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

GARY H. DUNCAN,1,2,3 RON C. KUPERS,2 SERGE MARCHAND,4,6 JEAN-GUY VILLEMURE,3 JAN M. GYBELS,7 AND M. CATHERINE BUSHNELL2,3,4,5

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

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

3326 0022-3077/98 $5.00 Copyright © 1998 The American Physiological Society

31-18-98 14:53:57 neupal LP-Neurophys
pain and thalamic-stimulation-produced paresthesiae. Subsequently, each patient participated in two PET scanning sessions, conducted on consecutive days. Each session consisted of four scanning conditions: a prestimulation baseline (BEFORE); an early stimulation scan (EARLY), started 1 min after onset of the thalamic stimulation; a late stimulation scan (LATE), conducted 30 min after onset of the stimulus but while the stimulus was still active; and a final scan (AFTER), which was started 5 min after thalamic stimulation was terminated. Patients gave VAS ratings of their pain immediately after each scan and a VAS rating of their paraesthesia. Patients refrained from therapeutic stimulation for 12 h before each scanning session.

Standard PET techniques were used to measure (without arterial blood sampling) rCBF after bolus injections of 30–40 mCu H15O (Fox and Mintun 1989). Subjects lay immobilized in the scanner with eyes closed. Scans began 15 s postinjection, lasted for 60 s, and were separated by 12–15 min to allow the tracer to decay to background levels.

Each subject’s PET volumes were transformed into the Talairach coordinate system (Talairach and Tournoux 1988) and coregistered with each other by using automated methods of Collins et al. (1994). Statistical brain maps comparing the various experimental conditions were derived from normalized data averaged across the five patients (Worsley et al. 1992). Directed searches of the subtracted brain volumes were subsequently performed assessing changes in CBF within thalamic and in cortical regions that receive somatosensory thalamic projections in primates (S1, secondary somatosensory cortex (S2), insular cortex, and anterior cingulate cortex). Subtractions of LATE–BEFORE and EARLY–BEFORE were performed to examine cerebral regions directly activated by therapeutic thalamic stimulation. The subtraction of AFTER–BEFORE was performed to reveal pain-related cerebral regions in which activity might be reduced as a result of thalamic stimulation. Threshold for statistical significance was set at $P < 0.05$, one-tailed, corrected for multiple comparisons.

Results

Pain relief and paresthesiae

Patient data are summarized in Table 1. All patients selected for the study reported satisfactory pain relief from thalamic stimulation for $\geq 3$ 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 $\sim 60\%$. 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 stimulat- or 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 pricking, 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).

Stimulation-related changes in rCBF

Table 3 describes response peaks observed in directed searches of thalamocortical somatosensory regions for subtractions of LATE–BEFORE and EARLY–BEFORE. The most evident change in rCBF related to thalamic stimulation was seen as a large, widespread activation in the region approximating the thalamic stimulation site itself (including VPL, internal capsule, and the lenticular nucleus) contralateral to the patient’s clinical pain problem. This increase in blood flow was present at the time of the EARLY scans, taken 1 min after stimulation began, but was much stronger toward the end of stimulation, as shown in the comparison of LATE and BEFORE scans (Fig. 1B).

Weaker activations were observed in cortical sites, but as with the blood flow changes near the thalamus these activations were more pronounced after continued thalamic stimu-

---

**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.
Thalamocortical activation sites

<table>
<thead>
<tr>
<th>Structure</th>
<th>Coordinates* x, y, z</th>
<th>t-Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LATE—BEFORE†</td>
</tr>
<tr>
<td>Thalamus/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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).

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.
TABLE 4. Comparison of activation sites for patients with \((n = 3)\) and without \((N = 2)\) immediate pain relief

<table>
<thead>
<tr>
<th>Coordinates and (t)-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></td>
<td>45, –7, 7 (t = 2.0)</td>
<td>37, –4, 0 (t = 1.7)</td>
</tr>
<tr>
<td>Anterior cingulate S1</td>
<td>Nothing†</td>
<td>Nothing†</td>
</tr>
<tr>
<td></td>
<td>13, –35, 74 (t = 2.3)</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate S2</td>
<td>Nothing†</td>
<td>Nothing†</td>
</tr>
</tbody>
</table>

\(P < 0.05\) \((t_u = 2.57,\) one-tailed, corrected for 10 multiple comparisons). † No peak with a \(t\)-value greater than 1.0.

DISCUSSION

In this study, we observed that low frequency \((< 100 \text{Hz})\) thalamic stimulation produces an increase in rCBF in and near the thalamus contralateral to the painful body site and in some cortical projection sites, with the effect being more prominent with continued stimulation. This increase in thalamic and cortical activity is similar to that observed by Katayama et al. (1986), who used lower-resolution PET in patients receiving ventroposterior thalamic stimulation for pain control. We also observed a decrease in thalamic activity after stimulation compared with before, which could reflect a decrease in nociceptive sensory transmission that might underlie the therapeutic effects of thalamic stimulation.

The original hypothesis of Mazars that thalamic stimulation may produce analgesia by activating tactile thalamocortical pathways that were inactivated by nerve or neuronal damage is only weakly supported by our data. Although there was a tendency for activation in the region of S1, this effect was nonsignificant and was stronger for patients who did not receive immediate pain relief. The differential placement of the patients’ electrodes within thalamus (to produce a paresthesia in the region of pain specific to that patient) would lead to slightly different S1 projections in each patient, which might partially account for the weak average S1 response. A significant S1 activation related to analgesic thalamic stimulation was found by Katayama et al. (1986) with lower resolution rCBF measures. Nevertheless, our data do not support the hypothesis that activation of tactile thalamocortical pathways is the sole mechanism underlying successful thalamic stimulation-produced analgesia.

In our study, the most prominent cortical increase in rCBF was found in the rostral insula, ipsilateral to the thalamic stimulation site. Although similar activation was observed for patients with and without immediate pain relief, it was somewhat stronger for those with immediate effects. Previous PET studies have shown that this region is activated during experimental pain (Casey et al. 1996; Coghill et al. 1994; Craig et al. 1996a; Derbyshire et al. 1994; Rainville et al. 1997) and neuropathic pain (Hsieh et al. 1995), but in addition it is activated by both warm and cool innocuous temperatures applied to the skin (Craig et al. 1996a). In monkeys, both nociceptive and thermoreceptive neurons were observed within the rostral insula (Dostrovsky and Craig 1996), and this region receives a strong projection from the VMpo thalamic nucleus (Bushnell et al. 1995), which is subjacent to VPM and contains both nociceptive and thermoreceptive neurons (Craig et al. 1994b). VMpo was identified anatomically in humans (Craig et al. 1994b), and stimulation in the region of human VMpo can evoke painful but more commonly thermal sensations (Davis 1996; Dostrovsky et al. 1992; Lenz et al. 1993). On the basis of evidence that cold inhibits pain processing (Bini et al., 1984; Osgood et al. 1990; Schoenfeld et al. 1985; Wahren et al. 1989; Yarnitsky and Ochon 1990) and the probable involvement of 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), Craig proposed that the temperature projection involving VMpo and anterior insula is an important pain-inhibitory pathway (Craig and Zhang 1996b; Craig et al. 1996a).

The activation of anterior insular cortex during thalamic stimulation of patients receiving long-term pain relief suggests that activation of temperature pathways may be an important component of the analgesia for some patients. This hypothesis was supported by the patients’ reports that, in addition to tactile paresthesias 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 bipolar stimulating electrodes used for pain relief could easily stimulate neurons within both the VMpo-insular and VPL/VMpo-S1 pathways.

The possible role of 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 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. Bélandier and P. Rainville for assistance in preparing the manuscript and illustrations.

Supported by grants from the Medical Research Council of Canada. Positron emission tomography was performed at McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada.
REFERENCES


Address for reprint requests: G. H. Duncan, Centre de recherche en sciences neurologiques, C. P. 6128, Succursale Centre-ville, Universite de Montreal, Montréal, Quebec, Canada, H3C 3J7.

Received 19 February 1998; accepted in final form 8 September 1998.

DUNCAN ET AL.