Narrative Review

Spinal Cord Stimulation for Chronic Neuropathic Pain: Research Progress in Molecular and Circuit Mechanisms

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Disclaimer: Yi Kang and Yidan Tang contributed equally to this work and share first authorship.
This study was supported by the National Natural Science Foundation of China (NO. 82301371 to Y.T.), Postdoctoral Research Project, West China Hospital, Sichuan University (No.2021HXBH059 to Y.T.), the Fundamental Research Funds for the Central Universities (No. 2023SCU12075 to Y.T.), the Science and Technology Plan Project of Sichuan Province (No. 2023NSFSC1780 to Y.T.), and the Key R&D projects of Sichuan Science and Technology Plan (No. 23ZDYF1157 to G.C.).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Background: Spinal cord stimulation (SCS) is an effective surgical intervention for treating chronic neuropathic pain conditions that are refractory to other management options, such as opioids, physical therapy, nerve blocks, or radiofrequency ablation. It is currently clinically approved as the main therapeutic procedure for persistent low back pain. As we understand these mechanisms better, SCS could have novel clinical applications. For this reason, an accurate understanding of research progress into the molecular and circuit mechanisms of SCS is indispensable for enhancing its effectiveness, safety, and future applications.

Objectives: This review aims to systematically discuss the molecular mechanisms of spinal cord electrical stimulation, from its action sites and transmitter interactions to the supraspinal circuit, to reveal the biological basis behind these mechanisms further and provide a more solid theoretical foundation and scientific basis for the clinical application of SCS.

Study Design: Narrative review.

Methods: Our research was conducted in PubMed, Ovid MEDLINE, and Embase. Boolean operators were used to combine MeSH (Medical Subject Headings) terms and keywords such as "spinal cord stimulation," "chronic neuropathic pain," "electric stimulation therapy," "analgesic mechanism," "spinal cord dorsal horn," "central sensitization," "neural circuits," and "neurotransmitter function".

Results: Numerous retrospective clinical studies and randomized controlled trials have yielded results supporting the remarkable efficacy and broad development prospects of SCS. However, the effectiveness and safety of SCS in certain diseases are still insufficiently studied, and the related molecular mechanisms are not well developed. We present a comprehensive, up-to-date overview and elaboration of the neurophysiological, biochemical, anti-inflammatory, and neurocirculatory mechanisms that have been associated with the use of spinal cord electrical stimulation for treating chronic pain.

Limitations: There exists an inconsistency in SCS animal experimental models.

Conclusions: Our findings from available studies include the molecular mechanisms involved in SCS on chronic pain, new paradigms for spinal cord electrical stimulation therapy, and explain their underlying biological processes, as well as the pros and cons of SCS in terms of its effectiveness in clinical use. With a better understanding of SCS's mechanisms, we may gain a more in-depth understanding of the current insights about the analgesic mechanisms of action underlying SCS for chronic neuropathic pain treatment.

Key words: Spinal cord stimulation, analgesic mechanism, chronic neuropathic pain, electric stimulation therapy, spinal cord dorsal horn, central sensitization, neural circuits, neurotransmitter function

Pain Physician 2025: 28:E371-E384

Authors' contributions: Y.K. and Y.T. contributed equally to this work. Y.K. drew the pictures. T.Z. and G.C. conceptualized the idea; Y.K. and Y.T. wrote and edited the manuscript. W.K. and Y.Q. supervised the work. All authors read and agreed to the published version of the manuscript.

Article received: 08-20-2024
Revised article received:
02-10-2025
Accepted for publication:
03-03-2025

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Neuropathic pain is caused by lesions or diseases of the somatosensory system, including peripheral fibers (Aβ, Aδ, and C fibers) and central neurons, and affects 6.9%–10% of the general population (1). Chronic neuropathic pain (CNP) is mainly characterized by refractory chronic pain lasting more than 3 months. Among patients with moderate to severe chronic pain, 74.1% are diagnosed with neuropathic pain (2). CNP has been a very active and productive area of clinical research over the past decades. CNP is often refractory and recurrent and can have a profound psychological effect on patients, leading to complications such as anxiety and depression. However, clinical data have shown that traditional drug therapy cannot resolve or reduce CNP, with less than a 50% pain relief response rate in more than 50% of patients (3). CNP encompasses various types, including Persistent Spinal Pain Syndrome, complex regional pain syndrome (CRPS), postherpetic neuralgia, diabetic peripheral neuropathy, and phantom limb pain.

The classic nociceptive pathway posits that peripheral nociceptive stimuli elicit activation of peripheral nerve terminals and their somata located in the dorsal root ganglia or trigeminal ganglia, hence creating electrochemical signals. Subsequently, primary neurons establish synaptic connections with second-order nociceptive neurons and excitatory and inhibitory interneurons located in the spinal dorsal horn (SDH). The production of several neurotransmitters triggers these connections. The axons of secondary neurons transmitting pain cross and ascend to various subcortical nuclei (the pons, medulla, midbrain, hypothalamus, and thalamus), ultimately projecting to the cerebral cortex (the central amygdala, prefrontal cortex, anterior cingulate cortex, insula, and primary somatosensory cortex), resulting in the perception of pain. Central sensitization and synaptic plasticity induced by peripheral nerve inflammation and other factors are currently widely accepted as the theoretical basis for CNP. Inhibitory interneurons in the SDH can suppress the transmission of nociceptive signals. Prolonged input of pain signals caused by various factors such as inflammation and nerve injury lead to plastic changes in the pain perception and modulation system within the spinal cord, resulting in allodynia and hyperalgesia, respectively.

Spinal cord stimulation (SCS), a well-established form of neuromodulation employed to stimulate the dorsal columns for modulating neural function associated with pain transmission (Fig. 1), originated with the Gate Control theory (4). According to this theory, the electrochemical information of peripheral pain is transmitted to the spinal cord through small-diameter, unmyelinated C fibers and a small number of myelinated A-δ fibers, terminating in the spinal cord dorsal horn's glial cells. At the same time, tactile or vibratory sensations are transmitted to the same region through large A-β fibers. The large afferent fibers activate both presynaptic inhibition and the activity of inhibitory interneurons in the spinal cord. Consequently, applying electrical stimulation that elicits activation of A-β fibers with a larger diameter results in suppressing signal processing originating from A-δ and C fibers with smaller diameters. Nonnociceptive afferents can suppress the spinal flow of noxious information to the brain by activating spinal inhibitory neurons.

The successful cases of SCS in clinical treatment provide a promising direction for addressing the challenges associated with CNP (5). However, the neurophysiological, biochemical, anti-inflammatory, and neurocirculatory mechanisms involved in SCS therapy for CNP have not been systematically and comprehensively explained. In this review, we will explain the relevant mechanisms of traditional SCS treatment for CNP and focus on novel targets that have been studied recently in order to find breakthroughs for increasing the clinical efficacy of SCS.

Spinal Cord Stimulation Target Sites

Spinal Dorsal Horn

The SDH, the first relay station for integrating somatosensory information, has been confirmed as a

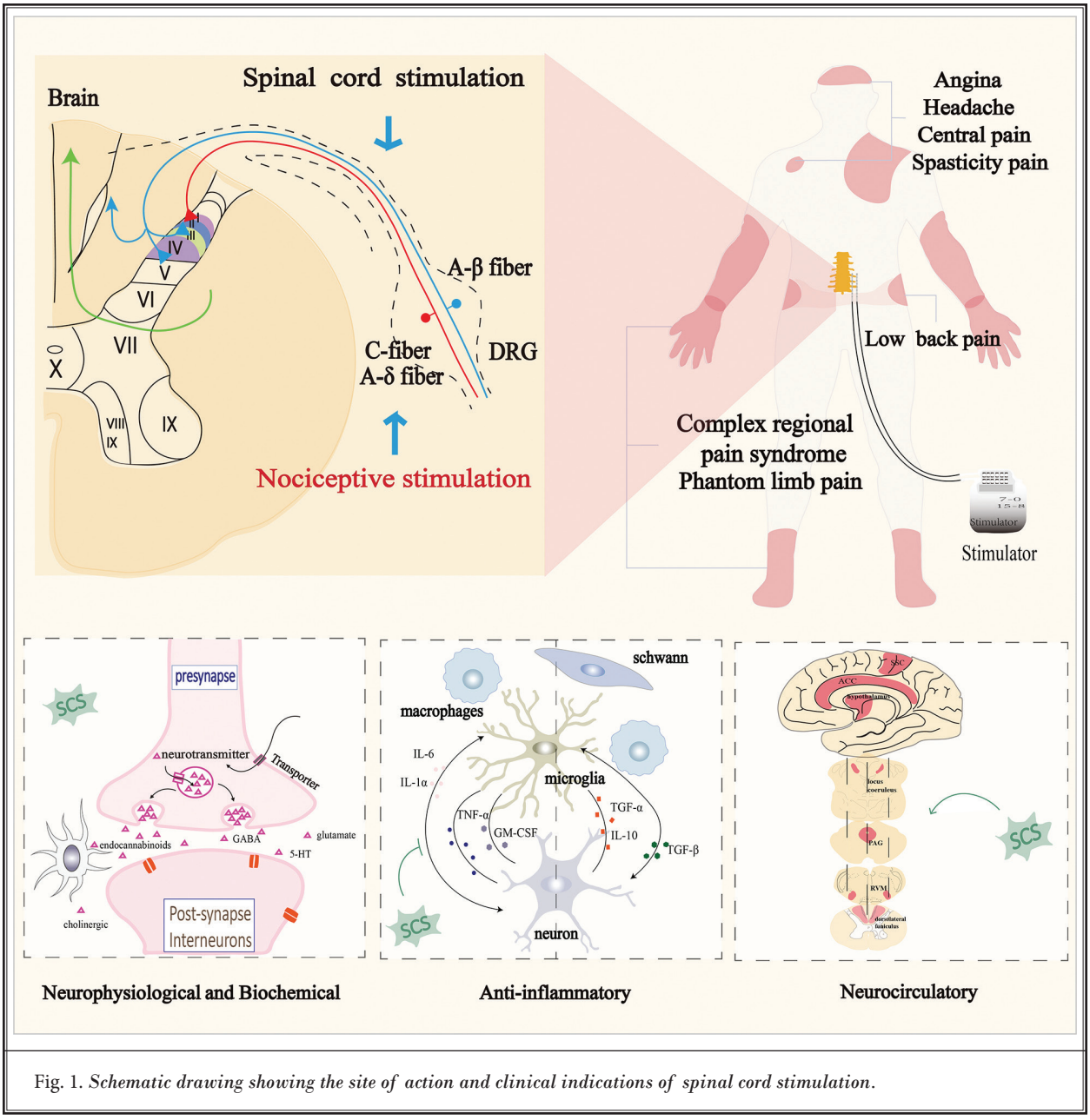

Fig. 1. *Schematic drawing showing the site of action and clinical indications of spinal cord stimulation.*

critical region for synaptic plasticity change (6). Based on the distinct characteristics of the pain receptive fields, the cells involved in pain processing within the SDH can be primarily classified into 2 categories: nociceptive-specific neurons, which predominantly receive high-intensity inputs related to noxious stimuli, and wide dynamic range neurons, which respond to a wide range of stimuli (7,8). According to the different functions of neurons, the SDH can be further divided into projection neurons that transmit nociceptive information to higher central structures, excitatory interneurons expressing vesicular glutamate transporter 2, and inhibitory interneurons expressing the inhibitory amino acid transporter (9).

The laminar organization of the spinal cord, defined by Bror Rexed in the 1950s, derived from patterns and groups of cell bodies, entails specific afferent connectivity. Thus, inputs from nociceptive and thermoreceptive afferents are predominantly seen in the superficial dorsal horn laminae (I and II), while in-

puts from mechanoreceptive and proprioceptive fibers mostly synapse in deeper dorsal horn laminae (III-V). The substantia gelatinosa, located in the II lamina of the SDH, serves as a central hub for regulating pain responses within different segments of the spinal cord. The labelled neurons with somata in lamina II exhibit diverse dendritic arrangements and orientations.

Five lamina II morphological categories were recognized based on characteristics of the dendritic arbor: islet, central, medial-lateral, radial, and vertical (10). Then, it was discovered that approximately 60% of γ(gamma)-aminobutyric acid (GABA)ergic neurons in this layer exhibit a dendritic arborization pattern known as islet neurons, while 5% display a vertical morphology (11). The dendritic arborization patterns of the remaining GABAergic neurons in the substantia gelatinosa have not been classified yet. Three types of dendritic arborization morphology (vertical, central, and radial) have been identified in glutamatergic neurons, whereas no excitatory neurons exhibited as islet neurons (12). These findings suggest that the dendritic morphology of neurons is at least partially related to the phenotype and function of the neurons. Jensen, et al (13) have proposed that the SDH is vital for SCS's analgesic effects; they postulate that GABAergic neurons with an islet-like dendritic morphology in the SDH have a prominent function in the pain-relieving effects (13).

Dorsal Column

Primary sensory afferent fibers process in the dorsal horn laminae III and IV via monosynaptic and polysynaptic connections onto projection neurons, which in turn project their axons via the dorsal column to the brainstem dorsal column nuclei (14,15). The dorsal column is one of the significant pathways conveying nonnociceptive sensory information, presenting an ideal target for stimulating primary sensory afferent fibers. The activation of dorsal column axons by epidural stimulation is recognized as part of the mechanism of analgesia for conventional SCS.

Large-diameter dorsal column axons drive subpopulations of inhibitory interneurons in the superficial dorsal horn to suppress the activation of projection neurons. Compared to conventional SCS, which produces paresthesia and pain relief by stimulating large myelinated fibers in the dorsal column, low-intensity, high-frequency (10 kHz) SCS has demonstrated long-term pain relief (16). Besides, SCS could elicit rapid epidural evoked compound action potentials representing dorsal column axonal activity (17). Dorsal column stimulation-induced suppression of wide dynamic range neuronal activity was linked to SCS-induced pain alleviation (18). A current study report that SCS of the dorsal column at the level where the damaged fibers enter the SDH provides significantly greater pain relief than SCS at more rostral levels (19).

Neurophysiological and Chemical Mechanisms of Spinal Cord Stimulation

Wide dynamic range (WDR) neurons are secondary neurons in the SDH that are involved in transmitting pain information. They are also the only neurons discovered in the spinal cord receiving input from multiple primary sensory fibers. WDR neurons transmit pain signals through the spinothalamic tract. In models of neuropathic pain, these cells exhibit sustained excitability and a predictable increase in firing frequency as pain intensity increases (19). Golgi staining reveals several morphological characteristics that may be present in WDR neurons: 1) they are situated in layers IV-V of the SDH; 2) the cell body diameter is between 20 μm–50 μm; 3) dendrites and dendritic spines appear to be continuous; 4) at least one dendritic spine extends into adjacent laminae; 5) at least half of the primary dendritic branches are in tissue slices (20).

Animal models have shown that SCS inhibits the hyperexcitability of WDR neurons in the SDH and induces the release of GABA in the SDH, thereby reducing the concentration of glutamate in the interstitium (21). The generation of neuropathic pain is closely associated with an imbalance between excitation and inhibition in spinal cord circuits (Fig. 2). The analgesic effects of SCS are still being explored in terms of which neurotransmitters it affects to maintain the excitatory-inhibitory balance in spinal cord circuits. Clarifying the interactions between various transmitter systems and the interconnections between SDH neurons may provide new insights into SCS treatment for CNP.

γ *(gamma)-aminobutyric Acid*

GABAergic interneurons are abundant in the deep layers of the SDH of the spinal cord and are of crucial importance in maintaining the excitatory-inhibitory balance. Stiller, et al (22) observed that intrathecal administration of the GABAB receptor agonist baclofen in rats with CNP, who were not responsive to SCS treatment, became sensitive to SCS therapy (22). Conversely, when intrathecal administration of the GABA receptor antagonist bicuculline was given, the sensitivity to SCS treatment was diminished. These experiments demon-

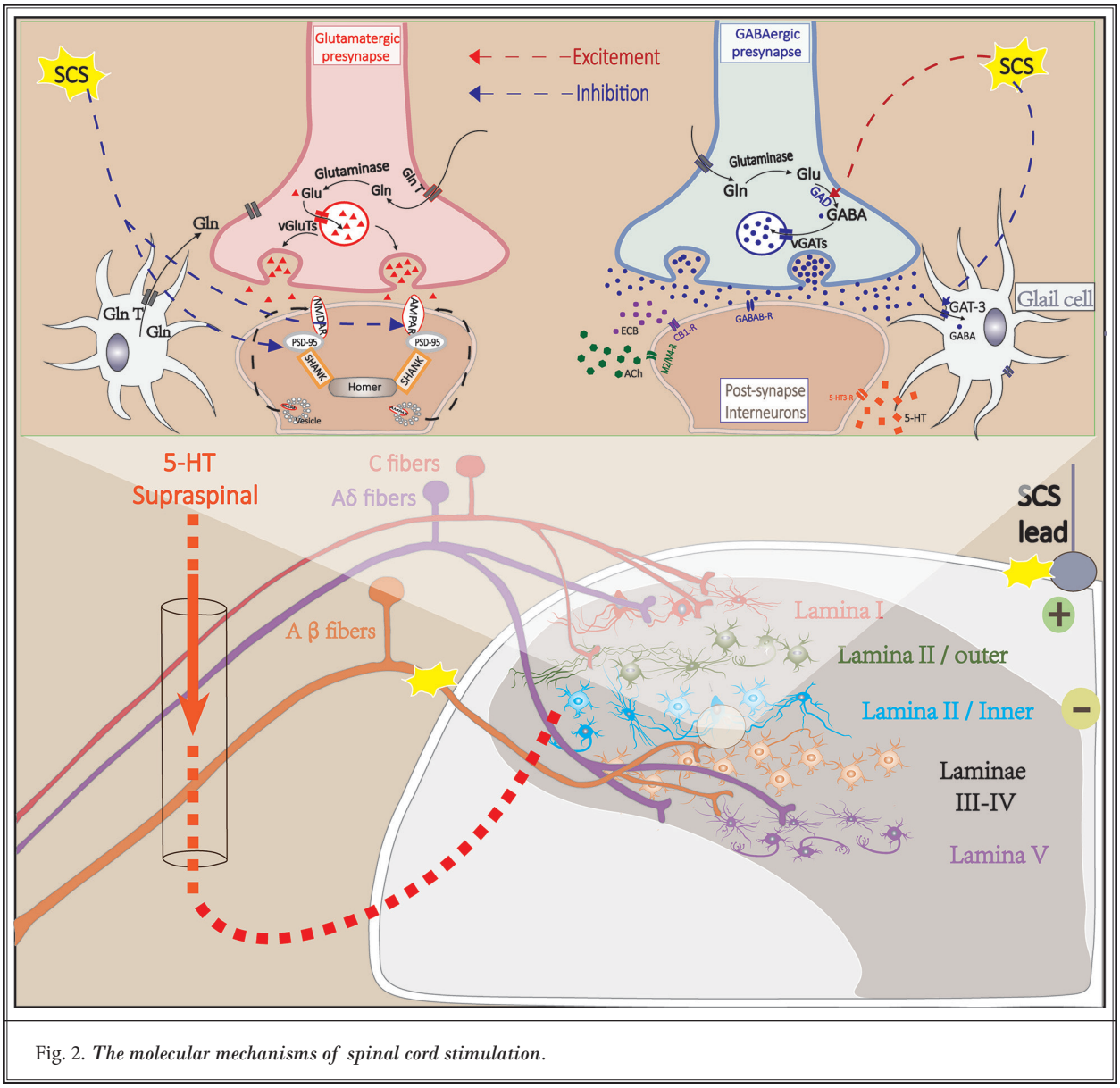

Fig. 2. *The molecular mechanisms of spinal cord stimulation.*

strate that SCS exerts its effects by enhancing the spinal GABAergic system, and there appears to be a stronger correlation with the GABAB receptor system (23,24).

One hypothesis for reduced spinal cord inhibition in CNP is the cell death of spinal cord GABAergic neurons following peripheral nerve injury. However, SCS increased GABA levels in the SDH, and even post-SCS, an extended elevation in extracellular GABA levels has been observed. Research suggests that SCS can influence the levels of GABA-synthesizing enzymes in the spinal cord. Western blotting and immunohistochemistry were used to analyze the levels of GABA-synthesizing enzymes, specifically glutamic acid decarboxylase (GAD)65 and GAD67. It was found that SCS may affect the accumulation of GAD65 in layer II in the SDH of patients who responded to SCS. This accumulation leads to an elevated GABAergic inhibitory tone in layer II, maintaining the effects of SCS and compensating for the peripheral release of GABA (25).

Some studies (26-28) also suggest that the increase in GABA concentration is associated with its reuptake mechanism. GABA transporter 3(GAT-3), a GABA transporter expressed on glial cells that mediates GABA reuptake, is encoded by Slc6a11. Stephens, et al (28) observed

downregulation of GABA reuptake-related genes, such as Slc6a1 and Slc6a11, in rats with neuropathic pain post-SCS treatment, which is similar to the results observed in rats with paclitaxel-induced peripheral neuropathy post-SCS therapy. According to the Gate Control theory, activating Aβ-fibers activates inhibitory networks in the SDH to prevent nociceptive transmission from occurring. Multiphoton microscopy in spinal cords extracted from mice expressing the genetically encoded calcium indicator GCaMP6s in glutamatergic and GABAergic populations found that Aβ-fiber stimulation initially recruits both excitatory and inhibitory populations, but has divergent effects on their activity. It augments the activity of a subset of GABAergic neurons residing in the SDH, which may explain how Aβ-fiber stimulation increases GABA release (29).

Glutamate

Neuroplasticity is the basic principle for the nervous system to learn and adapt to environmental changes. At least 5 different types of excitatory interneurons have been identified in the SDH and are currently involved in CNP (2). Synaptic plasticity between peripheral afferent fibers and second-order neurons forms the basis of central sensitization post nerve injury. Glutamate, the primary neurotransmitter for transmitting nociceptive information, exerts its effects through ionotropic receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors, as well as metabotropic glutamate receptors. Among them, NMDA receptors play an indispensable role in synaptic plasticity. The binding of NMDA-to-NMDA receptors induces the release of nitric oxide, a key mechanism involved in central sensitization generation and maintenance (30). In addition, scaffold proteins within the postsynaptic density (PSD), a dense protein network within the glutamatergic postsynaptic membrane, directly influence synaptic plasticity. Scaffold proteins are typically organized into 3 layers, each containing specific protein families (e.g., DLG4, DLGAP1–4, SHANK1-3), which is vital for the stability of NMDA and AMPA receptor clustering and the transmission of signals on the postsynaptic membrane.

PSD95 can anchor neuronal nitric oxide synthase to NMDA (31). The use of a PSD95-nNOS complex inhibitor, such as PCC-0105002, has been shown to effectively alleviate pain in a rat model of spinal nerve ligation (SNL). PCC-0105002 can modulate downstream signaling of NMDA receptors, including the NR2B/GluR1/CaMKIIα pathway and the Rac1/RhoA pathway, reducing synaptic plasticity structurally and functionally. This modulation of signaling pathways helps to restore the balance between excitatory and inhibitory neurotransmission, reducing the hyperexcitability and sensitization associated with CNP.

In the SDH of rats with chronic constriction injury, an upregulation of SHANK1 protein expression was observed (32). Inhibiting SHANK1 restored the pain threshold in chronic constriction injury rats to the pre-injury level (33). Additionally, Stephens, et al (28) first discovered that genes encoding scaffolding proteins within the PSD were down-regulated in chronic constriction injury rats post-SCS treatment. It is speculated that SCS may induce PSD instability, thereby attenuating the transmission of excitatory neurotransmitters.

Endocannabinoids

Endocannabinoids are bioactive lipid signaling molecules that regulate the transmission of nociceptive information and prolong synaptic plasticity, thereby affecting the duration of pain inhibition (34). Cannabinoid type 1 (CB1) receptors are essential for neuronal plasticity and pain modulation, but their involvement in the analgesic effects of SCS remains unclear (35). CB1 receptors are densely expressed in the terminals of primary afferent neurons and in excitatory and inhibitory interneurons within the substantia gelatinosa located in the SDH's II lamina.

The CB1 receptor antagonist AM251 can block the alleviation of mechanical hypersensitivity in SNL rats induced by SCS, while CB2 receptor antagonists do not have this effect (36). This suggests that the analgesic effects produced by SCS rely on the interaction between endocannabinoids and CB1 receptors. Furthermore, some studies have confirmed that the prolonged analgesic effects of repeated SCS are mediated by CB1 receptor specificity (37). This seems to be related to the ability of cannabinoids to reduce presynaptic glutamate release or interfere with the signaling pathways regulated by postsynaptic NMDA receptors (38). It can be concluded that cannabinoid receptors, especially CB1, may be important targets involved in the mechanisms underlying SCS-induced analgesia.

5-hydroxytryptamine, 5-HT

SCS exhibits a distinct segmental effect in the antinociceptive response of CNP models in rats, involving both spinal and supraspinal mechanisms. The descending antinociceptive system plays a crucial role in the

antinociceptive effects of SCS, mainly through the serotonergic pathway mediated by 5-HT (39). During SCS, the source of 5-HT in SNL rats is from supraspinal nuclei rather than local synthesis in the SDH.

SCS can activate and increase the number of serotonergic neurons in the dorsal raphe nucleus, which inhibits spinal nociceptive reflexes or attenuates the transmission of nociceptive information in the spinal cord. This suggests that the analgesic effects of SCS through the serotonergic pathway are achieved by activating the supraspinal component of the descending antinociceptive system rather than stimulating the spinal production of 5-HT (40,41).

The analgesic effects of 5-HT in CNP are partly mediated through spinal GABAergic and cholinergic mechanisms associated with different subtypes of 5-HT receptors (42,43). Song, et al (44) found that the activation of 5-HT2A, 5-HT3, and 5-HT4 receptors contributes greatly to alleviating neuropathic pain induced by SCS. The 5-HT3 receptor is an excitatory ligand-gated ion channel primarily located in the superficial layers of the SDH (44). The administration of selective 5-HT3 receptor agonists can increase the concentration of GABA in the spinal cord without altering glutamate and glycine levels, suggesting that the activation of 5-HT3 receptors occurs through spinal GABAergic interneurons (45). Moreover, compared to SCS alone, using serotonin reuptake inhibitors significantly elevates pain scores in patients receiving SCS treatment (46). This result supports the view that the serotonergic system is essential in SCS-induced analgesia.

Cholinergic

M receptor activation mediates an increase in intracellular Ca^{2+} in neurons, leading to increased neuronal nitric oxide synthase activity, thereby facilitating nitric oxide synthesis and release, which is involved in pain modulation. The elevation of intracellular calcium ions is also considered a critical triggering factor for synaptic plasticity, although the specific mechanisms are unclear.

In the SDH, a close functional relationship exists between cholinergic and GABAergic mechanisms. Intrathecal injection of muscarinic acetylcholine receptor (M) agonists or acetylcholinesterase inhibitors may exert analgesic effects by activating M receptors (mainly M2 and M4) on inhibitory interneurons in the SDH and increase local GABA release. Acetylcholine binding to presynaptic M receptors can inhibit excitatory signals to neurons in lamina II, requiring GABAB receptors' involvement. Activation of GABAB receptors contribute to the antinociceptive effects of M-receptor agonists (47).

By comparing the analgesic effects of central active M receptor agonists in wild-type mice and M2/M4 double knockout mice, Duttaroy, et al (48) confirmed that the combined action of M2 and M4 receptors in the spinal cord and supraspinal sites caused muscarinic analgesia. The effects produced by SCS can be entirely blocked by selective M4 receptor antagonists and partially attenuated by selective M1 and M2 receptor antagonists (49). In addition, SCS could inhibit relieved pain by inhibiting the C-fiber-evoked spinal local field potential post nerve injury in rats (50). These findings may guide the combination therapy of clinical SCS.

Neural Circuits Involved in Spinal Cord Stimulation for Chronic Neuropathic Pain

Anatomically and functionally, distinct medial and lateral pain pathways are among the 2 ascending and descending inhibitory circuits linked to pain (51). The dorsal anterior cingulate cortex and anterior insula serve as the primary hubs of the medial pain pathway, which encodes the unpleasantness and suffering associated with pain. The somatosensory cortex serves as the primary hub of the lateral route, which interprets pain based on its sensory component and discrimination. Furthermore, the rostral and prefrontal cingulate cortex, the hypothalamus, and the periaqueductal gray matter are linked to the downstream inhibitory circuit (52-54).

Ascending Pain Pathways Activated or Inhibited by Spinal Cord Stimulation

Chronic pain is an imbalance between the brain's ascending and descending pathways; burst SCS can normalize this imbalance in the brain. By normalizing the imbalance between the ascending and descending pathways in the brain, burst SCS may cause a notable alteration in electroencephalogram activity in both the left and right somatosensory cortex and the dorsal anterior cingulate cortex (53). Evoked potentials in the left primary somatosensory and anterior cingulate cortex might be markedly reduced by SCS, which would subsequently suppress neuropathic pain-related behavior (55,56). The release of GABA caused by SCS might stimulate inhibitory interneurons, reducing primary afferent transmission from the superficial dorsal horn to sympathetic output neurons in the intermediolateral nucleus (57).

Evidence in clinical research has shown that SCS may

achieve analgesia by enhancing alpha and gamma oscillations in the cortex, especially in the frontal lobe (58). Interestingly, SCS can regulate the cortical activity of patients who have had abnormalities of consciousness, such as changes in temporal complexity and natural frequency (50). Short-term SCS may enhance the intensity of slow oscillations in the right superior parietal gyrus to alleviate symptoms related to pain, sleep, and mood (59).

Additionally, animal experiments have proved that both tonic SCS and burst SCS augmented the levels of activation signals in the somatosensory cortex, premotor cortex, amygdala, anterior cingulate cortex, and insular cortex. Burst SCS caused a more significant rise in the brain locations stated before, compared to continuous SCS (60,61). The analgesic effect of SCS is related to an enhancement of cortical alpha and gamma oscillation, indicating a specific pattern of neural oscillation in individuals who respond positively to analgesia (62). Moreover, a study found an elevation in the frequency of alpha brain waves, an increase in the intensity of alpha brain waves, and a drop in the intensity of theta brain waves when comparing SCS to baseline, suggesting that the thalamocortical circuits were being influenced (63). In addition to this finding, a clinical study demonstrated that functional magnetic resonance imaging indicated anterior cingulate cortex activation in patients who experienced highly effective pain relief with SCS (64).

Descending Pain Pathways Activated or Inhibited by Spinal Cord Stimulation

The rostral ventromedial medulla, the primary source of descending serotoninergic innervation, is a crucial structure in pain control; it contains several well-characterized cell types related to the modulation of pain. The so-called ON cells facilitate, and OFF cells inhibit nociceptive signal transmission at the spinal segmental level. Other cell types are 5-HT-like cells and neutral cells (65). SCS significantly increases the discharge rate of OFF-like and 5-HT-like cells in the rostral ventromedial medulla of spared nerve injury rats (66). In parallel with the descending pain modulatory system originating in the rostral ventromedial medulla, spinally projecting noradrenergic pathways have been found to exert pain-controlling functions (67). Supraspinal noradrenergic projections from the locus coeruleus may play a role in SCS-induced pain reduction, perhaps via activating the locus coeruleus-periaqueductal gray- rostral ventromedial medulla loop, which may also contain thalamic relays (68). Activation of the dorsal column relay to supraspinal centers, involved in pain modulation, is probably via the descending fibers in the dorsolateral funiculi. Dorsolateral funiculi lesions inhibit the effect of SCS, suggesting it has an important role in SCS analgesia via spinal and supraspinal mechanisms (69).

Antineuroinflammation Effects

SCS may exert anti-inflammatory and analgesic effects by modulating the activation state of microglia or macrophages in animal models with neuropathic pain (70). According to Bakare, et al (71), SCS can alleviate paclitaxel-induced pain and transient gait impairment. This effect may be partially explained by reduced macrophage-mediated neuroinflammation and Schwann cell loss in the sciatic nerves (71). A recent study found that high-frequency SCS substantially reduces immune responses in the SDH by inactivating the Kaiso-P2X7R pathological axis in microglia, thereby promoting long-lasting pain relief (72). SCS can mitigate chemotherapy-induced peripheral neuropathy pain by modulating CX3CL1-macrophages (73).

In addition, SCS effectively inhibits the neuropathy-induced elevation of TLR4 and NF-κB p65, decreasing pronociceptive interleukin-1β, interleukin-6, and tumor necrosis factor-α proteins in the SDH, which alleviates pain hypersensitivity caused by diabetic neuropathy (74). A subsequent investigation revealed that the application of one-kHz SCS for 6 hours at a pulse width of 0.1 milliseconds was adequate to effectively reduce mechanical allodynia induced by nerve injury and to decrease interleukin-1β levels in both the serum and cerebrospinal fluid of rats (75).

Furthermore, an animal study that compared the effects and mechanisms of conventional frequency (50 HZ) and high frequency (1200 HZ) SCS on improving pain in diabetic painful peripheral neuropathy found that conventional, high frequency, or differential targeted multiplexed SCS (a combination of normal and high frequency) stimulation was effective in reducing mechanical hypersensitivity induced by diabetic peripheral neuropathy at 24 and 48 hours of continuous stimulation (76). Nevertheless, Con-SCS substantially increased TNF-α and demonstrated a shift in the inflammatory balance toward a pro-inflammatory state. In contrast, HF and DTM-SCS shifted the balance toward an anti-inflammatory state

Spinal Cord Vascular Changes in Response to Spinal Cord Stimulation

After applying functional ultrasonography, Tang et

al (77) observed significantly higher and faster blood volume changes in the dorsal regions of the spinal cord during SCS compared to the ventral regions of the spinal cord, independently of the parameters and electrode configurations; the spinal cord hemodynamic response was dependent on the frequency of the SCS, which was more responsive with low-frequency (20 Hz–40 Hz) stimulation.

Interestingly, many studies have reported on SCS, which is widely used to treat ischemic pain in peripheral, cardiac, and cerebrovascular diseases. SCS at lumbar segments (L2-L3) causes vasodilation in the lower limbs and feet, which is mediated by antidromic activation of sensory fibers, as vanilloid receptor type 1-containing fiber, as well as reduced sympathetic outflow (78-81). SCS could activate cell-signaling molecules such as extracellular signal-regulated and protein kinase (ERK) and protein kinase B (AKT) in the dorsal root ganglia. These kinases stimulate Transient Receptor Potential Vanilloid 1 (TRPV1), causing the release of vasodilators (e.g., calcitonin gene-related peptide [CGRP]), with a decrease in vascular resistance and an increase in local blood flow (82,83). In addition, prolonged SCS alleviated mechanical hypersensitivity in experimental painful diabetic polyneuropathy and increased peripheral cutaneous blood perfusion (84).

New Patterns of Spinal Cord Stimulation

Conventional SCS focuses on paresthesia-inducing stimulation that overlaps pain distribution with the intent of masking pain perception. Thus, the patient experiences paresthesia all over the pain area. Tonic SCS systems typically use frequencies within the range of 40 Hz–60 Hz and require patient feedback to adjust the stimulation location, pulse frequency, and other stimulation parameters. This reliance on comprehensive and enduring coverage of the paresthesia in the pain area determines the analgesic effect of conventional SCS. Moreover, patients need to tolerate these abnormal sensations to achieve effectiveness. In order to provide better treatment for patients with chronic pain, SCS has made breakthroughs and a paradigm shift from hardware to software to improve treatment efficiency and patient tolerability.

High Frequency Spinal Cord Stimulation

High frequency (HF) SCS is typically applied at frequencies ranging from one to 10 kHz, with a pulse width of around 30 milliseconds and an amplitude usually between one and 5 mA. This adjustment gives HF SCS distinct properties from paresthesia-based SCS, such as a more extended time course to response, implying the existence of an alternative mechanism of action beyond the gate control theory (85,86). The absence of paresthesia is probably because the dorsal column axons spike asynchronously, which is far less likely to activate the cortex (87).

Also, clinical evidence shows that different HF SCS frequencies can lead to significant pain relief (88-91). Animal experiments found that lysosomal function was impaired in the SDH of SNL rats after peripheral nerve injury. However, 4 hours of HF SCS treatment partially restored lysosomal function, activated autophagy, and alleviated pain sensitivity. Therefore, the effects of HF SCS on lysosomal function and autophagy may be one of the mechanisms by which HF SCS interferes with central sensitization's role in CNP (92).

Furthermore, HF SCS can alleviate activation of the inflammatory pathway on the injured side; the DRG appears to be a prominent site where HF SCS inhibits excessive mitogen-activated protein kinase (MAPK) phosphorylation (72). Labelling the neuronal activation marker c-Fos shows that HF SCS can directly or indirectly activate neurons in the injured-side dorsal horn. Recent studies, considering the involvement of the neurons in the superficial SDH in mediating the pain-relieving effects of HF SCS, suggested that HF SCS could improve the immunopathologic state in the superficial layer, and targeting the Kaiso-P2X7R axis may enhance conventional SCS therapy (85,93).

Burst Spinal Cord Stimulation

Burst SCS is a stimulation technique De Ridder, et al proposed in 2010 (93). The waveform of burst SCS consists of 5 closely spaced monophasic spikes, with a low stimulation frequency of 500 Hz and a burst stimulation frequency of 40 Hz. The pulse width is on millisecond, with a one millisecond interspike interval, and is delivered in constant current mode (94). De Ridder (95) believes that clustered or irregular discharges are more similar to regular neural activity. Furthermore, clustered stimulation is more efficient because less time is required for integration to activate cortical neurons.

Burst SCS has been proposed to modulate the spinomesencephalic pathway and activate cortical regions involved in pain modulation, such as the dorsal anterior cingulate and the right dorsolateral prefrontal cortex (64). Unlike tonic stimulation, the analgesic effect of burst SCS does not depend on GABAergic signaling. GABAB receptor antagonists can abolish the inhibitory

effect of tonic SCS on WDR neuron activity. However, this effect is not present in burst SCS (95). Furthermore, burst SCS has been shown to engage the activation of the anterior cingulate cortex (96).

Burst SCS may exert its effects on pain through the spinal-cortical-spinal loop, indirectly activating multiple pathways and resulting in central and spinal effects. The specific neurochemical mechanisms involved in burst SCS still require further investigation. A controlled crossover trial showed that burst SCS was superior to tonic stimulation in suppressing chronic refractory pain (97). Building upon this, one study has shown that in burst SCS, low-amplitude stimulation parameters are more effective in suppressing pain than high-amplitude stimulation, which provides a reference for the clinical selection of appropriate parameters for burst SCS (98).

Differential Target Multiplexed™ SCS, DTM-SCS

Differential target multiplexed (DTM™) (Medtronic) SCS programming mode is based on the differential gene expression in cells between pain and normal states. In DTM SCS, HF SCS and low-frequency stimulation are applied simultaneously to multiple spinal cord electrodes (99).

This combined stimulation mode aims to leverage the advantages of HF SCS, such as long-distance propagation and widespread activation of neurons, as well as the benefits of low-frequency stimulation, such as activation of the brainstem-spinal cord pathway and increased release of endorphins. The goal is to modulate pain signal transmission and control pathways by stimulating multiple target points. These target points can include the SDH, brainstem, cortex, and other pain-related regions.

DTM programming mode not only modulates neurons but also influences glial cells. A prospective, multicenter, open-label, randomized controlled trial with optional crossover reported improvements with DTM SCS in chronic low back pain and leg pain levels, functional disability, quality of life, patient satisfaction, and global impression of change were sustained, which is positive for patients with severe chronic low back pain who are ineligible for spine surgery (100). The specific molecular mechanisms involved in this process are not yet well understood and require further in-depth exploration.

Closed-loop Spinal Cord Stimulation

When patients are treated with SCS, physiological functions such as breathing, heartbeat, and changing posture alter the distance between the spinal cord target fibers and epidural SCS electrodes. This causes inconsistent therapy delivery, for example, under stimulation or overstimulation, as the spinal cord moves in and out of the unchanged electric field.

To overcome these challenges, closed-loop SCS that automatically adapts the pulse generator output for each pulse based on real-time measurements of evoked compound action potentials was created. Evoked compound action potentials are the sum of the action potentials of multiple nerve fibers activated by a given stimulus pulse and are the basis for determining target fiber activation (101) , which allows the system to effectively respond to the changing conditions of the spinal cord and ensure accurate and consistent activation at the desired evoked compound action potentials level. In a secondary analysis of a double-blind, randomized clinical trial, closed-loop SCS delivered a higher, more consistent neural response within the prescribed therapeutic window and demonstrated superior long-term improvements in pain relief and patient-reported outcomes, as well as meaningful opioid reduction (101). Compared with those receiving conventional SCS for managing chronic intractable back and leg pain, closed-loop SCS provided superior and durable outcomes in pain intensity, physical function, health-related quality of life, sleep quality, and emotional function at all time points (102). Compared with fixed-output, open-loop SCS at 36 months postimplant, greater neural activation and increased accuracy of spinal cord activation were observed with closed-loop SCS (103). The proofs above suggest closed-loop SCS may be an effective long-term therapy to alleviate chronic pain.

Conclusion

SCS offers pain relief for patients with chronic pain conditions, but its use should be carefully considered in collaboration with pain management specialists. Our review aims to summarize the neurophysiological, biochemical, anti-inflammatory, and neurocirculatory mechanisms underlying the analgesic effects of SCS. With this knowledge we hope that future research on the mechanisms of SCS-induced analgesia can provide additional insights, thereby improving and expanding the clinical efficacy of SCS based on specific pathological processes and become a treatment option for a broader range of patients with CNP.

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