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SEGRETARIA SCIENTIFICA
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n° 30 crediti assegnati per n° 8 Medici Chirurghi
Spinal cord stimulation (SCS) is commonly used for neuropathic pain. The patients had a mean follow-up rate of 33 months. 67% of patients achieved pain relief of at least 50%. The visual analog scale (VAS) was used to assess pain score reduction.
1st mechanisms of action:
SCS attenuated the increase of

- SP
- TRPV1 mRNA I
Role of TRPV1 in augmentation of cerebral blood flow by cervical spinal cord stimulation in rats
Xiaoli Yang1, Jay P Farber2, Mingyuan Wu2, Robert D Foreman2 and Chao Qin2

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ABSTRACT
Clinical experimental studies have indicated that upper cervical spinal cord stimulation (SCS) produces a significant increase in cerebral blood flow (CBF). However, the underlying mechanisms remain unclear. The aim of this study was to examine whether transient receptor potential vanilloid type 1 (TRPV1) was involved in the effects of SCS on CBF in rats. A spring-loaded unipolar ball electrode was placed on the left dorsal column at cervical spinal cord (C1–C2) in pentobarbital anesthetized, ventilated and paralyzed male rats. SCS with stimulus parameters (50 Hz, 0.2 ms, and 90% of motor threshold) was applied. Parietal craniotomy was performed to expose the left cortex for placement of laser Doppler flowmetry probe to measure CBF. Results showed that SCS increased CBF by 63.1±6.3% (P<0.01, n=24). Spinal transections at C6–C7 segments did not affect SCS-induced augmentation of CBF (53.8±11.7% vs 42.1±14.2%, n=7, P>0.05). Capsazepine (3 mg/kg, i.v.), an antagonist of TRPV1, reduced CBF-responses to SCS from 68.5±12.5% to 27.5±12.8% (n=8, P<0.05). After desensitization of TRPV1-containing fibers with resiniferatoxin (2 µg/kg, i.v), an ultra potent analog of capsicain, SCS-induced augmentation of CBF decreased from 65.0±9.5% to 27.4±7.2% (n=9, p<0.05). These data suggested that SCS-induced augmentation of CBF was mediated by TRPV1. (NIH grants: HL-075524 and NS-035471)

2nd mechanisms of action:
Clinical experimental studies have indicated that upper cervical spinal cord stimulation (SCS) produces a significant increase in cerebral blood flow (CBF). However, the underlying mechanisms remain unclear. The aim of this study was to examine whether transient receptor potential vanilloid type 1 (TRPV1) was involved in the effects of SCS on CBF in rats. These data suggested that SCS-induced augmentation of CBF was mediated by TRPV1.
Effects of Spinal Cord Stimulation with different frequencies on blood flow in the rat hind paw
jie gao1,2, mingyuan wu1, chao qin1, jay p farber1, Bengt Linderoth3 and robert d foreman1

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3 Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

ABSTRACT

Spinal cord stimulation (SCS) at a frequency of ~ 50 Hz is used to improve peripheral blood flow. However, it is unclear whether SCS at higher frequencies induces further increases vasodilation and enhances clinical efficacy. This study investigated effects of SCS at different frequencies on peripheral vasodilation. SCS was setup at the lumbar 2–3 spinal cord segments in rats. Cutaneous blood flows from both ipsilateral and contralateral hind foot pads were recorded with laser Doppler flow perfusion monitors. SCS at frequencies of 50, 200 or 500 Hz was applied through the ball electrode at 30%, 60% and 90% of motor threshold (MT). Resiniferatoxin (RTX), an ultra potent analog of capsaicin, was applied to block the transient receptor potential vanilloid receptor (TRPV1); Furthermore, calcitonin gene related peptide (CGRP)8–37, a CGRP-1 receptor blocker, was used to elucidate mechanisms of SCS vasodilation at a high frequency. SCS applied with the three frequencies produced similar MT. SCS at the frequency of 500 Hz induced a higher increase of cutaneous blood flow and decreased vascular resistance compared to that with the frequency of 50 and 200 Hz (P<0.05). RTX (2 µg/Kg. i.v.) as well as CGRP8–37 (2.37 mg/Kg. i.v.) significantly reduced SCS-induced vasodilation at this high frequency (500 Hz) (P<0.05). In conclusion, SCS at a high frequency significantly increased SCS-induced vasodilation effect without influencing the MT. Furthermore, effects of SCS at high frequency seem to be predominantly mediated via activation of TRPV1 containing fibers including a release of CGRP.

3th mechanisms of action:

- SCS at the frequency of 500 Hz induced a higher increase of cutaneous blood flow and decreased vascular resistance compared to that with the frequency of 50 and 200 Hz (P<0.05).
- Furthermore, effects of SCS at high frequency seem to be predominantly mediated via activation of TRPV1 containing fibers including a release of CGRP.
In recent years, software development has been key to the next generation of neuromodulation devices. In this review, we will describe the new strategies for electrical waveform delivery for spinal cord stimulation. A systematic literature review was performed using bibliographic databases, limited to the English language and human data, between 2010 and 2014. The literature search yielded three articles on burst stimulation and four articles on high-frequency stimulation. High-frequency and burst stimulation may offer advantages over tonic stimulation, as data suggest improved patient tolerance, comparable increase in function and possible success with a subset of patients refractory to tonic spinal cord stimulation. High-frequency and burst stimulation are new ways to deliver energy to the spinal cord that may offer advantages over tonic stimulation. These may offer new salvage strategies to mitigate spinal cord stimulation failure and improve cost-effectiveness by reducing explant rate.

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**Keywords**
High-frequency and burst stimulation are new ways to deliver energy to the spinal cord that may offer advantages over tonic stimulation.

- SCS at the frequency of 500 Hz induced a higher increase of cutaneous blood flow and decreased vascular resistance compared to that with the frequency of 50 and 200 Hz (P<0.05).

- SCS at high frequency seem to be predominantly mediated via activation of TRPV1 containing fibers including a release of CGRP.
Spinal cord stimulation reduces mechanical hyperalgesia and glial cell activation in animals with neuropathic pain.
Sato K1, Johansen LM, Sarada LS, Sluka KA

Abstract

BACKGROUND: Spinal cord stimulation (SCS) is commonly used for neuropathic pain; the optimal variables and mechanisms of action are unclear. We tested whether modulation of SCS variables improved analgesia in animals with neuropathic pain by comparing 6-hour vs 30-minute duration and 50%, 75%, or 90% motor threshold (MT) intensity (amplitude). Furthermore, we examined whether maximally effective SCS reduced glial activation in the spinal cord in neuropathic animals.

METHODS: Sprague-Dawley rats received the spared nerve injury model and were implanted with an epidural SCS lead. Animals were tested for mechanical withdrawal threshold of the paw before and 2 weeks after spared nerve injury, before and after SCS daily for 4 days, and 1, 4, and 9 days after SCS. Spinal cords were examined for the effects of SCS on glial cell activation.

RESULTS: The mechanical withdrawal threshold decreased, and glial immunoreactivity increased 2 weeks after spared nerve injury. For duration, 6-hour SCS significantly increased the mechanical withdrawal threshold when compared with 30-minute SCS or sham SCS; 30-minute SCS was greater than sham SCS. For intensity (amplitude), 90% MT SCS significantly increased the withdrawal threshold when compared with 75% MT SCS, 50% MT SCS, and sham SCS. Both 4 and 60 Hz SCS decreased glial activation (GFAP, MCP-1, and OX-42) in the spinal cord dorsal horn when compared with sham.

CONCLUSIONS: Six-hour duration SCS with 90% MT showed the largest increase in mechanical withdrawal threshold, suggesting that the variables of stimulation are important for clinical effectiveness. One potential mechanism for SCS may be to reduce glial activation at the level of the spinal cord.

PMID: 24361846 [PubMed - indexed for MEDLINE]  PMCID: PMC4297213  Free PMC Article
5th mechanisms of action:

4- and 60-Hz SCS, in part, work through opioid receptor mechanisms,
- with 4-Hz SCS activating μ-opioid receptors
- while 60-Hz SCS activated δ-opioid receptors.
**Article title:** What does the Mechanism of Spinal Cord Stimulation Tell Us about Complex Regional Pain Syndrome

**Author:** Joshua P. Prager, MD, MS

**Journal/Source:** Pain Medicine 2010: 11: 1278-1283

**Discussion:**

Neurostimulation has been used for several decades and become increasingly popular for the treatment of chronic intractable pain. A device that is commonly used is spinal cord stimulation (SCS). This is an implanted device containing spinal leads and a pulse generator. These leads can then be placed based upon the specific anatomic region. The mechanism of how pain relief is achieved through SCS is currently unknown. The following clinical review provided several possible mechanisms of action.

This clinical review included 25 case series and involved 500 patients with CRPS with implanted SCS systems. The patients had a mean follow-up rate of 33 months. 67% of patients achieved pain relief of at least 50%. The visual analog scale (VAS) was used to assess pain score reduction. SCS also provided measurable improvement in quality of life and functional ability. Out of eight studies, complications from the insertion of the SCS unit occurred in 33% of patients. Common complications include depletion of the pulse generator and lead migration.

The review of these studies showed the effectiveness of SCS in managing CRPS and also further exploring some possible explanations of how the effects of SCS are achieved. Some possible explanations include “gate control theory”, increased GABAergic or cholinergic activity in the spinal cord, and inducing peripheral vasodilation. The current available studies show that SCS can relieve pain and is of clinical benefit in CRPS and other pain syndromes. Further studies must be done to examine the role of the sympathetic stimulation in the pathophysiology of CRPS.

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A hypothesis on possible neurochemical mechanisms of action of cervical spinal cord stimulation in prevention and treatment of cerebral arterial vasospasm after aneurysmal subarachnoid hemorrhage

D. Yin, K.V. Slavin

Introduction

Hypothesis of effect of SCS on PDE5 activity

Evidence of effect of nitric oxide on cerebrovascular tone

Discussion

Summary

Conflict of interest

References

Abstract

Subarachnoid hemorrhage (SAH) is associated with the high incidence of development of cerebral vasospasm that results in morbidity and mortality due to delayed cerebral ischemia. So far there are no consistently effective therapies for treatment of vasospasm in patients suffering from SAH. It is well known that cervical spinal cord stimulation (SCS) can induce vasodilatation and increase cerebral blood flow (CBF). Based on the experiments in animals and the studies in humans, we have proposed the possibility to use SCS as a therapeutic strategy for prevention and treatment of cerebral vasospasm after SAH. However, the physiological mechanisms of action of SCS in this regard are poorly understood. Better understanding of the pathophysiology of vasospasm after SAH may provide insight into the role of SCS in such conditions. We hypothesize that effect of SCS on vasodilatation may be related to modulation of activity of phosphodiesterases 5 (PDE-5) and nitric oxide synthase (eNOS), resulting in enhancement of nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway, which may help prevent and/or treat vasospasm after SAH. Further investigations on the physiological mechanisms of action of SCS would be necessary to support this hypothesis.
Thank You Cagliari