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Supraspinal Mechanisms of Spinal Cord Stimulation for Modulation of Pain

Five Decades of Research and Prospects for the Future

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ABSTRACT

The field of spinal cord stimulation is expanding rapidly, with new waveform paradigms asserting supraspinal sites of action. The scope of treatment applications is also broadening from chronic pain to include cerebral ischemia, dystonia, tremor, multiple sclerosis, Parkinson disease, neuropsychiatric disorders, memory, addiction, cognitive function, and other neurologic diseases. The role of neurostimulation as an alternative strategy to opioids for chronic pain treatment is under robust discussion in both scientific and public forums. An understanding of the supraspinal mechanisms underlying the beneficial effects of spinal cord stimulation will aid in the appropriate application and development of optimal stimulation strategies for modulating pain signaling pathways. In this review, the authors focus on clinical and preclinical studies that indicate the role of supraspinal mechanisms in spinal cord stimulation–induced pain inhibition, and explore directions for future investigations.

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According to the American Association of Neurologic Surgeons, approximately 50,000 spinal cord stimulators are implanted per year, worldwide.[1] Growth of this field is moving at a rapid pace with an estimate of the worldwide neuromodulation systems market reaching more than 7 billion U.S. dollars by 2020.[2] As we pass the fiftieth anniversary since Norman Shealy implanted the first spinal cord stimulation system in 1967, the clinical effectiveness of spinal cord stimulation has made steady progress, with more significant advancements in the last decade.[3] In 1993, a 7-yr follow-up of 320 consecutive patients who had spinal cord stimulation placement for chronic intractable pain found that 52% still reported at least 50% relief of pain.[4] More than a decade later, it was reported that 48% of patients with failed back surgery syndrome who received conventional, paresthesia-guided spinal cord stimulation treatment had more than 50% pain relief at 6 months.[5] Considerable progress has been made since that time with reports of clinical effectiveness ranging from 60 to 85%.[6–10] Technological advancements in lead design, refinements of anatomical targeting (including structures outside the cord itself), and novel waveforms such as burst spinal cord stimulation and high-frequency paresthesia-free spinal cord stimulation are likely to have contributed to this continuous improvement.[10–12] Additionally, improved patient selection criteria likely amplified these results. Nevertheless, much room remains to enhance the success rate and expand the clinical application of spinal cord stimulation.

An important step in optimizing stimulation paradigms is to enhance our understanding of spinal cord stimulation mechanisms. Preclinical studies of electrical spinal stimulation can be broadly grouped based on their anatomical focus into three groups: (1) peripheral, distal to the dorsal root ganglion; (2) spinal/segmental, spinal cord and dorsal root ganglion; and (3) involvement of supraspinal structures. Although early studies tended to focus on the peripheral and spinal/segmental mechanisms of spinal cord stimulation, the study of supraspinal pathways will aid in the development of optimal stimulation paradigms for modulating neural activity in the pain signaling pathways and may help to characterize the links between pain, emotions, reward, and other higher functions in the brain. Additionally, the lack of clinical effectiveness of conventional spinal cord stimulation in acute nociceptive pain, pain inhibition extending beyond the stimulation period, the cumulative duration-dependent treatment effect size, and alleviation of pain from nonnoxious stimuli (*i.e.*, allodynia) cannot be readily explained by the spinal/segmental mechanism as proposed by Gate Control Theory alone.[13]

Materials and Methods

This review was conducted using a search of MEDLINE/PubMed, Medical Subject Headings, Cochrane Review, and Google Scholar. No date limits were applied, and the search was limited to the English language. Both preclinical and clinical sources were included if they were related to supraspinal mechanisms of spinal cord stimulation. The

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reference lists of the sources selected were also examined to identify the additional studies not found from the original search. We used discretion in this process with preference toward clinical and preclinical peer-reviewed articles in indexed medical journals. This search did not identify any review that specifically concentrated on supraspinal pathways that may be involved in mechanisms of action of spinal cord stimulation for pain treatment. Therefore, in this review, we examine the historical trend of clinical and preclinical studies that indicate a role for supraspinal mechanisms in spinal cord stimulation–induced pain inhibition, first in conventional spinal cord stimulation, then in newer spinal cord stimulation waveforms, and explore directions for future investigations.

1960s to 1980s: Conventional Spinal Cord Stimulation

We use the inclusive term spinal cord stimulation throughout this review rather than the historical term of dorsal column stimulation, which excluded involvement of neighboring neuroanatomical structures (table 1). Dorsal column stimulation restricted the stimulatory mechanism to those evoked by activation of the dorsal columns reaching the dorsal horns. "Central control" was briefly mentioned as an expression for supraspinal influences, but the previous focus was primarily on the spinal/segmental mechanisms.[14] The Gate Control Theory originally hypothesized that a combination of presynaptic inhibition and the actions of inhibitory interneurons within the spinal cord is activated by large diameter afferent fibers.[15] Thus, electrical activation of large-diameter afferents, A-β fibers, produces an inhibitory effect on the processing of signals from small-diameter A-Δ and C fibers, afferents.[16] Although this theory was the foundation for the development of conventional spinal cord stimulation (paresthesia-inducing tonic waveforms in which stimuli are delivered at a continuous frequency, pulse width, and amplitude), many gaps in our understanding could not be explained by this mechanism.[14,17]

Clinical

Supraspinal involvement was suggested by Nashold *et al.*[18] in their early work measuring electroencephalogram potentials evoked by stimulation of the dorsal column in humans (fig. 1). This was performed with subdural electrodes delivering

Table 1. Glossary of Neuroanatomical Structures Studied in Relation to Supraspinal Mechanisms of Spinal Cord Stimulation

Neuroanatomical Structure	Function
Anterior pretectal nucleus	Located in the pretectal midbrain near the thalamus, it is considered part of the reticular formation and is thought to exert descending mechanisms of pain control.
Cerebellar fastigial nucleus	A deep cerebellar nuclei involved in motor coordination.
Cingulate cortex	Involved with memory, learning, and emotion.
Diencephalon	An embryonic structure that develops into multiple forebrain structures including the thalamus, hypothalamus, epithalamus (includes pineal gland), and the pituitary gland.
Dorsal column	Ascending pathways relaying sensations of touch, vibration, and proprioception from the periphery.
Dorsolateral column	Also known as Lissauer's tract, a narrow axon tract located at the tip of the dorsal horn close to the entering posterior nerve roots.
Dorsolateral striatum	Involved in habitual behavior.
Gracile nucleus	A dorsal column nucleus located in the medulla that receives input from touch and proprioceptive neurons from the lower body.
Locus coeruleus	Located in the pons, it is the main site for norepinephrine production in the brain.
Mediodorsal nucleus of the thalamus	Associated with memory and cognitive processes.
Nucleus of the solitary tract	Sensory nuclei located in the medulla that receives input from viscera such as the respiratory, cardiovascular, and gastrointestinal systems.
Parafascicular nucleus of the thalamus	Involved in goal-directed behavior.
Parietal association area	Integrates information mostly involved with somatosensory and visual association sensory modalities.
Periaqueductal gray	Located in the midbrain surrounding the cerebral aqueduct, it serves multiple functions including descending pain inhibition and enkephalin production.
Prefrontal cortex	Involved in personality and higher cognitive functions.
Raphe nuclei	Midline brainstem nuclei that function to release serotonin and include the raphe obscurus, raphe magnus, median and paramedian raphe, raphe pontis, and dorsal raphe nuclei.
Rostral ventromedial medulla	Involved in the incorporation of descending signals to the spinal cord, it includes the nucleus raphe magnus, nucleus reticularis gigantocellularis, nucleus reticularis paragigantocellularis lateralis, and nucleus gigantocellularis pars alpha.
Spinothalamic column	An anterolateral or ventrolateral ascending tract that convey sensations of touch, pressure, pain, and temperature to the thalamus from the periphery.
Ventral posterolateral nucleus of the thalamus	The caudal nucleus processes visceral and nociceptive input, rostral nucleus processes proprioception, and the intermediate nucleus processes cutaneous input.
Ventromedial nucleus of the thalamus	Involved in motor control.

stimulation with a pulse duration from 0.1 to 0.3 ms, intensity from 0.1 to 30 volts, and frequencies less than 200 hertz. They suggested that spinal cord stimulation selectively "masks" neuropathic but not nociceptive pain as a result of processing at the cerebral level, diencephalon, or brainstem, rather than the spinal cord.[18,19] They also noted that when compared

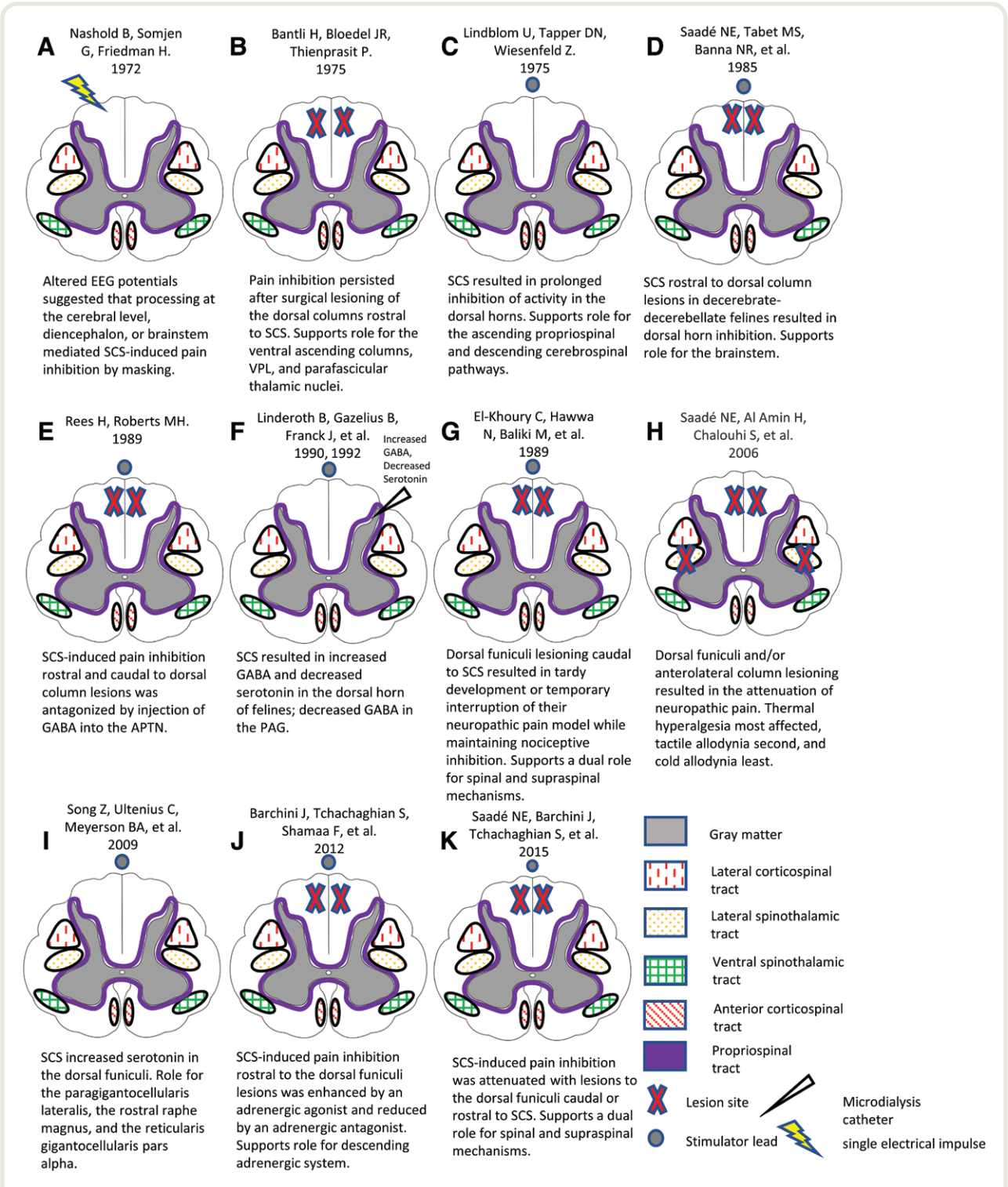

Fig. 1. Cross-sectional representations of experiments that have examined supraspinal mechanisms of spinal cord stimulator (SCS) therapy in chronological order. APTN, anterior pretectal nucleus; EEG, electroencephalogram; GABA, γ-aminobutyric acid; PAG, periaqueductal gray; VPL, ventral posterolateral nucleus of the thalamus.

to direct stimulation of the ventral posterolateral thalamic nucleus or sensory cortex, stimulation with single pulses at the dorsal column was consciously perceived at much lower intensities.[18] Before this study, researchers assumed that direct brain stimulation, as compared to peripheral stimulation, required lower amplitude intensities for patients to consciously perceive stimulation. These findings suggested the stimulation differs in mechanisms at the two sites examined. Significant reductions in somatosensory evoked potentials that correlate with pain inhibition were reported by Larson *et al.*[20] in humans receiving spinal cord stimulation, and many of these patients also developed hyperactive reflexes, which could indicate a weakening of tonic descending sensorimotor inhibition. This was also performed with subdural electrodes providing stimulation at frequencies of 70 to 100 hertz, a pulse width of 0.25 ms, and an estimated pulse current of 0.5 to 1.0 milliamps.

Preclinical

Although Larson *et al.* were not were not able to replicate their human somatosensory evoked potential findings when studying primates,[20] the authors postulated that the extended duration of both pain inhibition and reduced evoked potentials after stimulation involved supraspinal mechanisms. The ventral posterolateral and parafascicular nuclei of the thalamus were implicated in another primate study.[21] Investigators in this study measured evoked potentials within these nuclei after removing the dorsal cord rostral to the stimulation site so that only the ventral pathways ascended. The results implied that the dorsal columns may not mediate pain inhibition alone since evoked potentials in these nuclei remained consistent despite dorsal column absence (figs. 1B, 2, and 3).[21] While primarily studying the spinal mechanisms of spinal cord stimulation in the inhibition of spinothalamic neurons in primates, Foreman *et al.*[22] secondarily speculated that an ascending dorsal column signal may trigger inhibitory interactions at higher levels of the central nervous system. The involvement of supraspinal (*e.g.*, ascending propriospinal and descending cerebrospinal) systems was suggested based on observations in cats that spinal cord stimulation resulted in prolonged inhibition of a subpopulation of dorsal horn neurons,[23] which could not be explained by a spinal mechanism (figs. 1C, 3, and 4).[24,25]

Further characterization of the supraspinal pathways by Saadé *et al.*[26] occurred with decerebrate-decerebellate cats through spinal cord stimulation rostral to surgical lesions of the dorsal columns. Despite the dorsal column interruption, dorsal horn neuronal inhibition occurred below the lesioned level with multiple modalities of nociceptive stimuli. The brainstem was implicated as the supraspinal source of these effects because the specific preparation used excluded participation of the diencephalon, cerebral cortex, or cerebellum (figs. 1D, 2, and 3).[26] In a similar study, the same investigators observed inhibition of pain with dorsal column stimulation rostral to dorsal column lesions in an awake rat model.[27] The ascending pathway was attributed only to the dorsal columns because the low-intensity stimulation used did not spread beyond this region.[27] In their previous studies, the same group of investigators demonstrated the links between the dorsal column and the periaqueductal gray, nucleus raphe magnus, and reticular gigantocellular nucleus (figs. 2 and 3).[28–30] They also showed that unilateral spinal cord stimulation could modulate the activity of cochlear neurons

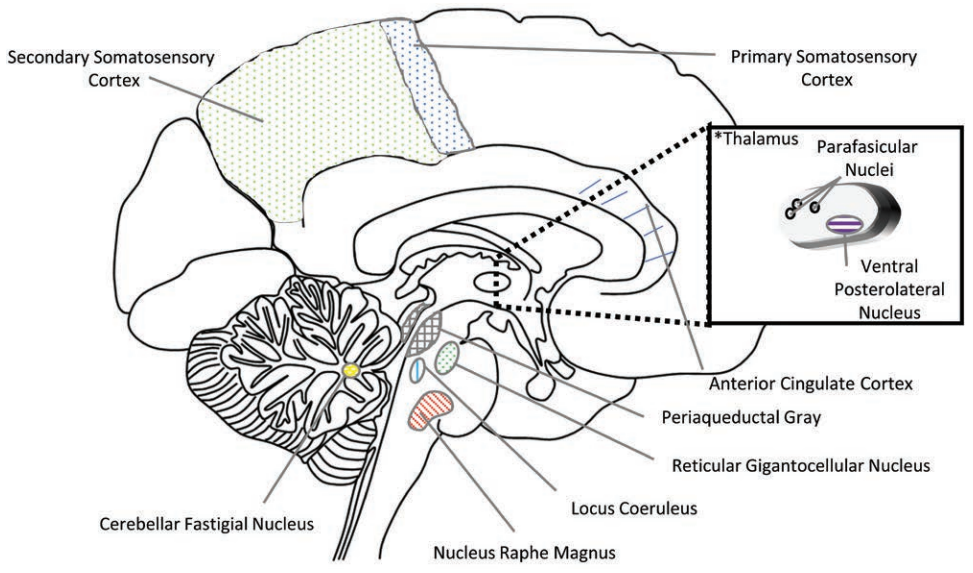

Fig. 2. Sagittal brain anatomy of regions involved in supraspinal mechanisms of spinal cord stimulation. *The thalamus insert depicts the thalamus corpus, which is situated laterally to the midsagittal section as illustrated.

bilaterally through direct projections, implying the potential for supraspinal mechanisms with widespread effects.[31]

The supraspinal effects of stimulation both rostral and caudal to dorsal column lesions in rats were further examined by Rees and Roberts,[32] particularly the possible involvement of the anterior pretectal nucleus (fig. 1E). They postulated that the short- and long-term inhibition of pain may result from two separate mechanisms. Long-term inhibition was antagonized by injection of γ-aminobutyric acid into the anterior pretectal nucleus, and was attenuated with stimulation caudal to the dorsal column lesion or lesioning of the ipsilateral dorsal column.[32] Thus, long-term inhibition was thought to be mediated by an ascending dorsal column pathway to the anterior pretectal nucleus, which then spurred descending inhibition, whereas short-term inhibition was thought to be mediated by antidromic spinal segmental mechanisms.[32–37]

There are perceivable limitations to the use of small animal models for spinal cord stimulation studies, which may reduce translatability to the clinical setting. It is also difficult to determine which areas of the spinal cord are stimulated, as the electrode to spinal cord size ratio is typically larger than that used in humans. Some models utilized subdural stimulation as opposed to the epidural location of human electrodes. Nevertheless, these models often serve as an important starting point for developing hypotheses to be further examined in large animals (*e.g.*, sheep) and in clinical trials. Although rat models of spinal cord stimulation tend to be most utilized, studies using larger animals may more closely resemble spinal cord stimulation in humans.

1990s: Broadening Applications of Conventional Spinal Cord Stimulation

Clinical

The 1990s brought much discussion regarding the effects of spinal cord stimulation on blood flow, including the

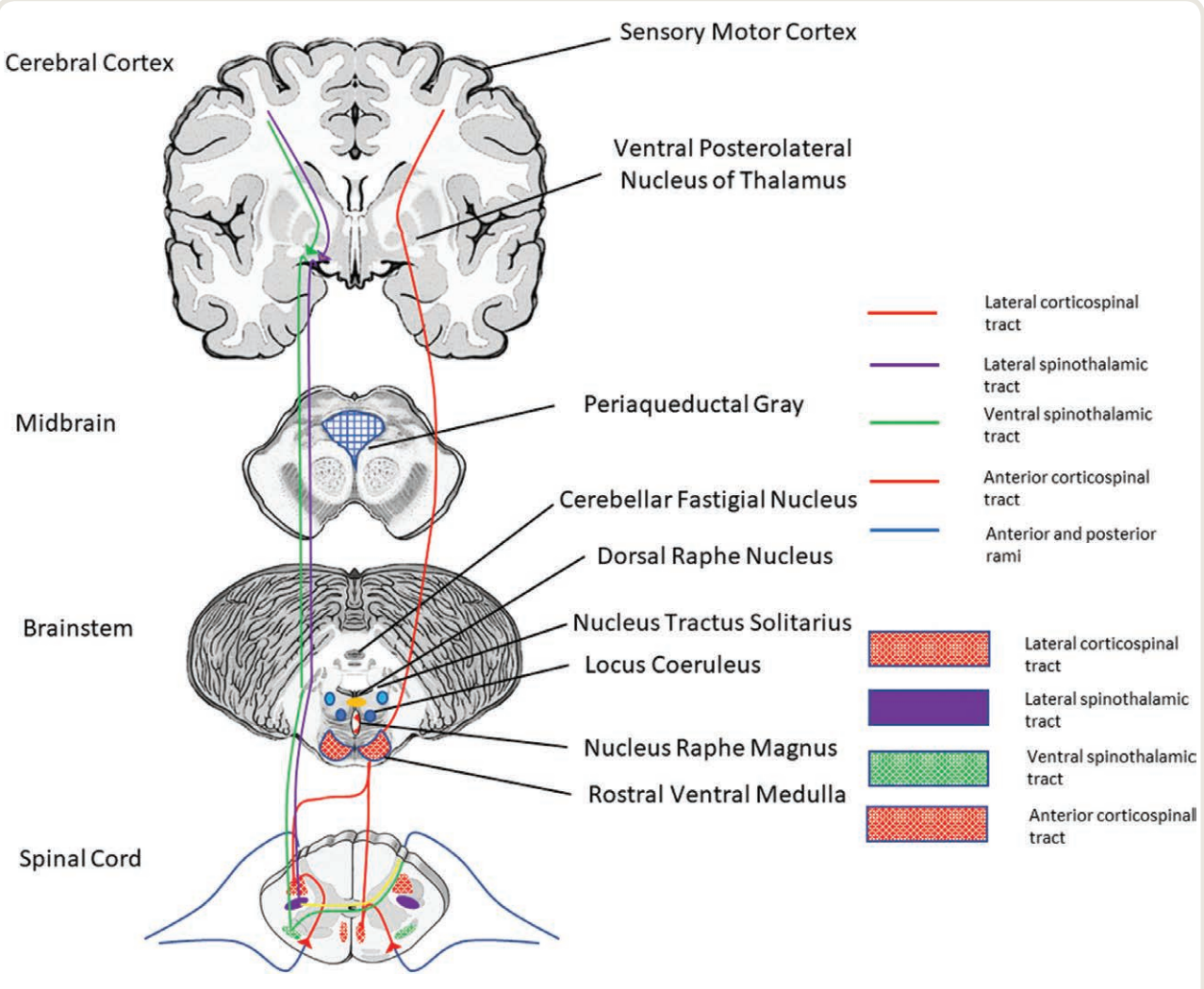

Fig. 3. Cross-sectional neuroanatomy of potential supraspinal pathways mediating spinal cord stimulation–induced pain inhibition.

mechanisms by which it altered cerebral blood flow.[38–42] Clinical applications included not only peripheral vascular disease and angina, but also the prevention of cerebral ischemia, for which high cervical stimulation (C3 and rostrally) had the most profound effects.[38,39] Coupling of cerebral blood flow to the sensorimotor regions activated by spinal cord stimulation was proposed as one possible mechanism contributing to these effects.[43] The use of neuroimaging approaches, such as positron emission tomography, allowed identification of specific regional cerebral blood flow changes with spinal cord stimulation in clinical studies.[40] In patients with chronic angina pectoris, spinal cord stimulation altered regional cerebral blood flow in multiple areas associated with cardiovascular control and nociception.[40] Regional cerebral blood flow was shown to differ across patient populations, anatomical locations of stimulation, and mode of stimulation.[40,43]

Preclinical

Rodent models of spinal cord stimulation–induced increase in cerebral blood flow were attributed to rostral activation of the medullary vasomotor centers or the cerebellar fastigial nucleus, which is known to influence cerebral blood flow (figs. 2 and 3).[44,45] During this same period, preclinical studies began revealing supraspinal neurochemical mechanisms of conventional spinal cord stimulation. Supraspinal mechanisms of spinal cord stimulation were examined by Stiller *et al.*, using microdialysis catheter techniques (fig. 1F).[46–49] Catheters placed stereotactically in the periaqueductal gray revealed significantly decreased levels of γ-aminobutyric acid (GABA) in freely moving rats receiving spinal cord stimulation (figs. 2 and 3).[47] An spinal cord stimulation–associated increase in GABA levels in the dorsal horn coupled with decreased levels in the periaqueductal gray may involve enhanced descending inhibition.[47,50] In a previous study, it was found that increased levels of serotonin but unaltered levels of substance *P* with spinal cord stimulation were present in the dorsal horns of decerebrate cats.[46] In intact cats, however, the substance *P* levels were instead increased both during spinal cord stimulation with "clinical parameters" and after pinch or noxious electrical nerve stimulation of a hind paw.[51] This finding suggested that both orthodromic dorsal column activation and activation of the spinothalamic tract could result in substance *P* release in the dorsal horn, probably after activation of quite different neuronal circuitry (figs. 1F and 3).[51]

Surrogate markers of neural activity with spinal cord stimulation were investigated by DeJongste *et al.*[52] through measurement of the rapidly transcribed oncoprotein c-Fos and the stress-induced heat shock protein 72. Although heat shock protein 72 concentrations were not detectable in neurons with or without spinal cord stimulation, limiting stress as a potential mechanism, c-Fos expression was increased in the spinal cord stimulation group within regions of the limbic system known to modulate emotions and pain.[52] Despite these findings, the authors were not in favor of a supraspinal mechanism because c-Fos expression was not increased in the ventrolateral medulla, the nucleus

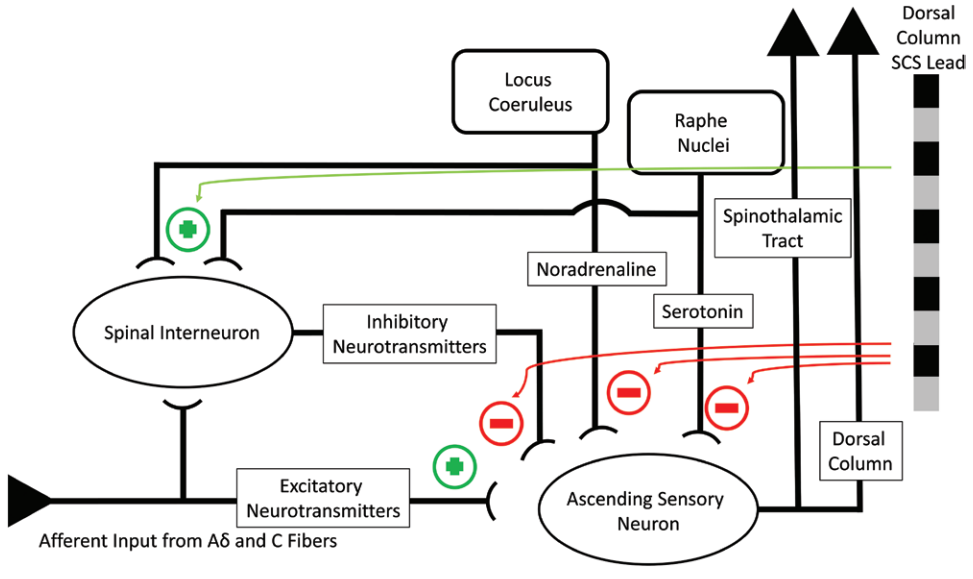

Fig. 4. Schematic of historical perspective on pain modulation by spinal cord stimulation (SCS). Dorsal column stimulation results in direct presynaptic inhibition of small-diameter sensory neurons and the activation of inhibitory interneurons producing an inhibitory effect on these neurons. Dorsal column stimulation also activates descending pain inhibitory pathways originating from the locus coeruleus and raphe nuclei.

of the solitary tract, or the nucleus raphe magnus (figs. 2 and 3). However, their conclusion may not be entirely valid because many other supraspinal structures are likely involved, and sites of central nervous system activation may differ based on the parameters of spinal cord stimulation application.[52] c-Fos expression is a nonspecific measure of neuronal activation with numerous limitations. For example, (1) a wide variety of stimuli cause nonspecific c-Fos expression, (2) expression is transient and lacks differentiating strength of activation, (3) activated neurons may not always express c-Fos, (4) there is no differentiation between activation of excitatory and inhibitory circuitry, and (5) neuronal inhibition is not measured.[53] Other neuronal activation markers such as phosphorylated extracellular signal–regulated kinase, a more dynamic marker and better indicator of central sensitization, may be worth examining in future studies.[54–56]

Contrary to a supraspinal hypothesis and findings by Saadé *et al.*,[57] a later study showed that the flexor reflex attenuation by spinal cord stimulation was mediated *via* spinal mechanisms, as complete cord transections rostral to the spinal cord stimulation application site did not significantly alter this attenuation.[57–59] The contradictory results may be the result of varying stimulation intensities used in the different studies.[57–59] Similar to studies by Rees and Roberts,[36] a model that surgically lesioned the dorsolateral column caudal to spinal cord stimulation found that pain inhibition was diminished, but not absent, which suggested a dual and additive role of spinal and supraspinal mechanisms.[60] Revisiting their previous study of flexion reflexes, Saadé *et al.*[61] found that nociceptive flexion reflexes are mediated by both spinal and supraspinal mechanisms. However, long-term inhibition may be particularly potentiated by a pons-brainstem-spinal loop. These studies are in contrast to a mechanistic review at the end of this decade, which concluded that the dorsal columns and the paresthesia elicited through them were a requirement for pain relief by conventional spinal cord stimulation in neuropathic pain.[62] Since then, some new spinal cord stimulation paradigms have shown that paresthesia may not be critical or indispensable to the success of spinal cord stimulation.[63–65]

2000s: New Tools for Elucidating Mechanisms

Clinical

The use of somatosensory evoked potential analysis with conventional spinal cord stimulation was revisited in a study of nine patients with failed back surgery syndrome undergoing concurrent tibial or sural nerve stimulation.[66] This analysis revealed that spinal cord stimulation attenuated somatosensory evoked potential signals in both the primary and secondary somatosensory cortices; however, somatosensory evoked potentials from the midcingulate cortex could decrease or increase depending on the parameters of the peripheral stimulation (figs. 2 and 3).[66] Consequently, spinal cord stimulation–induced pain inhibition may depend on the type of stimulus applied.[66] In a more extensive neurophysiologic assessment, plantar sympathetic skin response, F-wave, somatosensory-evoked potentials, H-reflex, and nociceptive flexion reflexes were assessed in a series of 20 patients receiving spinal cord stimulation for failed back surgery syndrome.[67] Particularly relevant to supraspinal mechanisms, the somatosensory evoked potential signals had reduced amplitudes, independent of nociceptive flexion- and H-reflexes, and increased latency during spinal cord stimulation.[67]

Using magnetic resonance spectroscopy in a group of 20 failed back surgery syndrome patients, an increase in GABA and a decrease in glucose concentrations in the ipsilateral thalamus were observed during spinal cord stimulation.[68] The increase in GABA was postulated to be due to effects on the spino-reticulo-thalamic-cortical pathway, part of the ascending reticular arousal system, which when modulated can interfere with the affective components of pain.[68] Poor responders also exhibited noticeable, yet less robust, changes in the GABA and glucose concentrations of the ipsilateral thalamus, calling into question the utility of this modality for predicting therapeutic response to spinal cord stimulation.[68] Although previous work used positron emission tomography to study spinal cord stimulation for angina pectoris, a recent study appears to be the first to investigate whether positron emission tomography can be used to determine neuronal activity before and after spinal cord stimulation for neuropathic pain.[40,69] Increases in regional cerebral blood flow, a marker of neuronal activity, were noted in the contralateral thalamus, bilateral parietal association area, anterior cingulate cortex, and prefrontal regions.[69] In contrast to the common methodology, regional cerebral blood flow was measured after rather than during spinal cord stimulation. They surmised that activation of thalamic and parietal association areas modulated pain thresholds while anterior cingulate cortex and prefrontal regions modulated the affective component of pain.[69] A recent review of the neurophysiologic and functional neuroimaging literature emphasized the need for large-scale controlled studies, but identified the thalamus and anterior cingulate cortex as key structures in the supraspinal mechanisms (figs. 2 and 3).[70]

Preclinical

Using microdialysis and immunohistochemical techniques, serotonin concentrations were examined with conventional spinal cord stimulation in nerve-injured rats.[71] The investigators observed increased serotonin in the dorsal horns of spinal cord stimulation responders immediately after stimulation, but not in responders before stimulation

or nonresponders at either time point. Furthermore, pain inhibition was enhanced in nonresponders with the exogenous administration of a serotonin agonist.[71] Yet, this effect was partially attenuated by concurrent administration of a GABA receptor type B antagonist. Increased serotonin concentrations may be attributable to a descending dorsolateral column pathway originating from the paragigantocellularis lateralis, the rostral raphe magnus, and the reticularis gigantocellularis pars alpha (figs. 1I, 2, and 4).[71,72] Focusing on the descending serotonergic inhibitory mechanism, the Karolinska group further sought to characterize which specific serotoninergic receptor subtypes mediate pain inhibition by conventional spinal cord stimulation.[73] They found that spinal cord stimulation-induced serotonin release mediated pain inhibition through multiple spinal serotonin receptors, including serotonin 2A, serotonin HT3, and serotonin HT4.[73] Activation of each of these receptors had differing effects on heat, cold, and mechanical hypersensitivity.[73]

Using immunohistochemical methods, a separate group also examined the role of serotonin in descending inhibition; however, they looked at the dorsal raphe nucleus, another source of serotonin, in the ventral periaqueductal gray matter rather than the nucleus raphe magnus or rostral ventromedial medulla (figs. 2, 3, and 4).[74] While additionally examining the role of the noradrenergic system *via* the locus coeruleus, they determined that spinal cord stimulation–induced antinociception is mediated by both serotonin and norepinephrine, with increased synthesis of these monoamines observed in the dorsal raphe nucleus and locus coeruleus, respectively (figs. 2, 3, and 4).[74] In another study, Barchini *et al.* concurrently lesioned the dorsal columns and administered antagonists known to inhibit the effects of descending pain pathway activation.[75] Pain inhibition by conventional spinal cord stimulation applied rostral to the lesion was partially attenuated by an adrenergic antagonist, and enhanced by an adrenergic agonist, suggesting that the supraspinal neurochemical mechanisms for spinal cord stimulation–induced pain inhibition at least partially involve the adrenergic system (fig. 1J).[75] In a rat model, a comparison of 100-, 60-, and 4-hertz spinal cord stimulation indicated that only the 4-hertz frequency increased expression of neural activity indicator c-Fos in the nucleus raphe magnus.[76] Contrary to the previous c-Fos study, no changes in expression level were noted in the periaqueductal gray (figs. 2 and 3).[76] Because the authors did not observe changes with 100-hertz stimulation in the supraspinal structures examined, they inferred that higher frequencies could alternatively mediate pain inhibition through spinal mechanisms.[76]

Conflicting results were noted by El-Khoury *et al.* in examination of spinal cord stimulation mechanisms with selective bilateral dorsal column lesioning.[77] They showed that pain inhibition was maintained after dorsal column lesioning caudal to spinal cord stimulation, which was applied with the electrodes on the dorsal aspect of the medulla at the level of the dorsal column nuclei. As in previous studies, these results demonstrated a role of descending supraspinal inhibitory influences. However, they noted a possible additional role of the dorsal columns in ascending nociceptive signaling as the lesioning itself produced tardy development or temporary interruption of their neuropathic pain model, a phenomenon called "spinal shock," which is frequently observed after manipulation in animal experiments (fig. 1G).[77] Members of the same group followed this study with investigations into selective unilateral and bilateral spinal cord lesioning of the dorsolateral column and/or spinothalamic column (fig. 1H).[78] Interruption of any combination of these tracts resulted in the attenuation of neuropathic pain, with thermal hyperalgesia most affected, tactile allodynia second, and cold allodynia least.[78] The effects of these lesions were normalized within 2 to 3 weeks, illustrating the plasticity of the nervous system.[78] These results oppose the hypothesis of supraspinal inhibitory influence of either tract because lesioning caused nociception attenuation, not facilitation.[78]

Building on previous lesioning studies, the Saadé research group applied spinal cord stimulation rostrally over the dorsal column nuclei or at the lumbar level. They similarly found attenuated spinal cord stimulation effects after dorsolateral column lesions, regardless of whether stimulation was applied rostral or caudal to the lesion (fig. 1K).[60,78,79] This finding supports the notion of a dual role for supraspinal and spinal mechanisms, as some antinociceptive effect was preserved after quite extensive lesions. The investigators observed that the suppressive effect of spinal cord stimulation on cold hypersensitivity was eliminated with these lesions, suggesting that cold hypersensitivity is alleviated *via* a supraspinal mechanism. Yet, this observation conflicts with a previous study, which suggested that an antidromic dorsal column mechanism mediates spinal cord stimulation–induced suppression of cold hypersensitivity.[75,79]

Because the spinal cord has limited numbers of serotonergic cell bodies, a previous study chose to examine the rostral ventromedial medulla,[80] which is known to be the main source of descending serotoninergic pathways (figs. 2, 3, and 4). In nerve-injured rats, the investigators conducted microelectrode recordings in the rostral ventromedial medulla and quantified the activity of the ON-cells, OFF-cells, serotonin-like cells, and neutral cells with spinal cord stimulation.[80] When they compared spinal cord stimulation responders and nonresponders, spinal cord stimulation selectively increased activity of the serotonin-like cells and OFF-cells (antinociceptive) in responders.[80] Therefore, responsiveness to spinal cord stimulation may be related to variable properties of the rostral ventromedial medulla in each individual patient. Microinjection of a GABA receptor type A agonist, but not an opioid antagonist, into the rostral ventromedial medulla

partially inhibited the spinal cord stimulation–induced pain inhibition in rats, indicating possible γ-aminobutyric acid–mediated control that may be related to the periaqueductal gray.[80] They also examined the role of the locus coeruleus in supraspinal descending inhibition by comparing locus coeruleus activation in spinal cord stimulation responders and nonresponders.[81] Although they noted a marked increase in activity of locus coeruleus neurons in spinal cord stimulation responders, noradrenergic concentration in the dorsal horn did not differ between groups, and neither α_1- or α_2-adrenergic antagonists administered intrathecally, nor "silencing" by microinjection of lidocaine into the locus coeruleus, reversed spinal cord stimulation–induced pain inhibition.[81] Therefore, they concluded that although there may be a supraspinal role (thalamus, periaqueductal gray, or rostral ventromedial medulla) for locus coeruleus neurons in spinal cord stimulation antinociception, it is not mediated by a direct descending spinal projection (figs. 2 and 3).[81] Another study in rats showed that anodal and cathodal spinal cord stimulation parameters had differing effects on somatosensory evoked potentials, suggesting that supraspinal mechanisms may be differentially engaged, depending on spinal cord stimulation parameters.[82,83]

Recent Developments: Continued Expansion of Applications and Novel Waveforms

Spinal cord stimulation has been successfully applied for the treatment of neurologic disorders other than pain, when the disease generator has strong indices for a cerebral dysfunction, thereby strengthening the argument for a supraspinal site of action. Spinal cord stimulation in vegetative and minimally conscious states has been studied for many years in Japan without evoking much interest in the Western world.[84] A particularly exciting new role for spinal cord stimulation has been in the treatment of movement disorders such as dystonia, tremor, multiple sclerosis, Parkinson disease, and painful legs and moving toes syndrome.[85–91] Seminal work in 2009 revealed that spinal cord stimulation restored locomotion in both dopamine-depleted and 6-hydroxydopamine–lesioned rat models of Parkinson disease.[86] They hypothesized that spinal cord stimulation disrupts the pathologic, synchronous low-frequency, oscillatory local field potential and neuronal patterns that are characteristic of the dorsolateral striatum and primary motor cortex in Parkinson disease.[86] This disruption occurs through spinal cord stimulation–induced activation of large cortical areas, which increases cortical and thalamic input to the striatum.[86] Spinal cord stimulation improved motor function similarly in a nonhuman primate model of Parkinson disease concurrently with neuronal activity desynchronization in the corticobasal ganglia circuitry.[91]

A recent study revisited the potential of spinal cord stimulation to treat cerebral ischemia using radiotracer techniques to extrapolate flow.[92] Removal of the superior cervical ganglion before stimulation did not attenuate stimulation-induced cerebral blood flow; however, profound attenuation occurred after spinal cord transection.[92] Thus, the effects on cerebral blood flow were attributed to a spinal ascending pathway to central vasomotor centers rather than a direct spinal effect *via* the superior cervical ganglion.[92]

Burst Spinal Cord Stimulation

Clinical. The burst stimulation application of spinal cord stimulation described by De Ridder *et al.*[64,93–95] has recently emerged as a waveform technology with a potential supraspinal mechanism. This modality employs bursts of five pulses, with an intraburst frequency of 500 hertz and a repetition frequency of 40 hertz.[64] Burst delivery was similarly used in transcutaneous electrical nerve stimulation in the 1970s.[96,97] The postulated supraspinal mechanism is based on electroencephalographic evidence from patients, which revealed activation of the dorsal anterior cingulate and dorsolateral prefrontal cortex.[94] Because the dorsal anterior cingulate cortex was activated, investigators inferred that burst spinal cord stimulation additionally modulates the medial pain pathways ascending to these regions (*via* the mediodorsal and ventromedial nucleus of the thalamus), which mediate pain-related affect and attention.[94,95] They acknowledged that this ascending pathway does not seem to involve the dorsal columns, as a recent study found that gracile nucleus activity is unaltered by burst spinal cord stimulation but markedly enhanced by conventional spinal cord stimulation parameters.[95,98] Instead, they proposed that burst spinal cord stimulation modulates the activity of C fibers terminating on lamina I dorsal horn neurons. A recent multicenter, randomized, unblinded, crossover study examining burst stimulation interestingly found an improvement in affect along with pain relief that could also support a mechanism involving medial thalamic activity.[99]

Preclinical. Much of the preclinical work regarding burst spinal cord stimulation was carried out after the human studies by De Ridder *et al.*[64,93–95] The effects of burst and conventional spinal cord stimulation on neuronal activity in the lumbosacral spinal cord and gracile nucleus and visceromotor reflexes were compared in an animal model of neuropathic pain.[98] From these findings, the investigators hypothesized that the absence of paresthesia reported in patients who receive burst spinal cord stimulation corresponded well with the lack of increasing spontaneous activity in neurons of the gracile nucleus found in their animal study.[98] Burst spinal cord stimulation attenuated visceral nociception better than conventional spinal cord stimulation when they measured visceromotor reflexes responses to noxious colorectal distention.[98] Because a component of

visceromotor reflexes involves supraspinal center modulation, they surmised that additional investigation into these supraspinal sites might elucidate the spinal cord stimulation mechanisms.[98] The parameters of burst spinal cord stimulation were studied by examining the effect of varying intraburst frequency (pulse frequency), burst frequency, burst width, burst amplitude, and pulses per burst (pulse number) on neuronal activity in rats.[100] The overall charge delivered to the spinal cord per burst, the integral of the current delivered with a single burst, positively correlated with increased efficacy of spinal cord stimulation.[100] Efficacy was measured by a reduction of wide-dynamic-range neuronal firing in rats, which was influenced by the parameters of pulse number, pulse width, and amplitude.[100] They subsequently discovered that, unlike conventional spinal cord stimulation, burst spinal cord stimulation does not increase spinal GABA release, as they observed no GABA elevation in peripheral blood. Furthermore, the effect of burst spinal cord stimulation was not abolished by a GABA receptor type B antagonist that did attenuate the effect of conventional spinal cord stimulation.[101]

Paresthesia-free High-frequency Spinal Cord Stimulation

Clinical. Since 2010, much attention has been paid to high-frequency spinal cord stimulation. The high-frequency stimulation paradigm is typically not programmed (*e.g.*, pulse width, amplitude) to produce paresthesia and has a frequency that is far beyond that of the endogenous central nervous system. Clinical trials have shown that this subparesthetic stimulation paradigm may be superior to conventional spinal cord stimulation for treating low-back and leg pain.[8,63] Using higher frequencies requires that the amplitudes and pulse widths be low because paresthetic stimulation beyond 800 hertz may be perceived as uncomfortable by patients.[102] High-frequency spinal cord stimulation encompasses an arbitrary range of frequencies; however, the commonly accepted boundary appears to be any frequency greater than 1 kilohertz. An exact definition of high-frequency spinal cord stimulation may eventually be refined as the mechanism of this waveform is further elucidated.

Preclinical. Most preclinical work to date has indicated that the primary mechanism of pain inhibition may occur at the spinal/segmental level.[103–108] A recent review of spinal cord stimulation summarized the working hypotheses that high-frequency stimulation (1) induces depolarization blockade (which occurs if high-frequency stimulation is applied to a single peripheral nerve), (2) causes desynchronization of afferent neural signaling, and (3) causes "membrane integration" whereby each individual stimulus is inadequate to depolarize a neuron, but multiple stimuli delivered during a length of time may cause depolarization.[96,109–113] To date, these hypotheses have received no support from computer simulation studies or preclinical experiments.[104,106] We found no published study that investigated a supraspinal mechanism of paresthesia-free high-frequency spinal cord stimulation. However, recent work has suggested that the variable preclinical results, sustained clinical effectiveness, and paresthesia-free stimulation with different combinations of stimulation parameters warrant investigation into whether possible supraspinal mechanisms participate in the creation of a pain-relieving effect.[10,96,114]

Previous studies of high-frequency spinal cord stimulation in rat models showed that intensities below the paresthesia threshold have an inhibitory effect on stimulus-evoked pain and that this stimulation paradigm does not activate or block transmission in the dorsal columns.[103,104] Furthermore, recent work has highlighted that a certain amount of electric charge transmission from the stimulator lead to the nervous tissue is essential for effect and that the waveform itself may not be critical.[65,83] Unpublished findings from preclinical research conducted by McMahon and his team[115,116] at King's College London have not included participation of supraspinal mechanisms. (Our knowledge of these unpublished findings is restricted to the following: [1] low-intensity 10-kilohertz spinal cord stimulation [20% of motor threshold] in rat models of persistent pain does not alter the excitability of normal myelinated primary sensory neurons or dorsal column neurons; [2] this stimulation may inhibit ectopic firing, in that recordings from lamina I neurons in the dorsal horn have shown that an inhibitory effect appears after 90 min of continuous stimulation; and [3] 60 min of low-intensity 10-kilohertz spinal cord stimulation suppressed response of deep dorsal horn neurons to wind-up stimuli.)

Conclusions

Understanding the supraspinal mechanisms of spinal cord stimulation will have important implications not only for improving the clinical effectiveness of spinal cord stimulation for pain treatment, but also for extending the indications beyond pain inhibition. For example, neuropsychiatric disorders, memory, addiction, behavior, cognitive function, other neurologic diseases, and performance enhancement are all being explored as new targets for spinal cord stimulation. Knowledge of spinal cord stimulation mechanisms will also enhance our overall understanding of the multiple unique and specialized areas in the brain.[117] The brain presents a challenge to researchers because invasive techniques require a high degree of skill, noninvasive imaging lacks spatial detail and temporal resolution, and *in vivo* experimentation with brain manipulation is problematic. Emerging technologies in neuroscience, such as single-cell RNA sequencing, optogenetics, dynamic imaging, and brain recording, may help overcome these obstacles. Initial preclinical attention may focus on the superficially located structures of the brain, as these are more readily accessible for experimental investigation. In the clinic, transcranial magnetic stimulation may serve as a bridge to knowledge of what deep

brain stimulation and spinal cord stimulation could achieve in the future.[118] This appears to be the moment for a new discussion of the potential supraspinal influences of spinal cord stimulation.

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Competing Interests

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