Alteration of pain processing by transcutaneous vagus nerve stimulation

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ClinicalTrials.gov Identifier: NCT01174498
Vagus nerve stimulation in awake rats reduces formalin-induced nociceptive behavior and fos-immunoreactivity in trigeminal nucleus caudalis

- 4 experimental groups
  - Left cervical vagus nerve stimulation (VNS)
  - Formalin injection into left vibrissal pad
  - VNS and formalin injection
  - Sham VNS

<table>
<thead>
<tr>
<th>Experimental groups</th>
<th>Fos-Immunoreactive neurons</th>
<th>Pain behaviour Cumulative time (sec)</th>
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<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Group 1 VNS only</td>
<td>20.4 ± 5.7</td>
<td>8.8 ± 3.6</td>
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<tr>
<td>Group 2 Formalin only</td>
<td>68.9 ± 17.6</td>
<td>7.3 ± 4.9</td>
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<tr>
<td>Group 3 VNS + Formalin</td>
<td>45.8 ± 14.4</td>
<td>14.6 ± 3.5</td>
</tr>
<tr>
<td>Group 4 Sham VNS</td>
<td>5.9 ± 1</td>
<td>3.7 ± 0.8</td>
</tr>
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</table>

- VNS inhibits sensory neurons in the brainstem and pain-related behavior on the ipsilateral side.
Left vagus nerve stimulation suppresses experimentally-induced pain

- 2 experimental groups
  - 10 patients with drug resistant epilepsy
  - 12 healthy, age-matched volunteers

- Experimentally-induced pain (hand)
  - Mechanical impact: pain threshold, wind-up
  - Tonic pressure (pinch)

- No effect on mechanical pain threshold.
- Reduction of wind-up.
- Reduction of tonic pressure pain.
- Results suggest influence of VNS on central pain processing.

Kirchner et al., Neurology 55: 1167-71, 2000
Transcutaneous vagus nerve stimulation (t-VNS)

Auricular branch of vagus nerve supplies the concha as shown by:

- **Intracranial section of the vagus nerve in man** (Fay, J Neurol Psychopathol 8: 110-23, 1927)
- **Isolated vagus nerve palsy with herpes zoster** (Ohashi et al., Rinsho Shinkeigaku 34: 928-9, 1994)
- **Auricular syncope** (Thakar et al., J Laryngol Otol 122: 1115-7, 2008)
- **Gastroauricular phenomenon** (Engel, Arch Psychiat Nervenkr 227: 271-7, 1979)
- **Referred, auricular pain secondary to lung neoplasms** (Eross et al., Cephalalgia 23:2–5, 2003)
t-VNS affects pain processing in man – Study design

- Randomized, controlled, crossover study (ClinicalTrials.gov Identifier: NCT01174498)
- 48 healthy volunteers: 24 female, 24 male, 23.3±2.1 years
- 2 sessions with or w/o active t-VNS in randomized order
- Quantitative Sensory Testing (QST) on left and right hand dorsum

![Diagram showing the study design with QST on left and right hand dorsum, and active and sham t-VNS sessions.]

**Active t-VNS (25 Hz, 250 μs, tingling)**

**Sham t-VNS (attached, no current)**
t-VNS affects pain processing in man – Results

- Increased pressure pain threshold (PPT) on left hand during t-VNS
  2-way ANOVA: interaction between stimulation and side, p<0.05 (sham vs. t-VNS: 402 vs. 432 kPa)
t-VNS affects pain processing in man – Results

- Increased pressure pain threshold (PPT) on left hand during t-VNS
  2-way ANOVA: interaction between stimulation and side, p<0.05 (sham vs. t-VNS: 402 vs. 432 kPa)

- Reduced mechanical pain sensitivity (stimulus-response function)
  2-way ANOVA: interaction between stimulation and side, p<0.05 (sham vs. t-VNS: 3.2 vs. 2.1)
t-VNS affects pain processing in man – Results

- **Increased pressure pain threshold (PPT) on left hand during t-VNS**
  2-way ANOVA: interaction between stimulation and side, p<0.05 (sham vs. t-VNS: 402 vs. 432 kPa)

- **Reduced mechanical pain sensitivity (stimulus-response function)**
  2-way ANOVA: interaction between stimulation and side, p<0.05 (sham vs. t-VNS: 3.2 vs. 2.1)

- **Reduced sensitivity for sustained heat pain**
  ANOVA: stimulation p<0.001, time p<0.0001

![Graph showing pain intensity over time](image)
Summary and Conclusion

- VNS in rats inhibits sensory neurons in the brainstem and pain-related behavior on the ipsilateral side.
- VNS in epilepsy patients inhibits wind-up and tonic pressure pain. Spinal or even supraspinal mechanisms may be involved.

- t-VNS inhibits deep muscle pain processing on the ipsilateral side.
- t-VNS flattens the stimulus-response function of pinprick pain.
- t-VNS reduces temporal summation of noxious heat.

- t-VNS affects pain processing but does not interfere with innocuous somatosensory processing.
- t-VNS seems to activate CNS mechanisms of pain modulation.
- Future studies will address potential analgesic effects in patients.