NeuroMod

Treating neuropathic pain with dorsal root ganglion stimulation


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KEY CONCEPTS

Pain is NOT A STIMULUS

There are NO PAIN FIBERS in nerves and NO PAIN PATHWAY in the brain.

The experience of pain is the final product of a complex information-processing network.

Perception of a particular stimulus depends not only on the nature of the stimulus, but also on the CONTEXT within it is experienced.

Pain is highly subjective and depends on previous experiences.
Chronic neuropathic pain is a critical health issue challenge.

Current treatments are inadequate.
Pain Lab Research: Foundations

1. How can you tell if a rat is in pain?

2. Where is the pain coming from?

3. What processes contribute to abnormal electrophysiology?

4. How we can modulate pain response?
Neuromodulation techniques rely on the application of electrical currents, in varying parameters, by means of implanted electrodes to achieve functional activation or inhibition of specific neuronal groups, pathways, or networks.

Treating neuropathic pain with dorsal root ganglion stimulation

With electrical currents Induced by SNL

Key location in chronic pain induction
THE TREATMENT OF SCIATICA BY GALVANIC ACUPUNCTURE,

BY

E. A. GOULDEN, M.D.,

LLANDRINDOD WELLS.
Proposed mechanism of action

**Activation of fast-conducting Aβ fibers** that convey sensations associated with low-threshold stimulation. These fibers possess both an ascending branch in the spinal cord dorsal column system and a collateral branch that enters the spinal cord grey matter. According to this hypothesis, **electrical stimulation of the ascending branch** results in antidromic activation of the descending collateral branch and produces synaptic interactions with **interneurons that inhibit transmission of nociceptive signals conveyed by slow conducting C fibers**.

But is there anything else?
Limits to the effectiveness of SCS

- Only partial relief or no reduction of pain at all.

- It is difficult to target paresthesias to a specific anatomic location.

- Stimulation leads migrate over time.

- The conclusion of the Cochrane review states that SCS might be effective for certain patients but that there is little evidence available to assess the benefits and harms of this treatment.

These considerations raise the question of whether stimulation-induced analgesia might be generated in a more reliable fashion with a more evident outcome.
Dorsal root ganglion (DRG) is an attractive target for electrical stimulation therapy.

Our previous results prove that:

- DRG is **important site for pathophysiologic changes** that lead to neuropathic pain,
- following nerve injury or inflammation, DRG neurons may become an important source of nociceptive signaling through **increased neuronal excitability and generation of ectopic discharges**, 
- the L5 and L4 DRGs in rats are **easily accessible** for drug application, are tolerant of trauma, including a needle insertion and injection.
DRG stimulation techniques are already in clinical use!!!

Stimulation of the DRG has been attempted in a small number of case studies with generally positive results. These cases have demonstrated 69% pain relief in a patient with discogenic back pain and 80% pain relief in a patient with postherpetic neuralgia.

Mechanisms of potential therapeutic action?
Main hypothesis

1. The electrical field stimulation of a dorsal root ganglion (DRG) may provide beneficial effects in a variety of painful conditions.

2. We will prove that the DRG stimulation is easier to perform, safer and more successful in terms of pain reduction compared to spinal cord stimulation.

3. We will show that the proposed neuromodulation approach can influence the filtering properties of the DRG T-junctions.
1. Construction of an implantable neural stimulator, development of implantation technique and stimulation protocols.
   1.1. Modify the existing stimulator and construct the prototype stimulator appropriate for DRG stimulation.
   1.2. Develop the software for control of the stimulator.
   1.3. Establish the protocol for implantation.
   1.4. Establish use of implantable stimulator.

2. Behavioral outcomes of DRG stimulation procedure in various pain models.
   2.1. Obtain behavioral data following in vivo stimulation in SNL model.
   2.2. Obtain behavioral data following in vivo stimulation in carrageenan inflammation model.

3. Investigate the inflammatory potential of the electrode placement and GFS.
   3.1. Establish electrochemical reaction products at the electrode surface
   3.2. Establish if implantation induces inflammatory reaction
   3.3. Establish if implantation induces neuronal death in DRG
   3.4. Establish a link between morphological and electrophysiological changes.

4. *In vitro* electrical field stimulation of the injured DRGs
   4.1. Establish if GFS decreases nerve excitability
   4.2. Identify a distinct DRG population with particular sensitivity to GFS.

5. Properties of T-junction under GFS
   5.1. Obtain data on the effect of GFS on AP propagation at the level of T-junction.
   5.2. Define protocol for DRG cultivation on MEA substrate.
   5.3. Demonstrate (using MEA) filtering properties of the T-junction.
Electrical stimulation of the DRG decreased somatic excitability and increased filtration of high-frequency afferent AP trains.

Neuromodulation 2013; 16: 304–311
Electrical stimulation of the DRG activates sensory neurons, causing Ca2+ influx that triggers Ca2+-dependent processes leading to decreased somatic excitability and increased filtration of high-frequency afferent AP trains.

Neuromodulation 2013; 16: 304–311
Nociceptors
Anatomically and physiologically specialized peripheral sensory neurons which respond to noxious stimuli. There are two main categories:
- A$\delta$ mechanical nociceptors
- C polymodal receptors
Anesthesiology. 2005 Aug;103(2):360-76.
INCREMENTAL DEPOLARIZING CURRENT PULSES

Aδ-type neuron from L4 (non injured) DRG

Aδ-type neuron from L5 (injured) DRG

Anesthesiology. 2005 Aug;103(2):360-76.
AFTERHYPERPOLARIZATION

Anesthesiology. 2005 Aug;103(2):360-76.
T-junction is a regulator of afferent impulse traffic.

Diminished filtering of AP trains at the T-junction of C-type neurons with axotomized peripheral processes could enhance the transmission of activity that is ectopically triggered in a neuroma or the neuronal soma, possibly contributing to pain generation.


Reduction and even elimination of soma excitability proved to have no detectable effect on the reliability of spike conduction past the DRG and into the spinal cord


The somatic/perisomatic hyperpolarization, together with the low-pass filtering properties of the t-junction, can interfere with action potential propagation.

Two basic techniques for measuring electrical activity in cultured electrogenic cells:

- transmembrane measurements,
- extracellular measurements, and
- indirect methods – voltage sensitive or fluorescence dyes.
3Brain GmbH, Switzerland, www.3brain.com

Istituto Italiano di Tecnologia (IIT)
Neuroscience and Brain Technologies (NBT-NTECH)
**BioChip 4096S:**
- A microelectrode array that integrates **4096 electrodes** on 2.67mm x 2.67mm centered in a 3mm x 3mm working area.
- Allow recording from **4096 electrodes**: real-time acquisition and visualization up to the capacity of the hard drive.
- Stimulating through a maximum of **16 electrodes**: an external stimulator can be connected to the BioCAM.
- The software ("BrainWave") lets you configure the electrodes out of 16 stimulating electrodes.

![Functional Imaging with Electrodes](image-url)
Supplemental Movie 5
DIV 21

Propagating action potential in an RFP expressing neuron evoked by electrical stimulation.

Recording configurations were scanned across the neuron. The median voltage per electrode (colored pixels) in response to stimuli applied to a single electrode (white plus) 90 times per configuration are plotted. An evoked action potential (yellowish) travels along an axon toward the soma and into the dendrite. The largest voltage was at the axon hillock. Scale bar: 100 um.
A) High-density microelectrode array (MEA) that is used for neuronal plating.
B) and E) Preliminary results showing adult DRG neurons planted over the MEA substrate (red – β-tubulin; blue – Hoechst). C) Tissue culture test plate with MEAs. D) Two MEAs under the coverslip ready for the immunofluorescence analysis. Scale bar: 50mm.
The invention concerns a device to stimulate living tissue with an array of microelectrodes.
Reviewer 1:
In this project a non-pharmacological intervention has been described to be used and studied for the management of neuropathic pain. Therefore, the selection of the animal model should be aligned with the aim of the study. Carrageenan-induced inflammation model is a model for acute inflammation. Use of a nerve injury model such as Chronic Constriction Injury (CCI) is recommended to be used instead to study the effects of neuronal stimulators.

Reviewer 2:
One of the stated goals “We will prove that the DRG stimulation is easier to perform, safer and more successful in terms of pain reduction compared to spinal cord stimulation” is not met in this proposal. This head-to-head comparison is not there in terms of efficacy, breadth of relief (e.g., distal regions), and addressing safety is only touched on briefly. Other than rotarod, how will this differentiation be addressed?
HVALA NA POZORNOSTI