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# Dorsal Root Ganglionic Field Stimulation Relieves Spontaneous and Induced Neuropathic Pain in Rats

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**Abstract: Dorsal root ganglion (DRG) electrical stimulation (ganglionic field stimulation [GFS]) is effective in relieving clinical pain, but its mechanism is unknown. We therefore developed a rat model for GFS to test analgesic effects in the context of neuropathic pain. GFS was applied with a bipolar electrode at L4, using parameters replicating clinical use (20 Hz, 150-μs pulse width, current at 80% of motor threshold). Neuropathic pain was generated by tibial nerve injury (TNI). Pain behavior was monitored by determining the threshold for withdrawal from punctate mechanical stimuli, by identifying hyperalgesic responses to noxious mechanical stimuli, and by hypersensitivity to cold. The affective dimension of pain was measured using conditioned place preference. We found that electrode insertion caused no behavioral evidence of pain and produced no histological evidence of DRG damage. GFS reversed TNI-induced hypersensitivity to cold and mechanical hyperalgesia and allodynia. Allodynia remained diminished 15 minutes after GFS. Conditioned place preference showed that GFS was not rewarding in uninjured control animals but was rewarding in animals subjected to TNI, which reveals analgesic efficacy of GFS for spontaneous pain. We conclude that GFS relieves neuropathic pain in rats. This model may provide a platform for identifying mechanisms and novel applications of GFS.**

***Perspective:** We show that electrical stimulation of the DRG in rats reverses neuropathic pain behavior and provides a rewarding effect to animals with spontaneous neuropathic pain. This confirms analgesic efficacy of DRG stimulation in an animal model, and provides a platform for preclinical exploration.*



***Key words:** Dorsal root ganglion, neuromodulation, neuropathic pain, conditioned place preference, analgesic stimulation.*

Chronic pain is a major cause of suffering, disability, lost work, and health care expenses. Because chronic pain is poorly treated, development of new therapeutic options is a high priority. Spinal cord stimulation (SCS) is a treatment modality that has earned a place in advanced treatment when noninvasive approaches have failed.[8] Its appeal has expanded as implantation techniques and neuroaugmentation technology have advanced. However, SCS is effective against only a limited range of conditions and often provides incomplete relief. Furthermore, when SCS is successful in providing analgesia, therapeutic efficacy typically fades with time, often due to loss of paresthesia distribution into the painful area.[1,8,27]

To address these limitations, a new clinical approach has been developed in which electrical stimulation is applied at the level of the dorsal root ganglion (DRG). Initial clinical findings using this experimental therapy, hereafter referred to as ganglionic field stimulation (GFS), are promising. In clinical trials so far (>500 subjects overseas and a complete US Investigational Device Exemption pivotal trial), GFS with electrodes placed adjacent to the DRG in the intervertebral foramen has been

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highly effective for treating pain associated with complex regional pain syndrome, causalgia, failed back surgery syndrome, and chronic postsurgical pain.[25,31,37,39] A notable difference from SCS is stable analgesic efficacy long after initiating treatment.[24,31,37] This distinction may in part be due to greater mechanical stability of GFS lead placement compared with SCS.[21] However, another factor contributing to the eventual loss of effectiveness of SCS analgesia may be the inherent plasticity of central nervous system synaptic mechanisms upon which SCS analgesia depends.[28] A difference in mechanisms of GFS and SCS is suggested by predictable GFS pain relief for conditions in which SCS is often ineffective, such as pain localized to the feet or inguinal region,[24,31] and GFS has been successful in subjects for whom SCS failed.[7] An additional indicator of different mechanisms is a generally lower stimulation frequency for optimal analgesia in GFS (approximately 20 Hz)[36] versus SCS (40–60 Hz). In an ongoing prospective, randomized, controlled, multicenter trial, GFS had significantly greater efficacy than SCS in complex regional pain syndrome.[23]

The mechanism of GFS analgesia is unknown, although our previous in vitro experiments show that field stimulation can block the passage of impulse trains through the sensory neuron T-junction where the peripheral process and central process join the stem process.[20] To explore the underlying mechanisms of GFS analgesia in a relevant in vivo setting, we developed a rat model that incorporates key features of the clinical approach. In this article, we report initial findings that validate this model. Our findings not only provide a potentially useful research tool for mechanistic studies of GFS and further development of this analgesic modality, but also give support to the efficacy of GFS for treating neuropathic pain in an experimental system that minimizes placebo effects that may cloud interpretation of clinical studies.

## Methods

### Animal Subjects

All animal experiments were performed according to protocols approved by the Institutional Animal Care and Use Committee of the Medical College of Wisconsin. Male Sprague Dawley rats weighing 200 to 250 g were obtained from The Taconic Farms Biosciences (Rensselaer, NY), and were maintained and used according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and in compliance with federal, state, and local laws. Table 1 shows the number of animals used in the protocols. Animals were housed in a pathogen-free facility, 2 animals per individually ventilated cage, in a room maintained at 22°C ± 1°C at 35 to 45% humidity, with a 12/12-hour day/night cycle. Animals had free access to food (irradiated commercial rodent diet "5001"; LabDiet, St. Louis, MO) and water, and bedding was aspen wood chips. At the termination of the study, euthanasia was performed by decapitation during deep anesthesia.

**Table 1. Rat Groups and Number of Animals Per Group**

| Test | Sham TNI and GFS | TNI and Sham GFS | TNI and GFS |
|---|---|---|---|
| Behavior (von Frey, pin, cold) | 6 | 6 | 9 |
| CPP | 6 | 0 | 9 |

### Injury Model Preparation

Tibial nerve injury (TNI) was on the basis of a previous report.[22] Animals were anesthetized with isoflurane and the right leg was shaved and disinfected. A 2-cm incision was made on the lateral midthigh and the underlying muscles separated to expose the sciatic nerve and the point at which it divides into its distal branches. At a distance 5 mm distal to this branch point, the tibial nerve was ligated with 6.0 silk suture and 2 to 3 mm of the nerve was removed distal to the ligation. The sural and common fibular nerves were preserved and contact with them was avoided. Muscle and fascia were closed in layers, and skin was closed with staples. Sham TNI control rats had exposure of the nerves but no ligation.

### DRG Stimulator Implantation

Each electrode was fashioned from 2 platinum-iridium wires (.010 inch and .005 inch) from which the insulation was removed at their termini (Fig 1A), and their other ends were secured in a standard plastic connection hub (PlasticsOne, Roanoke, VA). The terminus of the larger wire was folded back upon itself and the smaller wire was wrapped helically over the insulated portion of the larger wire behind its terminus. This design is approximately axially symmetric, and thereby provides bipolar contact in apposition to the DRG independent of rotational position. Insertion of the GFS electrodes, which were sterilized using a steam autoclave, was performed aseptically, during inhalation anesthesia (isoflurane 2% in oxygen), while maintaining body temperature at 36.5°C. A paramedian incision was made to expose the external aspect of the intervertebral foramen at the level of the fourth lumbar (L4) spinal nerve, and the accessory process overhanging the foramen was removed. A probe with a .4-mm diameter was inserted into the intervertebral foramen dorsolateral to the DRG, to create a space into which the electrode was inserted in juxtaposition to the DRG. A stainless steel ligature (.25 mm diameter) was used to bind the electrode to a screw (.86 mm diameter, 3.2 mm long) inserted into the transverse process caudal to the foramen. The leads, which were contained in 2.3-mm (outer diameter) flexible plastic tubing (Tygon; Saint Gobain Performance Plastics, Paris, France) for protection from excess flexion, were tunneled to the head, where the connection hub was secured to the skull with dental cement and screws.