Spontaneous neuronal hyperactivity in the medial and intralaminal thalamic nuclei of patients with deafferentation pain

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Electrical activity was recorded from single cells in the thalamus of 10 patients with chronic pain associated with deafferentation. Under local anesthesia, these patients underwent either electrode implantation or thalamotomy for treatment of their pain. In eight of the 10 patients, single units were identified as discharging spontaneously in high-frequency, often rhythmic, bursts. The discharges were of two types: short bursts comprised of two to six spikes with a burst frequency of one to four per second; and long trains of 30 to 80 spikes of similar frequency. Reconstruction of electrode trajectories indicated that recordings were made from the region corresponding to the lateral aspect of the mediodorsal thalamic nucleus, the central lateral nucleus, a small part of the central median nucleus, and the parafascicular nucleus. In the eight patients in whom spontaneous neuronal burst activity was exhibited, it was impossible to study activity evoked by natural cutaneous stimulation due to the continuous spontaneous neuronal discharges.

Both animal and human studies have suggested that pain related to deafferentation is accompanied by spontaneous hyperactivity in the dorsal horn of the spinal cord and in the ventral posterior thalamic nuclei. The authors present evidence of spontaneous neuronal hyperactivity in the intralaminal thalamic nuclei of patients with pain related to deafferentation. The findings suggest that spontaneous neuronal discharge in patients with pain related to deafferentation is more widespread in the central nervous system than has been previously appreciated. The results have important implications for the surgical treatment of chronic pain.

Key Words • pain • thalamus • neurophysiology • neuron

Chronic intractable pain is often observed in patients following various forms of deafferentation. Such pain is usually referred to as "central pain" and has been found in various conditions such as avulsion of the brachial and lumbosacral plexuses, post-herpetic neuralgia, spinal cord injury, injury to peripheral nerves, and cerebral infarctions located in the somatosensory pathways. The pathophysiological basis for pain following deafferentation is unclear. It has been more than 20 years since Loeser, et al. demonstrated spontaneous hyperactive and bursting neurons located in the spinal cord of a patient who suffered chronic pain related to spinal cord injury. They proposed that these spontaneously hyperactive neurons might be the generator mechanism for the pain experience in deafferentation. Abnormal brain activity associated with chronic pain syndromes was described in a number of patients by Nashold and Wilson and Gucer, et al. Subsequent animal experiments confirmed that deafferentation by means of peripheral neurectomy or rhizotomy results in spontaneous neuronal hyperactivity. Tasker and colleagues recently described spontaneous neuronal hyperactivity in the thalamic nucleus ventralis posterolateralis of patients with chronic deafferentation pain.

The present study reports the finding of spontaneous neuronal hyperactivity in the central lateral, central median, and parafascicular nuclei in eight of 10 patients with intractable pain related to deafferentation. Our study suggests that spontaneous neuronal hyperactivity is much more widely distributed throughout somatosensory pathways than has previously been described. The findings have important implications for surgical treatment of pain related to deafferentation.

Throughout this paper the nomenclature and parcelation of thalamus suggested by Hirai and Jones is employed unless the work of others is being described. Thus, the nucleus centralis thalami of Hassler is termed
the central median nucleus, the nucleus medialis dorsalis is the mediodorsal nucleus, the nucleus intralaminaris is the central lateral nucleus, and the nucleus parafascicularis is the parafascicular nucleus. They are all considered by Jones to be associated with the internal lamina.

Clinical Material and Methods

Recordings were performed in 10 patients who underwent either chronic electrode implantation or thalamotomy for treatment of intractable pain (Table 1).

FIG. 1. Trajectories typical of those calculated for chronic electrode implantation in periventricular gray matter (PVG) or for thalamotomy in the central median nucleus (CM). The heavy solid lines represent the position of the cannula through which the recording electrode is introduced and guided through the brain. The broken lines represent the extent and path of the electrode for recording as it emerges from the cannula, 8.5 mm above the target (solid circles, lower). The medial track (PVG) is positioned at a lateral angle of 19° relative to the midsagittal plane and, because of its angle, passes through up to 5.5 mm before reaching the target, shown here by several frontal sections (F.p 5 to F.p 10). The more lateral track (CM) is positioned at a lateral angle of 10° relative to the midsagittal plane and, because of its anterior angle, would actually terminate 2 mm anterior to the frontal section shown (F.p 10). The frontal plane sections are modified from Schaltenbrand and Wahren and are calculated in millimeters posterior to the midpoint of the anterior commissure-posterior commissure line.

The extent of deafferentation varied from a small localized region related to a femoral neurectomy to an entire upper limb in a patient with brachial plexopathy associated with a pulmonary apex tumor. Also included was complete hemibody deafferentation in a patient with a cerebral infarction. As described in previous reports by Young, et al., prior to consideration for electrode implantation or thalamotomy, all patients had been exposed to numerous alternative treatment procedures in an attempt to provide relief for their pain.

All operative procedures were performed under local anesthesia. The patients received intermittent intravenous sedation with midazolam (a short-acting benzodiazepine) and fentanyl (an opioid analgesic) as necessary throughout the procedure. All patients responded normally to verbal communication. The Leksell stereotactic system was employed for electrode implantation and both computerized tomography (CT) scans and magnetic resonance (MR) images were utilized for target localization. Ventriculography was also employed in several of the patients. Target sites were located in the periventricular gray matter (PVG) and the thalamic
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Fig. 2. Action potentials typical of those recorded from cells encountered in the trajectories for the periventricular gray matter (PVG). These units were both recorded from the mediodorsal nucleus of a patient with chronic pain in the left arm and shoulder related to brachial plexus injury following rib resection for vascular insufficiency. In both cases, the units fired in an intermittently rhythmic pattern and were typical of bursting types described in the text. **Upper Left:** A unit recorded 6 mm above the target (see arrow in Fig. 1, F.p 7) showing short bursts of four to six spikes with durations of 10.6 to 22 msec and interspike intervals of 3 to 4.5 msec. The burst frequency was two to three/sec. Scale: vertical, 50 μV; horizontal, 0.1 sec. **Lower Left:** Detail of an individual burst from recording at upper left. Scale: vertical, 50 μV; horizontal, 20 msec. **Upper Right:** A unit recorded 7 mm above the target (see arrow in Fig. 1, F.p 5) showing longer bursts of 38 to 81 spikes with a burst duration of 200 to 430 msec and interspike intervals of 4 to 8 msec. The burst frequency was one to two/sec. Scale: vertical, 50 μV; horizontal, 0.1 sec. **Lower Right:** Detail of an individual burst similar to those shown at upper right. Scale: vertical, 50 μV; horizontal, 50 msec.

medial nuclei, primarily the central median. The final target for electrode placement in the PVG was 2 mm anterior to the posterior commissure, 1 to 2 mm lateral to the third ventricular wall, and at the level of the anterior commissure-posterior commissure (AC-PC) plane. For intralaminar thalamotomy, the target was 8 mm posterior to the midpoint of the AC-PC line, 1 to 4 mm above the AC-PC plane, and 6 to 9 mm from the midline. Target coordinates were varied in relation to size of the third ventricle and thalamus in each patient.

In all patients, the angle of approach of the electrode to the target was approximately 30° anterior with reference to the coronal plane and 10° to 39° lateral with reference to the sagittal plane. The electrodes were introduced via a burr hole located just anterior to the coronal suture and 15 to 25 mm lateral to the midline. Electrode trajectories were reconstructed using the Schaltenbrand and Wahren stereotactic atlas.29 Figure 1 depicts the typical recording trajectories.

Single-unit activity was recorded in unipolar fashion with a tungsten microelectrode which was advanced with a hydraulic microdrive. Recordings were begun 8.5 mm in advance of the intended target. Conventional amplification and recording techniques were used to store data digitally on magnetic tape for postoperative off-line analysis of individual cell activity. Monopolar electrical stimulation was delivered with a Grass stimulator and isolation unit.*

### Table 1
Results of electrode recordings in 10 patients with deafferentation pain

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Location of Pain</th>
<th>Etiology</th>
<th>Neuronal Hyperactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>arm &amp; shoulder lower brachial plexus injury C8–T1</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>leg</td>
<td>femoral neurectomy</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>trigeminal</td>
<td>post-herpetic neuralgia</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>trigeminal</td>
<td>post-herpetic neuralgia</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>hemibody</td>
<td>cerebral infarction</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>arm</td>
<td>spinal cord injury</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>C2–4</td>
<td>post-herpetic neuralgia</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>back &amp; leg</td>
<td>radiculopathy</td>
<td>yes</td>
</tr>
<tr>
<td>9</td>
<td>back &amp; leg</td>
<td>radiculopathy</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>arm</td>
<td>pulmonary apex tumor</td>
<td>no</td>
</tr>
</tbody>
</table>

**Results**

A total of 81 cells were observed. In eight of 10 patients with chronic pain, single cells were observed discharging with the action potentials organized in bursts. The frequency of these bursts varied from one to four/sec and they were often intermittently rhythmic depending on the individual unit (Fig. 2 upper traces).

*Model SU48 stimulator and Model SIU7 isolation unit manufactured by Grass Instrument Company, Quincy, Massachusetts.
The bursts were of two types: 1) short bursts made up of 2 to 6 spikes per burst with an intraburst frequency of 200 to 400/sec (Fig. 2 left and Fig. 3); and 2) long trains of 30 to 80 spikes with an intraburst frequency of 125 to 250/sec (Fig. 2 right). Occasionally, the two types of burst activity were recorded simultaneously from different cells and, when this occurred, both units had the same interburst frequency. Most cells encountered were the short-burst type.

Reconstructions of typical PVG and central median recording trajectories are shown in Fig. 1. For the more lateral trajectory, we calculated that the first bursting cells were encountered at the junction between the lateral portion of the mediodorsal and centralis lateralis-central mediodorsal area of the thalamus. They were present consistently until the inferior level of the central median nucleus was reached (Fig. 3). The firing characteristics of the cells did not seem to be affected by the patient’s state of wakefulness. Bursting units were recorded in patients during periods of quiet sleep as well as during arousal and, in fact, during periods of spontaneous physical activity and speech. Units with similar characteristics were encountered in the more medial trajectory in the mediodorsal and parafascicular nuclei (Fig. 2).

Cellular activity elicited by natural stimulation was impossible to study when spontaneously active bursting neurons were encountered. On the contrary, in the two patients in whom burst activity was not observed, peripheral receptive fields were identified for several cells in the intralaminar nuclei. In one patient, individual units in the parafascicular nucleus could be activated using light, brisk taps to the chin. The peripheral field was bilateral; tapping, but not stroking or brushing, evoked cellular unit responses. The number of action potentials per response was greater on contralateral than on ipsilateral stimulation. Cells with the same peripheral field localization were found during a total trajectory of about 750 μ in the medial thalamic nuclei. Just proximal to this recording point, units were identified which were activated by taps applied to the contralateral shoulder. Repetitive natural stimulation initially produced fairly rapid accommodation with a marked decrease in unit firing until the unit finally became refractory to further stimulation. When electrical stimulation (0.5 msec duration at 200 Hz and 0.04 mA to 0.05 mA) was applied to the same thalamic recording locus, it provoked a sensation of “pulling” in both sides of the face and in the shoulder and neck. This was a subjective sensation without any objective motor activity and at threshold was not painful. In another patient, recordings in the central median nucleus revealed many spontaneously bursting neurons with no identifiable peripheral fields (Fig. 3). Stimulation at this site produced a tingling in the contralateral hand. As the electrode was lowered another 2 mm, stimulation tests evoked a throbbing sensation, first in the arm, then in the shoulder.

Discussion

Neuronal Hyperactivity from Intralaminar Nuclei in Patients with Deafferentation Pain

This report describes for the first time spontaneously hyperactive neurons in the region of the intralaminar thalamic nuclei of patients with chronic pain related to deafferentation. Previous patient series have focused on the ventral posterior (lateral sensory) thalamus in relation to pain.

In the present study, reconstruction of the stereotactic coordinates based on CT and MR studies indicated...
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that the cells described were located mainly in a zone along the lateral border of the mediodorsal nucleus, the centralis lateralis, the medial border of the central median nucleus, and in the parafascicular nucleus. Neuronal hyperactivity was recorded from single units in the medial thalamic nuclei in eight of 10 patients with chronic pain related to deafferentation. In general, these units could not be activated by natural or electrical stimulation of any body region. Electrical stimulation of this region sometimes provoked a sensation of movement, throbbing, or pulling in the contralateral upper extremity and face. Ipsilateral sensory phenomena were not evoked.

The only other study of units in the medial thalamus focused on evoked unit activity in seven patients, of whom four suffered from intractable pain and three from spasmodic torticollis or seesaw nystagmus. To our knowledge, no recordings have been reported from this same area in normal subjects. Thus, it is impossible at this time to confirm that the burst activity observed in the present study represents definite pathology. We are suspicious, however, that the activity is pathological in character based on its similarities to the previously recorded pathological activity in the lateral sensory thalamus, as well as its similarity to the neuronal hyperactivity recorded in animal models of deafferentation.

In studies of neurons from these areas in animal models, some cells demonstrated a type of burst firing associated with the sleep-waking cycle and alerting responses. In preliminary studies, the units from which we recorded activity showed no changes in their firing patterns related to the arousal states of our patients and therefore most likely do not represent cells involved in arousal.

Thalamic Intralaminar Nuclei and Pain

From a physiological perspective, Albe-Fessard and Besson suggested that the intralaminar nuclei, centrum medianus, and parafascicular complex might play a role in nociception based on the demonstration that, in the monkey and cat, many neurons in these nuclei had heterotopic convergent responses, showing spatial and modality convergence and responses to noxious or rapid onset stimuli. Other animal studies verified the large receptive fields and responses to nociceptive stimuli in intralaminar regions. It has been suggested that the intralaminar nuclei most likely play a role in the affective-motor response or the detection of potentially harmful stimuli rather than in the sensory-discriminative aspects of pain. Axonal transport tracing techniques and physiological studies suggest that the primary efferent projections of the intralaminar nuclei are striatal, while there are also light and somewhat diffuse projections to the cerebral cortex. In addition, recent studies by Hirai and Jones have identified tachykinin- and/or enkephalin-immunoreactive fibers in human intralaminar nuclei with the exception of the centre median, thus linking these nuclei to the endogenous opiates.

Jones divided the intralaminar nuclei into a rostral group (central medial, paracentral, central lateral, and rhomboid nuclei) and a caudal group (central medial and parafascicular nuclei). Projections from the spinthalamo-thalamic tract and the trigeminal nuclei caudalis terminate in the central lateral nucleus and the adjacent so-called paralamellar portion of the mediodorsal nucleus. The latter is actually a posterior extension of the large-celled component of the central lateral nucleus. The central lateral thalamic nucleus is not represented per se in standard stereotactic atlases of the human brain; however, this general region has been designated the n. paralamellaris. In a new parcellation of the human thalamic nuclei, Hirai and Jones clearly identified the central lateral nucleus as a significant component of the intralaminar thalamic nuclei.

Neuronal Hyperactivity of Lateral Thalamic Nuclei and Deafferentation Pain

As mentioned above, past explorations of the human thalamus in relation to pain have focused on lateral sensory nuclei of the thalamus which form the primary receiving areas in the brain for sensory systems associated with painful stimuli. Tasker and colleagues, Lenz, et al., Hirayama, et al., and Gorecki, et al. described spontaneously hyperactive neurons in the lateral thalamic nuclei of a number of patients suffering from chronic pain related to deafferentation. Most of the cells investigated were located in the ventroposterolateral nucleus but a significant number were also located in the nucleus ventralis intermedius, with smaller numbers in the nucleus ventralis caudalis parvocellularis, nucleus ventralis oralis posterior, and zona incerta. Alteration in somatotopic organization of the deafferentated thalamus characterized by empty, displaced, and reorganized receptive fields was also described. These studies point to a distinct population of neurons which fired in bursts and were located in the lateral sensory thalamus of patients with pain due to deafferentation.

Clinical Implications

Deafferentation hyperactivity of central neurons has been identified in the thalamic intralaminar nuclear group (medial thalamus) as well as in the spinal cord and lateral somatosensory thalamus. The findings of a dual representation of neuronal hyperactivity in the lateral and medial thalamic is perhaps not surprising in view of the fact that these are the two primary thalamic targets for pain-related relays from the spinal cord, carried by the neospinothalamic and paleospinothalamic systems. The widespread nature of this neuronal hyperactivity, if it is truly a generator of the spontaneous burning pain of which such patients often complain, may explain why therapeutic measures such as dorsal root entry zone lesions in the spinal cord,

thalamic lesions in the lateral or medial thalamus, and electrical stimulation in the lateral thalamus fail to resolve pain in deafferentation states in a relatively high proportion of patients.

Perhaps a combination of therapies, possibly including thalamotomy in the intralaminar nuclei and chronic stimulation in the lateral nuclei, might produce higher success rates in the treatment of chronic pain due to deafferentation than either approach alone. In our experience, simultaneous electrical stimulation in the PAG and sensory thalamus provides a slightly increased success rate compared to sensory thalamic stimulation alone. As our knowledge of the altered physiology which accompanies such states expands, we may find abnormalities even more widespread than the current study suggests.

Acknowledgments

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