies

Electrical stimulation of the DRG using electrical fields can have numerous effects, among them activation of low-threshold nerve fibers, alteration of conduction properties of axons and axonal T-junctions, and modulation of the properties in the DRG neurons and non-neuronal cells. Koopmeiners and colleagues[171] showed that exposing rat DRG to brief periods of field stimulation caused calcium influx, attenuated the intrinsic excitability of DRG neurons, and increased filtering of action potentials through the DRG. Pan et al.[172] examined the effects of DRG stimulation in a rat model of nerve injury. They implanted the DRG stimulation lead in situ such that rats could be maintained awake and ambulatory. Thirty minutes of DRG stimulation reversed mechanical (to pin and von Frey) and cold hypersensitivity, and the effect outlived stimulation by 15 minutes. The experimental design allowed the authors to study the affective components of pain by setting up a conditioned place preference assay, in which rats were conditioned to receive DRG stimulation in one of two chambers for 4 days. After conditioning, rats spent significantly more time in the chamber where they received DRG stimulation, whereas sham-stimulated rats showed no chamber preference, strongly suggesting that DRG stimulation in this model relieves pain. Using the same implanted DRG stimulation lead model, this group performed BOLD fMRI imaging in rats that received an acute painful stimulus to the hind paw, with or without stimulation.[173] Stimulating the DRG significantly attenuated the response across multiple brain regions, whereas the stimulation itself, when administered at clinically relevant parameters, had little effect on the fMRI response. These findings confirm the hypothesis

that DRG stimulation decreases action potential propagation, likely at the level of T-junctions.[171]

These studies substantiate the concept that DRG stimulation has direct effects on dorsal root axonal transmission of painful inputs, and reverses pathologic activity found in neuropathic states. Additional studies are needed to delineate mechanisms, specifically the role of calcium influx on DRG neurons and support cells.

CONCLUSIONS AND FUTURE DIRECTIONS

There is little doubt that SCS represents a safe and effective therapy for patients with neuropathic pain conditions, especially those with FBSS. The accumulating clinical evidence is overwhelmingly positive, and with the introduction of burst, HF10, and DRG SCS, patients have more options than ever before. In high-quality RCTs, burst stimulation and HF10 have been shown to be provide pain relief superior to that of conventional SCS for patients with FBSS.[10, 11, 51] Other stimulation paradigms such as high-density[174–176] and 3D-guided[15] SCS have shown great promise as well, although larger randomized studies are needed to confirm preliminary findings. Large, non-industry-sponsored clinical trials comparing the available options are urgently needed to establish what stimulation paradigms are superior for specific neuropathic conditions. In addition, more attention should be directed to better understand the loss of efficacy that occurs over short and long durations.[46, 177, 178] Future studies should also attempt to better characterize treatment failures, in addition to successes.[179]

Quantitative sensory testing has shown promise in defining pain phenotypes[180, 181] and in guiding pharmacologic treatment.[182] It might be useful for predicting SCS analgesia,[66] although larger studies are needed.[60] Other neurophysiologic measures such as SEPs and the RIII reflex support the idea that SCS modulates segmental nociceptive processing in humans. It will be interesting to determine if these measures can be used to guide patient selection and improve treatments. This topic deserves further study, particularly with paresthesia-free waveforms. Accumulating evidence supports the idea that SCS mediates analgesia at the systems level by modulating corticolimbic activation, and technical advances that include paresthesia-free waveforms combined with MRI compatibility hold great promise. Future fMRI studies with placebo-controlled designs should further delineate cortical and spinal mechanisms of action, predict responders, and optimize stimulation parameters.

Preclinical studies have deepened our understanding of the mechanistic basis of SCS, at times with direct translational implications.[183] Although multiple neurotransmitters have been implicated in segmental and supraspinal mechanisms of conventional SCS, and pharmacologically augmented SCS proved successful in small studies,[184] a detailed understanding of neuronal pathways involved and circuit-level effects is still lacking. Early and late SCS may have distinct mechansims[115] that are relevant to the loss of efficacy observed clinically. Much less is known about the neural pathways activated in patients, and noninvasive imaging studies should address these questions.[75]

The observed clinical efficacy of burst and HF10 SCS combined with basic research findings that these stimulation paradigms do not activate or inhibit dorsal columns when used at clinically relevant parameters, strongly supports mechanisms of action other than the traditional gate control mechanism.[17, 98] Additional studies are needed to determine these mechanisms, their overlap, and how they relate to conventional SCS.[185] As these novel therapies do not appear to follow linear relationships between charge delivery and behavioral outcomes,[151, 164] it will be important to identify the critical waveform parameters that are relevant to pain relief.[11, 162] Electrical field effects of DRG stimulation on nearby neurons were shown in an *in vitro* model, and these changes may be secondary to calcium influx and subsequent changes in intrinsic excitability.[171] It remains to be determined if burst and HF10 impart similar field effects on dorsal horn neurons, and how these effects vary depending on neuronal type, electrode geometry, and stimulation parameters. These questions have significant translational relevance. For example, they point to the importance of placing the leads anatomically. However, studies are needed to determine the critical spinal segments for different pain pathologies (the T9–10 disc space is targeted in current practice to treat axial back pain when using HF10 stimulation), whether there are inter-individual variations, and if these segments differ for distinct waveforms.[29, 98]

Chronic neuropathic pain is a common, diverse condition[186] that is difficult to treat[187] and associated with significant impairments in quality of life.[188] The importance of having safe and effective therapies has been highlighted recently in discussions about the opioid epidemic.[189, 190] Understanding the biologic basis of SCS through improved communication and collaborations between the clinical and scientific communities will be critical for identifying appropriate candidates, optimizing pain relief, and maximizing societal benefit (Table 5).

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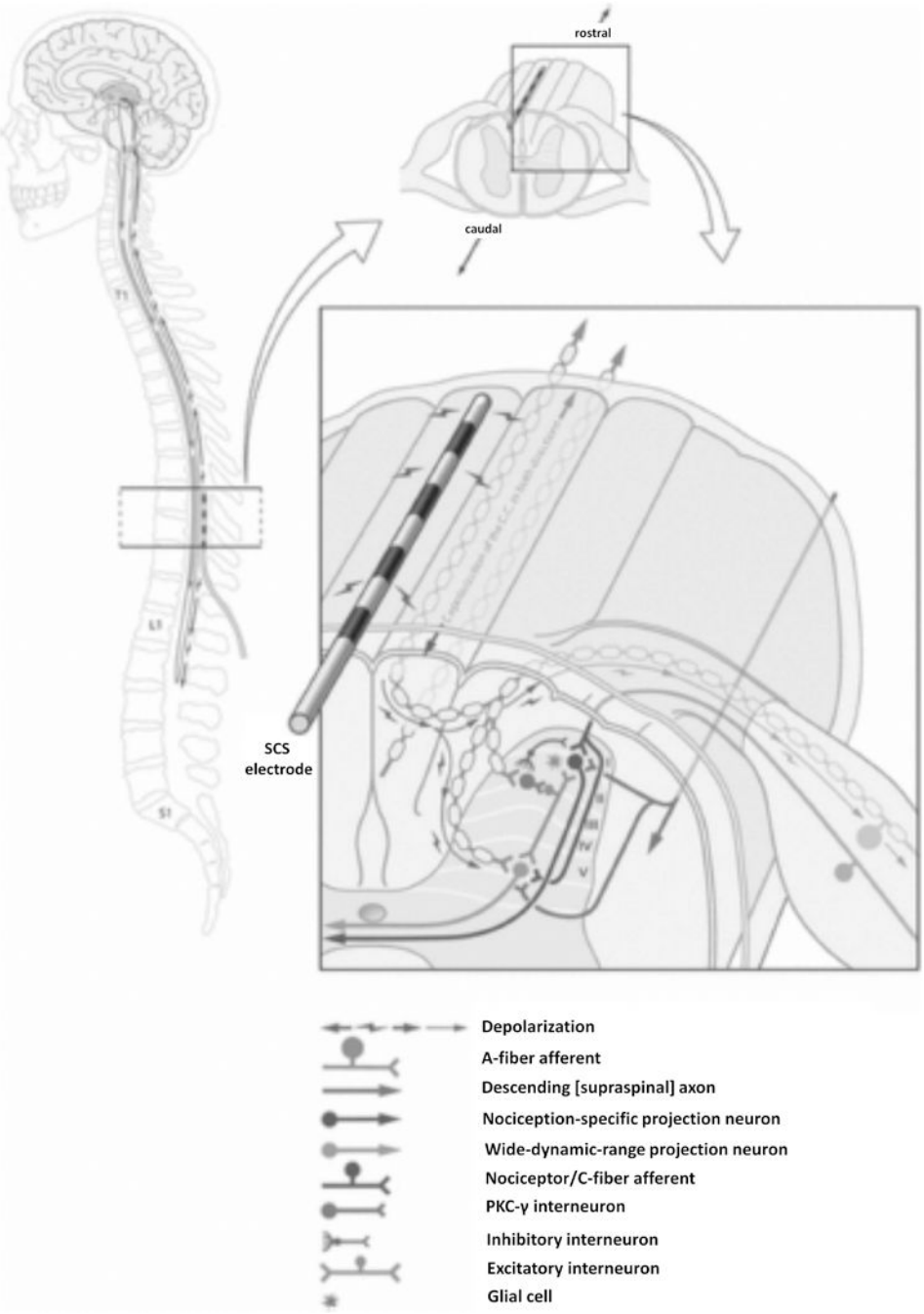

Fig. 1. Spinal cord stimulation lead position.

The electrical lead sits in the epidural space, and the electrical stimuli activate fibers directly below it. This causes initiation of orthodromic and antidromic action potentials and supraspinal and segmental effects. Adapted from Smits et al., 2013.[2]

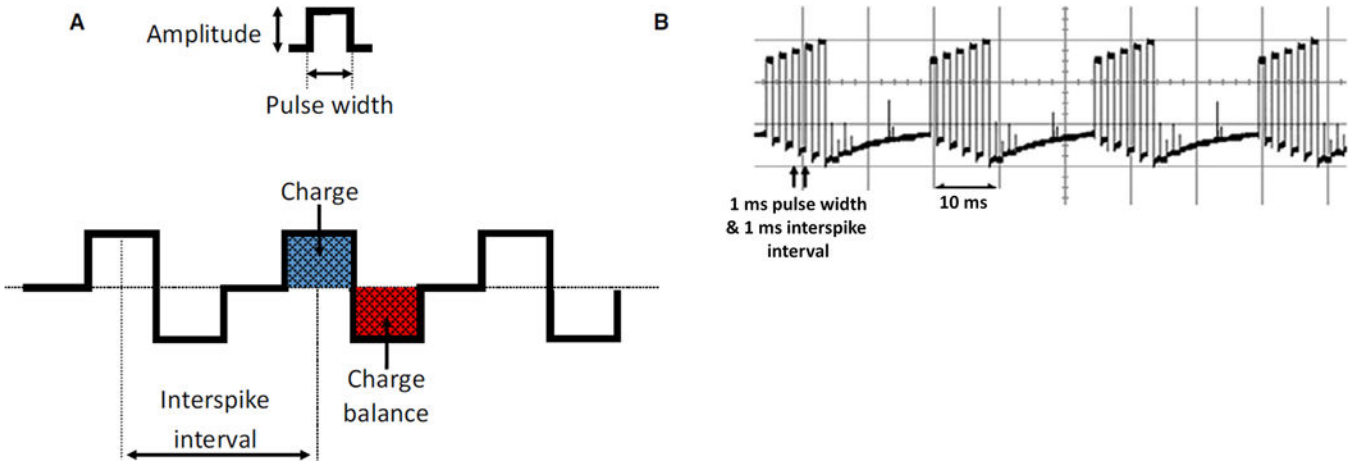

Fig. 2. Waveform properties.

(A) The amount of charge delivered to tissues depends on pulse properties: shape, amplitude, and duration. The lower panel illustrates the concept of frequency and charge balance. (B) Burst waveform, adapted from De Ridder et al.[3] The waveform represents five, 1-ms-long pulses, delivered at 500 Hz, while the burst frequency is 40 Hz. Charge balance occurs after the five pulses.

Table 1.

Randomized controlled trials in spinal cord stimulation

SCS type	Failed back surgery syndrome	Complex regional pain syndrome	Diabetic neuropathy
Conventional	North,[40] Kumar,[36] Rigoard,[42, 43] *Turner[191]	Kemler[45,46]	De Vos,[47] Slangen[48]
HF10	Kapural,[10] De Andres[136]		
Burst	Deer,[51] Schu[157]	Kriek[158]	
Dorsal root ganglion		Deer[12]	

*Final results available at https://clinicaltrials.gov/ct2/show/results/NCT01697358HF10,

HF10, high frequency at 10 kHz; SCS, spinal cord stimulation.

Table 2.

Effects of spinal cord stimulation on sensory testing

Study	SCS type	Mechanical detection	Mechanical pain	Thermal detection	Thermal pain	Electrical detection	Electrical pain	Other
Shealy[53]	Conventional	=	↓				↑	
Larson[58]	Conventional	↓						
Lindblom[54]	Conventional	↑	=					
Doerr[65]	Conventional					↑	↑	
Marchand[63]	Conventional			↑	↓			
Mironer[66]	Conventional					=	↑	
Alo, 2000[67]	Conventional					↑		
Kemler[61]	Conventional	↑ (initially)	=	=	=			↓ (mechanical hyperalgesia)
Eisenberg[55]	Conventional	↑					↑	
Rasche[59]	Conventional	↓	=	Cold ↑ Warm ↓	=			
Meier[57]	Conventional							= (wind up-like pain)
Ahmed[62]	Conventional			↑	↑			
Campbell[60]	Conventional	=	=	=	=			↓ (thermal temporal summation)
Manresa[192]	Conventional						=	
Youn[143]	High Frequency	↑	↑	=	=			

*200–1200 Hz.

↑ Increased; ↑ Decreased; = No change; SCS, spinal cord stimulation.

Table 3.

Neurophysiologic effects of spinal cord stimulation in humans

Study*	Sympathetic skin response	H reflex	RIII reflex	F wave	Notes
Garcia-Larrea[73]			Suppressed in 52.4%		Analgesia correlated with RIII attenuation
De Andrade[68]	Increased amplitude; decreased latency	Increased threshold and latency; decreased amplitude	Increased threshold; decreased area	Decreased latency	Analgesia correlated with RIII attenuation
Manresa[192]			Increased threshold		

All studies used conventional spinal cord stimulation.

Table 4.

Basic mechanisms of spinal cord stimulation-induced analgesia

SCS type	Neurotransmitters	Synaptic depression	WDR	Glial cells	Supraspinal	Axonal conduction
Conventional	Acetylcholine,[108, 193] dopamine,[126] cannabinoids,[115, 122] GABA,[96, 102–105] serotonin[110–112, 126, 194]	Presynpatic,[195, 196] postsynpatic[120, 122]	Wind-up,[116, 151, 197] excitability,[116, 117] long-term potentiation[198]	Activation[199]	Descending modulation[125, 127, 128, 150, 200, 201]	
High frequency			Excitability[152]			Block[147,151,202]
Burst			Excitability[162,163]			
Dorsal root ganglion						Block[171,173]

Table 5.

Future directions (developed with help from the International Association of Pain's Neuromodulation Interest Group).

1. What are the segmental and distal circuits engaged by spinal cord stimulation (SCS)?
   We need circuits to be defined by modern, genetically identified cell types.
   - What are the biological roles of these circuits?
2. How are these circuits engaged by different stimulation paradigms (i.e., variations in frequency, and/or intensity, and/or pulse width)?
   - What are the spike trains that are generated by various SCS paradigms?
   - How do these spike trains translate into long-term changes?
   - How do spike trains alter the activity of output neurons at spinal (wide dynamic range, nociceptive specific) and supraspinal (rostroventral medulla) sites?
3. How do SCS mechanisms differ in acute versus long-term stimulation states?
   - Although animal models generally focus on early SCS, it is more relevant clinically to study late SCS, as loss of efficacy with long-term use is a significant clinical problem.
4. Testing of effects and pain relief based no longer on Hargreaves and von Frey tests (response-mediated effects) but on operant testing of behavior. The latter includes affective-emotional and cognitive aspects of pain and will likely improve clinical translation of findings.
5. Imaging (fMRI, PET-scan) studies of supraspinal areas with various SCS paradigms need to be correlated with pain relief and used to link observed behavioral and cellular effects to selected brain areas.