Genetics of Pain and Spinal Cord Stimulation: A Review of the Literature

Corresponding Author:
Dr. Gentian M Vyshka,
Lecturer, Biomedical, Faculty of Medicine, Rr Dibres 371 - Albania

Submitting Author:
Dr. Gentian M Vyshka,
Lecturer, Biomedical, Faculty of Medicine, Rr Dibres 371 - Albania

Article ID: WMC001635
Article Type: Systematic Review
Submitted on: 26-Feb-2011, 06:20:40 PM GMT  Published on: 27-Feb-2011, 06:48:43 PM GMT
Article URL: http://www.webmedcentral.com/article_view/1635
Subject Categories: NEUROLOGY
Keywords: Chronic Pain, Spinal Cord Stimulation, Analgesia, Dorsal Columns, Electrostimulation, Regional Pain Syndrome

How to cite the article: Vyshka G M. Genetics of Pain and Spinal Cord Stimulation: A Review of the Literature . WebmedCentral NEUROLOGY 2011;2(2):WMC001635

Source(s) of Funding:
No funding has been received.

Competing Interests:
No competing interests to declare.
Genetics of Pain and Spinal Cord Stimulation: A Review of the Literature

Author(s): Vyshka G M

Manuscript

1. Genetics of pain and genetic mediation of pain-related traits
There is a number of genetic models displaying large divergence in analgesic sensitivity; and the investigations into the genetic mediation of pain-related traits have gained clinical consistency and diagnostic value more and more. These pain-related traits, whose genetic basis has been supposed and studied, are mainly based on experimental data gathered on mammals such as knock-out mice (Mogil, 1996). The two main issues in discussing and studying the genetics of pain-related traits have been:

a. Nociceptive and neuropathic pain sensitivity
b. Sensitivity to endogenous and exogenous analgesics.

Because the large number of subjects required for sustainable genetic investigations, the studies have been performed by using the hot-plates and/or tail-flick tests of nociception. In a previous study, without entering in genetic details, we studied the pain and temperature threshold, whose relevance for different neurological diseases is clearly approved (Vyshka, 2003). The study was made on healthy probands, but the correlations with clinically important human pain states were not tested, if there were correlations to be found at all.

Among the human diseases with genetic effect of pain, different authors mention:
1. Hereditary sensory neuropathy type I,
2. Familial hemiplegic migraine,
3. Painful congenital myotonia.

Genetic traits of the above mentioned diseases have been reliably formulated; HSAN (Hereditary Sensory & Autonomic Neuropathies) as a large and non-homogenous group provide the most interesting nosology, mainly due to the fact that the disease affects only small fiber loss; safeguarding some large-fiber functionality assures the efficacy of spinal cord stimulation, as we shall further discuss. HSAN molecular diagnostics suggested a dominant inheritance, traits related to the Chromosome 9q22.1-q22.3; and an enzyme named serine palmitoyltransferase, long-chain base subunit 1 (SPTLC1) has been accused as important in the pathogenesis of the disease. (Reilly, 1998). Studies have interested other neuropathies as well as complex regional pain syndromes.

The analysis of a genetic model of chronic pain is clinically important and well worth of the efforts made up to now. There have been confirmed relationships between a murine gene and pain-related traits for pro-opio-melanocortin and opioid stress-induced analgesia, but as said before, studies have been mainly focused on knockout mice. This for some authors is not a disadvantage, since 80% of mouse genome is estimated to match conserved regions of human genome (Copeland, 1993).

The use of hot-plates and tail-flick tests of nociception might reflect only poorly important human pain situations, but they predict the effectiveness of analgesics (Hammond, 1989). Considerable evidence suggests that different types of nociception are mediated by separable physiological mechanisms (Dennis, 1979). Therefore we might well expect that the genetic mediations of sensitivity to these pain modalities will be different as well. Genetic factors also play an important role in the sensitivity expressed toward opiate inhibition of different pain modalities (Jacob, 1983; Oliverio 1975); as indicators of lower or higher sensitivity have been used the latencies of responses gathered during application of hot-plates and tail-flicks in KO mouse (Mogil, 1996).

Investigations into the genetic mechanics of pain-related traits should somehow provide relevant clinical data; the sensitivity toward opiate administration, or spinal cord stimulation, or whatever analgetic measure to be conducted, will become a screening pre-test before entering the patient in a long-term pain therapy.

2. Neuropathic pain and dorsal horn alterations
Neuropathic pain might become manifest, persist and seriously hurt the patient, even in the absence of any evidence of peripheral tissue damages. There have been several neural mechanisms suggested in triggering and upholding the neuropathic pain in general:

--- at the peripheral nerve stage, the deafferentation might be the cause. The loss of sensory axons due to post-herpetic neuralgia, will reflect not only the sensory deficit, but the severe pain the patients will suffer thereafter (Oaklander, 1998).
--- Neuroma formation and axonal damages may
generate ectopic impulses; a very common process during different types of neuropathies. These ectopic impulses will reenter antiodromically in a process known as ephaptic transmission.

---the hyper-expression of α-adrenergic receptors has been suggested as a pathological mechanism in the CRPS (complex regional pain syndrome), as it happens after a partial peripheral nerve damage (Woolf, 1999).

---central structures might become hypersensitive as well; dorsal horn, periaqueductual substance, thalamus, rostro-ventral medulla, all these structures have shown deficiency in modulating the pain perception through the serotoninergic descending pathways that normally filter the painful experiences. Anatomic and functional changes in the dorsal horn of medulla have been widely discussed; there is evidence that the interneurons of second lamina of Rexed undergo a massive apoptosis after peripheral nerve damage, maybe through an excitotoxic mechanism (Sugimoto, 1990). Opioids, GABA-enhancing drugs, clonidine and spinal cord stimulation might quite well mimic the descending pain inhibition in such cases. NMDA receptors have been accused as well, because NMDA antagonists (dextrometorphan, ketamine) will remove the hypersensitivity toward pain in patient with neuropathy (Nelson, 1997).

At the level of actual knowledge, it is widely accepted that the dorsal horn undergoes anatomic and functional changes, causing hyperexcitability and hyperalgesia (Yakhnitsa, 1999); genetic traits of analgesic efficacy should be clinically very important in providing relief and in suggesting the patients a specific analgesic treatment, such as the spinal cord stimulation.

3. Spinal cord stimulation as a rostral extension of peripheral nerve stimulation

Since the Melzack-Wall gate theory of pain (1965), there have been several attempts to translate the neurophysiological findings in the clinical practice. Spinal Cord Stimulation (SCS) was introduced as a rostral extension of peripheral nerve stimulation, with the precise aim to stimulate the spinal dorsal columns. Through this stimulation, an activation of large-caliber myelinated fibers (Ab) will follow, fibers that on the other hand will modulate or inhibit pain transmission in small-caliber unmyelinated (C) and thin myelinated (Ad) nerve fibers.

Fig. 1 – Left side: raports of C and Ad fibers with Ab fibers in the dorsal root ganglion and dorsal horn. Right side: further pain processing in the spinohalamic tract.

The above figure (no.1) illustrates the raports of C and Ad fibers with Ab fibers and other structures of the dorsal horn (Mense, 2004), and further pain processing in the spinohalamic tract (Paulev, 2000). In order for the SCS to be effective, there should be considered following points:

(A) The patient has to undergo a trial period, during which percutaneous temporary electrodes will be implanted. The patients have to refer at least 50% improvement in the pain (Kim, 2001; North, 2002), through questionnaires such as VAS and other pain rating scales.

(B) Pain relief occurs only in areas where the stimulation produces paresthesias. Therefore the patient is kept awake during the device implantation (Giller, 2003; Van Buyten, 2001) so that the electrode position can be modified as needed. However, other surgeons prefer the general anesthesia during the surgical implantation of the SCS device, and therefore a monitoring way of electrode placement has been widely required. The use of antidromic evoked potentials has been reported as a reliable way to precise placement of dorsal cord disc electrodes (Yingling, 1986). According to authors, antidromic recordings are preferable to orthodromic ones, for the purpose of intraoperative evaluation of dorsal cord electrode placement.

There are still some technical problems regarding the paresthesias’ obtaining in the painful areas:

***Achieving stable paresthesias can be difficult, due to the complexity of the pain pattern (Giller, 2003);

*** The electrodes can migrate;

*** Other intrinsic reasons for failure of the implanted device can play a role.

A major technical issue that may limit and influence the clinical efficacy, is the range of stimulation amplitudes between the perception threshold (PT) and the discomfort threshold (DT) – often preventing a complete coverage of the painful area by paresthesia to provide maximum therapeutic effect (Holsheimer 1997). Another technical problem will be that of stimulating the dorsal root instead of / or as well as – stimulating the dorsal columns, which is the main purpose of the stimulation (Ibid.).

Theoretical Framework for SCS way of acting and efficacy

Over the years, there have been several hypothesis regarding the neurotransmitters’ action during the spinal cord stimulation – Stanton-Hicks (1997).
stimulation via percutaneous leads has been but in cervical regions as well. High cervical has found wide use mainly in thoracolumbar regions, paresthesia in order to relieve painful situations, SCS According to the territory that has to be covered by sympathetic activity. Locally-acting modulators such as modulation of the autonomic function (decrease in vasodilatation, but it can be seen as well as a antidromic stimulation of dorsal root afferents causing increased micro-circulation. The latter is a result of reduction as a secondary phenomenon due to ischemic pain, Vaarwerk (1998) explains the pain responsiveness (due in part to the deafferentation behavior of the device. So, a SCS induced release of GABA can be the explanation for the suppresion of allodynia observed in rats after SCS (Vaarwerk, 1998). There is generally a large consensus regarding the efficacy of SCS in neuropathic pain treatment, in a variety of nosologies that can specifically produce the clinical picture of neuropathic pain (and of the behavioral manifestations accompanying that picture, i.e., tactile & termal allodynia and hyperalgesia). Taking for proven a pronounced hyperexcitability in dorsal horn neurons (enlargement of their receptive fields; transsynaptic degeneration of cell bodies in dorsal horn; increased responsiveness of dorsal horn neurons to mechanical stimuli ecc.), Yakhnitsa et al., (1999) have tried to explain the intrinsic mechanism of SCS. According to the authors, hyperexcitable neurons are prone to being modulated by SCS. There is also a suppressive effect of SCS on afterdischarges, as well as on spontaneous activity in dorsal horn neurons. Other authors as well (Galer, 1997) have included the spontaneous ectopic impulse generation and the progressive increase of dorsal horn responsiveness (due in part to the deafferentation hyperactivity) as some of the principal mechanisms of neuropathic pain.

Regarding the actually widely proven efficacy of SCS in ischemic pain, Vaarwerk (1998) explains the pain reduction as a secondary phenomenon due to increased micro-circulation. The latter is a result of antidromic stimulation of dorsal root afferents causing vasodilatation, but it can be seen as well as a modulation of the autonomic function (decrease in sympathetic activity). Locally-acting modulators such as VIP, substance P & CGRP may play some role as well.

The antisympathetic effect of SCS is mentioned from Simpson (1997) as well, and according to the author it is apparent in peripheral ischaemia, cardiac ischaemia & CRPS (reflex sympathetic distrophy & causalgia).

**Technical Issues**

According to the territory that has to be covered by paresthesia in order to relieve painful situations, SCS has found wide use mainly in thoracolumbar regions, but in cervical regions as well. High cervical stimulation via percutaneous leads has been suggested from Simpson (1997) for a very particular situation, such as persistent vasospasm after subarachnoid haemorrhage – no further data, to our knowledge, have investigated further in this matter. The figure no. 2 shows the model designs of SCS electrode implants that are actually in use (both percutaneous and plate electrodes – from North, 1997).

The majority of the authors agree that the insulated plate electrodes are superior to the percutaneous electrodes, in terms of pain relief providing as well as in avoiding stimulation-evoked discomfort, typical to the percutaneous electrodes (North, 1997). In a later article, North et al., (2002), compared the percutaneous and laminectomy electrodes, and demonstrated performance advantages for insulated arrays implanted via laminectomy, in comparison with percutaneous electrodes.

Reviewing the technical outcomes of SCS implantation, North (2002) compared the percutaneous and laminectomy electrodes. The permanent electrode was positioned at the same radiographic level as the temporary electrode for each patient. The right / left position of the electrode was established not only radiologically but also physiologically via intraoperative testing of the conscious patient under local anesthesia. The fig. no. 3 represents the successive implantation of percutaneous (A) and insulated (B) electrodes.

While implanting the electrodes under local anesthesia as well, Van Byuten (2001) suggests the patient to stay in a sitting position, for the following reasons: (a) the sitting position is more comfortable for both the patient and the physician; (b) allows better communication with the patient; (c) results in more accurate lead placement than the prone position, which does not correspond to the patient’s usual daily situation.

We’re not aware if other authors prefer the implantation with the patient in a sitting position, like Van Byuten et al.

Fig. 2: representative contemporary SCS designs from Medtronic Inc., (left-hand column) and Quest ANS (right-hand column). Upper arrow: percutaneous model 3478A Pisces Quad; Lower arrow: late design 3587 A Resume.

Working with computer-based models, Holsheimer (1997) tried to propose a solution to a major drawback of the SCS system: the generally limited paresthesia coverage. As mentioned above, dorsal root stimulation can be a problem. According to the author, dorsal column stimulation can be enhanced: (1) through optimization of the geometry of a rostrocaudal epidural array or (2) by the use of a transverse tripolar epidural array, as
well as (3) through ensuring a small electrode-to-spinal cord distance, resulting in a high ratio of DT:PT (discomfort threshold : perception threshold).

PATIENT SELECTION
SCS is applied worldwide to 15,000 patients annually (5,000 in Europe). Therefore a good selection of patients will ensure high efficacy, avoidance of unrealistic expectations as well as of unnecessary economic costs. Gybels et al., in a consensus statement (1998), provide following inclusion and exclusion criteria for neurostimulation generally and SCS in particular:
1- failure of more conservative pain treatments;
2- partial sparing of dorsal column fibers, where SCS is considered;
3- the presence of other stimulating devices (pacemakers etc.) is considered a contraindication for SCS;
4- severe coagulopathies and immunodeficiencies may be contra-indicative;
5- major psychiatric disorder, poor compliance and / or drug abuse are contra-indicative;
6- the life expectancy of a patient selected for SCS has to be longer than a year.

The inclusion and exclusion criteria quoted above are summarized in the Table 1.

Kumar et al., (1998) in his inclusion criteria includes the no.1 and no.5 from the above list, as well as the following:
1- a defined non-malignant, organic cause of pain;
2- the capacity to give informed consent for the procedure.

In selecting patients for treatment of chronic intractable pain through SCS, North (2002) used the following criteria:
1- chief complaint of the patients was a radicular pain;
2- there should be an objective basis for the complaint of pain such as:
   A- abnormal diagnostic imaging results; or
   B- neurological deficit consistent with the patient’s pain complaints & history; or
   C- well-documented history of surgery for appropriate indications;
3- exhaustion of all available conservative treatments before SCS (same criteria as no.1 in Gybels, see above).

INDICATIONS
There is a substantial difference between the principal criteria of implanting a SCS device in Europe – where the vascular indications are growing more and more numerous – and USA, where the ‘failed back surgery syndrome’ is still the principal indication of SCS. In the abovementioned consensus statement, Gybels et al. (1998) included following criteria for neurostimulation:
- peripheral nerve lesion,
- entrapment of peripheral nerves,
- stump pain after amputation,
- post-herpetic neuralgia,
- post-radiation plexopathy,
- polyneuropathies,
- failed back surgery syndrome,
- intractable angina pectoris,
- peripheral vascular disease (Raynaud, frostbite, Buerger’s disease).

Other diseases with some relief of the pain (anyway doubtful) are:
- pain due to incomplete lesions of spinal cord,
- chronic cervical and sacral radiculopathy.

Do not respond:
- pain due to root avulsion,
- pain due to syringomyelia.

Kim (2001) reports following indications for SCS:
- nonspecific limb pain,
- disc disease neuropathic pain,
- peripheral nerve neuropathic pain,
- cord lesions neuropathic pain,
- cauda equina neuropathic pain,
- post-thoracotomy pain,
- amputation-related pain,
- complex regional pain syndrome type I (CRPS I).

Kumar (1998) included in the quoted article the following clinical painful situations, with good responses after successful implantation of SCS:
- failed back syndrome,
- pain due to multiple sclerosis,
- reflex sympathetic dystrophy (CRPS),
- peripheral neuropathy,[1]
- pain caused by peripheral vascular disease.

In this study of 235 patients, several other indications were examined for SCS implantation:
- spinal cord lesion,
- perirectal pain,
- cauda equina lesion,
- bone and joint syndromes,
- stump pain,
- phantom limb pain.

Takahashi et al., (2002) reported that epidural SCS may be considered as the treatment of choice for:
- painful legs and moving toes.

Kumar et al. (1997); Forouzanfar et al (2004); have also confirmed the efficacy of SCS in the management of reflex sympathetic dystrophy (CRPS).

Simpson (1997) reports that the efficacy of SCS is ‘most effective’ and ‘extraordinary’ in following conditions:
- intractable angina pectoris
- intractable pain due to deafferentation & autonomic disturbances
- specific conditions with a success rate of 70-90% such as:
  ANGINA
  ISCHAEMIC LIMB PAIN
  CRPS
  BRACHIAL PLEXUS DAMAGE
  PHANTOM LIMB
  DIGIT PAIN
  BATTERED ROOT SYNDROME

The author also reports some very particular conditions, where SCS may be used, but the efficacy has still to be proven:
- persistent vasospasm after subarachnoid hemorrhage;
- prolonged coma and persistent vegetative state (cervical SCS).

The same author refers the efficacy of SCS with high frequencies of stimulation (1100-1400 Hz) in:
- extrapyramidal disorder & spasticity.

Other authors, nevertheless, have considered the use of SCS for the control of spasticity in spinal cord injury, as lacking the long-term efficacy and as being not cost-effective (Midha et al., 1998).

The concluding table (Table 2) below includes all indications, discussed and approved as successful from the majority of the authors, as well as some from the other indications that are not considered to bring any relief for the specific purpose they're initially proposed and used for.

References

1. Belmont John W., Genetics of Primary Pain Disorders; online edition.
Illustrations

Illustration 1

Fig. 1 – Left side: raports of C and Ad fibers with Ab fibers in the dorsal root ganglion and dorsal horn. Right side: further pain processing in the spinothalamic tract.

Illustration 2

Fig. 2: representative contemporary SCS designs from Medtronic Inc. (left-hand column) and Quest ANS (right-hand column). Upper arrow: percutaneous model 3478A Pisces Quad; Lower arrow: late design 3587 A Resume.
Illustration 3

Table 1

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA for SCS</th>
<th>EXCLUSION CRITERIA for SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of more conservative pain treatments;</td>
<td>The presence of other stimulating devices (pacemakers etc.);</td>
</tr>
<tr>
<td>Partial sparing of dorsal column fibers;</td>
<td>Severe coagulopathies and immunodeficiencies;</td>
</tr>
<tr>
<td>Life expectancy of the patient is longer than a year;</td>
<td>Major psychiatric disorder;</td>
</tr>
<tr>
<td>A defined non-malignant, organic cause of pain is detectable;</td>
<td>Poor compliance;</td>
</tr>
<tr>
<td>Chief complaint of the patients is a radicular pain;</td>
<td>Drug abuse.</td>
</tr>
<tr>
<td>An objective basis for the complaint of pain is found;</td>
<td></td>
</tr>
<tr>
<td>The capacity of the patient to give informed consent for the procedure.</td>
<td></td>
</tr>
</tbody>
</table>
### Illustration 4

Table 2

<table>
<thead>
<tr>
<th>Situations where SCS use has been proven effective</th>
<th>Situations where SCS use has some, or a doubtful efficacy</th>
<th>Situations that do not improve through SCS use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve lesion (following entrapment); Post-herpetic neuralgia; Brachial plexus damage (and post-radiation plexopathy); Peripheral polyneuropathies (with preservation of some large fiber function); Failed back surgery syndrome; Intractable angina pectoris; Peripheral vascular disease (Raynaud, Buerger's); Nonspecific limb pain; Complex regional pain syndrome type I (CRPS I); Disc disease neuopathic pain (and battered root syndrome).</td>
<td>Pain due to incomplete lesions of spinal cord; Chronic cervical and lumbosacral radiculopathy; Peri neural pain; Cauda equina lesions; Bone and joint syndromes; Stump pain; Phantom limb pain; Vasospasm after subarachnoid hemorrhage and prolonged coma &amp; persistent vegetative state (high cervical SCS); Extrapyramidal disorder &amp; spasticity; Painful legs and moving toes; Pain due to multiple sclerosis.</td>
<td>Complete spinal cord transection; Pain due to root avulsion; Pain due to syringomyelia; Spasticity in spinal cord injury.</td>
</tr>
</tbody>
</table>

1. Nociceptive forms of pain are more likely to benefit from other therapeutic procedures.
2. Stump pain after amputation is — anyway — an indication in the consensus statement of Gybels et al., 1998.
3. Some authors consider the condition as having a high success rate of pain relief through SCS implantation.
4. The use of SCS with high frequencies (1100-1400 Hz) – such as reported successful in treating extrapiramidal conditions – seems practically out of everyday scope.
Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.