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Mechanisms for the Clinical Utility of Low-Frequency Stimulation in Neuromodulation of the Dorsal Root Ganglion

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ABSTRACT

Background: Dorsal root ganglion stimulation (DRG-S) involves the electrical modulation of the somata of afferent neural fibers to treat chronic pain. DRG-S has demonstrated clinical efficacy at frequencies lower than typically used with spinal cord stimulation (SCS). In a clinical study, we found that the frequency of DRG-S can be tapered to a frequency as low as 4 Hz with no loss of efficacy. This review discusses possible mechanisms of action underlying effective pain relief with very low-frequency DRG-S.

Materials and Methods: We performed a literature review to explore the role of frequency in neural transmission and the corresponding relevance of frequency settings with neuromodulation.

Findings: Sensory neural transmission is a frequency-modulated system, with signal frequency determining which mechanisms are activated in the dorsal horn. In the dorsal horn, low-frequency signaling (<20 Hz) activates inhibitory processes while higher frequencies (>25 Hz) are excitatory. Physiologically, low-threshold mechanoreceptors (LTMRs) fibers transmit or modulate innocuous mechanical touch at frequencies as low as 0.5–5 Hz, while nociceptive fibers transmit pain at high frequencies. We postulate that very low-frequency DRG-S, at least partially, harnesses LTMRs and the native endogenous opioid system. Utilizing lower stimulation frequency decreases the total energy delivery used for DRG-S, extends battery life, and facilitates the development of devices with smaller generators.

Keywords: Dorsal root ganglion, frequency, low back pain, neuromodulation, pathway, stimulation, transmission

Conflict of Interest: The authors have nothing to disclose.

INTRODUCTION

Technology in the field of spinal cord stimulation (SCS) has advanced rapidly over the past decade, leading to better treatment outcomes for chronic pain. Conventional SCS uses tonic stimulation, in which pulses are delivered at approximately 40–60 cycles per second. In recent years, the advent of stimulation paradigms such as dorsal root ganglion stimulation (DRG-S), burst SCS, high-density (HD-SCS) and high-frequency kilohertz stimulation (HF-SCS) have led to renewed interest in studying SCS waveforms and stimulation parameters to better understand how energy delivery to the nervous system influences clinical outcomes with these newer modalities.

The programmable stimulation parameters that determine the charge delivered in neuromodulation are amplitude, pulse width, and frequency. Additional variables used to manipulate the electrical field include, among others, the number of contacts activated, spatial relationship between the contacts, lead placement, pulse shape, and pulse recharge strategy. The basic unit of electrical charge delivery is referred to as the pulse. The amplitude is the strength of the pulse, measured in milliamperes (mA). The pulse width is the amount of time each pulse is delivered over, measured in microseconds (μsec). The stimulation frequency is the number of pulses delivered per second, measured in hertz (Hz).

Newer modes of SCS waveforms have shifted the focus of the charge delivery concept to one that relies on all the stimulation parameters being considered together to determine the "dosing" strategy being employed. This is done by calculating the electrical charge (coulombs [C]) delivered 1) per pulse (amplitude × pulse width), and 2) per second (C/s) (amplitude × pulse width × frequency) (1,2). For example, tonic SCS settings provide a higher dose of charge per pulse because of the higher amplitude typically used for paresthesia, while HF-SCS provides a lower charge per pulse while delivering a higher dose of charge per second (2).

While SCS can be applied with several different waveforms, SCS lead placement is limited to the epidural space, where bending of

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the vertebral column and ample cerebrospinal fluid (CSF) space can vary the distance between the leads and the dorsal column fibers of the spinal cord. DRG-S involves applying an electrical field using tonic stimulation at or near the somata of afferent fibers (3). Multiple interactions occur at the level of the DRG, which are believed to inhibit nociceptive transmission. Spinal mechanisms at points of neural convergence enable DRG-S with a single lead to cover multiple spinal segments (4). The electrical signal also propagates action potentials (APs) both orthodromically into the dorsal horn and antidromically to the peripheral nerve, for which the potential effects are yet to be elucidated.

In regards to charge delivery strategies, there are several factors to consider; the width of the CSF space, exposure to spinal cord movement, and propensity for lead migration, all of which can reduce the charge delivered from stimulator electrode to target tissue (5). Furthermore, axon characteristics such as diameter, degree of myelination, and distance from the stimulus govern the charge amount necessary to activate the target neuron and the stimulation frequencies the neuron will optimally respond to (5). When comparing DRG-S and SCS, these aforementioned reasons allow DRG-S to require significantly less charge per pulse to stimulate neurons than SCS (5). SCS preferentially recruits Aβ fibers, which are large-diameter and thickly myelinated. Conversely, as the DRG houses the somata of all afferent nerves, DRG-S can target smaller unmyelinated C fibers and thinly myelinated Aδ fibers in addition to the Aβ fibers.

Currently, there is a paucity of research regarding the stimulation parameters used for DRG-S, particularly with pulse frequency. The Neuromodulation Appropriateness Consensus Committee described the best practice for programming in general principles since individual patients may require different patterns, amplitudes, and spatial arrays of stimulation (6). Pulse frequency on current FDA-approved DRG-S devices have a programmable range of 4–80 Hz with a default value of 20 Hz based on the median frequency used for patients diagnosed with complex regional pain syndrome or causalgia in the lower extremities from the ACCURATE trial (7).

Our empirical observations in the clinic suggest that lower frequency stimulation may be as efficacious in DRG-S: a retrospective analysis of 20 consecutive patients with low back pain maintained their pain relief after tapering their stimulation frequency to 4 Hz (8), which is the lowest device setting for the Proclaim DRG-S system (9). Here, we review the literature to discuss the implications of these observations regarding a mechanism of action to explain the effectiveness of very low-frequency DRG-S for pain relief.

SENSORY NEURON SIGNALING

Sensory neurons convert external stimuli into corresponding internal signals. Peripheral sensory receptors are activated by physical modalities such as touch, heat, and physical contact, or by chemical signals such as capsaicin. The relay of a stimulus from the skin begins with stimulus-induced graded changes in the transmembrane voltage potential of a cutaneous receptor causing it to reach its activation threshold. Once the threshold is reached, an AP in the afferent fiber propagates to the DRG, spinal cord, and brain. Characteristics such as the intensity and duration of the stimulus at the sensory receptor determine the frequency and firing patterns of APs. This is then responsible for the selective release of neurotransmitters from the corresponding nerve terminals that signal propagation or inhibition depending on the postsynaptic receptors they activate (10) (Fig. 1a).

At the synapse, neurotransmitters bind to receptors on the postsynaptic neuron. Depending on the type and number of receptors involved, this leads to excitation/depolarization or inhibition/hyperpolarization of the postsynaptic neuron, generating an excitatory or inhibitory postsynaptic current (EPSC or IPSC). The postsynaptic neuron in turn receives input from multiple primary afferents and interneurons, with each synapse generating an EPSC or IPSC. If the sum of this graded input, referred to as spatial summation, reaches the threshold of the postsynaptic neuron, a postsynaptic AP is generated (Fig. 1b).

Receptor sensitivity, the duration of a neuron's refractory period, fast- vs. slow-adapting fibers, and temporal and/or spatial summation of successive receptor potentials determine the strength of the receptor potential. Because APs are an all-or-nothing signal, any AP generated by a given neuron has a fixed amplitude and duration. It is, then, the frequency and/or pattern of APs that "code" for the strength of the stimulus, making neural signaling frequency dependent. The stronger the stimulus, the higher the frequency at which APs are generated, up to a maximal rate.

Neural coding is the process by which the nervous system discriminates between various modalities and strengths of stimuli. Although the breadth of neural mechanisms involved is still poorly understood, individual primary afferent neurons code the intensity and type of input they transmit through the timing or pattern of APs known as temporal coding (11), and their firing rate, or frequency coding (12). For example, a nonpainful stimulus, such as simple touch, transmits APs at lower frequencies compared to a stronger or noxious/painful stimulus. Multiple sensory neurons with different firing properties are involved in transmitting a given stimulus. Therefore, the frequency code and temporal code of the APs transmitted by each neuron will vary in response to that stimulus. The collective set of responses by the sensory neurons involved is referred to as population coding. Population coding therefore consists of a unique set of temporally coded and frequency coded signals generated by a group of neurons over time to a specific stimulus (13).

Primary sensory neurons with somata in the DRG can fire APs at frequencies up to 200–300 Hz under physiological conditions (14–17). Maximum frequency is dependent on the duration of the total refractory period (absolute and relative). If the receptor potential achieves suprathreshold strength, the maximum frequency is only limited by the duration of the absolute refractory period. Because the absolute refractory period typically lasts 1–2 msec, the maximum AP frequency an individual neuron can achieve is 500–1000 Hz.

Newer SCS paradigms such as burst take advantage of this physiological characteristic since these programs run at frequencies approaching a neuron's maximal firing rate capabilities. With neuromodulation, the pulse frequency also influences how often a neuron being stimulated fires in response. A neuron can entrain or synchronize its AP firing to match the pulse frequency within a limited range (2). This is referred to as phase locking. Different nerves have different phase locking properties regarding the stimulation frequencies they can synchronize to. At lower stimulation frequencies, groups of neurons can better synchronize to a train of electrical pulses and fire simultaneously. Higher stimulation frequencies result in asynchronous firing in which individual neurons respond to different pulses within the electrical stimulation train.

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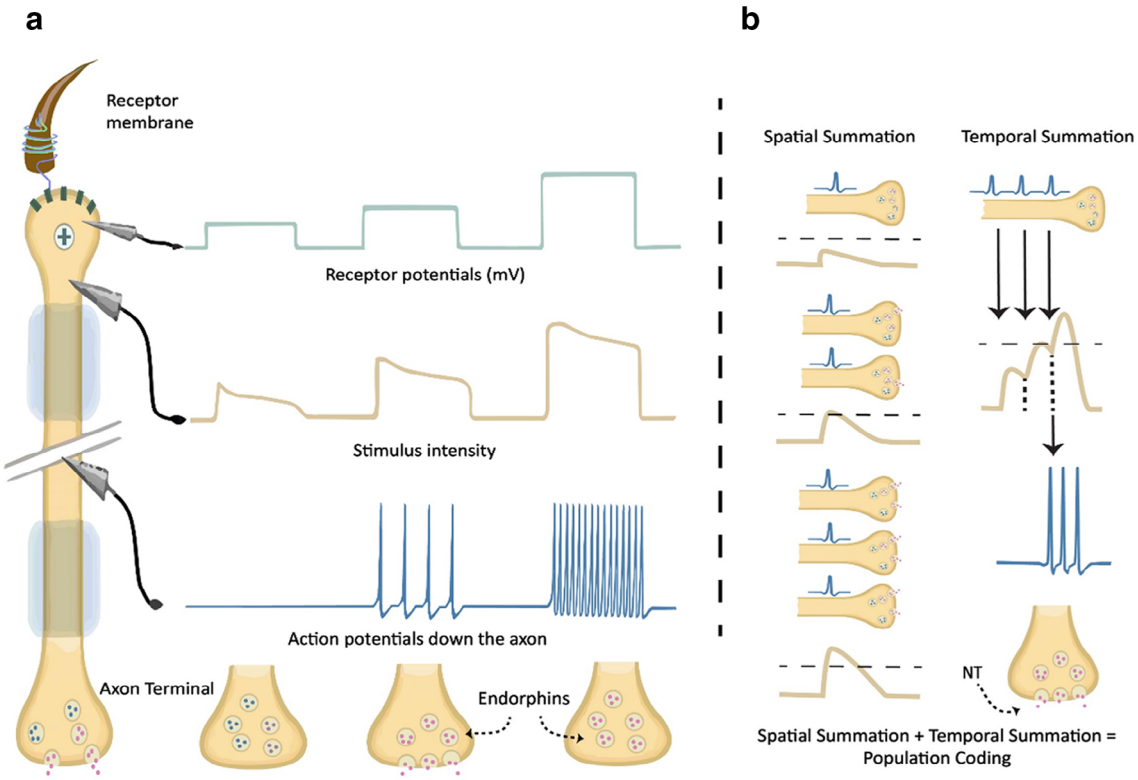

Figure 1. a. Stimulus-induced amplitude-graded receptor potentials at receptors of the primary sensory neuron. Frequency-dependent response at the nerve terminals causing the selective the release of neurotransmitters such as endogenous opioids. The greater the receptor potential, the higher the frequency of APs generated. b. Spatial summation occurs when multiple presynaptic neurons together release enough neurotransmitter to create a cumulative amplitude-graded postsynaptic receptor potential in the postsynaptic neuron. Temporal summation is the product of a single neuron sending repeated action potential to the nerve terminal causing a cumulative response on the second-order neuron.

This is especially true at the DRG which houses Aβ, Aδ, and C fiber sensory neurons, all of which have different AP firing properties.

LOW-THRESHOLD MECHANORECEPTORS

Primary sensory neurons are highly specialized to detect and transmit a specific type of touch or pain sensation. One subset of Aβ-, Aδ- and C-fiber neurons, referred to as low-threshold mechanoreceptors (LTMRs), transmit and fine tune cutaneous touch sensation, whereas nociceptive Aδ and C fiber afferents transmit pain and temperature. When comparing nerve fiber types, there are considerable differences between them regarding the frequencies at which they typically transmit signals. In the normal healthy state, LTMRs physiologically fire at low to very low frequencies in response to tactile stimuli. For example, nonpainful mechanical stimulation of Aδ- and C-fibers produce an average neural firing rate of 15 Hz or less (18–20), and Aβ LTMR fibers rarely fire above 20 Hz during sustained touch stimulation (21). Mechano-thermal Aδ fibers respond with low-frequency APs (below 10 Hz) for nonpainful steady-state temperatures and for cooling impulses (22). C-LTMRs are typically found on hairy skin follicles and are associated with the pleasant, or "emotional" aspect of touch (23–25). The pleasant sensations to brush stroke of hairy skin transmitted by C-LTMRs occurs at firing frequencies below 20 Hz (26) but much lower (below 10 Hz) for nonpainful steady state temperatures and for cooling impulses. In contrast, nociceptive primary afferent fibers fire at higher frequencies to transmit pain. Heat stimulation elicits up to 50 Hz AP firing rates in C-fibers (18). Mechano-thermal Aδ fibers fire at 40–50 Hz with increasing painful heat temperatures (22). Painful mechanical stimulation elicits afferent fiber firing rates above 50 Hz (27). These studies indicate that pain sensation is frequency dependent, with nonpainful stimuli associated with low-frequency firing rates and painful stimuli associated with high-frequency firing rates. Table 1 lists the typical physiologic firing rates of afferent fibers to encode innocuous vs. nociceptive stimuli.

In addition to transmitting cutaneous light touch and mechanosensation through low-frequency AP signaling, LTMRs also inhibit pain signaling in the superficial dorsal horn, in part by signaling endogenous opioid release that bind inhibitory presynaptic or postsynaptic opioid receptors (28–30) (Fig. 2). The basis for developing SCS, the Gate Control Theory, proposed that Aβ fibers inhibit pain transmission through activation of dorsal horn inhibitory interneurons (31). While this was subsequently demonstrated in empirical testing (32,33), Aδ- and C-LTMRs have also been shown to inhibit nociceptive transmission in a frequency dependent manner in preclinical studies (24,25,29,34,35). Work by Arcourt et al. demonstrated that maximal LTMR-mediated pain inhibition is achieved at 5 Hz stimulation frequency or less, while LTMR activity hardly affects pain behavior at stimulation frequencies above 5 Hz (36). Moreover, experimental *in vivo* recordings show that nonpainful brush stimulation activates Aδ and C fiber LTMRs to generate IPSCs in substantia gelatinosa (SG) nociceptive neurons (37). In addition, Aδ and C fiber dorsal root stimulation at one spinal level produce IPSCs in the SG of rostrocaudal spinal

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Table 1. Typical Physiologic Firing Rates for Afferent Nerve Fiber Types Under Non-noxious vs. Nociceptive Conditions.

Afferent fiber type	Type	Myelination	Skin type location	Firing frequency	
				Mechanical/light touch	Nociceptive thermal/pain
Aβ	SAI-LTMR	Thick	Glabrous, hairy	≤ 20 Hz (21)	–
	LTMR	Thick	Glabrous		
Aδ	HTMR	Thin	Glabrous, hairy	≤15 Hz (20,27)	>40–50 Hz (22,27)
	LTMR	Thin	Hairy		
C	HTMR	Unmyelinated	Glabrous, hairy	-	>50 Hz (18)
	LTMR/C-tactile	Unmyelinated	Hairy	<20 Hz (26)	–

LTMR: low-threshold mechanoreceptor; SAI: slowly adapting type I; HTMR: high-threshold mechanoreceptors.

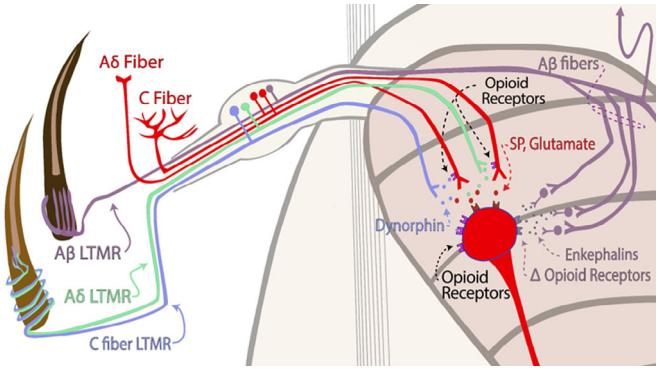

Figure 2. Activation of LTMR sub-sets of all fiber types leads to the release of endogenous opioids in the dorsal horn of the spinal cord.

levels (38,39). These Aδ- and C-afferent-mediated inhibitory projection fields spread more in the rostro-caudal axis than the excitatory projection fields, indicating a lateral inhibitory network exists to restrict the rostrocaudal broad excitation of the SG neurons evoked by noxious stimuli (40).

VERY LOW FREQUENCY AND NEUROMODULATION

That the activation of pain-relieving mechanisms is dependent on the frequency of incoming APs (2) has been demonstrated in various electrical stimulation therapies, including SCS (41–43). This may be mediated by endogenous opioids. Sato et al. demonstrated that SCS at 4 Hz in the rodent model provided efficacious pain relief and triggered the release of endogenous ligands that activate mu opioid receptor pathways, whereas 60 Hz SCS activated delta opioid receptor pathways (41). Electro-acupuncture and transcutaneous stimulation demonstrate that stimulation at 2–10 Hz recruits mu opioid receptor pathways while higher frequencies (100 Hz) elicit delta opioid receptor system activation (42–45). In allodynic animal models, SCS and DRG-S both increase paw withdrawal thresholds, suggesting pain relief (46–49). Additionally, DRG-S at 1 Hz, 20 Hz, and 1000 Hz were equally efficacious in blocking pain in rats, with 1 Hz having a longer wash out period (49). These studies underscore Ikeda et al.'s findings that very low- and high-frequency electrical stimulation to the same primary afferent fibers can trigger different pathways or mechanistic responses within the spinal circuits (50).

Application of the same stimulation frequency to different neuroanatomic locations along pain pathways may not utilize the same mechanisms to achieve pain relief. 50-Hz SCS increases GABA release in the dorsal horn (46), whereas 50 Hz DRG-S does not (46,48) (Fig. 3). Likewise, lower frequency neuromodulation has been shown clinically and experimentally to produce inhibition in physiologic conditions other than pain. In animal studies of the genitourinary system, very low-frequency stimulation of LTMR fibers at 3–5 Hz promotes inhibition of bladder hyperactivity compared to higher frequencies (51,52) and sacral neuromodulation for bladder and bowel dysfunction is typically programmed between 10 and 20 Hz (53–56). Somatocardiac reflexes were inhibited at <4 Hz (34). Vagal nerve stimulation typically use ranges from 10 to 30 Hz to treat depression and seizures (57,58). In 1975, Adams showed that pain relief mediated with deep brain stimulation at 10 Hz could be reversed with naloxone. Today, deep brain stimulation as low as 1 Hz is used to prevent seizures in epilepsy (59–64). In all, these modalities demonstrate the effects of very low-frequency stimulation in neuromodulation interventions. Additionally, through animal and human studies, these modalities suggest that the endogenous opioid system plays a role in the mechanisms of action.

VERY LOW-FREQUENCY DRG-S: SPINAL INHIBITION

Processing of pain signals occurs within the superficial dorsal horn (DH) of the spinal cord, where the neuronal architecture is complex and has not been fully elucidated. Primary afferent axons branch into multiple terminals to synapse on second order neurons and interneurons. Likewise, neurons in the DH can receive input from multiple primary afferents as well as interneurons, modulating the net signal via population coding (65). This frequency-dependent volley of multiple excitatory and inhibitory neurotransmitters and/or ligands onto second order neurons may result in excitation or inhibition. Animal studies have demonstrated that low-frequency stimulation activates inhibition in the dorsal horn at <20 Hz (34,66–70), while >25 Hz produces excitation (51,52,67,71).

Most pain signaling in the spinal cord is processed in Lamina II, the substantia gelatinosa (SG). Very low-frequency stimulation at 1 Hz to primary afferents results in inhibition of SG neuron output that is blocked by low dose naloxone, a nonspecific opioid antagonist, but unaffected by GABA and glycine antagonists (50,68,70). Inhibition of SG neuron output with 100 Hz stimulation to the same fibers is reversed by GABA and glycine antagonists, but

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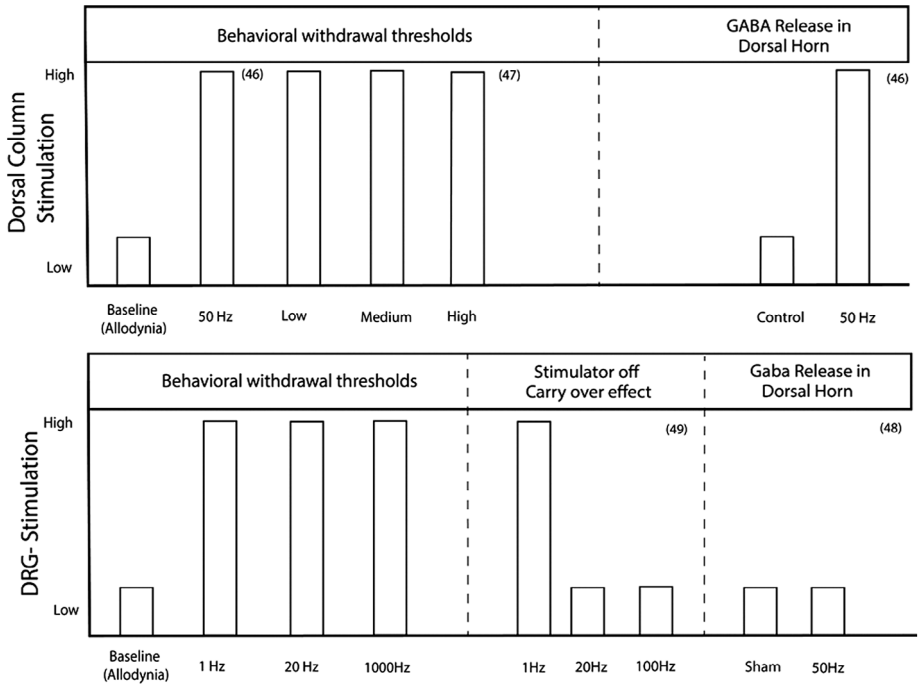

Figure 3. Behavioral and neurotransmitter consequences of SCS vs. DRG-S. Both SCS and DRG-S increase paw withdrawal thresholds in allodynic animals. However, only low-frequency (1 Hz) DRG-S has apparent frequency-dependent effectiveness in delayed washout of effect. The release of GABA in the DH is marked during SCS but not DRG-S.

unaffected by low dose naloxone, indicating different mechanisms are at play (50). These results demonstrate inhibition with very low-frequency stimulation is endogenous opioid dependent, whereas higher frequency stimulation relies on GABAergic/glycinergic mechanisms. Consistent with these findings, when comparing analgesic effects of 1 Hz to 20 Hz and 1000 Hz DRG-S in an animal model of painful diabetic polyneuropathy, equivalent antinociceptive effects across all frequencies were found. However, only at 1 Hz was a delayed washout effect observed, suggesting an additional or alternative mechanism of action (49). The study surmised that the delayed washout effect seen with 1 Hz frequency stimulation was due to induction of an Aδ fiber-mediated long-term depression of dorsal horn nociceptive transmission. This was previously demonstrated experimentally by Sandkuhler et al. (68) (Fig. 4). Additionally, only low stimulation frequency of the DRG at 5 Hz *in vitro* elicits APs in all three classes of Aβ-, Aδ- and C-fiber neurons, while higher stimulation frequencies do not (72). Based on these observations, we hypothesize that one of the primary pain-relieving mechanisms of DRG-S is the selective activation of Aβ-, Aδ- and C-LTMR fibers at very low frequencies. By generating APs at low physiological frequencies in these fibers, DRG-S may engage the LTMR's dual role of inhibiting pain signaling in the dorsal horn through non-GABAergic mechanisms, namely opioid receptor activation.

The frequencies at which DRG neurons can be activated and phase lock to stimulation pulses for pain relief are determined by the neurons' intrinsic firing properties (2,36); it may be the case that phase-locked propagation of APs results in different treatment outcomes than asynchronous stimulation. LTMRs were shown experimentally to phase lock at stimulation frequencies from 0 to 20 Hz; coincidentally this includes the frequency range that is most effective in DRG-S (73). Higher stimulation frequency resulted in asynchronous firing rates and a proportional decrease in propagation of APs above 30 Hz (36) (Fig. 5). Therefore, higher stimulation frequencies, which fall outside of the phase-locking range, may be less efficient at stimulating DRG neurons, specifically LTMR fibers, to promote pain relieving effects. This very low

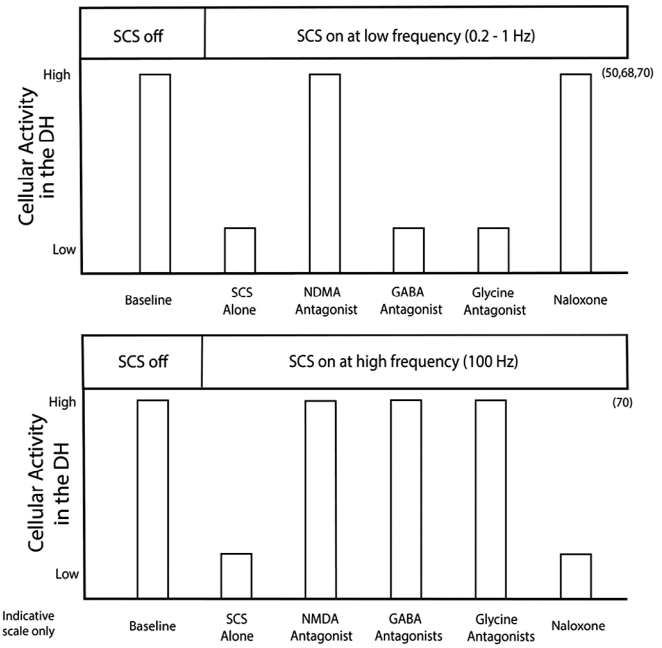

Figure 4. Differential effects of low- and high-frequency stimulation in Lamina II of the DH. Inhibition by high-frequency stimulation (but not low frequency) is GABA/glycine-dependent, while inhibition by low-frequency stimulation (but not high-frequency) is naloxone dependent.

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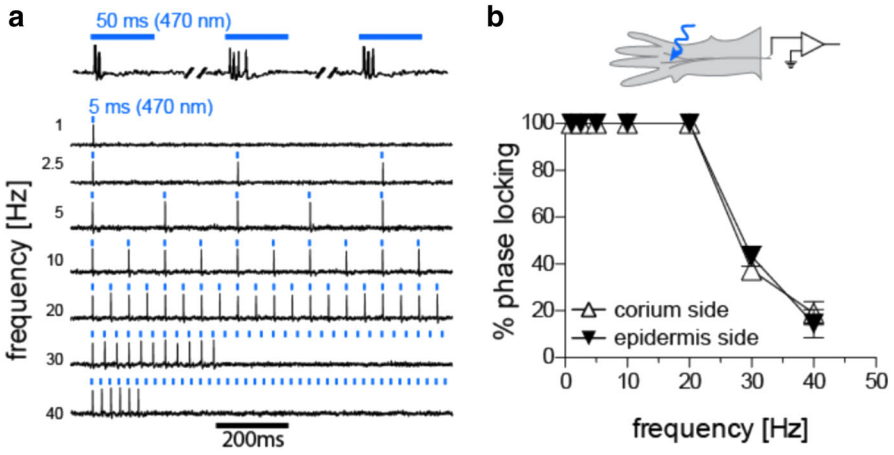

Figure 5. Phase locking is the ability of certain frequencies of a stimulus to activate an action potential in a neuron, and here the neurons are optogenetically identified LTMRs. The stimulus is represented by the blue lines above the electrical tracings (a). Note that LTMR phase lock 1:1 up to 20 Hz with a rapid loss of synchrony above 30 Hz (a and b). Reproduced with permission from Arcourt et al. (36). [Color figure can be viewed at wileyonlinelibrary.com]

frequency dependent nerve fiber type activation was recently demonstrated in the rodent model, where C fiber propagation into the dorsal horn was entrained up to 20 Hz, and further activation was not achieved up to 100 Hz (74). Additionally, it was demonstrated that hypersensitivity to mechanical stimulation normalizes with DRG-S, a phenomenon recently demonstrated in patients implanted with DRG-S using pressure pain threshold testing (74,75).

These findings, combined with the observation that LTMR input has a strong analgesic effect at low firing frequencies but hardly affects pain behavior evoked at stimulation frequencies above 5 Hz (36), suggest that very low-frequency DRG-S may be optimal for pain relief while also being the most efficient for charge delivery. With DRG-S, clinical therapeutic benefit occurs in the same low frequency range, from 4 to 20 Hz, achieving equivalent pain control to higher frequencies while limiting the electrical dose being utilized (8).

In summary, DRG-S has several mechanisms of action to provide analgesia at the level of the stimulated DRG (76–79), but the broader coverage of multiple spinal segments seen with DRG-S at certain levels is not explained by these mechanisms alone (4,80–82). Stimulation at very low frequencies (≤ 5 Hz) can generate APs in all LTMR fiber types (72) and trigger more of the body's own physiologic inhibitory systems through opioid receptor activation (24,25,34,36). This mechanism is distinct from SCS since dorsal column stimulation targets only Aβ fibers and is limited to adjoined gating mechanisms. Furthermore, synchronous AP firing rates can be generated at up to 20 Hz, though equivalent or potentially improved therapeutic benefit may be achieved at 5 Hz or less (36); frequency ranges where good DRG-S outcomes have been observed. Therefore, very low-frequency DRG-S can entrain all LTMR fiber types, which then harness mechanisms including intraspinal inhibition via endogenous opioid receptor recruitment (4,34,82,83). This may explain the success of DRG-S observed in post-surgical pain syndromes that typically have a component of nociceptive pain (82,84,85). The ability to phase lock or capture selective nerve fiber types to achieve a desired outcome can potentially alter our current approach to neuromodulation. In addition, lower stimulation frequency would decrease the total energy delivery, extending battery life, and facilitating the development of devices that can have smaller generators, which may be associated with lower complication rates and better cost-effectiveness.

CONCLUSIONS

Currently, optimal stimulation parameters for DRG-S are not defined. Our clinical observations consistently demonstrated good outcomes at very low frequencies. The human nervous system is frequency modulated, which in turn determines which circuits and mechanisms are activated in the dorsal horn. Physiologically, LTMR fibers transmit or modulate innocuous mechanical touch at low frequencies while nociceptive fibers transmit pain at high frequencies. Our observations are consistent with very low-frequency DRG-S harnessing LTMRs and the native endogenous opioid system. Utilizing the lowest electrical dose is invaluable, and more research is needed to further elucidate the effects of frequency in DRG-S, and in turn, possibly expand indications for DRG-S.

Authorship Statements

Kenneth B. Chapman prepared the manuscript draft with important intellectual input from Tariq A. Yousef, Allison Foster, Michael D. Stanton-Hicks, and Noud van Helmond. Kenneth B. Chapman, Tariq A. Yousef, Allison Foster, Michael D. Stanton-Hicks, and Noud van Helmond edited the manuscript. All authors approved the final manuscript.

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COMMENTS

Low frequency stimulation has been in use for many years in the percutaneous electrical stimulation field, including PENS and Pulsed RF. However, the exciting opportunity afforded by long term depression of A-delta fibers should not overlook potential applications of implantable neuromodulation devices for treating mechanical pain as well as neuropathic pain.

Further clinical work along these lines is needed to justify recommendations for clinical implementation, but the potential appears to be considerable across a variety of disease states.

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Just when we thought everything that needed to be discussed with DRG stimulation had been put into print, researchers and clinicians continue to find new and innovative ways to maximize this impressive therapy and improve clinical outcomes for patients. Well done!

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