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# Response to spinal cord stimulation in variants of the spared nerve injury pain model

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**Abstract**

Spinal cord stimulation (SCS) is a treatment given to patients with drug-resistant neuropathic pain, in particular pain resulting from peripheral nerve injury. However, the reasons why some patients develop neuropathic pain and why SCS is not effective in all patients with this chronic pain are not fully understood. The present study compares the response to SCS and the yield of neuropathic animals in variants of the spared nerve injury (SNI) model introduced by Decosterd and Woolf (I. Decosterd, C.J. Woolf, Spared nerve injury: an animal model of persistent peripheral neuropathic pain, Pain 87 (2000) 149–158). Sprague–Dawley rats were prepared with various types of lesions of different branches of the sciatic nerve and then tested for paw mechanical hypersensitivity. A miniature electrode system for SCS was implanted at the T10-T11 vertebral level. Stimulation was applied in awake, freely moving animals with parameters comparable to those employed clinically. Suppression of paw hypersensitivity was considered a positive response to SCS. The incidence of mechanical hypersensitivity ("allodynia") in the different models was: SNI 53%; peroneal axotomy 45%; tibial axotomy 68%; tibial tight ligation 73% and partial tibial tight ligation 50%. "Mirror phenomena" with contralateral paw hypersensitivity was present in about 20% of the animals. The response to SCS differed between models with the lowest response rate in the original SNI model (8%) while the others demonstrated rates in the order of 40–50%. There was a tendency that the efficacy of SCS in suppressing allodynia was inversely related to the severity of hypersensitivity. In conclusion, modifications of the SNI model provide a reproducible incidence of neuropathic hypersensitivity and an increased responsiveness to SCS. These variants may prove suitable for future research on the mechanisms involved in pain relief with SCS.


*Keywords:* Allodynia; Neuropathic pain; Spared nerve injury model; Rat; Spinal cord stimulation

Numerous animal models of peripheral neuropathy have been developed that involve injury to the main trunk of the sciatic nerve [1,3]. In contrast, the so-called spared nerve injury model (SNI) [6] is produced by sectioning the tibial and common peroneal branches of the sciatic nerve, while leaving the sural and the saphenous nerves intact. Lee et al. [13] reported that selective injury to the sural or tibial nerves produced the highest incidence of prominent and long-lasting signs of neuropathy. Recently, variants of the latter model have been further explored [10].

Over the years we have conducted a series of experimental studies aimed at elucidating neurophysiological and biochemical mechanisms involved in the relief of neuropathic pain by spinal cord stimulation (SCS). In these studies different rat models of mononeuropathy have been employed [3]. Animals displaying hypersensitivity to innocuous tactile or thermal stimuli, "allodynia", have been subjected to SCS applied with "clinical stimulation parameters", which can produce suppression of the hypersensitivity. However, the number of responders has been highly variable, partly dependent on the nerve injury model used. For example, animals with photochemically induced ischemic sciatic nerve lesion (the Gazelius model) [9] have been almost invariably unresponsive to SCS [3,26].

The SNI model has been reported to yield a very high incidence of robust, long-lasting signs of neuropathy, and it has also been used in studies of neuropathic pain mechanisms, drug testing and electrical CNS stimulation (e.g. [7,24,27]) Therefore, we performed several pilot SCS experiments using this model, but it

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appeared that these animals rarely responded with the expected "allodynia" suppression. The present study was undertaken with the aim of exploring whether variants of the SNI model are more likely to respond to SCS. A further aim was to examine a possible relationship between the degree of hypersensitivity and the effect of SCS.

The study was approved by the local ethics committee for animal research. Male adult Sprague–Dawley rats (200–230 g, B&K Universal AB, Sollentuna, Sweden), housed in a 12-h light/dark cycle with free access to food and water, were used.

All surgical procedures were performed under general anesthesia induced with 4% halothane and maintained with 1–2% of this anesthetic in $O_2$/air (1:1) delivered by an open-mask system at a rate of approximately 2 l/min. Body temperature was maintained at $37.5 \pm 0.5\,C^{\circ}$ by using an automatic heating device (CMA/150, CMA Microdialysis AB, Stockholm, Sweden).

The nerve lesions were produced unilaterally on the left hind limb. The method of creating the original SNI model has been described in detail previously [6]. After making a skin incision the sural, common peroneal and tibial nerves, were exposed. The tibial and common peroneal nerves were then tightly ligated with 6/0 silk (Ethicon, Germany) and 3–4 mm of the nerves distal to the ligation were removed (SNI). Alternatively, only the common peroneal (PA) or the tibial (TA) nerves was tightly ligated and sectioned (axotomy). In another variant, the tibial nerve was ligated without sectioning (TL) or merely 1/3 to 1/2 of its diameter was ligated (PTL).

Five groups of animals were created: (1) 30 with SNI; (2) 20 with PA; (3) 57 with TA; (4) 26 with TL; (5) 20 with PTL. An additional group of five animals was subjected to a sham operation which merely exposed the common peroneal and tibial nerves. The animals were tested for hind paw sensibility after 1 week of habituation to the laboratory environment. Implantation of a spinal electrode was performed 7–11 days after nerve injury when the presence of robust hypersensitivity was confirmed. One testing session was performed on the day before electrode implantation to obtain basal values. The rats were then tested 2, 4, 7 and 11 days after surgery and subsequently once a week for up to 15 weeks. Not all rats that presented with mechanical hypersensitivity according to the predetermined criteria (see below) could be followed with regular testing to the time end-point because some were lost as a result of fractured electrode leads or, in a few cases, adverse neurological sequelae after spinal electrode implantation or wound infection.

All tests were performed in a quiet room where the animals were also housed. The same experienced team member performed all the tests. During testing, the rats were placed in a circular, plexi-glass cage with a metal mesh floor to allow for stimulation of the lateral plantar surface of the paw (innervated by the spared sural nerve). The animals were adapted to the testing situation for at least 15 min before the session started.

A series of von Frey nylon monofilaments with stiffness corresponding to 0.8, 1.5, 2.7, 4.5, 5.5, 7.0, 8.5, 10, 12.5, 15, 18.5, 22, 26 and 30 g bending force (MARSTOCKnervetest®, Marburg, Germany) were applied to the lateral plantar surface of both hind paws in ascending and descending order (up-and-down method). An advantage of these filaments is that their tip diameters are identical (0.5 mm). A brisk withdrawal of the hind limb was considered a positive response. Similarly to our previous studies the withdrawal threshold was defined as the application force at which the rat withdraws the paw three times out of five consecutive stimuli. A withdrawal threshold of 5.5 g or less was classified as representing "allodynia". This upper threshold level to define "allodynia" has been used in our previous studies [4,25] and corresponds to that specified in several other, comparable reports (e.g. [2,12]). A further reason is that this stimulation intensity is presumably subthreshold for activation of cutaneous C-nociceptors [14].

A small laminectomy was performed at T11 and a SCS cathode (oval silver disc with a larger diameter of 2 mm; thickness 0.25 mm) was positioned onto the dura. The anode (4 mm silver disc) was placed subcutaneously on the chest wall. Two connecting wires (teflon-coated, plaited stainless steel wire) with micro-contacts were passed subcutaneously to the neck. Rats displaying adverse signs of neurological sequelae after electrode implantation were euthanized.

The SCS parameters (50 Hz and 0.2 ms) were selected to be comparable to those used clinically. The stimulation intensity was 90% of that evoking a motor response (a local twitching of abdominal muscles and/or stretching of hind limbs), as determined individually in each animal 20 min before the SCS sessions began in the observation cage.

The effect of SCS on the withdrawal thresholds to mechanical stimuli was first assessed 2 days after implantation of the electrode system. The animals were placed in the plexi-glass testing cage, and the SCS electrodes were connected to the stimulation unit via an electric swivel mounted on a balance arm enabling the animal to move around freely. The baseline thresholds to the von Frey filaments were assessed 20 min before SCS. SCS was then applied for 30 min. The thresholds were assessed just before stimulation and then in 10 min intervals up to 100 min. The testing was terminated when the thresholds at two consecutive determinations had returned to the levels obtained before SCS. SCS-induced reduction of "allodynia" corresponding to a threshold increase to 15 g or more in the nerve-injured paw was regarded as a positive response. Normal intact animals rarely react to the application of filaments below 30 g bending force and never with a paw withdrawal comparable to the brisk response after nerve injury. In several recent studies 15–26 g filaments have been used as cut-off stimulation intensity [12,16,21], and therefore we selected the 15 g filament as a criterion to represent "normalization" of the sensitivity resulting from the SCS treatment.

Fisher's Exact Test was used to compare the rates of hypersensitivity to nerve injury and response to SCS responders between the different animal groups. Values of $p < .05$ were regarded as significant.

From a total of 153 operated animals, 93 (61%) developed mechanical hypersensitivity ("allodynia") which was most conspicuous on the lateral side of the nerve-injured hind paw. Nineteen (20%) of these allodynic rats also developed hypersensitivity in the contralateral paw ("mirror allodynia"). In the five sham-operated animals normal sensibility was retained in both hind paws. The incidence of allodynia in the different models

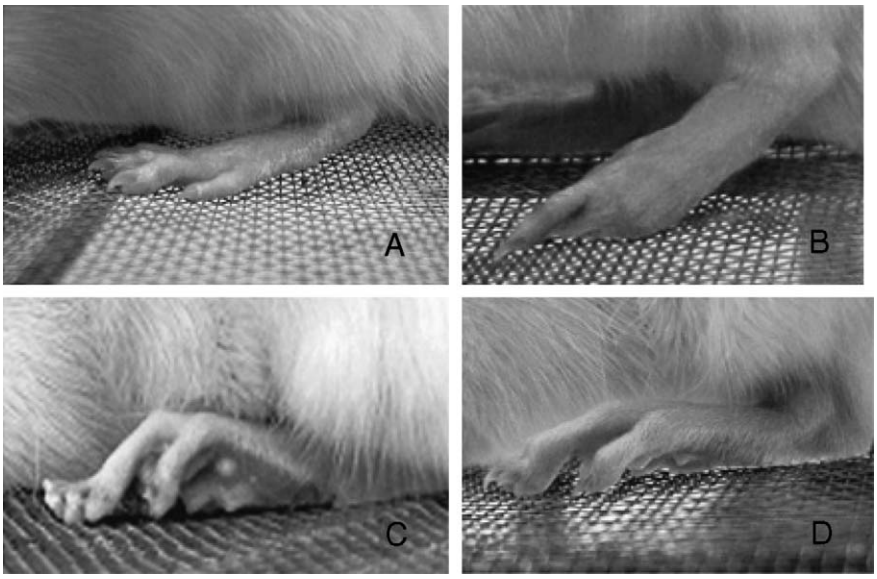


Fig. 1. Photographs of rat paw's position 24 h after nerve lesion. (A) In sham operated rats, the foot and toe pads on the operated side were pressed against the floor just the same as on the contralateral side. (B) In rats with peroneal axotomy, the affected paw had an inverted posture. (C and D) In SNI, tibial axotomy and tibial ligation rats, the affected paw instead presented an eversion posture, which was less prominent in some of the rats with partial tibial ligation (D).

about 2 weeks after surgery is shown in Table 1. There were no statistically significant differences between the groups but there was a tendency that tibial nerve ligation and axotomy produced a somewhat higher incidence of allodynia ($p > 0.05$, Fischer's Exact Test). In general, allodynia was present within 1 week after surgery. It stabilized after another week up to 10 days and peaked during the second or third week, persisting for 7–10 weeks except after partial tibial ligation where it did not last for more than about 3 weeks.

Regardless of whether or not mechanical allodynia was present the posture of the nerve-injured paw was conspicuously altered within 24 h after surgery in all the different models (Fig. 1). In rats with peroneal axotomy, the affected paw presented an inverted posture (Fig. 1B) and it was often dragged behind during locomotion, which made plantar testing for withdrawal difficult. In the SNI model and after tibial axotomy and tibial ligation, the affected paw instead demonstrated an eversion posture (Fig. 1C). A majority of the partial tibal ligation animals presented with a less prominent everted paw posture (Fig. 1D). It should be noted that "mirror" allodynia affecting the contralateral paw was never associated with any postural abnormality in that paw.

Severe allodynia (withdrawal threshold <1.5 g) often related to behavioral signs suggesting the presence of spontaneous pain: such animals seemed to avoid using the affected paw both as support and grooming at rest and during locomotion, and they could exhibit a sudden spontaneous, sustained withdrawal; they also frequently licked the paw.

The SCS system was successfully implanted in 57 rats with allodynia. Stimulation sessions were performed once weekly for up to 6–7 weeks, or as long as the allodynia persisted. Only three of the PA model rats were implanted because the inverted paw posture made it difficult to properly evaluate the effect, i.e. testing of the lateral part of the plantar paw in our examination cages, and these data are not included in the analyses.

In the present study the SCS effect on mechanical hypersensitivity was assessed only in the nerve-injured paw. The time courses of the SCS-induced suppressive effect on the mechanical hypersensitivity were similar in all the models, and a typical example (TA model) is shown in Fig. 2.

Table 1
Incidence of mechanical hypersensitivity in different nerve injury models

| | Rat model | | | | |
|---|---|---|---|---|---|
| | SNI | PA | TA | TL | PTL |
| No. operated | 30 | 20 | 57 | 26 | 20 |
| Incidence hypersenstivity (%) | 53 | 45 | 68 | 73 | 50 |
| Incidence mirror hypersenstivity (%) | 25 | 25 | 13 | 21 | 40 |

SNI: spared nerve injury [6]; PA: peroneal axotomy; TA: tibial axotomy; TL: tibial ligation; PTL: partial tibial ligation.

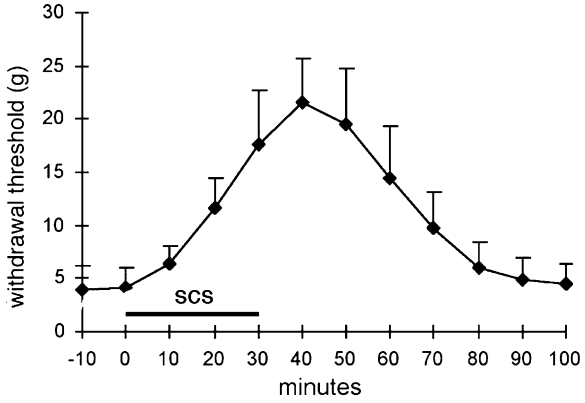


Fig. 2. Effects of SCS on the mechanical hypersensitivity represented by withdrawal thresholds in rats ($n = 10$) subjected to tibial axotomy. Data presented as mean and S.E.M.

Table 2
Rates of SCS responders in different models

| | Rat model | | | |
|---|---|---|---|---|
| | SNI | TA | TL | PTL |
| No. of SCS rats tested | 13 | 24 | 9 | 8 |
| No. of responders | 1 | 10 | 4 | 4 |
| Responder rate (%) | 8 | 42 | 44 | 50* |

* $p < 0.05$; compared with SNI group (Fischer's Exact Test).

Table 3
Rates of SCS responders at different time points

| | Weeks | | | | |
|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | ≥6 |
| No. of SCS sessions | 24 | 27 | 24 | 13 | 20 |
| Responder rate (%) | 17 | 19 | 21 | 39 | 35 |

Pooled data from all models (except SNI).

Only one of the tested 13 SNI rats could be classified as a responder (Table 2). The incidence of responders in the TA, TL, PTL groups was much higher although a statistically significant difference ($p < 0.05$, Fischer's Exact Test) was found only in the PTL group; there were no statistical differences between the TA, TL and PTL groups. Therefore, data from all models except from the original SNI could be pooled. The incidence of responders in the total number of SCS sessions was then analysed over time. There were no statistical differences between the time points (Table 3, Fischer's Exact Test).

In total, 158 sessions of SCS were performed. The sessions were pooled and divided into five groups according to the magnitude of the baseline withdrawal thresholds, and subsequently the number of positive SCS responses (threshold increase to ≥15 g) was determined. Compared with the 0.8 g group (0/43), the 2.7 g (5/35), 4.5 g (10/23), and 5.5 g (9/30) groups differed significantly (Fig. 3). We also analysed the relationship between

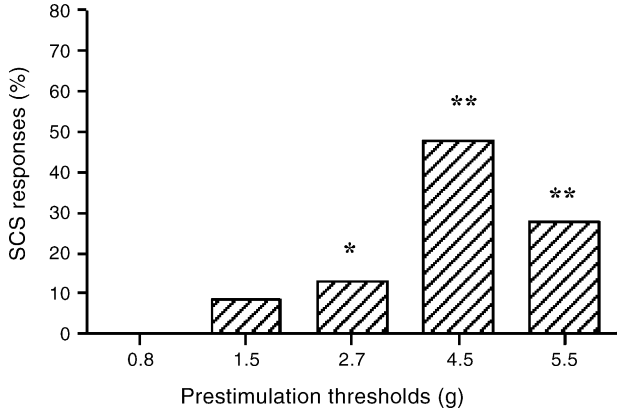


Fig. 3. Percent of positive SCS responses related to magnitude of prestimulation withdrawal thresholds. Compared with the 0.8 g group (0/43), the 4.5 g (10/23), 5.5 g (9/30) and 2.7 g (5/35) groups showed significant differences ($^{*}p < 0.05$, $^{**}p < 0.01$). Note that the numbers on the *Y*-axis do not refer to rats but to outcome in percent of the total number of stimulation sessions since most rats were tested several times, and one and the same rat could display somewhat different baseline withdrawal thresholds at different occasions.

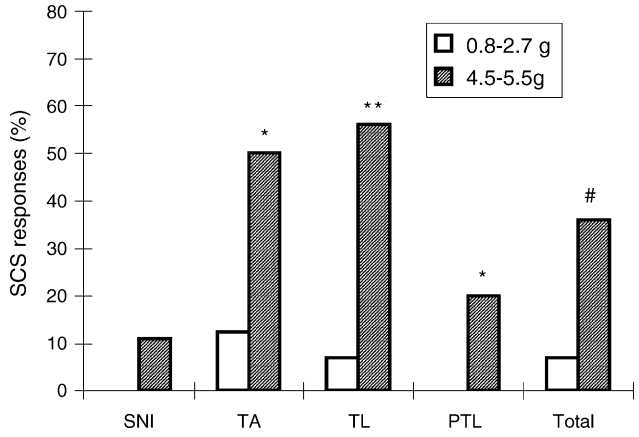


Fig. 4. Percent of positive SCS responses in two subgroups of withdrawal thresholds in the different models. The 0.8–2.7 g threshold group compared with that of 4.5–5.5 g differed significantly in the TA, TL ($^{**}p < 0.01$) and PTL ($^{*}p < 0.05$) models. Compared with the SNI model the pooled data of these three models ("Total") also differed significantly ($^{\#}p < 0.05$). PA: peroneal axotomy; TA: tibial axotomy; TL: tibial ligation; PTL: partial tibial ligation. (Numbers on the *Y*-axis, see legend to Fig. 3).

the prestimulation threshold values, and the likelihood of a SCS response in each of the different nerve injury models. For this, the threshold values were divided into two classes: 0.8–2.7 g and 4.5–5.5 g, respectively, in each model and related to the outcome of SCS. These results, in percent, are shown in Fig. 4. There were significant differences between the two threshold classes in all the models.

In the current study the overall incidence of hypersensitivity was about 60%, and this is higher than that recorded in our earlier studies using the Seltzer and the Bennett models [3,4,19]. In the original report on the SNI model by Decosterd and Woolf [6] virtually all the animals presented with neuropathic signs. The tibial injury nerve model, which is identical to the TA procedure in the present study, has also been reported to produce mechanical hypersensitivity in all animals [10]. There are several reasons for this differential occurrence of hypersensitivity; besides genetic (strain) and environmental factors, food composition, etc., there were differences in the testing protocol and criteria for classification of hypersensitivity ("allodynia"). Inadvertent lesioning of the sural nerve is also possible but a less likely cause of this difference. In line with our earlier studies [3,25] the criterion for allodynia was somewhat stricter then that applied in the original SNI study [6] in that we required a clear withdrawal be produced with three out of five stimuli instead of one out of five. The former proportion of positive responses for assessing the threshold value also has been used in another study utilizing the SNI model and then only about 80% were classified as hypersensitive [8].

Considering that in humans, injury to peripheral nerves only occasionally gives rise to evoked and/or spontaneous pain it is not unexpected that experimental nerve injury in rats does not always result in painful hypersensitivity; actually, a model and procedure resulting in a moderate symptom rate may appear more clinically relevant. Furthermore, chronic neuropathic pain due to nerve injury is associated with cutaneous hypersensitivity only in about 20% of the patients (e.g. [22]).

We failed to demonstrate any statistically significant differences in hypersensitivity incidence between the different models though there was a clear tendency that extensive lesioning (axotomy) of the tibial nerve was most effective in providing pronounced and long-lasting "allodynia" (cf. [10]).

The so-called mirror tactile hypersensitivity was recorded in a substantial proportion of the animals. In contrast, this phenomenon has not been observed neither in the original report on the SNI model nor in a study on different varieties of the same model [6,13]. However, mirror hypersensitivity was frequently recorded in a later study performed on the SNI model [8]. These contralateral effects following unilateral, peripheral nerve injury are poorly understood, and we have, as yet, no explanation why it was relatively common in the SNI variants described in the present study (cf. [15]; review, see [11]).

Rats subjected to injury of the sciatic nerve, its branches or the corresponding spinal nerves are often referred to as "models of neuropathic pain". However, as a rule these animals behave normally and rarely exhibit signs of ongoing pain. Therefore, the exaggerated responses to peripheral stimuli conceivably mimic evoked rather than spontaneous pain. The different types of nerve injury described here all resulted in characteristic changes of paw posture. It is highly probable that these changes are due to different types of motor axon injury and not primarily related to the presence of pain. At variance with an earlier study by Na et al. [20] a dissociation between motor deficit and pain is further supported by the observation that mirror hypersensitivity in the contralateral paw observed in our study was not associated with a change in paw posture.

A salient finding was that the SNI rats were considerably less likely to respond to SCS than were the other models examined. This was an unexpected finding in view of a recent publication where it was demonstrated that electrical stimuli applied to the dorsal column nuclei may significantly attenuate several signs of neuropathy in the SNI, as well as in the Bennett model [7]. However, in our studies the electrode was applied onto the spinal dorsal columns similarly to clinical practice. It is likely that electric stimuli applied at the level of the obex activate different neuronal circuits than does low thoracic SCS. It is presently not possible to determine definitely whether or not the chosen different stimulation targets account for the conflicting results in the two studies.

Previously we also reported that the Gazelius model, i.e. photochemically induced ischemic sciatic nerve lesion, which yields a consistently high incidence of mechanical and thermal allodynia, hardly ever responds to SCS [9,26]. In the SNI model at least 80% of the sciatic fibers are axotomized whereas in the TL and PTL models only about 50 and 30%, respectively, of the axons are injured (cf. [23]). Also the ischemic lesion in the Gazelius model presumably involves a large part of the sciatic fibers [9]. Thus, one possible factor influencing response probability may be the extent of axonal injury, and we hypothesize that the poor responsiveness to SCS in the SNI model is due to the large proportion of injured fibres. It should be noted in this context that the pharmacological profile of this model is somewhat different from most other models in that the tactile hypersensitivity responds poorly to gabapentin [5].

Clinically, pain due to peripheral nerve injury is a cardinal indication for SCS treatment [17]. A puzzling observation is that patients suffering such pain and presenting with seemingly almost identical symptomatology comprising abnormalities in sensitivity, may respond quite differently to SCS. It is tempting to hypothesize that the variable incidence of SCS-responders depend on partially different mechanisms involved in the development and perpetuation of signs of neuropathy both in the patients [17,18] and also reflected in the different animal models [5].

In conclusion, modifications of the SNI model may provide a higher incidence of neuropathic hypersensitivity than models involving the sciatic nerve trunk and display increased responsiveness to SCS. Some of these variants may prove useful in the further exploration of pathophysiological mechanisms differentially responsive to SCS.

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