Pain After Surgery—New Directions in Neuromodulation

PHYSIOLOGY OF NEUROMODULATION

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DISCLOSURES

- Boston Scientific
- Respicardia
- W. L Gore & Associates
PHYSIOLOGY OF NEUROMODULATION

• Neuromodulation and the Gate Control Theory
• Use of Animal Models
• Translational Research
• Examples of Models Using SCS
  – Peripheral Neuropathy and SCS
  – Peripheral Vascular Disease and SCS
  – Irritable Bowel Syndrome and SCS
  – Selecting Parameters—Burst-Tonic
GATE CONTROL THEORY: THE “STIMULUS” FOR DEVELOPING NEUROSTIMULATION FOR PAIN RELIEF
GATE CONTROL THEORY

Noxious Pinch Skin

Touch

Pain

Stimulate Touch Fibers
SPINAL CORD STIMULATION (SCS): Proposed Mechanisms

Antidromic Activation of the Large Primary Afferent Fibers

Activation of the “Classical Gate Control Mechanism” of Melzack & Wall

In: Linderoth & Meyerson, 1995
Gate-Control Theory 1965


First Clinical Report 1967

Neuromodulation and the Gate Control Theory

Use of Animal Models

Translational Research

Examples of Models Using SCS
- Peripheral Neuropathy and SCS
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USE OF ANIMAL MODELS
Pros:

- Use of analyses that cannot be applied to humans (LD 50; histology; lesional studies; various surgeries and pharmacological treatments, etc)
- Large numbers of subjects can be used
- Life time studies take short time
- Simple, or simplified systems may be studied
- Genetically manipulated animals available
- Small animals more economical/less public interest
USE OF ANIMAL MODELS

- **Cons:**
  - No verbal communication—Only behavioural, anatomical, histological and chemical studies
  - Animal systems different from human
  - Animal systems differ between species
  - Ethical problems; especially primate studies
  - Can the results be transferred to the human situation??
ACTUAL AND POTENTIAL ANIMAL MODELS

- Neuropathic pain
- Peripheral ischemia
- Cardiac ischemia
- Diabetes
- Visceral Dysfunction
- Inflammatory Pain
- Cancer Pain
- Skeletal Pain
- Arthritic (Joint) Pain
- Other Models?
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THE CONSTANT DEBATE
Relevance of Animal Models

• Clear differences exist between most animal models and clinical conditions they resemble

• Paucity of direct collaboration among scientists, clinicians, and engineers

• Collaboration is needed to develop models, design experiments and discuss results

• Collaboration would facilitate translation of studies between bench and bedside
FRIEND, COLLEAGUE, "TRANSLATOR"

Dr. Bengt Linderoth, MD, PhD
Karolinska Hospital
Stockholm, Sweden
NEUROSURGEON
Visiting Professor
University of Oklahoma HSC
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ANIMAL MODELS OF PERIPHERAL NEUROPATHY

- **A**: Axotomy
- **B**: Bennett
- **C**: Seltzer
- **D**: Chung
- **E**: Gazelius

**F**: Sural nerve
- **DRG**
- **Common peroneal nerve**
- **Spared nerve injury**
- **Spinal nerve**
- **Tibial nerve**
ANIMAL MODELS OF NEUROPATHIC PAIN
Spinal Nerve Ligation (SNL)
INCREASED SENSITIVITY TO INNOCUOUS TACTILE STIMULI IN AN ANIMAL MODEL OF MONONEUROPATHY

Partial Sciatic Nerve Ligation

Miniature SCS system $\rightarrow$ Test of SCS response

Spinal Cord Stimulation (SCS) Parameters: 66%, 200 us, 50 Hz

Cui & Linderoth.

![Graph showing withdrawal threshold over time with SCS stimulation]
ANIMAL MODEL OF MONONEUROPATHY
EFFECT OF SCS ON
WIDE DYNAMIC RANGE SPINAL NEURONS

Yakhnitsa et al., 1999
MICRODIALYSIS PROBE PENETRATION INTO THE DORSAL HORN

Cui et al., Pain 73: 87-95, 1997
If the Gamma-Amminobutyric Acid (GABA)-B receptor is blocked, the reduction of GLU is abolished.

Cui et al., Pain 73: 87-95, 1997
UPDATE OF SCS MECHANISMS FOR NEUROPATHIC PAIN MODULATION

Ach—Acetylcholine
Aden—Adenosine
DLF—Dorsolateral Funiculus
NE—Norepinephrine
5-HT—Serotonin
X—future transmitters or modulators

Adapted from Linderoth & Meyerson, Anesthesiology 2010
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PERIPHERAL VASCULAR DISEASE

Pre-implant  3 months SCS  1 year SCS
Peripheral Arterial Occl. Disease (PAOD)—caused by atherosclerosis and expressed as reproducible ischemic muscle pain (intermittent claudication) and inadequate blood flow

Diabetic Angiopathy—calcification of the media of larger vessels and major effects in the microcirculation

Buerger’s Disease—rare—combination of inflammation and clots in blood vessels that impairs blood flow

Vasopastic Disorders—several pathologies involving intermittent localized vessel spasm that affects blood supply—walls of the blood vessels look normal

Raynaud’s Disease—causes fingers, toes, tip of the nose and ears to feel numb and cool in response to cold temperatures and stress. Arteries supplying these areas narrow

Frostbite—extreme cold damages skin and severely constricts blood vessels
CLINICAL HISTORY
Peripheral Vascular Disease

- Cook et al., 1976 Introduced the treatment
- Meglio, 1981
- Tallis et al., 1983
- Augustinsson, 1985
- Broseta et al., 1985
- Jivegard et al., 1987
- Galley et al., 1988
- Jacobs et al., 1988
CLINICAL RESULTS
Limb Salvage: improvement

- Rickman et al. *Journal Vascular Nurs* 1994
- Jivegard et al. *Eur J Vasc Endovasc Surg* 1995
- Gersbach et al. *Eur J Vasc Endovasc Surg* 1997
- Ubbink et al. *J Vasc Surg* 1999
- Amann et al. *Eur J Endovasc Surg* 2002
SCS OUTCOMES:

- Vasospasm > 70%
- Arterial Insuff. 60 – 70%

SCS AND PERIPHERAL VASODILATION

Mechanisms

• Inhibition of Sympathetic Efferent Activity (Linderoth)

AND/OR

• Antidromic Activation of Sensory Afferent Fibers releasing CGRP (Foreman)
Linderoth et al., 1991

Stim on

Cutaneous Vasodilation
in the ipsilateral footpad

Stim off

SCS Left Side
~66% MT
L1-L2 segments

Ventilator
Laser Doppler Flowmeter
Stimulator
Computer And A/D Converter
Purpose: Transection of the sympathetic efferent fibers eliminates peripheral vasodilation. This result suggests that SCS occurs as a result of sympathetic inhibition.

Hexamethonium (nAch receptor antagonist which acts in autonomic ganglia) also markedly attenuates vasodilation.

This is further evidence that the sympathetic nervous system is involved in peripheral vasodilation.
FOREMAN TEAM
Spinal Cord Stimulation at 30%, 60%, and 90% MT
Antidromic Activation of Dorsal Root Afferents:
Release of CGRP

CGRP-(8-37)—Calcitonin Gene-Related Peptide Antagonist

Tanaka, Barron, Chandler, Linderoth & Foreman, 2001
To Agree or Disagree, that is the Question
A Toast to the Team that solved the “Root” Problem


THE "ROOT" OF THE PROBLEM
Stockholm—Cold; Oklahoma City—Warm
Role of Sensory Afferents and Sympathetic Efferents

Cooled Paw (20-25°C)  Normal (31°C)

Blood Flow

Antidromic Activation

Sympathetic Inhibition

SCS ≤ 60% of MT

CS

CONCLUSION

Endothelial cells
Relaxation of Vascular smooth muscle cells

Nitric Oxide

Sympathetic Efferent Fibers

CGRP

Dorsal Root Aδ & C Afferents
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CHRONIC VISCERAL PAIN

- Chronic visceral abdominal pain is common in disorders such as
  - Chronic pancreatitis
  - Irritable bowel syndrome (IBS)

- Conventional approaches for treating chronic visceral pain have limited efficacy and poor side effect profiles
IRRITABLE BOWEL SYNDROME (IBS)

- Chronic disorder of unknown origin
  - Abdominal pain
  - Abnormal bowel habits
  - Comorbid somatic pain
  - Associated with anxiety
  - Exacerbated by emotional stress
  - Subset of patients develop symptoms following an enteric infection, early life stress.

  U.S. prevalence: up to 20%
  - Up to 40% of military veterans

- Cost: ≥ $1.2 billion/year

Grundmann & Yoon (2010); Choung & Locke (2011)
Yunus (2011); Tuteja et al (2009); White et al (2010)
VISCERAL HYPERSENSITIVITY IN IBS

- Colorectal balloon distention in humans

(Mertz, 2003a from Ritchie, 1973)
In a freely moving rat colorectal distention (CRD) produces a visceromotor response (VMR) that is dependent on the distention pressure.

VMR: behavioral response induced by colorectal distention,

(Ness and Gebhart, 1988)
SPINAL CORD STIMULATION ATTENUATES COLONIC HYPERSENSITIVITY

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Department of Physiology, OUHSC,
Oklahoma City, OK 73014

Dept. of Neurosurgery, Karolinska Institutet and Karolinska University Hospital, Stockholm Sweden.

Basic Animal Model Data Published in 2003 and 2005.
The OUHSC Physiology Team
EXPERIMENTAL SETUP

A. Chronic Implantation of Stimulating Electrode
B. Strain Gauges implanted in Abdominal Muscle- 3-7 days later
C. Colorectal distention

Stimulator
Preamplifier
Grass Chart Recorder

90% MT, 200 µs, 50 Hz

Measures Visceromotor Reflexes (Muscle Contractions)
METHODS

Implantation of Strain Gauges

Recovery

30 min

CRD

10 min

SCS

30 min

CRD

10 min

VMR to CRD

Strain-gauge force transducer

Colorectal balloon catheter
EFFECT OF SCS ON NOCICEPTIVE PRESSURES OF COLORECTAL BALLOON DISTENTION

# of contractions/10 min

![Graph showing the effect of SCS on nociceptive pressures.
Pre-SCS: 25 contractions/10 min; Post-SCS: 5 contractions/10 min. The difference is statistically significant (**).]
EFFECT OF SCS ON DURATION

# of contractions/10 min

No SCS  10 min.  30 min.  50 min.  70 min.  90 min.

Balloon Distention (60 mmHg)
Following SCS (90% MT/30 min)
A, SCS on C1-C2 or L1-L2 segments; B, cell recording at L6-S2 segments; C, colorectal distention
S1 SPINAL NEURON RESPONSES TO SCS

SCS on C1-C2

SCS on L2-L3

SCS: 90% MT, 50 Hz, 0.2 ms, 3-5 min
NEURAL HIERARCHY ORIGINATING FROM C1-C2 SEGMENTS

Spinal Cord Stimulation
90%MT, 200 us, 50 Hz
NEURAL HIERARCHY ORIGINATING FROM L5-S2 SEGMENTS

Spinal Cord Stimulation
90%MT, 200 us, 50 Hz

L5-S2

Spinal cord

Excitation

Inhibition
1. Briefly anesthetize with isoflurane

2. Give sedated animal an enema of trinitrobenzenesulfonic acid (TNBS)

3. This treatment produces:
   a. Active inflammation from 3-5 days
   b. Post-inflammatory visceral hypersensitivity for 21-60 days

4. Animals were studied 30 days post enema.

SCS INHIBITS POST-INFLAMMATORY COLONIC HYPERSENSITIVITY

Balloon Distention (30 mmHg for 10 min)

TNBS = Trin trobenzenesulfonic acid
• SCS (90% MT/30 min):
  - Normalizes the response to nociceptive distention in the colon.
  - Does not alter colonic compliance.
  - Normalizes the hypersensitive response to non-nociceptive distention in the sensitized colon.
Intractable IBS in a 43 yr old female
  - Abdominal Pain and Severe Diarrhea

Based on our Study (Greenwood et al 2003), SCS was used for treatment of this “hopeless” case
  - 2 week trial
    - Diarrhea free
    - 75% Pain Reduction
  - 6 months
    - Diarrhea Free
    - Pain Reduction not as effective

After 1 yr accidental IPG turn-off happened and the symptoms relapsed.
After resuming SCS symptoms again were controlled.
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Burst stimulation: 40 Hz burst mode with five pulses at 500 Hz per burst and a pulse width of 1ms with 1ms interspike interval

Figure from De Ridder et al., Neurosurgery 2010;66:986–990.
A, SCS (90% MT, 0.2 ms, 40 Hz or Burst) on L2-L3 segments; B, EMG recordings from abdominal muscle; C, **Noxious (60 mm Hg)** Colorectal Distention (CRD)
## MOTOR THRESHOLD OF ANIMALS in Microamperes (μA)

<table>
<thead>
<tr>
<th>SCS</th>
<th>VMR group</th>
<th>Lumbosacral group</th>
<th>Gracile group</th>
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<tr>
<td>Burst</td>
<td>182.5 ± 30.3</td>
<td>159.5 ± 19</td>
<td>135.7 ± 8.6</td>
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<tr>
<td>Tonic</td>
<td>328.0 ± 48.5*</td>
<td>366.8 ± 38.8*</td>
<td>353.6 ± 18.5*</td>
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*compared to burst SCS, p<0.05
EMG RECORDINGS FROM ONE ANIMAL

Before SCS

IEMG left
IEMG right
REMG left
REMG right
CRD

Immediately after SCS

IEMG left
IEMG right
REMG left
REMG right
CRD

Recovery

Burst

Tonic

IEMG—Integrated EMG
REMG—Raw EMG
SUPPRESSIVE EFFECT OF TONIC AND BURST SCS OF VMR RESPONSES TO CRD

A VMR response suppressed by SCS

B Recovery time of VMR response

Reduction of AUC (%)

Recovery time (min)

Ipsilateral    Contralateral

*
A, Dorsal Column Nuclei (DCN); Cell recording from the Gracile Nucleus of the DCN; B) SCS (60%MT, 0.2 ms 40 Hz or Burst) L2-L3 Segments

EXPERIMENTAL SETUP
Gracile Nucleus—Paresthesia?

Diagram:
- Computer
- CED 1401 Data Acquisition System
  - Spike 2 software package
- Oscilloscope
- Discriminator
- WPI Stimulator
- Microelectrode
GRACILE NEURON TRACING SHOWING SPONTANEOUS ACTIVITY

A
Without SCS

B
With Tonic SCS

C
With Burst SCS

Extracellular Action potential

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Extracellular Action potential
SUMMARY OF SPONTANEOUS ACTIVITY DURING TONIC AND BURST SCS

**A: WDR neuron**

- Spontaneous activity (imp/sec) before and during tonic SCS.
- Spontaneous activity (imp/sec) before and during burst SCS.
- n=10

**B: LT neuron**

- Spontaneous activity (imp/sec) before and during tonic SCS.
- Spontaneous activity (imp/sec) before and during burst SCS.
- n=10

* indicates a statistically significant difference.
CONCLUSIONS

• Burst SCS is more efficacious than tonic SCS in attenuating visceral nociception

• Reduced or abolished paresthesia in patients may be due in part to burst SCS not increasing spontaneous activity of neurons in the gracile nucleus
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