Spinal Cord Stimulation Paradigms and Pain Relief

Neuromodulation: Technology at the Neural Interface

Received: January 5, 2022 Revised: March 11, 2022 Accepted: April 7, 2022

https://doi.org/10.1016/j.neurom.2022.04.049

Spinal Cord Stimulation Paradigms and Pain Relief: A Preclinical Systematic Review on Modulation of the Central Inflammatory Response in Neuropathic Pain

Thomas J. de Geus, MSc[1,2]; Glenn Franken, PhD[1,2]; Elbert A.J. Joosten, PhD[1,2]

ABSTRACT

Objectives: Spinal cord stimulation (SCS) is a last-resort treatment for patients with chronic neuropathic pain. The mechanism underlying SCS and pain relief is not yet fully understood. Because the inflammatory balance between pro- and anti-inflammatory molecules in the spinal nociceptive network is pivotal in the development and maintenance of neuropathic pain, the working mechanism of SCS is suggested to be related to the modulation of this balance. The aim of this systematic review is to summarize and understand the effects of different SCS paradigms on the central inflammatory balance in the spinal cord.

Materials and Methods: A systematic literature search was conducted using MEDLINE, Embase, and PubMed. All articles studying the effects of SCS on inflammatory or glial markers in neuropathic pain models were included. A quality assessment was performed on predetermined entities of bias.

Results: A total of 11 articles were eligible for this systematic review. In general, induction of neuropathic pain in rats results in a proinflammatory state and at the same time an increased activity/expression of microglial and astroglial cells in the spinal cord dorsal horn. Conventional SCS seems to further enhance this proinflammatory state and increase the messenger RNA expression of microglial markers, but it also results in a decrease in microglial protein marker levels. High-frequency and especially differential targeted multiplexed SCS can not only restore the balance between pro- and anti-inflammatory molecules but also minimize the overexpression/activation of glial cells. Quality assessment and risk of bias analysis of the studies included make it clear that the results of these preclinical studies must be interpreted with caution.

Conclusions: In summary, the preclinical findings tend to indicate that there is a distinct SCS paradigm–related effect in the modulation of the central inflammatory balance of the spinal dorsal horn.

Keywords: Glial cells, inflammation, neuropathic pain, spinal cord stimulation, stimulation paradigms

Conflict of Interest: The authors reported no conflict of interest.

BACKGROUND

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system."[1] The disease is present in approximately 8% of the adult population and is a major burden on the patient and health care system.[2,3] Damage to the nervous system may lead to an increased peripheral and/or central inflammatory response[3,4] and, with that, severely affect the nociceptive network. Consequently, the inflammatory response aids in both the development and maintenance phases of neuropathic pain.[5] Treatment of neuropathic pain remains a major challenge in current medicine. Because the central inflammatory response plays such a pivotal role, both the characterization and modulation of the inflammatory response are important and may alleviate pain in patients with neuropathic pain.

Central Inflammation and Glial Cells in Neuropathic Pain

An increased central inflammatory response in the spinal dorsal horn is a common and important part of the underlying mechanism of neuropathic pain.[5–8] The activation of spinal glial cells results in the release of proinflammatory and anti-inflammatory cytokines, neurotrophic factors, and chemokines.[9] An optimal balance of pro- and anti-inflammatory molecules is among the most important prerequisites to avoid or minimize the development of neuropathic pain.[10,11] When this balance is in favor of proinflammatory molecules, this will result in the development and maintenance of neuropathic pain. Increased levels of anti-inflammatory molecules could restore

Address correspondence to: Thomas J. de Geus, MSc, Maastricht University, Universiteitssingel 50, Rm F1.148, 6229 ER Maastricht, The Netherlands. Email: t.degeus@maastrichtuniversity.nl

[1] Department of Anesthesiology and Pain Management, Maastricht University Medical Centre, Maastricht, The Netherlands; and
[2] Department of Translational Neuroscience, School of Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

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Source(s) of financial support: The authors reported no funding sources.

the balance, which may ultimately prevent the development and maintenance of neuropathic pain.[10,11]

In the central nervous system (CNS), pro- and anti-inflammatory cytokines are secreted by neuroglial cells.[12,13] The neuroglia makes up 70% of the cells in the CNS and consists of two types, microglia and macroglia, the latter of which can be subdivided into astrocytes and oligodendrocytes.[14,15] Upon nerve injury, the affected tissue at the injury site immediately starts to release chemokines. The release of chemokines and inflammatory mediators almost instantaneously activates local microglial cells, which are situated around the central terminals of the affected fibers. The activation of microglial cells and their release of proinflammatory cytokines are a fast response, which, in a normal state, is followed by the release of anti-inflammatory cytokines.[11,12,16] These anti-inflammatory cytokines restore the inflammatory balance between pro- and anti-inflammatory molecules, ultimately preventing neuropathic pain. When this balance is not restored, neuropathic pain may be further and continuously induced by a persistent release of proinflammatory markers and the increased activity of glial cells, including the astrocytes.[17] After a peripheral or central nerve injury, the activation of the microglia peaks between day 4 and day 7 postinjury, which strongly suggests that the microglia are involved in the development phase of neuropathic pain.[18]

Microglial cells may activate neighboring astrocytes and, with that, further extend the cascade of reactions to the initial nerve injury.[19] The activation of the astrocytes peaks during the second week postinjury.[18] The timing of astroglial activation suggests that these cells are involved in not only the onset but also the maintenance of neuropathic pain. Furthermore, there might be a potential role for the oligodendrocytes in the modulation of the inflammatory response as related to the maintenance of neuropathic pain.[20,21] Because the evidence for oligodendrocytes in neuropathic pain as related to spinal cord stimulation (SCS) is not found in the literature, this is not part of this systematic review.

The activated astrocytes contribute to the neuropathic pain state in a variety of ways, eg, by secretion of proinflammatory cytokines, by regulation of receptors such as the Toll-like receptor-4 (TLR-4), and by increasing transmission of Ca2+ that results in central sensitization.[22,23] Clearly, targeting either the activated microglial and/or astroglial cells may restore the balance between pro- and anti-inflammatory cytokines, and this may ultimately result in pain relief in patients with neuropathic pain. Neuromodulation and, in particular, SCS is a promising technique which might restore this inflammatory balance.

SCS and Modulation of Central Inflammatory Response in the Treatment of Neuropathic Pain

Electrical neuromodulation based on SCS of the dorsal columns is commonly used as a last-resort treatment option for patients with neuropathic pain. SCS has been found to be an effective treatment option for several neuropathic pain disorders, including, but not limited to, complex regional pain syndrome (CRPS),[24] failed back surgery syndrome or persistent spinal pain syndrome,[25] and painful diabetic peripheral neuropathy.[26,27] The use of SCS with conventional settings (conventional SCS [Con-SCS]) typically results in approximately 50% pain reduction in 50% to 70% of patients. The mechanism underlying the pain-relieving effect of SCS is far from understood. Nevertheless, it is documented that, in line with the gate control theory, anti- and orthodromic activation of Aβ-fibers play an important role.[28] Furthermore, the activation of spinal gamma-aminobutyric acid (GABA)ergic inhibitory interneurons and a descending serotonergic feedback loop, both of which interfere with the process of central sensitization, have been shown to be involved.[28] Interestingly, the implementation of new technical tools and genetic analyses boosted the field of SCS and revealed a pivotal role of central glial cells and/or the balance between pro- and anti-inflammatory molecules in the mechanism underlying SCS-induced pain relief.[28] In recent years, new SCS waveforms or paradigms such as high-frequency SCS (HF-SCS) (>500 Hz), differential targeted multiplexed SCS (DTM-SCS) (a combination of different frequencies), and Burst-SCS (bursts of five pulses delivered at an intraburst frequency of 500 Hz, with these bursts repeated at an interburst frequency of 40 Hz) have been developed. These paradigms are thought to have different mechanisms of action and potentially different effects on the inflammatory balance in neuropathic pain.[29,30] It is the aim of this review to collect and summarize all preclinical studies investigating the modulatory effects of SCS paradigms on the central inflammatory response and glia activity in neuropathic pain models. This review may act not only as an overview of the current status of SCS-induced pain relief and the possible role of central inflammation but also as a template for further research.

MATERIALS AND METHODS

Search

A systematic search in the MEDLINE, Embase, and PubMed data bases was performed to select relevant articles from 1950 through November 19, 2021. The search was performed to select all studies evaluating the central inflammatory response and glial activity after SCS in experimental models for neuropathic pain. Search terms are described in the Supplementary Data Appendix. Duplications were removed.

Inclusion Criteria

Preclinical peer-reviewed articles, published in the English language, were selected. The following criteria were defined for inclusion: 1) the study was performed in an animal model for neuropathic pain; 2) SCS treatment was performed in at least one of the groups (regardless of SCS paradigm); and 3) the central inflammatory response and/or astrocyte and/or microglia activity was measured in any form (Fig. 1 provides the flowchart). Our systematic search resulted in a selection of preclinical studies. Clinical evidence and studies on this subject are very limited and thus not included in our review. However, for a complete overview, these clinical studies are discussed in the Discussion section.

Selection of Studies

Two independent researchers selected the articles on the basis of several inclusion criteria described above, after reading the title and the abstract. If the selection was not evident, based on the title and abstract, the article was read in its entirety. In the case of disagreement, a consensus was reached, or a third party was consulted.

Risk of Bias Analysis

The quality of the literature was assessed by two individual researchers using the SYRCLE Risk of Bias (RoB) tool for animal studies.[31] Ten items related to performance bias, selection bias, attrition bias, detection bias, reporting bias, and other biases are included in the RoB tool. Each item was scored as low risk, high risk,

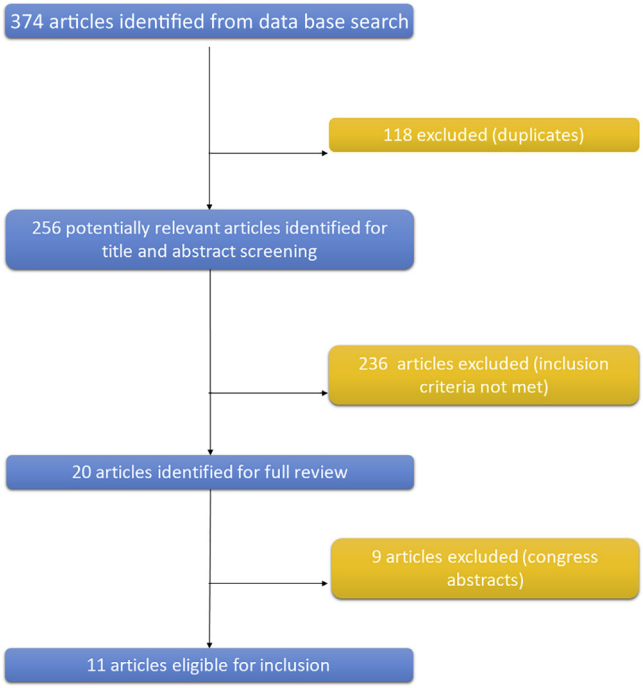

Figure 1. Flowchart of the included studies. [Color figure can be viewed at www.neuromodulationjournal.org]

or unclear. In the case of disagreement, a consensus was reached, or a third party was consulted.

Data Extraction

Data were extracted using an extraction form. Characteristics reported in each study were noted; these included pain model used, rat strain, study groups, lead placement, SCS settings, and SCS duration. Furthermore, outcome measurements were extracted, which included the effects of SCS on pro- and anti-inflammatory cytokines, microglia, and astrocyte markers. We classified these effects as inhibition or decrease, no change, upregulation or increase, and not known.

RESULTS

Using the online search, 374 articles were identified as eligible for this review (Fig. 1). Of these articles, 118 were excluded because of duplications. A total of 236 articles were excluded because the inclusion criteria were not met, and nine were excluded because they were poster abstracts. A total of 11 articles were eligible for inclusion (Fig. 1).

Characteristics of Included Studies

The included studies and relevant characteristics are depicted in Table 1. The articles show many similarities, such as the animal strain and pain model used. On the contrary, variability exists because some studies describe a relatively short induction time of the neuropathic pain model as related to the start of SCS treatment: after three to five days,[29,32–36] whereas other studies wait up until 14,[37,38] 18,[39,40] or even 36 days[41] before stimulation is started. Furthermore, the stimulation duration varies over the studies, ranging from a single session of six hours of stimulation[36] to a treatment based on 72 hours of continuous stimulation.[32,35] To understand the effect of various SCS paradigms and/or frequency of SCS and their related mechanism, the effects of the following SCS settings are described: Con-SCS (50–60 Hz),[29,32–41] HF-SCS (>500 Hz),[29,33,34] low-frequency SCS (LF-SCS) (<4 Hz),[39] and DTM-SCS[29,33,34] (which is essentially a variable combination of Con- and HF-stimulation).[30] Furthermore, lead placement was comparable in all articles (T13–L2),[29,32–35,37,39–41] except for one study, where leads were implanted more caudally (L4–L5).[36] One article did not specify the location of the leads.[38] In addition, outcome measurement or analysis for determination of central inflammatory markers and/or glial markers varies between either protein or gene expression levels. Moreover, some studies use general protein or genetic markers for glial cell activation such as IBA-1, OX-42, GFAP, or MCP-1,[36,39,40] which indirectly correlate with the inflammatory balance, whereas other articles describe the use of transcriptomic or proteomic analysis and more specifically identified glial or inflammatory-related markers such as p-p38 MAPK, TNF-α, TLR4, or IL-1β.[29,32–35,37–41]

RoB Analysis

The RoB was assessed using the SYRCLE RoB tool for animal studies (Table 2).[31] From this analysis, it can be concluded that randomization (sections 1, 4, and 6) was generally poorly reported. Also, concealment (section 3) and blinding of the outcome assessor (section 7) were poorly described. In contrast, sufficient blinding of the experimenter was often noted (section 5). Predominantly all baseline characteristics were adequately reported (section 2), and studies were mostly free of selective outcome reporting (section 9). Moreover, missing data were poorly (or not) described (section 8), and articles suffered from a potential other bias, especially owing to conflict of interest, because studies were often financially supported by company funding (section 10).

Effect of Experimental Neuropathic Pain and SCS Paradigms on Central Inflammation and Glial Cell Activity/Expression in the Spinal Dorsal Horn

The results of induction of the neuropathic pain model (with or without sham stimulation) on the expression of pro- and anti-inflammatory cytokines, microglia markers, and astrocyte markers are depicted in Table 3. The effects of induction of neuropathic pain using various experimental models like chronic constriction injury, sciatic nerve injury, or paclitaxel-induced peripheral neuropathy tend to result in an increase in the proteomic and transcriptomic profile toward proinflammatory cytokines.[33,34,40] At the same time, a decrease in the RNA levels of anti-inflammatory cytokines is noted.[34,40] All studies included in this review report that the expression of microglial markers, which include p-p38 mapk, OX42, TLR4, NF-κB, proteomic and genomic profiles, and IBA-1, is increased after the lesion of the peripheral nerve and the induction of the neuropathic pain model.[29,32–41] Furthermore, the induction of neuropathic pain has shown to result in a significant increase in astrocyte marker levels, which include transcriptome analysis, *Gfap*, and *Mpc-1* markers.[33,37,39–41] It needs to be stressed that not all studies reported such a difference in the activity of these astrocyte markers.[32,36]

Con-SCS in animals with chronic neuropathy for three hours on three consecutive days or 48 hours continuously was shown to result in an increase in transcriptomic profiles toward a proinflammatory state.[33,34] Furthermore, an increase in genes that

Table 1. Study Characteristics.

Author (year)	Pain model	Rat strain	Onset/duration SCS	SCS protocol	Lead placement	Outcome measurements
Cedeño et al[33] (2020)	SNI	♂ SD (275–315 g)	48 h of stimulation, 5 d post injury/lead implantation	Con: 50 Hz (150 ms PW) HF: 1200 Hz (50 ms PW) DTM: LF + HF	L1-L2	Transcriptomics
Sato et al[39] (2014)	SNI	SD (250–350 g)	14 d post SNI, 6 h of stimulation, 4 d in a row	Con: 60 Hz 90% MT LF: 4 Hz 90% MT	L1-L2	IHC: OX42 & p-p38 MAPK (microglia), GFAP & MCP-1 (astrocytes)
Shinoda et al[36] (2020)	SNI	♂ SD (6-wk-old)	6 h stimulation 3 d post SNI	Con: 60 Hz, 240 μs PW, 80% MT	L4-L5	IHC: IBA1(microglia) & GFAP (astrocytes)WB: IBA1(microglia)
Shu et al[40] (2020)	CCI	♂ SD	3 h/d, day 18-20 post CCI	Con: 50 Hz, 0.2 ms PW, 80% MT	T13-L1	IHC: GFAP (astrocytes), OX42 (microglia). PCR: *Gfap* (astrocytes, *Ox42* (microglia), *Inos*, *Cd16*, *Cd32*, *Arg1*, *Cd163*, *Tgf-b*, *Tnf-a*, *Il-b* (pro inflammatory markers. *Il-4, Il-10* (anti-inflammatory markers).
Sivanesan et al[37] (2019)	PIPN	♂ SD	8 h/d, 14 d Paclitaxel injection after 1, 3, 5 and 7 d	Con: 50 Hz, 0.2 ms PW, 80% MT	T13-L1 spinal level	RNA sequencing
Smith et al[34] (2021)	SNI	♂ SD	48 h of stimulation, 5 days post injury/lead implantation	Con: 50 Hz (150 ms PW) HF: 1200 Hz (50 ms PW) DTM: LF + HF	L1-L2	Transcriptomics
Stephens et al[41] (2018)	CCI	♂♀ SD	3 d, 2 session/d 120 min/ sesssion day 36–38 post CCI	Con: 50 Hz, 0.2 ms PW, 80% MT	T13-L1 spinal level	RNA-sequencing
Tilley et al[35] (2021)	SNI	♂ SD	72 h of stimulation, starting 4 d post SNI	Con: 50 Hz 70% MT	L1-L2	proteomics
Vallejo et al[29] (2020)	SNI	♂ SD	48 h of stimulation, 5 d post injury/lead implantation	Con: 50 Hz (150 ms PW) HF: 1200 Hz (50 ms PW) DTM: LF + HF	L1-L2	RNA-sequencing
Vallejo et al[32] (2016)	SNI	♂ SD	72 h of stimulation, starting 4 d post SNI	Con: 50 Hz, 20 us PW, 70% MT	L1-L2 spinal level	Microarray analysis
Yuan et al[38] (2014)	CCI	♂ SD	30 min, for 3 d, 14 d post CCI	Con: 50 Hz, 200 ms PW, 66% MT	Not specified	WB: TLR4 NF-kB p65. PCR: *Tlr4*, *Nf-kB*. IHC: NF-kB p65. Elisa: IL-1B, IL-6, TNF-a

CCI, chronic constriction injury; IHC, immunohistochemistry; MT, motor threshold; PCR, polymerase chain reaction; PIPN, paclitaxel-induced peripheral neuropathy; PW, pulse width; SD, Sprague Dawley; SNI, sciatic nerve injury; WB, Western blotting.

Table 2. RoB Assessment.

SYRCLE's RoB	1	2	3	4	5	6	7	8	9	10
	Selection bias 1	Selection bias 2	Selection bias 3	Performance bias 1	Performance bias 2	Detection bias 1	Detection bias 1	Attrition bias	Reporting bias	Other potential Bias
Cedeño et al[33] (2020)	⊖	✓	⊖	⊖	⊖	⊖	⊖	⊖	✓	⊖
Sato et al[39] (2014)	⊖	⊖	⊖	⊖	⊖	✓	⊖	⊖	✓	✗
Shinoda et al[36] (2020)	⊖	✓	⊖	⊖	✓	✓	✓	✗	✓	✓
Shu et al[40] (2020)	⊖	✓	⊖	⊖	✓	⊖	⊖	⊖	✓	⊖
Sivanesan et al[37] (2019)	⊖	⊖	⊖	⊖	✓	⊖	⊖	✗	✓	⊖
Smith et al[34] (2021)	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	✓	⊖
Stephens et al[41] (2018)	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	✓	⊖
Tilley et al[35] (2021)	⊖	✓	⊖	⊖	✓	⊖	⊖	⊖	✗	✗
Vallejo et al[29] (2020)	⊖	✓	⊖	⊖	✓	⊖	⊖	✗	✓	✗
Vallejo et al[32] (2016)	⊖	✓	⊖	⊖	✓	⊖	⊖	✗	✓	⊖
Yuan et al[38] (2014)	⊖	✓	⊖	⊖	✓	⊖	⊖	✓	✓	✓

1: ✓ = adequate randomization; ⊖ = randomization but no details; ✗ = no evidence of randomization. 2: ✓ = all baseline characteristics given; ⊖ = not all baseline characteristics given; ✗ = baseline characteristics not given. 3: ✓ = evidence of adequate concealment of groups; ⊖ = no information on concealment allocation; ✗ = evidence of inadequate concealment allocation. 4: ✓ = evidence of random housing of animals; ⊖ = unknown if housing arrangement was random; ✗ = no information about housing agreement at all. 5: ✓ = evidence of caregivers blinded to intervention; ⊖ = unknown if caregivers were blinded; ✗ = evidence of inadequate blinding of caregivers. 6: ✓ = evidence of random selection for assessment; ⊖ = unknown if assessment was randomly selected; ✗ = evidence of non-random selection for assessment. 7: ✓ = evidence of assessor blinded to intervention; ⊖ = unknown if assessor were blinded; ✗ = evidence of inadequate blinding of assessor. 8: ✓ = explanation of animal missing data; ⊖ = no information if all animals were included in final analysis; ✗ = no explanation of missing animal data. 9: ✓ = free of selective reporting based on methods/results; ✗ = selective reporting. 10: ✓ = free of other high bias risk; ⊖ = insufficient data to determine risk of other bias; ✗ = existence of problems with potential for high risk of bias.

Table 3. Effect of Various SCS Paradigms on Activation and Expression of Pro- and Anti-inflammatory Cytokines, Microglia, and Astrocytes.

Paradigm	Pro-inflammatory cytokines	Anti-inflammatory cytokines	Microglia	Astrocytes
Model/sham SCS	⊕ [34,38] ◎ [40]	⊖ [40]	⊕ [29,32–41]	⊕ [33,37–41] ◎ [32,36]
Con	⊕ [33,34,40] ⊖ [38]	◎ [40] ⊖ [34]	⊕ [32,42,37,40,41] ⊖ [29] ⊖ [34–36,38,39]	⊕ [37,41] ◎ [32,33,40] ⊖ [36,39]
LF	?	?	⊖ [39]	⊖ [39]
HF	⊖ [34]	⊕	⊖ [29,33,34]	⊖ [33]
DTM	⊖ [34]	⊕	⊖ [29,33,34]	⊖ [33]

⊖ = inhibition or decrease; ◎ = no change; ⊕ = upregulation or increase; ? = unknown.

express proinflammatory cytokines *Il-1b* and *Tnf-α* in the spinal dorsal horn was reported after three days of three hours per day of Con-SCS.[40] On the contrary, short application of Con-SCS (three consecutive days for 30 minutes) was shown to result in a decrease in proinflammatory cytokines.[38] The presence of anti-inflammatory cytokines in the spinal dorsal horn, measured with the use of transcriptomics, tends to decrease after 48 hours of Con-SCS.[34] On the contrary, the messenger RNA (mRNA) levels of identified anti-inflammatory molecules *Il-4* and *Il-10* were not changed after three days of three hours per day Con-SCS.[40]

The effects of Con-SCS, varying from three days of three hours per day to 72 hours of duration, on microglia marker expression in the spinal dorsal horn have been shown to increase based on transcriptomic profiles or mRNA analysis of *Ox42*, *Inos*, Cd16, and *Cd32*.[29,32,33,37,40,41] However, one article reports a weak decrease in the transcriptomic profile of the activated microglia after 48 hours of Con-SCS.[34] Moreover, even a significant decrease in microglia markers after three consecutive days of 30 minutes and 48 hours of continuous Con-SCS by proteomic analysis or p-p38 MAPK, OX42, TLR4, NF-κB, MAPK10, and IBA1 protein levels have been noted.[35,36,38,39] Short application of Con-SCS (three days of 30 minutes) resulted in a decrease in mRNA levels of microglia markers *Tlr4* and *Nf-κB*.[38]

An increase in the transcriptome related to astroglial markers was noted after three days of four hours per day and 14 days of eight hours per day of Con-SCS.[37,41] On the contrary, six hours of Con-SCS has been shown to result in a decreased activation of GFAP astrocyte marker.[36,39] Furthermore, no changes in astrocyte markers have been reported after 48 hours, 72 hours, and three days of three hours per day of Con-SCS.[32,33,40]

LF-SCS (six hours for four days) resulted in a decrease in general microglia and astrocyte markers OX-42, GFAP and MCP-1.[39] No data on the effects of LF-SCS on pro- and anti-inflammatory cytokines have been reported.

HF-SCS for 48 hours has been shown to result in a decrease in transcriptomic profiles of proinflammatory cytokines, microglia, and astrocyte markers in the spinal dorsal horn.[29,33,34] A similar effect was noted with the use of 48 hours of DTM-SCS, although the effect might even be more pronounced than with HF-SCS.[29,33,34] Interestingly, one study reported an increase in anti-inflammatory markers after 48 hours of HF- and DTM-SCS.[34]

Study Characteristics and the Effects of Con-SCS on Microglia and Astrocyte Expression and/or Activity

The results of the studies on the effect of Con-SCS on microglia and astrocyte marker expression report either an increase, decrease, or no change. To further understand the conflicting results, the characteristics of each individual study as related to the effects on the microglia and astrocytes are summarized in Table 4. Although there is variation in the location of the SCS electrode, duration and timing of the treatment, frequency, pulse width, and intensity of the Con-SCS paradigm, these differences cannot explain the conflicting results on measured microglia or astrocyte expression/activity. Nevertheless, a relation between the method used to assess microglia markers and the effect of Con-SCS is noted (Table 4): When RNA sequencing or mRNA analysis of identified inflammatory markers *Cd16*, *Cd32*, and *iNos*[32,33,40] is used, an increase in microglia expression or activity is noted after Con-SCS. With the use of proteomic profiling and protein levels of IBA-1, TLR4, or NF-κB, a decrease in microglia-related expression or activity is noted with Con-SCS.[35,36,38,39] However, very short stimulation with Con-SCS (three days of 30 minutes per day) seems to result in a decrease in both microglial mRNA and protein markers *Tlr4* and *Nf-κB*.[38] Furthermore, Con-SCS tends to result in a decrease in immunohistochemical staining intensity of the microglia markers OX42, p-p38 MAPK, and IBA-1.[36,39,40] A similar effect on the astrocytes was noted, where Con-SCS tends to result in an increase in astrocyte-related RNA profiles[37,41] and at the same time a decrease in protein marker GFAP.[36]

DISCUSSION

To our knowledge, this is the first systematic review on the use of SCS and modulatory effects on the central inflammatory response in animal models for neuropathic pain. In general, the neuropathic pain models used show an upregulation of proinflammatory markers, microglia, and astrocytes and at the same time a downregulation of anti-inflammatory markers in the spinal dorsal horn nociceptive network. The use of Con-SCS results in an upregulation of proinflammatory cytokines and, concurrently, a downregulation of anti-inflammatory cytokines. Con-SCS furthermore results in a decrease in microglia-related protein expression or activity, whereas microglial-related mRNA expression is generally increased. HF-SCS and DTM-SCS tend to downregulate proinflammatory cytokines, microglia, and astrocytes. LF-SCS results in a decrease in general microglia and astrocyte markers OX-42, GFAP, and MCP-1, but more research is needed to substantiate these results and to study the detailed effects on pro- and anti-inflammatory cytokines.

The results from this systematic review suggest that DTM- and HF-SCS are better in restoring the inflammatory imbalance in animals with neuropathic pain than Con-SCS. This may underlie the beneficial pain-relieving effects of these paradigms.

Effects of Neuropathic Pain on the Pro- and Anti-inflammatory Balance in the Spinal Dorsal Horn

The results of the studies included show that induction of neuropathic pain results in an increased proteomic and

Table 4. Characteristics of the Studies and Effect of Con-SCS on Microglia Activity/Expression.

Author (year)	Location (spinal cord)	Duration	Start SCS	Frequency (Hz)	Pulse width (μsec)	Intensity (% of MT)	Method	Effect on microglia	Effect on astrocyte
Cedeño et al[33] (2020)	L1-L2	48 h	5 d post SNI	50	150	70	RNAseq	⊕	⊙
Sato et al[39] (2014)	L1-L2	6 h, for 4 d	14 d post SNI	60	?	90	IHC	ⓘ	ⓘ
Shinoda et al[36] (2020)	L4-S1	6 h	3 d post SNI	60	240	80	WB & IHC	ⓘ	ⓘ
Shu et al[40] (2020)	T13-L1	3 h, for 4 d	18 d post CCI	50	200	80	IHC & rtPCR	⊕	⊙
Sivanesan et al[37] (2019)	T13-L1	8 h/d for 14 d	Day before PIPN	50	200	80	RNAseq	⊕	⊕
Smith et al[34] (2021)	L1-L2	48 h	5 d post SNI	50	150	70	Transcriptomics	ⓘ	NA
Stephens et al[41] (2018)	T13-L1	120 h 2× per day, for 3 d	36 d CCI	50	200	80	RNA-seq	⊕	⊕
Tilley et al[35] (2021)	L4-L5	72 h	4 d post SNI	50	20	70	Proteomics	ⓘ	NA
Vallejo et al[29] (2020)	L1-L2	48 h	5 d post SNI	50	150	70	RNAseq	⊕	NA
Vallejo et al[32] (2016)	L1-L2	72 h	4 d post SNI	50	20	70	RNAseq	⊕	⊙
Yuan et al[38] (2014)	?	30 min for 3 d	12 d post CCI	50	200	66	qPCr, WB	ⓘ	NA

ⓘ = inhibition or decrease; ⊙ = no change; ⊕ = upregulation or increase.
IHC, immunohistochemistry; MT, motor threshold; NA, not available; qPCR, quantitative polymerase chain reaction; RNAseq, RNA sequencing; rtPCR, real time polymerase chain reaction; WB, Western blotting.

transcriptomic profile toward a proinflammatory state. Furthermore, a decrease in the anti-inflammatory markers IL-4 and IL-10 was noted. This is in line with literature reviews where an increase in proinflammatory cytokines and a decrease in anti-inflammatory cytokines were reported.[5,43,44] A prolonged increased expression of proinflammatory cytokines is known to induce neuropathic pain.[13,14] Furthermore, a decrease in anti-inflammatory cytokines also is related to the development and maintenance of neuropathic pain.[5] This disbalance between pro- and anti-inflammatory molecules as a result of peripheral nerve injury is crucial in the development and chronification of neuropathic pain. The reported disbalance in inflammatory molecules is further supported by the increased expression of microglia and astrocyte markers, suggesting a further activation and participation of these glial cells in the development of neuropathic pain. The microglia and astrocytes are crucial in the development and maintenance of neuropathic pain and are pivotal for the inflammatory balance. Altogether, the results show that peripheral nerve injury pushes the central inflammatory balance in the spinal dorsal horn toward a proinflammatory state, and this may facilitate the development and maintenance of neuropathic pain.

Con-SCS and Modulation of the Central Inflammatory Balance

The effects of Con-SCS on identified pro- and anti-inflammatory markers and its balance are counterintuitive. Con-SCS has been shown to alleviate pain in animal models, and this would suggest a restoration of the central inflammatory balance between pro- and anti-inflammatory molecules. From this, a decrease in proinflammatory markers and an increase in anti-inflammatory markers after application of Con-SCS in chronic neuropathic pain are expected. However, based on this review, it is concluded that Con-SCS does not result in a decreased proinflammatory state but instead results in an increase in proinflammatory molecules in the spinal dorsal horn of rats with chronic neuropathy (Table 3).[33,34,40] It must be noted that in contrast to longer stimulation, very short stimulation did result in a decrease in proinflammatory cytokines.[38] However, these results, in general, implicate that the mechanism involved in Con-SCS–induced pain relief is likely not related to an accelerated restoration of the disbalance between pro- and anti-inflammatory molecules in the spinal dorsal horn. Previous research shows that the mechanism underlying Con-SCS and pain relief acts through the modulation of GABAergic as well as serotonergic inhibition of the spinal nociceptive network.[28,42] Clearly, the fact that Con-SCS does activate the proinflammatory response in the spinal dorsal horn does not further add to its pain-relieving effect and might even be counteractive in the long term.

The increased effect of Con-SCS on the inflammatory balance toward a proinflammatory state is further supported by the effects on gene expression of microglia markers.[32,33,40] This is with the exception of very short stimulation (30 minutes for three days), which resulted in a decrease in the mRNA levels of microglia-related markers *Tlr4* and *Nf-κB*.[38] This differential effect of short-term stimulation may be a possible explanation for the reported wash-in effect of Con-SCS.[45] Interestingly, as can be deduced from Table 4, Con-SCS results in a decrease in microglial marker protein levels.[35,36,38] The microglia are known to be crucial in the development phase of neuropathic pain.[5] Gene-expression change is a fast response, a matter of hours, and can stay changed for several days.[46,47] Protein-expression changes are slower and prolong longer.[5,43] It could therefore be expected that short-term Con-SCS (hours) would lead to a decrease in microglia marker gene

expression, and long-term Con-SCS (days) also would lead to a decrease in protein expression markers. In the available literature, the shortest stimulation period is 30 minutes for three consecutive days,[38] which indeed results in a decrease in both microglia-related mRNA and protein markers. Longer stimulation, starting at 48 hours continuously or three hours for four days, results as expected in a decrease in protein levels.[36,39] However, this is generally not reflected in gene expression levels.[32,33,40] A possible explanation for the results could be that not all genes transcribed will be translated to proteins. Based on the results of this review, Con-SCS potentially interferes with the translation of these genes and may thereby reduce microglial activity. The latter must be studied using an approach that investigates both gene and protein expression after Con-SCS.

Effects of LF-, HF-, and DTM-SCS on the Inflammatory Balance

Use of HF- and DTM-SCS results in a decrease in proinflammatory markers, microglia, and astrocytes after stimulation.[29,33,34] In contrast with Con-SCS, these paradigms thus result in a decrease in gene expression and proteomic profiles of microglia and proinflammatory markers.[32,33,37,40,41] Behavioral data reported a better pain alleviation with the use of not only HF- but especially DTM-SCS than with the use of Con-SCS.[29] It must be emphasized that these findings are based on a few studies and need further confirmation and investigation.

LF-SCS showed a decrease in staining intensity of microglia and astrocyte immunohistochemical markers after four days of six hours of stimulation. This is in line with the results with Con-SCS in this review.

For now, these results from our review implicate that HF- and DTM-SCS are superior to Con-SCS in restoration of the central inflammatory balance, and this may underlie a possible better pain relief as reported in various animal behavior studies.[29,32,35]

Glial cells are known to be affected by electrical stimulation. Their membranes can be depolarized by external electric fields.[48] The effects of the different paradigms on the depolarization of the microglia in the spinal cord are not known. Nevertheless, based on the findings of this review, different paradigms and stimulation frequencies might have different effects on the depolarization of glial cells, which may explain the different effects on the inflammatory balance.

Clinical Studies on SCS and Central Inflammatory Response

The important role of the inflammatory balance and glial cells in the development and maintenance of neuropathic pain has previously been described.[5,43] However, research describing the effects of SCS on inflammatory markers in patients experiencing neuropathic pain is scarce but not absent. An analysis of the cytokines from artificial skin blisters before and after Con-SCS (40 Hz) in patients with CRPS showed a significant decrease in the proinflammatory cytokine IL-15 after stimulation.[49] Furthermore, other proinflammatory cytokines (including IL-2, IL-12, and INF-γ) showed a trend toward decreased levels.[49] Moreover, the anti-inflammatory cytokines IL-4, IL-5, and IL-10 also showed a trend toward decreased levels over time.[49] Protein measurements of the cerebrospinal fluid (CSF) showed an increase in dickkopf-related protein 3, a contributor to an immunosuppressive microenvironment.[50] These results show that neuromodulation techniques such as SCS might be able to restore the central inflammatory balance by decreasing pro- but not anti-inflammatory cytokine expression in patients with neuropathic pain. These results are partly in contrast with the findings of this review because we also find a decrease in anti-inflammatory cytokines but an increase in proinflammatory cytokines. This difference may be explained by the location of the examination because in patients, it is not possible to measure directly in the spinal cord. Based on the findings of this review, it is pivotal to investigate the effect of different SCS paradigms in a clinical setting as related to the modulation of central inflammatory balance. Understanding the effect of different SCS paradigms on the inflammatory balance may improve the clinical outcome of this therapy.

Limitations and Methodologic Quality of the Studies

The major limitation with the reviewed studies is mainly the methodologic quality assessment. Most RoB items are scored "unclear" owing to poor reporting. In general, blinding and randomization were poorly reported, as well as missing outcome data. Reporting of the exact methods used is required in future research to improve the quality of animal studies. Furthermore, the study characteristics vary between most studies, making it difficult to directly compare them. Reporting of the characteristics was adequate, making it possible to identify explanations for differences between studies. Because of these limitations, the results of the studies as included in this systematic review should be interpreted with caution. Furthermore, to our knowledge, the effects of LF-SCS on the inflammatory balance in neuropathic pain were only researched in one published article, and the effects of other paradigms such as Burst-SCS, closed-loop, and 10 kHz have not yet been studied. Owing to limited available clinical data, this review only focused on preclinical research. Future clinical research will not only provide insights into the clinical effects of SCS paradigms on the spinal inflammatory balance but also put the results of the experimental findings into perspective regarding translatability. Hence, clinical studies could, for example, focus on the analysis of inflammatory markers in CSF as related to SCS in neuropathic pain.

CONCLUSIONS

In summary, the preclinical studies included in this review report an imbalance toward a proinflammatory state in animals with neuropathic pain and an increase in glial cell markers. Con-SCS does further induce the proinflammatory state and not restore this central inflammatory imbalance in the spinal dorsal horn. The use of new SCS paradigms that use increased stimulation frequency, such as HF- and DTM-SCS, tends to result in a more optimal restoration of the central inflammatory balance between pro- and anti-inflammatory molecules and in an improved management of the central glial response and, with that, ultimately in better pain relief. The preclinical findings and effect of SCS paradigms not only need to be further confirmed with future animal studies but also may initiate new clinical studies, optimizing the treatment of patients with chronic neuropathic pain.

Authorship Statements

Thomas J. de Geus, Glenn Franken, and Elbert A.J. Joosten designed and conceptualized the study. Thomas J. de Geus, Glenn Franken, and Elbert A.J. Joosten determined and performed the systematic literature search. Thomas J. de Geus and Glenn Franken

performed the study inclusion and assessed the quality of the included manuscripts. Thomas J. de Geus wrote the manuscript. All authors have approved the final version of the manuscript.

How to Cite This Article

de Geus T.J., Franken G., Joosten E.A.J. 2022. Spinal Cord Stimulation Paradigms and Pain Relief: A Preclinical Systematic Review on Modulation of the Central Inflammatory Response in Neuropathic Pain. Neuromodulation 2022; ■: 1–10.

SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.04.049.

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COMMENT

This is a very important and complete overview that gives a perfect overview of what we know now of the impact of inflammation and how we can modulate this with neuromodulation. This is the basic for future research in SCS.

Jan Kallewaard, MD, PhD
Arnhem, The Netherlands