Stimulation of Human Thalamus for Pain Relief: Possible Modulatory Circuits Revealed by Positron Emission Tomography

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1Département de stomatologie, Faculté de médecine dentaire and 2Centre de recherche en sciences neurologiques, Université de Montréal, Montréal, Québec, Canada, H3C 3J7; 3Department of Neurology and Neurosurgery, Faculty of Medicine, 4Faculty of Dentistry, and 5Department of Anesthesiology, Faculty of Medicine, McGill University, Montréal, Québec, Canada; and 6Université du Québec en Abitibi-Témiscamingue, Rouyn-Noranda, Québec, Canada; and 7Department of Neurology and Neurosurgery, University Hospital, Gasthuisberg, Louvain, Belgium

Duncan, Gary H., Ron C. Kupers, Serge Marchand, Jean-Guy Villemure, Jan M. Gybels, and M. Catherine Bushnell. Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography. J. Neurophysiol. 80: 3326 ± 3330, 1998. Stimulation of the somatosensory thalamus was used for more than 2 decades to treat chronic pain in the human. However, despite clinical reports of successful results, little is known about the actual mechanisms mediating this form of stimulation-produced analgesia. To reveal possible neuronal pathways evoked by thalamic stimulation, we measured regional changes in cerebral blood flow (rCBF) in five patients who received successful long-term relief of chronic pain with somatosensory thalamic stimulation. Positron emission tomography during thalamic stimulation revealed significant activation of the thalamus in the region of the stimulating electrodes as well as activation of the insular cortex ipsilateral to the thalamic electrodes (contralateral to the patients’ clinical pain). For these patients, thalamic stimulation also evoked paresthesiae that included thermal sensations in addition to tingling sensations. Results of this study indicate that in some cases somatosensory thalamic stimulation may activate a thalamocortical pain modulation circuit that involves thermal pathways. These results are consistent with other recent reports suggesting that activation of thermal pathways may contribute to modulation of nociceptive information.

INTRODUCTION

The first reports of direct electrical stimulation of the somatosensory thalamus (ventroposterior lateral and medial; VPL/VPM) to treat chronic pain in the human appeared in the early 1970s (Hosobuchi et al. 1973; Mazars et al. 1973, 1974). This procedure is most often employed for treating neuropathic pain and was used with varying success during the last 3 decades. Nevertheless, despite numerous clinical studies reporting pain relief, the success of thalamic stimulation for the treatment of chronic pain remains unpredictable (see Duncan et al. 1991; Gybels and Kupers 1995; Kumar et al. 1997). Furthermore, evaluation of stimulation-produced pain relief is difficult because there can be a large placebo effect (Marchand et al. 1992). Mazars originally stimulated the ventroposterior thalamus in patients suffering from deafferentation pain, based on the theory that such pain is caused by lack of proprioceptive stimuli reaching the thalamus (Head and Holmes 1911). Stimulating the primary somatosensory pathway at this thalamic site was an effort to compensate for the lack of normal sensory input (Mazars et al. 1974). The gate control theory (Melzack and Wall 1965) further championed the idea that stimulation of low threshold somatosensory pathways inhibits pain; thus direct stimulation of this pathway at the thalamic level would be expected to reduce neuropathic pain, which is characterized by loss of such input after damage in the peripheral or CNS. Physiological studies in anesthetized animals confirmed that stimulation in VPL thalamus inhibits the activity of both spinthalamic nociceptive neurons in monkey (Gerhart et al. 1981, 1983) and thalamic parafascicular nociceptive neurons in rat (Benabid et al. 1983). However, there is little behavioral evidence in animals confirming the predicted stimulation-produced analgesia, although Kupers and Gybels (1993) found that VPL stimulation in rat reduces mechanical allodynia in a model of neuropathic pain.

To elucidate cerebral mechanisms potentially associated with VPL/VPM-produced analgesia, this study utilizes positron emission tomography (PET) to examine, in human subjects, regional changes in cerebral blood flow (rCBF) evoked by thalamic stimulation. Results of this study were reported in abstract form (Duncan et al. 1997).

METHODS

Participants in this study were five patients (4 females, 1 male; mean age: 58 yr, range: 43–78 yr), for whom electrical stimulation of the somatosensory thalamus produced satisfactory long-term relief from chronic neuropathic pain. Only subjects having pain relief for ≥3 yr were studied to reduce the possibility of placebo effects contributing to the analgesia. The regions of pain involvement included the face, hand, low back, and leg. Before any testing, patients gave informed consent for their participation in this study, which was approved by the local ethics committee of the Montreal Neurological Institute.

During preliminary sessions, patients were trained to use 100-mm visual analog scales (VASs) to rate their levels of clinical
Mic stimulation for pain relief and paresthesiae. Weaker activations were observed in cortical sites, but as typically guided by the patient's report of paresthesiae, which are evoked by electrical stimulation as the electrode advances through the thalamus.

Patient data are summarized in Table 1. All patients selected for the study reported satisfactory pain relief from thalamic stimulation for ≈3 yr (mean duration: 4.5 yr). With normal regular use of the thalamic stimulators in their home environment, they reported a mean reduction in clinical pain of ~60%. However, this relief was not always immediately time locked to the onset of stimulation but rather reflects a global comparison of pain between periods of regular stimulator use and periods during which the stimulators were not used at all. During scanning sessions, three of five subjects had an immediate reduction in pain on onset of the thalamic stimulation, whereas two subjects did not. Nevertheless, both of these latter subjects reported substantial long-term relief with repeated stimulation. All participants reported paresthesiae during thalamic stimulation. A postexperiment questionnaire (a single-blind checklist allowing responses concerning a variety of possible sensations) mailed to the patients several months after the scans revealed that during regular home use thalamic stimulation produced sensations of prickling, tingling, hot, warm, or cold (based on the responses of 3 of 5 patients questioned; of the remaining 2, 1 died and 1 could not be reached; see Table 2).

**Table 1. Study participants**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pain Site</th>
<th>% Pain Relief at Home</th>
<th>Pain Intensity* Before Thalamic Stimulation</th>
<th>Pain Intensity* During Thalamic Stimulation</th>
<th>Paresthesia* Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Face</td>
<td>90</td>
<td>35</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>C</td>
<td>Low back, leg</td>
<td>69</td>
<td>24</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>A</td>
<td>Face</td>
<td>70</td>
<td>20</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>D</td>
<td>Face</td>
<td>25</td>
<td>43</td>
<td>53</td>
<td>72</td>
</tr>
<tr>
<td>S</td>
<td>Hand</td>
<td>60</td>
<td>15</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

* Numerical value on a 100-mm visual analog scale.

**Table 2. Temperature paresthesiae**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Paresthesia</th>
<th>Rating*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Hot</td>
<td>3</td>
<td>Heats more when I turn it up</td>
</tr>
<tr>
<td>D</td>
<td>Warm</td>
<td>5</td>
<td>First Tingling, then after a few seconds... face becomes warm</td>
</tr>
<tr>
<td>S</td>
<td>Cold</td>
<td>8</td>
<td>Painful hand becomes cold, like touching marble</td>
</tr>
</tbody>
</table>

* Numerical ratings on a 0 (no sensation) to 10 (extremely intense) scale.

1 During surgical implantation, placement of the thalamic electrode is typically guided by the patient's report of paresthesiae, which are evoked by electrical stimulation as the electrode advances through the thalamus. Electrodes are normally targeted within thalamus so as to maximize these sensory paresthesiae projected to the site of clinical pain. This induction of stimulation-produced paresthesiae is frequently considered a prerequisite for pain relief with thalamic stimulation.

2 PET scans were obtained with the Scanditronix PC-2048 system, which provides 15 image slices 6.5 mm apart with a transverse image resolution of 4.6–6.4 mm and an axial resolution of 5.4–7.1 mm (Evans et al. 1989, 1991). Data were collected in two sequential frames of 40 and 20 s; data presented here are derived from the 40-s frame, which yielded the better signal-to-noise ratio.
TABLE 3. Thalamocortical activation sites

<table>
<thead>
<tr>
<th>Structure</th>
<th>Coordinates*</th>
<th>t-Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x, y, z</td>
<td>LATE—BEFORE†</td>
</tr>
<tr>
<td>Thalamus/lenticular nucleus</td>
<td>25, −12, 0</td>
<td>4.8§</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>43, 10, −3</td>
<td>3.0§</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>0, 2, 33</td>
<td>2.2</td>
</tr>
<tr>
<td>S1</td>
<td>17, −26, 65</td>
<td>2</td>
</tr>
<tr>
<td>S2</td>
<td>40, −15, 15</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* Stereotaxic coordinates, based on Talairach and Tournoux (1988), for activation peaks observed in LATE—BEFORE subtraction (x, medial—lateral; y, anterior—posterior; z, superior—inferior).
† t-scores for peaks related to thalamic stimulation after 30 min.
‡ Maximum t-scores observed within the target region after 1 min of thalamic stimulation.
§ P < 0.05 (tα = 2.57, one-tailed, corrected for 10 multiple comparisons).

lation. The largest and only significant cortical activation site was localized within the rostral insula, ipsilateral to the thalamic stimulation (Fig. 1C). There were smaller nonsignificant blood flow increases in S1 cortex (Fig. 1A), the major output target for tactile information traveling through the sensory thalamus. Although this activation was weak, it was centered in the region of S1 ipsilateral to the site of thalamic stimulation, as predicted by the presence of localized tingling paresthesiae. Another nonsignificant activation was present near the midline in the anterior cingulate cortex. Finally, in the region of S2, the stimulation-related increase in blood flow yielded a t-value of only 0.8, suggesting no tendency for activation in this area.

Subtractions of AFTER—BEFORE did not reveal significant changes in S1, S2, insula, or anterior cingulate cortex. However, there was a significant reduction in posterior thalamic activity ipsilateral to the stimulation, after it was terminated compared with before it began [Talairach coordinates: 6, −29, 0 (t = 3.89); 12, −7, 7 (t = 2.9)].

Because only three patients showed immediate pain relief at the time of stimulation, additional separate analyses were performed for patients with and without immediate pain reduction. Table 4 shows that, although both groups had significant activation in the region of thalamus during stimulation, this activation was more robust and somewhat more rostrally located in the patients with immediate pain relief. In addition, the three patients with immediate relief showed significant activation in the rostral insula, whereas those without immediate relief showed a lesser, nonsignificant activation in a similar region. However, the larger number of subjects contributing to the analysis in the relief group could explain the larger t-values, which do not necessarily mean that activation was stronger. Although neither group showed a significant activation in S1, S2, or anterior cingulate cortex, the subjects without immediate relief showed a tendency toward increased rCBF in S1 cortex. One of these subjects experienced an intense tingling paraesthesia during stimulation (Table 1), which may be reflected in these data. Separate analyses of AFTER—BEFORE for patients with and without immediate pain relief did not reveal significant differences in rCBF in any pain-related areas for either group. The thalamic decreases observed in the larger group analysis were no longer significant when the subjects were divided into two groups.
evidence that cold inhibits pain processing (Bini et al., 1984; Hsieh et al., 1995), but during experimental pain (Casey et al., 1996; Coghill et al., 1997). The importance of different modulatory pathways for the relief of neuropathic pain is the sole mechanism underlying success in the relief of chronic neuropathic pain (Craig et al., 1994b; Davis et al., 1997). The activation of anterior cingulate cortex (ACC) activation in stimulation-produced pain relief involved the temperature-related activation of the insular cortex in an illusion of pain produced by a combination of warm and cool skin stimulation (Craig and Bushnell, 1994a; Craig et al., 1996a). The hypothesis was supported by the patients’ reports that, in addition to tactile paresthesiae that was originally targeted during electrode placement, they also perceived thermal sensations of cold and warm during thalamic stimulation. The close proximity of microstimulation sites evoking tactile and thermal sensations, observed by Lenz et al. (1993) and Dostrovsky et al. (1992), indicates that the thalamus is an important pain-inhibitory pathway (Craig and Zhang, 1996b; Craig et al., 1996a).

The possibility of an anterior cingulate cortex (ACC) activation in stimulation-produced pain relief is not clear. We observed a (nonsignificant) trend toward activation in ACC with thalamic stimulation; however, neither nonpainful thermal nor tactile stimulation was observed to activate this region (Casey et al., 1994; Coghill et al., 1994; Craig et al., 1996a), whereas painful stimulation reliably activates it (Casey et al., 1996; Coghill et al., 1994; Craig et al., 1996a; Derbyshire et al., 1994; Hsieh et al., 1995; Jones et al., 1991; Rainville et al., 1997; Talbot et al., 1991). The possibility exists that the patients’ recognition of the thalamic stimulation conditions triggered attention-related processes within the ACC that were observed to be distinct from those related to nociceptive processing (see Davis et al., 1997).

In conclusion, the results of this study suggest that in some patients stimulation of somatosensory thalamus may activate thalamocortical circuits involved in thermal as well as tactile processing. Whereas the original theoretical basis for analgesic thalamic stimulation involved activation of tactile thalamocortical pathways, the current data suggest that the activation of thermal pathways may provide an important contribution to a consistent long-term pain relief in some patients. Further studies of larger patient groups with different electrode placements would be necessary to determine the relative importance of different modulatory pathways for the relief of chronic neuropathic pain.

We express our appreciation to Dr. K. Kumar for help in identifying appropriate patients for this study, Medtronic Canada for financial support of patients’ travel arrangements, and F. Belanger and P. Rainville for assistance in preparing the manuscript and illustrations.

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### Table 4

Comparison of activation sites for patients with (n = 3) and without (N = 2) immediate pain relief

<table>
<thead>
<tr>
<th>Coordinates and r-Scores</th>
<th>Immediate relief</th>
<th>No immediate relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus/lenticular nucleus</td>
<td>23, −18, 0, t = 5.5*</td>
<td>20, −28, 0, t = 3.3*</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>31, 0, 21, t = 2.8*</td>
<td>41, 4, 10, t = 1.7</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>45, −7, 7, t = 2.0</td>
<td>37, −4, 0, t = 1.7</td>
</tr>
<tr>
<td>S1</td>
<td>Nothing†</td>
<td>Nothing†</td>
</tr>
<tr>
<td>S2</td>
<td>13, −35, 74, t = 2.3</td>
<td>Nothing†</td>
</tr>
</tbody>
</table>

P < 0.05 (t = 2.57, one-tailed, corrected for 10 multiple comparisons).

† No peak with an r-value greater than 1.0.
REFERENCES


WILLIS, W. D. Inhibition of primate spinothalamic tract neurons by stimulation in ipsilateral or contralateral ventral posterior lateral (VPL) thalamic nucleus. Brain Res. 229: 514–519, 1981.


