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The Pathways and Processes Underlying Spinal Transmission of Low Back Pain: Observations From Dorsal Root Ganglion Stimulation Treatment

Kenneth B. Chapman, MD*†‡; Pauline S. Groenen, BS*§; Kris C. Vissers, MD, PhD¶; Noud van Helmond, MD* ; Michael D. Stanton-Hicks, MD††**

Background: Dorsal root ganglion stimulation (DRG-S) is a novel approach to treat chronic pain. Lead placement at L2 has been reported to be an effective treatment for axial low back pain (LBP) primarily of discogenic etiology. We have recently shown, in a diverse cohort including cases of multilevel instrumentation following extensive prior back surgeries, that DRG-S lead placement at T12 is another promising target. Local effects at the T12 DRG, alone, are insufficient to explain these results.

Materials and Methods: We performed a literature review to explore the mechanisms of LBP relief with T12 DRG-S.

Findings: Branches of individual spinal nerve roots innervate facet joints and posterior spinal structures, while the discs and anterior vertebrae are carried via L2, and converge in the dorsal horn (DH) of the spinal cord at T8-T9. The T12 nerve root contains cutaneous afferents from the low back and enters the DH of the spinal cord at T10. Low back Aδ and C-fibers then ascend via Lissauer's tract (LT) to T8-T9, converging with other low back afferents. DRG-S at T12, then, results in inhibition of the converged low back fibers via endorphin-mediated and GABAergic frequency-dependent mechanisms. Therefore, T12 lead placement may be the optimal location for DRG-S to treat LBP.

Keywords: Convergence, dorsal root ganglion, low back pain, neuromodulation, pathway, stimulation, T12, transmission

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INTRODUCTION

Low back pain (LBP) gives rise to a large morbidity burden worldwide (1–3) and is one of the top five most common reasons for physician visits in the United States (1–3). Since the causes of LBP remain elusive in the majority of cases, no disease-specific treatments exist (1). In the last two decades, spinal cord stimulation (SCS) has become a reasonable treatment option for patients with refractory LBP (4–6). However, multiple studies show that approximately 40% of the patients continue to have pain after implantation with SCS (7,8). The mechanisms of action of SCS, particularly for paresthesia-free paradigms, are enjoying renewed scientific interest and investigation (9).

More recently, dorsal root ganglion stimulation (DRG-S) has been shown to be an effective treatment for selected pain syndromes. In this intervention, leads are placed adjacent to the DRG in the vertebral foramen. DRG-S is currently only FDA-approved for the treatment of complex regional pain syndrome (10,11). However, DRG-S is also effective for back pain, and a number of published "off-label" cohorts have included back pain cases (12–14). Typical DRG-S lead placement is at the spinal levels corresponding to the dermatomal level of pain. Current hypotheses for a DRG-S mechanism of action suggest modulation of nociceptive transduction at the level of the stimulated DRG (15), with recommended parameters of 250 μsec pulse widths at 20 Hz, and amplitudes individualized to sub-paresthesia levels (16).

Recently, several reports with promising results of DRG-S in axial LBP have been published. In these reports, leads were placed at L2. For example, Huygen et al. (17) performed DRG-S at the L2 level for LBP with good results based on the concept of sympathetic convergence at the L2 level and sympathetic innervation of the lumbar discs

Address correspondence to: Kenneth B. Chapman, 1360 Hylan Boulevard, Staten Island, NY 10305, USA. Email: chapmanken@spinepainny.com.

* The Spine & Pain Institute of New York, New York City, NY, USA;
† Department of Anesthesiology, New York University Langone Medical Center, New York City, NY, USA;
‡ Northwell Health Systems, New York City, NY, USA;
§ College of Medicine, Radboud University, Nijmegen, the Netherlands;
¶ Department of Anesthesiology, Pain, and Palliative Medicine, Radboud University, Nijmegen, the Netherlands;
** Department of Anesthesiology, Cooper Medical School of Rowan University, Cooper University Hospital, Camden, NJ, USA; and
†† Department of Pain Management, Cleveland Clinic, Cleveland, OH, USA

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(17–21). In that study, seven out of 12 patients who had a successful trial maintained good outcomes after one year, which implies their theory was reasonable. A subsequent study also employed L2 DRG-S based on the concept of sympathetic convergence at this level, in this instance for isolated discogenic pain. Kallewaard et al. (22) followed 14 patients—with positive discography, negative facet joint injection, and no prior back surgery—for a year. For strictly discogenic pain, the significant improvements exceeded those of the other L2 study (17). A third DRG-S study at L2 for chronic pain following lumbar discectomy reported an average of 72% pain relief after 12 months of treatment (23). It was hypothesized that stimulation at L2 harnesses the convergence of somatic and sympathetic afferents based on spinal nerve anatomy (17).

Recently, we have reported our findings for LBP treatment with DRG-S at another nonconcordant spinal level: T12 (24). We programmed our DRG-S patients with low stimulation frequencies: at a mean of 14 Hz. In our report, all patients had undergone multiple injections or procedures for pain in the previous two years, with the majority having had prior surgeries including multilevel instrumentation. Mean baseline pain was 92.5 mm on a standard 0–100 visual analog scale (VAS), with concomitant serious limitations in function and health-related quality of life. After an average of 8.3 months of treatment, mean pain ratings declined to 20.0, which is lower than the definition of remitter of 25 mm (25). Furthermore, all patients responded with at least 50% pain relief and more than half responded at 80% or better pain relief at their last follow-up. Functional and quality of life outcomes also dramatically improved, with all mean values approximating those of nonpain population norms (see Fig. 1; (24)). These improvements exceeded those in other published reports. For example, high-frequency SCS treatment for 12 months (SENZA trial) reduced back pain to a similar level, but from a lower baseline than ours (7.6 on a 10-cm VAS). Moreover, the average reduction in disability, 16.5 ODI points, was eclipsed by the improvement of more than 50 points that we observed (25). Our increase in EQ-5D scores from 0.30 to 0.84 spanned the entire range of EQ-5D ratings from two recent reports of DRG stimulation for LBP: one reported an improvement from 0.31 to 0.50 (17) while another reported an improvement from 0.61 to 0.84 (22). The increase was similar to the change from 0.34 to 0.80 in nine patients with failed back surgery syndrome (23). Two studies with tonic SCS demonstrated improvements in the physical and mental components of the SF-36 of roughly 20%, while our patients demonstrated 100% improvements in those categories, with T12 DRG-S patients having a mean score of 60 at last follow-up, which was greater than the normalized population mean of 50 (26,27).

There is currently no consensus about the ideal spinal cord level for DRG-S lead placement to cover the low back. We propose that the mechanism of action for T12 DRG-S for axial LBP is dependent

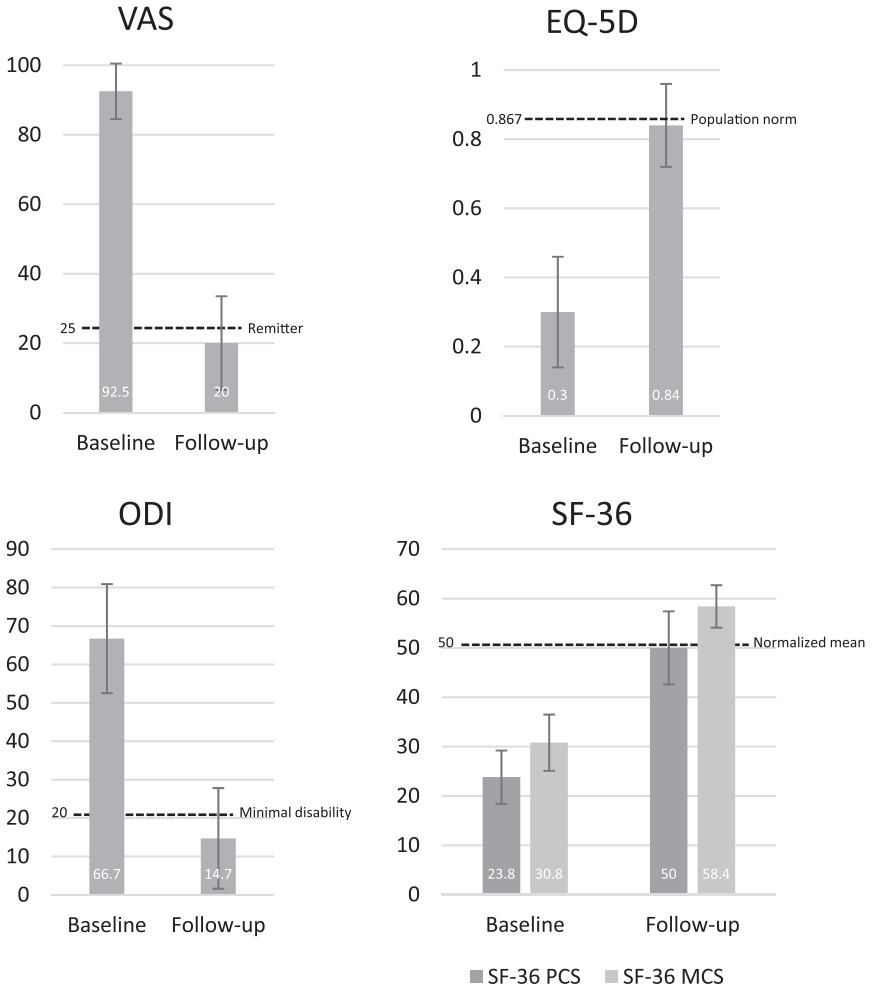

Figure 1. Summary of the published T12 DRG-S for LBP study demonstrating robust improvements in pain, quality of life, and disability with DRG-S. Reproduced with permission from Chapman et al (24).

on deep LBP fibers entering Lissauer's tract (LT) at their given level and converging with the T12 afferents within the dorsal horn (DH), as discussed below. The convergence of low back fibers in LT with T12 encompasses the L2 spinal nerve afferents, as previously discussed, in addition to other nerve roots, thus providing relief for a more diverse patient population than seen with L2 DRG-S for discogenic pain, which depends on sympathetic convergence at that level. The purpose of this article is to present a narrative review of anatomical and neurophysiological pathways to support our hypothesis that the T12 level is the ideal location for DRG-S lead placement specific to LBP.

ANATOMY AND PHYSIOLOGY

The sensory innervation of the low back is relatively nondetailed and represents a small region of the primary sensory cortex (28–31). Patients cannot typically discriminate among, for example, disc-related pain, facet pain, or muscle strains due to a lack of discrete sensory input, which suggests that pain signals for this large area must converge onto small targets, in a manner similar to that seen in visceral pain syndromes (32,33). The T12 dermatome covers a significant portion of the skin and soft tissue of the low back. This fact is not widely appreciated due to misconceptions of low back cutaneous innervation perpetuated in multiple dermatomal maps published over the past 120 years (28–30). For example, a commonly used dermatomal map, that of Keegan and Garrett (34), shows that much of the lumbar spine and buttocks are innervated by lumbar nerve roots, not T12. However, the 1898 work of Head and Campbell demonstrated that shingles rashes that covered the low back corresponded to the T12 DRG (35). Later, meticulous dissections by Maigne et al. also found that much of the skin of the low back and upper buttock was innervated by T12 and L1 (36). With this information, Lee et al. published an evidence-based dermatomal map showing much of the skin and subcutaneous tissue of the low back is innervated by the T12 spinal nerve (37). As the lumbar and sacral nerve roots from the cauda equina enter the spinal cord between the T11-L1 vertebral levels, the T12 nerve roots actually enters the spinal cord at the mid- to lower-T10 vertebral level (see Fig. 2a) (28,30,38,39).

The innervation of the lumbar spine is from multiple sources including superficial nerves, sympathetic/autonomic nervous system inputs, and branches of somatic nerve roots, which comprise at least a medial branch nerve, sinuvertebral nerve and basivertebral nerve (28,29,40). Sensory input passing through the DRG to the DH of the spinal cord is predominantly cutaneous in nature. Swett et al. demonstrated in rats that 19% of input of sciatic nerve DRGs was from muscle, 5% from joints, and the remaining 76% from cutaneous afferents (41). Afferent nerve fibers are somatotopically organized at the DRG (15), and this is maintained within the DH, with the distal limbs organized medially and the trunk laterally. The nerves related to the lumbar spine are located in the lateral aspect of the DH, as are the visceral terminations in the thoracic spine (42–44). In addition, laterally located second-order neurons have the capability to receive input from all lumbar spinal nerve roots, whereas the nerves on the medial aspect of the DH receive input from their corresponding level (45). Somatotopic organization is maintained at all points along afferent pathways, including the spinal nerve, DRG, nerve rootlet, DH, spinothalamic tracts, thalamus, and somatosensory cortex (30,42,43,46–49) (see Fig. 3a).

Nociceptors are peripheral receptors that are able to sense pain; nociception is the transmission of those pain signals to the central nervous system (30,46,48,50). Nociceptive neurons comprise thinly myelinated Aδ nerve fibers, which are able to conduct fast mechanical stimuli (light touch), thermal stimuli, and acute pain (30,46,48,50), and unmyelinated C-fibers that conduct slower, chronic pain sensations and are able to conduct any type of painful stimuli due to their polymodal receptors (30,46,48,50). A subset of Aβ, Aδ, and C-fibers neurons are low threshold mechanoreceptors (LTMR), involved with touch sensation and localization (51). LTMR afferent terminals are found around hair follicles, while their central synapses are in lamina 2 and 3 (30,46–48,51).

The DRG is located outside the spinal cord at the axonal T-junction and contains the cell bodies of all sensory neuron afferents, including those of nociception, vibration, fine touch, and proprioception (15,52,53). Gnostic sensory information travels from the DRG toward the ipsilateral dorsal column (DC), while pain and temperature modalities enter the DH and travel toward the brain via the anterolateral system and spinothalamic tracts (15,53). Before nociceptors synapse in the gray matter of the DH, they may enter LT, a rostrocaudal tract located between the tip of the DH and the dorsal root entry zone; also known as the dorsolateral funiculus (30,46–48). Axons may enter LT and ascend one or two segments before entering the gray matter of the spinal cord segment, or they may synapse in the DH and then enter the LT, as demonstrated in Brown Sequard Syndrome (30,47,48,54–58) (Fig. 2b). In some cases, C-fiber pain may ascend up to as many as six segments in LT (46,48,56,59–62). This is the anatomical substrate for intersegmental processing (63). Once in the DH, the nociceptors synapse in Rexed laminae I and II of the gray matter, the posteromarginal nucleus and the substantia gelatinosa (30,46–48), and from there they synapse on second-order neurons. After convergence and processing, second-order neurons make their way to the ascending tracts of the anterolateral system and eventually synapse in the thalamus (30,46,47). See Fig. 2 for a summary of the points in this section.

One of the spinal targets of sensory afferents are neurons that receive multiple diffuse inputs: wide dynamic range (WDR) neurons that are thought to play a pivotal role in pain processing. The lateral DH has a preponderance of WDR neurons that receive both noxious and nonnoxious stimuli, as opposed to nociceptor-specific neurons (49). GABA and glycine are the primary inhibitory neurotransmitters in the DH (64–66). Up to 80% of the cells of the substantia gelatinosa have the potential to be inhibitory (67), via GABA (68,69). DRG-S may activate the inhibitory potential of this preponderance of small fiber cutaneous afferents, making the DH a putative site of mechanism for DRG-S. Also present in pre-synaptic terminals and interneurons throughout the DH are endorphins and enkephalins, which are endogenous opioids that bind to μ, γ, and κ opioid receptors to decrease nociceptive transmission and the experience of pain (see Fig. 4) (70–81). Exogenous opioid pain medications target these same receptors in the DH to decrease mechanical pain.

T12 DRG-S FOR AXIAL LBP: INTEGRATING THE EVIDENCE

DRG-S hyperpolarizes the T-junction of the primary sensory neuron at the DRG, which would explain why DRG stimulation may be effective in the distribution of the concordant spinal nerve, but not why stimulation at a distant DRG, such as T12, would provide pain relief for LBP (32,52,82–91).

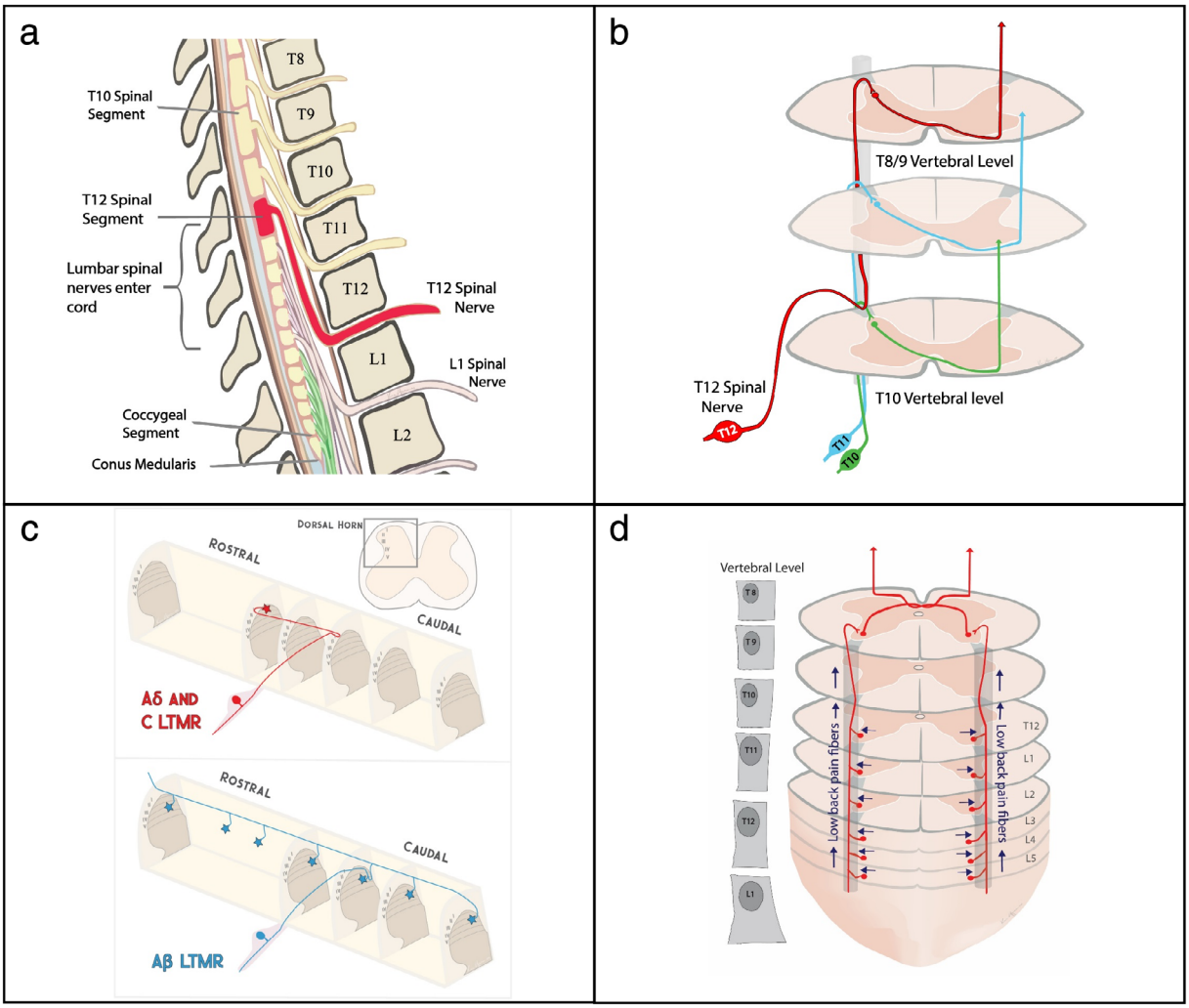

Figure 2. (a) T12 nerve roots enter the vertebral column and ascend to enter the spinal cord at the lower T10 vertebral level. (b) T12 spinal nerve Aδ and C fibers entering the spinal cord at the T10 level and ascending in Lissauer's tract to enter the DH at the T8-9 level. This is the classic level detailed in Brown Sequard syndrome. (c) LTMR fiber tracing through the spinal cord shows that Aδ and C fibers ascend one to two levels to then enter the superficial DH, while Aβ fibers enter the DC and send collaterals rostrally and ventrally at multiple adjacent levels. Modified with permission from Abraira et al. (58). (d) Lumbar spinal cord segments demonstrating LBP fibers at all lumbar levels exiting the DH to travel together in Lissauer's tract to converge at the T8/9 level. [Color figure can be viewed at wileyonlinelibrary.com]

Convergence

We hypothesize that convergence, defined as the merging of multiple inputs onto a single target location or neuron, is a hallmark of back pain transmission. Lumbar C- and Aδ nociceptive nerve fibers arising from nerve roots of multiple spinal segments may converge in the substantia gelatinosa (lamina II) of a single segment, and nociceptive nerve fibers arising from one dermatome can travel through different spinal nerves and enter the spinal cord at different segmental levels, converging on a common target neuron in the substantia gelatinosa (see Fig. 3b) (59). Similarly, nociceptive input from deep low back structures across several segments converges cranially (92,93).

Placement of traditional SCS for low back coverage typically has lead placement at the top of the T8 vertebral body with the contacts extending into the body of T9, most commonly using contacts at the T8/9 interspace. SCS, as a segmental phenomenon, is predicated on the antidromic inhibition within the DH from the DC at or near the location of the active contacts. As discussed in a previous section, this is approximately the same level where low back fibers converge and enter the DH (84).

DH fibers enter from lateral to medial within the DC and proceed centrally, then extend deeper into the DC (94). Given the smaller amount of proprioception and light touch sensation represented in the lumbar spine, there is likely less representation of lumbar fibers in the DC. This makes the placement of SCS leads, and the ability to manipulate the electrical field, important. Recent improvements in stimulation technology have made capture of the low back more successful, but in a portion of cases, achieving adequate pain relief and improvement in function with SCS for axial LBP remains elusive.

Wall and Shortland demonstrated physiologically that the T12 dorsal root has neural connections to the DHs of all levels of the lumbar spine (95). This, combined with the evidence presented above, leads us to postulate that convergence of the diffuse innervation of the deep low back is an analog for stimulation of the T12 DRG, a single distant pathway, to achieve pain relief. Specific to T12, the nerve roots enter the spinal canal at T12 and enter the spinal cord at the level of mid/lower T10 (see Fig. 2a) (28,29,38,39). The T12 low back Aδ and C fibers then enter LT and

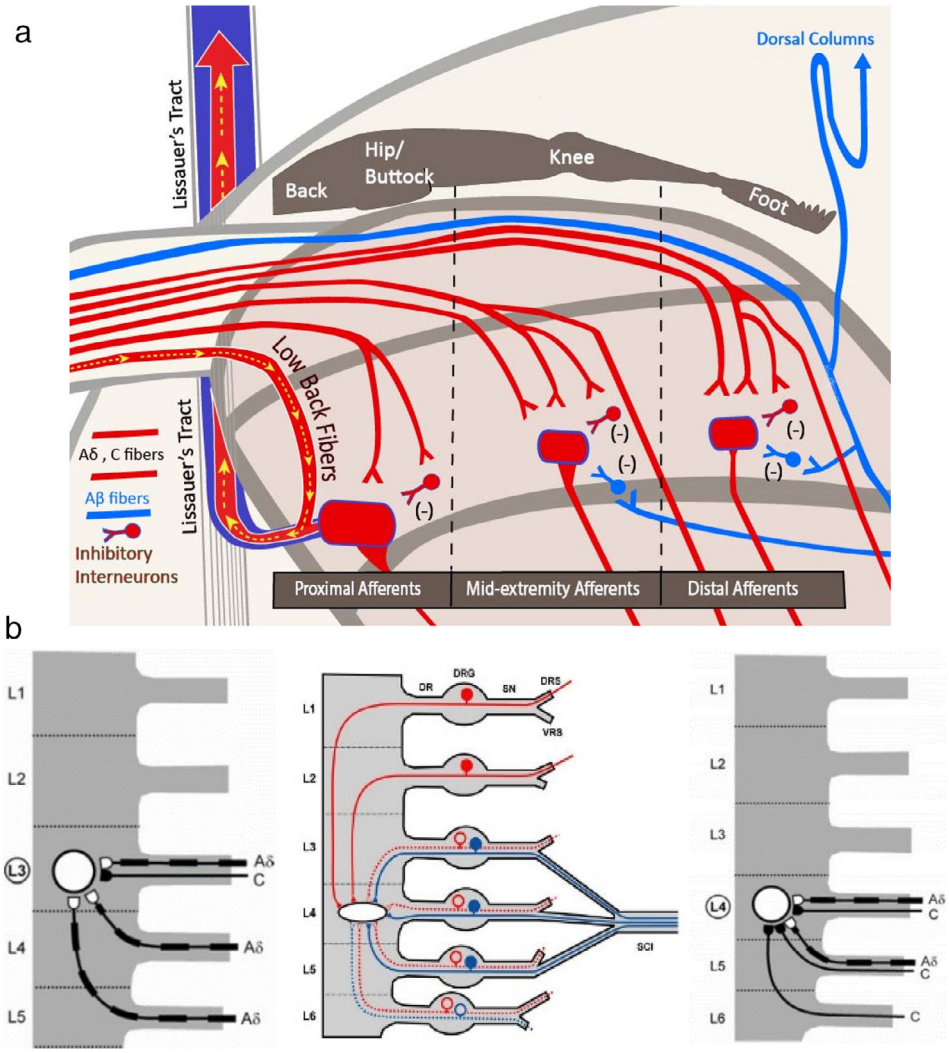

Figure 3. (a) The somatotopic organization within the DH places distal input medially with proximal, or truncal, input laterally. Laterally located low back fibers exiting the DH to Lissauer's tract. (b) Convergence of afferents within the spinal cord from multiple levels converging on the same second order neuron From Pinto et al. (59); reproduced with permission. [Color figure can be viewed at wileyonlinelibrary.com]

travel rostrally to the T8/9 region where they enter the DH (see Fig. 2b). At this level, the converged pain fibers from the deep structures of the low back then converge with the final piece of sensory information from the low back, the cutaneous fibers arising from T12 spinal nerve. This represents the full complement of low back sensory afferents.

Neurons from the lateral portion of the DH have been shown to exit the DH and travel in a rostrocaudal pathway for intersegmental processing (96). We postulate that the deep lumbar spine nociceptive signals deriving from the lumbar nerves, including the L2 nerve root carrying the sympathetic afferents (40,92,93), do not travel to the ascending tracts at their corresponding level but rather exit the DH and travel rostrally together in LT. See Figs. 2d and 3a.

Inhibition

In normal states there is resting inhibition mediated though tonically firing inhibitory cutaneous afferents (85). However, in painful states, increased nociceptive input may override the inhibitory control and reach the brain. The normal inhibitory mechanisms are overwhelmed and there are less inhibitory neurotransmitters (GABA and glycine) available (97). Stimulation of the T12 DRG, which provides cutaneous innervation to much of the lumbar spine though LTMR neurons, is able to suppress the converged pain fibers from the deep lumbar spine where they converge and provide a dense inhibition of the downstream nociception.

When a painful stimulus is repeated, the WDR neurons become more easily excitable, leading to the pathological state of "wind up" (98–103). SCS and dorsal root stimulation suppressed hyperexcitable responses of both WDR neurons and the spinothalamic tract in neuropathic rats (90,104,105), demonstrating the same potential location for a mechanism of action in both types of stimulation.

Segmental inhibition is accepted as a presumed mechanism of action of traditional SCS (67,84,90,105–113). Thus, antidromic inhibition at the T8/9 level from the DCs though interneurons may be indirect and incomplete at lamina I and II, as compared to the denser populations of these myelinated proprioceptive cells in lamina III, IV, V and VI. The DRG and its nerve root carry all types of sensory stimuli (52,53). DRG-S modulates orthodromic firing in the DRG of afferent neurons, with direct access to Aβ, Aδ and C-fiber

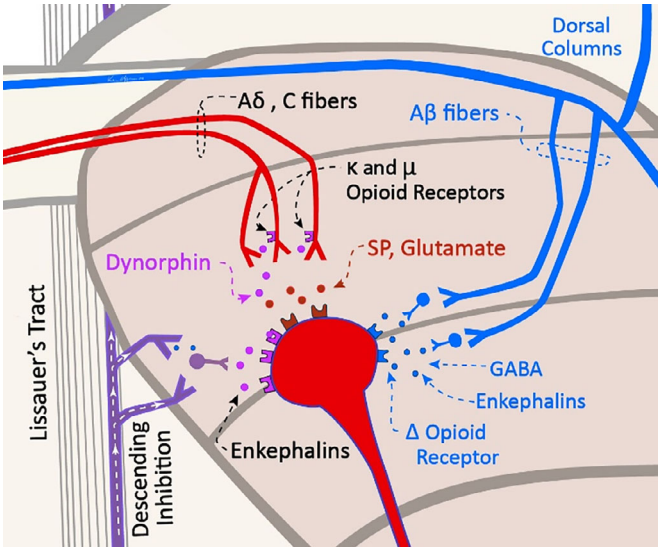

Figure 4. Normal DH processing of input on second-order neurons: Excitatory transmission via substance P and glutamate from Aδ and C nociceptive afferents. Inhibitory input from GABA, descending inhibition via enkephalins, and Aδ and C fiber LTMR-mediated inhibition via dynorphin and enkephalin. [Color figure can be viewed at wileyonlinelibrary.com]

neurons, and the potential to harness the inhibitory mechanisms of all afferent fibers, and thus create a greater post-synaptic inhibition on second order neurons (62,84,90,96,107,113–116). The significance of nerve fiber type has been demonstrated in several studies. Yang et al. stimulated Aβ fibers at the dorsal root entry zone and attenuated the C-component, of the WDR neural response at 50 Hz (115). Combining stimulation of Aβ fibers in the DC together with selective Aβ stimulation from the dorsal root did not appear to provide additional inhibition compared to DC stimulation alone, which suggests that neither method was more effective in inhibiting additional fibers (117). These findings, along with the segmental collateral input from Aβ fibers (see Fig. 2c), suggest that DRG-S should at least give a localized pain relief similar to SCS. Furthermore, it should be noted that these findings were generated with 50 Hz stimulation; if the experiments were repeated with low-frequency stimulation (lower than 20 Hz), it is possible that the effects would be potentiated. The impact of frequency on DRG-S will be discussed below.

An interconnected system of LTMR neurons contribute to lateral inhibition which fine tunes the localization of sensory inputs, as is seen in vision, touch, and pain (118–120). Within the DH, the first processing unit of the spinal cord is a robust circuitry of interneurons that integrate stimuli, similar to that seen in the retina (67,85). These LTMRs are also an important form of inhibition that may be harnessed with DRG-S. Also within the superficial DH, we have descending inhibition from the rostroventral medulla (RVM) involving DH interneurons that use a two-phase inhibition of pain transmission, although it is unlikely to be influenced by DRG-S. The first rapid phase is mediated by GABA. The second longer-lasting phase is mediated by enkephalins acting on the δ opioid receptor in primary afferent terminals (75).

Sensory afferent neurons show increased frequency of action potentials with increasing intensity of a stimulus (121–123). Non-painful mechanical stimulation of Aδ and C fibers produces an average neural firing rate of 15 Hz or less (124–126), and Aβ afferent fibers rarely fire above 20 Hz during sustained touch stimulation (127). In contrast, nociceptive primary afferent fibers fire at higher frequencies to transmit pain information. Heat stimulation elicits C fiber firing rates up to 50 Hz (124). Mechanothermal Aδ fiber unit action potentials fire at 40–50 Hz with increasing painful stimuli (128).

Inhibition in the DH is mediated at very low frequencies, typically lower than 20 Hz (81,88,129–132), and cells that tend to be excitatory are activated at higher frequencies (>25 Hz) (130,133–135). Low-frequency stimulation (0.5-5.0 Hz) of afferent nerve fibers favors presynaptic inhibition in the spinal DH in cats (136). In addition, very low frequency electrical stimulation (1 Hz) of Aδ primary afferent fibers inhibits excitatory DH interneurons through spinal opioid system activation (131,132). LTMRs also exert inhibitory control on mechanical pain signaling at very low frequencies (20 Hz or lower), while stimulation at frequencies above 20 Hz was less effective at eliciting LTMR action potentials (137). In our report of DRG-S at T12, we stimulated at a mean of 14 Hz, which is consistent with these recent studies, and is in contrast to traditional SCS frequencies of ~50 Hz.

GABA levels are elevated in the DH with SCS and these are thought to be related to its mechanism of action (138,139). Burst SCS especially elevates GABA levels (140). However, administration of GABA and glycine antagonists do not block inhibition by very low frequency (<20 Hz) stimulation (131,132). A recent study demonstrated that DRG-S does not induce GABA release in the DH (141). Thus, DRG-S, especially at very low frequencies, is likely to be less dependent on GABAergic mechanisms.

LTMR activation can inhibit afferent transmission including nociception using the endogenous opioid system; namely through the release of endorphins and/or enkephalins (67,131,142). C-LTMRs are believed to be responsible for mediating "emotional touch," or the pleasurable/affective component of touch though κ opioid receptors and dynorphin (143–148). The very low frequency LTMR action potentials elicited by activation of hair follicles and release of endorphins are responsible for the pleasurable effect of lightly brushing the hairy skin, as opposed to the same touch applied to glaborous (non-hairy) skin, which would be Aβ mediated (149).

Aβ, C, and Aδ LTMRs use endorphins to inhibit nociceptive transmission. Aβ neurons are associated with δ opioid receptors, which are activated by enkephalins. Aδ and C LTMRs stimulate the release of dynorphin, which activates the κ opioid receptors (78). μ opioid receptors are expressed presynaptically on specific types of Aδ and C fibers and postsynaptically on second-order neurons in laminas I and II and are responsive to endorphins and enkephalins (70). Naloxone has high affinity for the μ and κ opioid receptors and low affinity for the δ opioid receptor (150). Traditional SCS activates Aβ fibers from the DCs and thus is likely limited in its therapeutic effects to the inhibitory potential of the Aβ fibers (89,90). Low-dose naloxone was ineffective at blunting 60 Hz SCS, but naltrindole, a δ opioid receptor selective antagonist, reversed the effects of SCS. Naloxone, which reverses LTMR inhibition (151), reversed Aβ mediated SCS but only at very high doses (150).

Afferent neuronal fibers can differentially release neurotransmitters in response to low- and high-frequency afferent signals. Low-frequency afferent signals can activate the inhibitory system, while high-frequency afferent input (noxious) can activate both excitatory and inhibitory circuits that are GABA or glycine dependent where the net effect can change under varying conditions (152,153). Therefore, we propose that very low frequency DRG-S activates Aδ, C, and Aβ LTMR-mediated release of both dynorphin and enkephalins to act on μ, κ, and δ opioid receptors in humans.

The above evidence combined with the results of our case series lead us to conclude that DRG-S is an effective, focal means of achieving inhibition within the superficial layers of the DH. Conceivably, this very low frequency stimulation is mimicking LTMR signaling, thus activating innate inhibition.

Integration and Summary

Using the data presented above, we hypothesize that DRG-S at subthreshold doses downregulates firing in the DRG as previously reported (154), therefore working at a local level, while also inducing firing of Aδ, C, and Aβ LTMR fibers to cause inhibition through endorphin-mediated mechanisms (see Fig. 5). The proposed mechanism of action of DRG-S at the T12 DRG not only potentially demonstrates the manner in which LBP is transmitted to the brain but also can be extrapolated to explain several other SCS-related phenomena.

The mechanism of convergence-related inhibition mechanistically is similar to that seen in referred pain (48,155,156), but rather than an experience of pain, it is the convergence of the pain-signaling low back neurons with inhibition induced by T12 DRG-S that produces the opposite result: pain interruption. The 1949 convergence-projection theory of Ruch (157) theorized that visceral fibers and cutaneous fibers converge on the same second-order neurons. Pain from the viscera takes the place of input from the skin; thus, the brain would perceive only the cutaneous pain from that dermatome. For example, when the diaphragm is irritated by air in the peritoneum, or by inflammation of the gallbladder, the patient complains of shoulder pain (C3-4-5), or with angina, left arm pain (T1). The same phenomenon occurs when neurons within lamina I receive input from lower lumbar nerves and integrate this information with the muscles and joints (63,96). Somatic and visceral C-fibers also converge onto the same neurons in the lamina II; therefore, C-fibers of different origin can inhibit each other (32). Deep somatic structures converge with cutaneous input (63,158) and inhibit each other. For example, intercostal afferent stimulation inhibits visceral afferents from the heart and esophagus (159). Stimuli arising from the sympathetic chain and from the corresponding cutaneous regions also inhibit one another. Such cutaneous counter-irritations are able to inhibit visceral pain (160). Luz et al. demonstrated that somatic (cutaneous) and visceral (deep structures) afferents converge in lamina I neurons, which showed inhibitory responses upon stimulation (85). Furthermore, lamina I neurons may receive both excitatory visceral inputs (such as the pain arising from the facet joints) and inhibitory somatic inputs (such as the DRG stimulation of the "cutaneous" T12 root). This phenomenon is known as somatovisceral inhibition and sets the stage for convergence of the low back fibers with cutaneous input (32).

This hypothesis of convergence-related inhibition may explain why the patients in our study responded similarly to subjects in previous L2 DRG-S studies (17,22) but had a fuller and more complete success rate. At the L2 level, DRG-S may only be able to cover sympathetic afferents, which would treat discogenic pain and, perhaps, a portion of the Aδ and C fibers entering at that level. These L2 fibers would also enter LT and ascend to the T8/9 level with the converged low back fibers from all levels of the lumbar spine, therefore coverage of LBP by the T12 DRG encompasses discogenic pain, in addition to LBP arising from origins more than just the disc itself.

Selective activation of Aβ fibers from the dorsal root inhibited noxious C fibers postsynaptic currents but did not alter Aδ stimulation (89). Antidromic stimulation in the DC causes little Aδ activation (90). This lack of capture of Aδ fibers with SCS may also have led to poorer outcomes with Type 1 CRPS patients with brush stroke allodynia at one year, because this is an Aδ mediated signal (161). The ability to stimulate Aδ fibers and their corresponding inhibitory interneurons

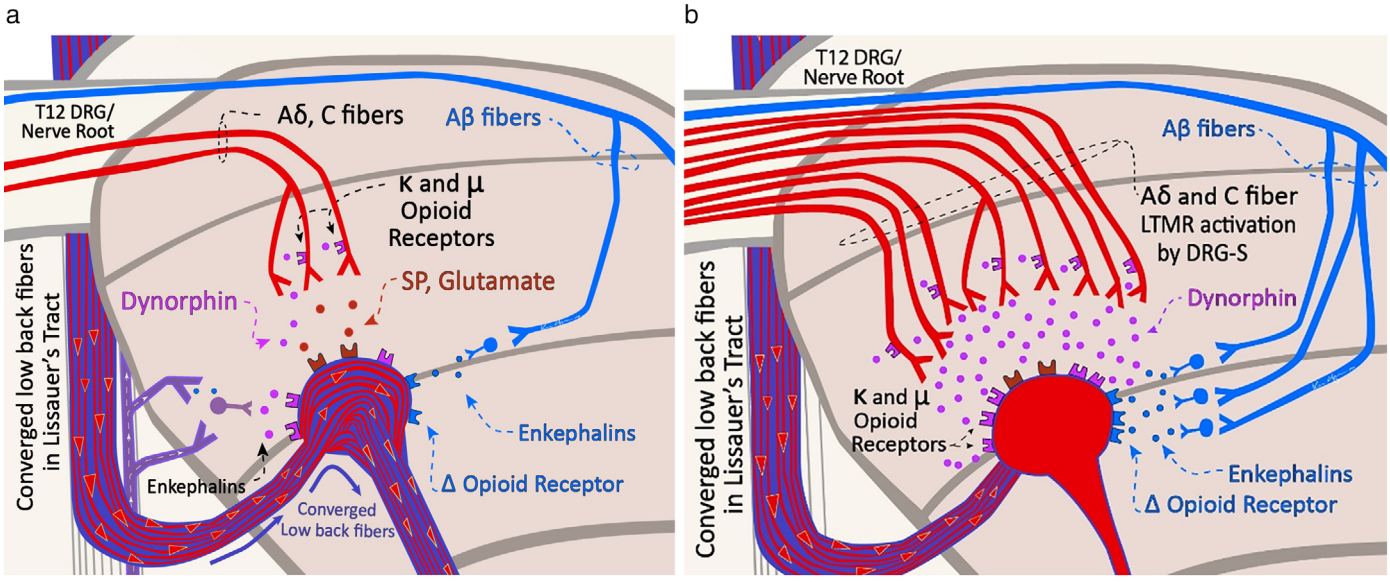

Figure 5. (a) T12 spinal nerve skin and normal subcutaneous tissue input to the converged LBP fibers at the T8/9 level. Excitatory and inhibitory input from the T12 spinal nerve provides the final piece of sensory input to the converged low back fibers (dark blue) as they enter the DH. The converged low back fibers in their entirety then travel to the corresponding ascending pathways. (b) DRG-S at very low frequencies activates LTMRs at the DRG, causing a massive release of inhibitory ligands on the converged low back fibers, in turn, causing a dense inhibition of LBP transmission (dark blue to red). Under normal conditions, LTMRs release dynorphin and enkephalins, which inhibit mechanical input in order to localize touch and fine tune the touch process. [Color figure can be viewed at wileyonlinelibrary.com]

with DRG-S, along with the inability to recruit Aδ fibers with Aβ stimulation would lead us to conclude that this interaction has a significantly different mechanism from that of SCS.

The results of our prior case series and our theory also postulate that the effects of DRG-S are not limited to the DRG itself. As demonstrated with T12 DRG-S for LBP, we hypothesize that inhibition is also occurring within the DH through a mechanism involving the endogenous opioid system. This activity combined with convergence and/or re-convergence of peripheral nerves can be one mechanisms behind the phenomenon of coverage of an adjacent dermatome with DRG-S and thus can explain the misnomer, "cross-talk" which is used to explain why DRG-S can cover more than one dermatome. A better understanding of the convergence of autonomic fibers with cutaneous fibers can also potentially lead to a more effective treatment of sympathetically mediated conditions with neurostimulation in the future.

Providing this denser, more specific block of the cells of the DH, through LTMRs, the body's natural mechanism to inhibit mechanical pain, may also explain why DRG-S may be having an effect on some traditionally somatic pain syndromes and not just neuropathic pain (17,22–24,30,162,163). Unlike traditional SCS, in which nociceptive neurons are indirectly affected through supraspinal and segmental mechanisms of action, DRG-S may modulate all afferent input.

It has been demonstrated in rodents, that exogenous opioid use leads to μ receptor internalization, and in turn tolerance, however, these same receptors did not demonstrate this to endogenous opioids, and therefore did not develop tolerance for endogenous opioids (164). This lack of tolerance to endogenous opioids may be responsible for the fact that DRG-S is associated with less habituation, or tolerance, than SCS at one year in patients with CRPS I (165).

In the previous report from our group, DRG-S at T12 resulted in excellent pain relief and functional improvement for low back complaints, especially when contrasted with recent notable SCS reports, albeit with the caveat that important differences exist in treatments, study designs, and subject selection criteria (24). It is possible that activation of the endorphin system may play a role in these dramatic psychological testing scores and this warrants further investigation. Within this context, then, our evidence for T12 DRG-S in LBP suggests that this treatment is a highly robust treatment to reduce pain, but arguably more importantly, to reverse disability and restore a meaningful quality of life.

CONCLUSIONS

Considering the complicated neuroanatomy of the nociceptive pathways arising from the low back, we postulate that the T12 DRG is the optimal location for lead placement for axial LBP, regardless of origin. Evidence for the individual steps detailing the transmission of low back fibers in LT have been demonstrated in prior research, but it was not until the degree of improvement with DRG-S at the T12 level was observed that the hypothesis could be generated that they converged at the T8/9 level with the T12 cutaneous afferents. Additionally, the paucity of Aβ-mediated input from the low back and the subsequently smaller proportion of dorsal column fibers representing the low back necessitates specific lead placement for stimulation. These facts, in combination with our theory of LBP transmission may also explain the current best practices in stimulating the T8-9 interspace with SCS for low back coverage (see Fig. 6).

Our case series illustrates that T12 DRG lead placement results in substantial and significant pain relief. Our continued clinical follow-up of those patients indicates that the results have been robustly maintained. Although our preliminary outcomes demonstrate superior VAS and functional improvement, we suspect at least similar results to SCS for axial LBP, given the Aβ fiber recruitment, and this technique may present an alternative means of stimulation for low back coverage. We encourage neurophysiological researchers to focus on the nociceptive pathways arising from the low back with special interest in the role of the T12 spinal cord level and DRG-S in those pathways, in its use for mechanical

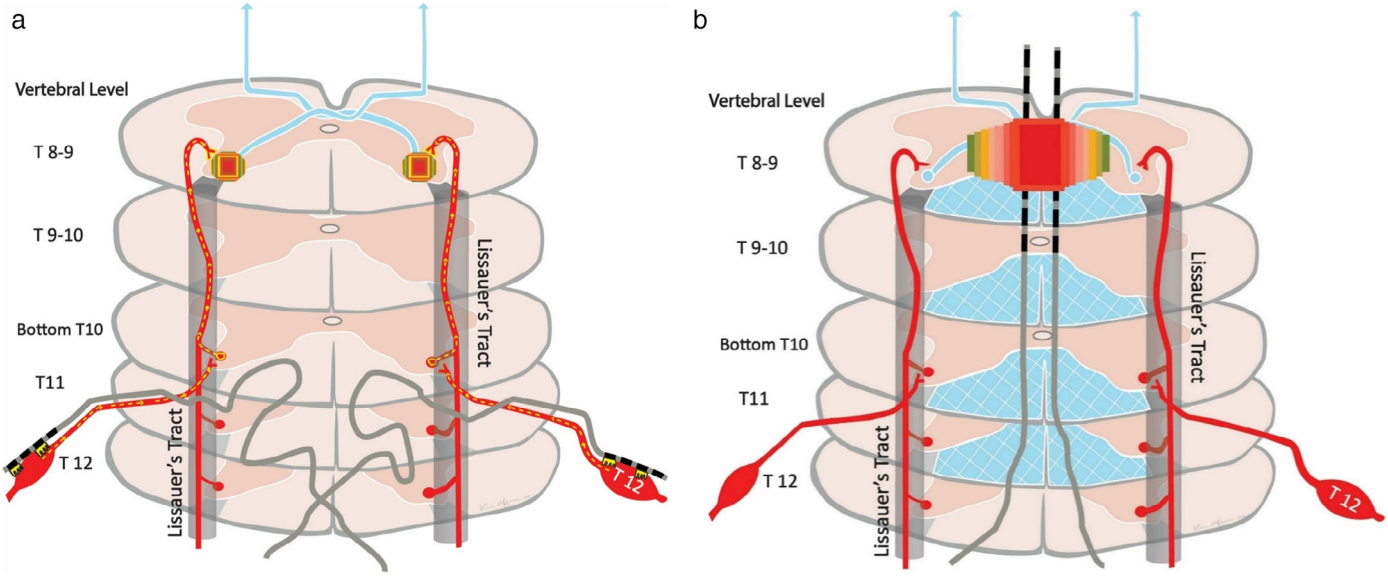

Figure 6. (a) Effect of DRG-S at T12 creating focal inhibition within the superficial DH at the convergence point of the low back fibers at the T8-9 level. (b) Segmental mechanism of action of dorsal column SCS with activation of DC fibers and anterograde effects within the DH at the T8-9 level. The focal targeted activation of inhibitory fibers in the DH with DRG-S allows for a denser inhibition but with a much lower total charge delivered than that of SCS. [Color figure can be viewed at wileyonlinelibrary.com]

pain syndromes, and other potential places where convergence may occur, such as abdominal pain, pelvic pain, sympathetically mediated pain and axial thoracic and cervical pain.

Authorship Statement

Kenneth B. Chapman was the primary author, with the assistance of Pauline S. Groenen. All authors contributed to the concept and approved the final version of the manuscript. The authors thank Allison Foster, PhD, an independent medical writer, for her intellectual contribution to the drafting of the manuscript.

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COMMENTS

Chapman et.al have provided a novel stimulation option for targeting refractory low back pain along with detailed neuro anatomical dialogue to support an hypothesis that may explain the extraordinary results obtained in his case series – previously published in *Neuromodulation* (1).

Paul Verrills, MBBS
Melbourne, Australia

Reference

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This review article contains perfectly written, important, new information that can bring us a step further in treating low back pain with neuromodulation, and in this case DRG stimulation. I am looking forward to follow up studies.

Jan Kallewaard, MD
Arnhem, the Netherlands

