Reorganization in the Cutaneous Core of the Human Thalamic Principal Somatic Sensory Nucleus (Ventral Caudal) in Patients With Dystonia

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INTRODUCTION

Dystonia is a movement disorder characterized by sustained muscle contractions that lead to twisting movements and abnormal postures (Fahn 1988). Many observations suggest that dystonia is characterized by abnormal processing of sensory information (reviewed by Hallett 1995). Abnormal sensory activity, in fact, has been found in the CNS of patients with dystonia (dystonia patients) studied by positron tomography (Tempel and Perlmutter 1995). Monkeys with dystonia-like movements resulting from overtraining in a gripping task. We investigated whether similar reorganization occurs in the somatic sensory thalamus of patients with dystonia (dystonia patients). We studied recordings of neuronal activity and microstimulation-evoked responses from the cutaneous core of the human principal somatic sensory nucleus (ventral caudal, Vc) of 11 dystonia patients who underwent stereotactic thalamotomy. Fifteen patients with essential tremor who underwent similar procedures were used as controls. The cutaneous core of Vc was defined as the part of the cellular thalamic region where the majority of cells had receptive fields (RFs) to innocuous cutaneous stimuli. The proportion of RFs including multiple parts of the body was greater in dystonia patients (29%) than in patients with essential tremor (11%). Similarly, the percentage of projected fields (PFs) including multiple body parts was higher in dystonia patients (71%) than in patients with essential tremor (41%). A match at a thalamic site was said to occur if the RF and PF at that site included a body part in common. Such matches were significantly less prevalent in dystonia patients (33%) than in patients with essential tremor (58%). The average length of the trajectory where the PF included a consistent, cutaneous RF was significantly longer in patients with dystonia than in control patients with essential tremor. The findings of sensory reorganization in Vc, thalamic caudal parvocellular nucleus (Vcpc) (Lenz et al. 1999). Therefore, Vc was thoroughly examined in both patient groups. Analysis was restricted to the cutaneous core of Vc, defined as the region where the majority of cells respond to innocuous, cutaneous, mechanical stimuli. This region probably corresponds to Vc and thalamic ventral caudal parvocellular nucleus (Vcpc) (Lenz et al. 1988b, 1993b). The previously described operative, physiological, and analytic methods are outlined briefly here (Lenz et al. 1994b). The protocol used in these studies conforms to the principles stated in the Declaration of Helsinki regarding the use of human subjects and is reviewed and approved annually by the Johns Hopkins University Joint Committee on Clinical Investigation.

METHODS

Twenty-six patients were studied during the physiological exploration that precedes stereotactic thalamotomy for treatment of dystonia or essential tremor. The somatic sensory thalamus was explored in these patients to determine the anterior and inferior borders of Vc, which predict the borders of the thalamic nucleus ventral intermediate (Vim) and the thalamic nucleus ventral oral posterior (Vop), which are the nuclei to be lesioned during thalamotomy for dystonia or tremor (Bertrand and Lenz 1995; Hua et al. 1998; Lenz et al. 1994b; Zirh et al. 1999). Therefore, Vc was thoroughly examined in both patient groups. Analysis was restricted to the cutaneous core of Vc, defined as the region where the majority of cells respond to innocuous, cutaneous, mechanical stimuli. This region probably corresponds to Vc and thalamic ventral caudal parvocellular nucleus (Vcpc) (Lenz et al. 1988b, 1993b). The previously described operative, physiological, and analytic methods are outlined briefly here (Lenz et al. 1993, 1994b). The protocol used in these studies conforms to the principles stated in the Declaration of Helsinki regarding the use of human subjects and is reviewed and approved annually by the Johns Hopkins University Joint Committee on Clinical Investigation.

Operative procedures

The stereotactic coordinates of the anterior commissure-posterior commissure line were determined by computerized tomography or magnetic resonance imaging. The target region was explored with a microelectrode that was advanced along trajectories made through a burrhole located 1.5 cm lateral to the midline at the level of the coronal suture (Lenz et al. 1988a). The first trajectory was toward Vc,
the most reliable landmark for the exploration. Next, the regions anterior to Vc—presumed Vim and presumed Vop—were explored to identify the optimal lesion site. Physiological exploration with the microelectrode involved both recording of neuronal activity and stimulation at microampere current levels (Lenz et al. 1994b).

During recordings, we examined two aspects of neuronal activity in particular: spontaneous firing pattern and neuronal activity during somatic sensory stimulation. The somatic sensory examination included stimulation of both cutaneous structures and structures deep to the skin. Cutaneous sensory cells responded to touch or pressure applied to the skin. Deep sensory cells responded to joint movement and/or squeezing of muscles or tendons but did not respond to stimulation of the skin deformed by these stimuli.

Microstimulation was delivered through the microelectrode in trains of approximately 1 s duration at 300 Hz by means of a biphasic pulse consisting of a 0.2 ms anodal pulse followed 0.1 ms later by a 0.2 ms cathodal pulse of the same magnitude. The effect of the stimulation on dystonia was assessed with the patient’s arm elevated. Additionally, during stimulation, patients were asked if they felt anything. If any effect was observed, the current was first decreased in a series and then increased in a series until a threshold for the effect was established (threshold microstimulation; see Lenz et al. 1993). The quality and location of the evoked sensation (projected field, PF) was then determined.

The lesion site in dystonia patients was chosen at sites anterior to Vc where cells displayed activity related to the dystonia and had deep RFs, and where stimulation evoked changes in the patient’s dystonia. One or more lesions were made at sites with these properties. Lesions were made by introducing a radiofrequency lesioning electrode (outside diameter 1.1 mm, exposed length 3 mm) with a thermistor at the tip to monitor temperature (TM electrode, Radionics Inc., Burlington, MA). To make each lesion, the temperature of the electrode was held at 70° and then at 80° centigrade for 1 min for each temperature. Neurological examinations stressing pyramidal tract, sensory, speech, and cerebellar functions were carried out before, during, and after each lesion.

**Data analysis**

In this study, Vc in patients with essential tremor was compared with that in patients with generalized dystonia. Somatotopic organization was assessed by the number of different body parts included in PFs or in RFs, the match between RF and PF at one site, and the length of the trajectories with consistent RFs or PFs. A multiple-part RF for a single neuron is defined by the presence of two or more separate cutaneous parts of the body and a multiple-part PF is defined by the presence of two or more separate cutaneous parts of the body. In identifying parts of the body, we followed the conventions used in previous studies (Byl et al. 1996b; Lenz et al. 1988b). Specifically, separate parts of the body included separate digits, thenar eminence, hypothenar eminence, palm, forearm, upper arm, lip, chin, outer surface of the cheek, inner surface of the cheek, nose, forehead, tongue, gums, ear, thigh, lower leg, foot (excluding toes), and toes. When the RF and PF were limited to the same part of the body, they were said to form a match. When the RF and PF included both the same part of the body and other separate body parts, they were said to have a partial match. When the RF and PF did not overlap, they were said to form a mismatch.

Two sites were said to have a consistent RF if the RF of both sites included the same part of the body. The length of a trajectory with consistent RFs is the distance along the trajectory where each RF continues to include the same part of the body. The part of the body chosen for any trajectory length was the part that maximized the length of the trajectory with a consistent RF. The same convention was applied to PFs. Human thalamic somatotopy in Vc is a function of the mediolateral plane and rows of trajectories were aligned in parasagittal planes (Lenz et al. 1988b). The maximal distance along a trajectory over which the RF or the PF stays consistent is longer for body parts with larger representations (Lenz et al. 1994a). This technique of estimating the size of representations is arbitrary, but it conforms to our previous studies in humans (Lenz et al. 1994a, 1998b). The same conventions were applied to all patients studied.

**RESULTS**

These data describe the results of cellular recordings at 382 sites along 45 microelectrode trajectories for 15 patients with essential tremor and at 388 sites along 49 microelectrode trajectories through the cutaneous core of Vc in 11 dystonia patients (Table 1). Figure 1 is a map of RFs and PFs in the region of Vc for a patient with essential tremor; sites 77–97 constitute the cutaneous core of Vc. This map shows the representation of the digits and lip. As is common in patients with tremor (tremor patients), no neurons had multiple-part RFs in the cutaneous core of Vc. Multiple-part PFs occurred at

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**TABLE 1. Characteristics of dystonia patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Distribution</th>
<th>Etiology</th>
<th>Associated Signs</th>
<th>Age (Duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Face, neck, all limbs (especially RUE)</td>
<td>Idiopathic sporadic</td>
<td>None</td>
<td>64 (18)</td>
</tr>
<tr>
<td>B</td>
<td>LUE, LLE</td>
<td>Posthemiplegic</td>
<td>Left hemiparesis (including face), mild atrophy LLE</td>
<td>31 (29)</td>
</tr>
<tr>
<td>C</td>
<td>LUE</td>
<td>Probable corticobasal degeneration</td>
<td>Parkinsonism</td>
<td>65 (3)</td>
</tr>
<tr>
<td>D</td>
<td>LUE, LLE</td>
<td>Posthemiplegic</td>
<td>Left hemiparesis</td>
<td>13 (9)</td>
</tr>
<tr>
<td>E</td>
<td>RUE, RLE</td>
<td>Presumed encephalitis</td>
<td>Right hemiparesis, right Babinski, right hemiatrophy</td>
<td>37 (35)</td>
</tr>
<tr>
<td>F</td>
<td>LUE, LLE, RUE, neck, speech</td>
<td>Idiopathic sporadic</td>
<td>None</td>
<td>33 (25)</td>
</tr>
<tr>
<td>G</td>
<td>LUE, LLE, jaw</td>
<td>Idiopathic sporadic</td>
<td>None</td>
<td>36 (2)</td>
</tr>
<tr>
<td>H</td>
<td>All limbs, neck</td>
<td>Idiopathic familial</td>
<td>None</td>
<td>26 (18)</td>
</tr>
<tr>
<td>I</td>
<td>All limbs right &gt; left, trunk</td>
<td>Cerebral palsy</td>
<td>Right hemiplegia, increased reflexes throughout</td>
<td>21 (19)</td>
</tr>
<tr>
<td>J</td>
<td>LUE, LLE</td>
<td>Viral encephalitis</td>
<td>Left hemiplegia and Babinski</td>
<td>36 (30)</td>
</tr>
<tr>
<td>K</td>
<td>LUE, LLE</td>
<td>Posthemiplegic</td>
<td>Left hemiparesis</td>
<td>24 (20)</td>
</tr>
</tbody>
</table>

Age and duration of dystonia are at operation (in years). Patients D, E, F, and G were operated on twice. LUE, left upper extremity; RUE, right upper extremity; LLE, left lower extremity; RLE, right lower extremity.
FIG. 1. Map of cutaneous receptive fields (RFs) and projected fields (PFs) in the region of the thalamic ventral caudal nucleus (Vc) in a patient with essential tremor, displayed in the parasagittal plane. A: position of the trajectory relative to nuclear boundaries as predicted radiologically from the position of the anterior commissure-posterior commissure (AC-PC) line. The AC-PC line is indicated by the nearly horizontal line; the trajectory is shown by the oblique line. Left side of A represents anterior, top represents dorsal. Positions of the nuclei are inferred from the AC-PC line and therefore are only an approximate indication of nuclear location. ML, medial lemniscus; PC, posterior commissure; STN, subthalamic nucleus; Vc-por, thalamic nucleus ventral caudal portae; Vim, thalamic nucleus ventral intermediate; Vop, thalamic nucleus ventral oral posterior; WM, white matter. B: location of the cells, stimulation sites, and trajectories (S2) relative to the AC-PC. Locations of the stimulation sites are indicated by tick marks to the left of the trajectory and those of recorded cells by tick marks to the right of the trajectory. Cells with RFs are indicated by long tick marks and those without RFs by short tick marks. Scales are as indicated. Each site where a cell was recorded or stimulation was carried out, or both, is indicated by the same number in B and C. C: site numbers, with PF to the left of the vertical and RF to the right for a site. NR, no activity related to active movement or sensory stimulation.
5 of 8 stimulation sites (63%). The RF representation of the third digit (sites 77–81) was 0.95 mm long and the second digit (sites 82 and 83) was 0.31 mm long. The PF representation of the third digit (sites 77–80) was 0.5 mm long and the second digit (sites 83–92) was 2.8 mm long. Examples of mismatches are seen at sites 85 and 92.

A map for a patient with dystonia is shown in Fig. 2. The trajectory traversed the representation of cutaneous structures in the hand in the core of Vc (sites 14–22). In this patient, 5 of 9 cells (55%) in the cutaneous core of Vc had multiple-part RFs (thenar or hypothenar and palm, fourth/fifth and thumb/second digit). This patient had multiple-part PFs at 7 of 8 sites.

**FIG. 2.** Map of RFs and PFs in the region of the Vc in a patient with dystonia. Conventions as in Fig. 1. A phasic dystonia response is an increase in cellular activity occurring at the time of a transient increase in the patient’s dystonia, usually related to active movement.
Evidence of somatotopic reorganization: multiple-part RFs

The differences in the presence of multiple-part RFs and PFs for patients with essential tremor and those with dystonia are summarized in Table 2. Significantly more neurons with multiple-part RFs (chi square, $P < 0.00001$) and significantly more stimulation sites with multiple-part PFs occurred in dystonia patients than in tremor patients (chi square, $P < 0.0002$). Thus PFs and RFs involving more than one part of the body were significantly more common in dystonia patients than in tremor patients.

Length of trajectories with RFs or PFs

Figure 3 provides a visual representation of the length and distribution of the trajectories with consistent neuronal RFs for the controls and the dystonia patients. The trajectories with consistent PF were significantly longer [Fig. 3B, $P < 0.05$, Kruskal Wallis analysis of variance (ANOVA) by ranks] for dystonia patients than for controls with essential tremor. Lengths of trajectories with consistent RFs did not differ significantly (Fig. 3A, $P > 0.05$, Kruskal Wallis ANOVA by ranks) between these two patient groups.

Match between RFs and PFs

Each of the neuronal RFs and the PFs at a site was coded according to body parts (Fig. 4, inset), and all were plotted against each other (Fig. 4). For this section of the analysis, all digits together (labeled “multiple digits” in the inset) and the hand excluding digits (labeled “palm/hand” in the inset) were considered as separate parts of the body. The PF of a stimulation site where a cell was not recorded was paired with the RF of the closest recorded cell. For example, in Fig. 1, stimulation at site 88 was paired with the RF for the cell recorded at site 89. For any RF/PF pair, we plotted the part of the body to which the RF of the recorded cell was closest against the part of the body involved in the PF (Fig. 4A, essential tremor; Fig. 4B, dystonia). Thus points on the 45°-angle line indicate thalamic sites where the RF and PF matched or partially matched.

Table 2. Proportion of neurons associated with multiple-part receptive fields and stimulation sites associated with multiple-part projected fields: comparison of controls and dystonia patients

<table>
<thead>
<tr>
<th></th>
<th>PFs ($P &lt; 0.0002$)</th>
<th>RFs ($P &lt; 0.00001$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential tremor ($P &lt; 0.00001$)</td>
<td>47% (132/279)</td>
<td>11% (14/126)</td>
</tr>
<tr>
<td>Dystonia ($P &lt; 0.00001$)</td>
<td>71% (168/238)</td>
<td>29% (44/151)</td>
</tr>
</tbody>
</table>

$P$ values (chi square) apply to the row or column labeled.

The number of such sites was significantly higher (chi square, $P < 0.002$) in patients with essential tremor (36 of 62 or 58%) than in patients with dystonia (33 of 103 or 32%).

Effects of duration and age of onset of dystonia on reorganization

The effect of duration and age of onset of dystonia on reorganization in the cutaneous core of Vc was examined. The population of patients with duration of dystonia $<5$ yr ($n = 2$) was compared with that with duration of $>5$ yr ($n = 9$). The patients with the longer duration of dystonia had a significantly greater (chi square, $P < 0.001$) percentage of cells with multiple RFs (35.7%) than did patients with the shorter duration of dystonia (7.4%). Differences between these two groups in mismatches of RFs and PFs and in numbers of trajectories with constant RF length $>1$ mm were not significant.

The population of patients with onset at age $<10$ yr ($n = 8$) was compared with the population with age of onset $>33$ yr ($n = 3$). The patients with the younger age of onset had a significantly greater (chi square, $P < 0.001$) percentage of cells with multiple RFs (29.7%) than did the patients with later onset (6.7%). Differences between these two groups in mismatches of RFs and PFs and in numbers of trajectories with constant RF length $>1$ mm were not significant.

Discussion

The findings from this study suggest that significant somatotopic reorganization of Vc occurs in patients with dystonia. Given the input from Vc to the primary sensory cortex (Jones 1985), this finding is consistent with reports of somatic sensory reorganization in cortical area 3b in monkeys with focal dystonia caused by overtraining for a gripping task (Byl et al. 1996a,b, 1997). These results thus lend support to the suggestion that somatic sensory reorganization occurs in thalamocortical circuits as a result of, and perhaps as a cause of, dystonia.

Methodologic considerations

Time constraints in the operating room greatly limit mapping the human thalamus as compared with mapping the monkey cortex. To obtain enough data to draw conclusions about sensory reorganization, we collected data from a relatively large number of patients ($n = 26$). However, the total number of neuronal RFs and PFs for each patient was limited. Therefore, interindividual differences may significantly influence the results. For patients with essential tremor, there are no known neurological abnormalities other than tremor and the population is relatively homogeneous (Watts and Koller 1998). Maps of the thalamic location of RFs (Lenz et al. 1988a) and PFs (Lenz et al. 1993) are similar in essential tremor and many other disorders, but we have no way of knowing how such maps would compare with those of normal controls. An earlier detailed analysis of motor thalamus in the dystonia patients reported here suggested that characteristics of dystonia and sensory properties of neurons were relatively constant in this population (Lenz et al. 1999). Thus the major features of sensory organization may be similar among patients within each of the two groups. Finally, because our conclusions depend on comparisons of the two populations, the statistical techniques should account for the variability within each population.
The location of the core of Vc rests entirely on the physiological criteria. The region where the majority of cells respond to innocuous cutaneous stimuli probably corresponds to Vc and Vcpc (Lenz et al. 1988b, 1993); this is our inference based on comparisons with monkey studies employing histological confirmation of recording sites (Jones 1985, Kaas 1991). Of course, we have no way of anatomically confirming the location of the region described in this report.

Somatic sensory activity: somatotopic reorganization

Interruption of somatic sensory inputs leads to reorganization of somatotopic maps in the principal sensory nucleus of
the thalamus in monkeys and humans. Monkey or raccoon ventral posterior lateral pars caudalis, corresponding to human Vc (Jones 1985), has been studied after adult nerve injury or digit amputation (Garraghty and Kaas 1991; Rasmusson 1996). Increased representation of the stump of an amputated digit was found with large RFs that included both the stump and adjacent digits. In humans, major reorganization of inputs to Vc occurs in patients with chronic pain after spinal transection (Lenz et al. 1994a) or amputation (Davis et al. 1998; Lenz et al. 1998). Representations of the part of the body next to the area of sensory loss are increased and PFs are poorly matched to RFs. Thus changes in human thalamic organization are consistent with those found in animals after interruption of somatic sensory inputs.

The present results suggest that thalamic sensory organization is plastic and thus can be altered by dystonia, as it can be by deafferentiation. In this study involving sampling of cells from Vc, the cellular RFs were more likely to have multiple body segments represented in each RF in dystonia patients than in tremor patients. In addition, there was a poorer match between RFs and PFs at any site. Similar alterations in sensory organization in Vim in many of these same dystonia patients have been briefly described (Lenz et al. 1999). To our knowledge, that study and the present one are the only reports of
thalamocortical plasticity in the presence of alterations in motor behavior.

Neural plasticity in response to interruption of sensory input and motor behavior is better established in the cortex where it may arise, in part, as a result of thalamic reorganization. It is well known that cortex, specifically area 3b, adapts to interruption of sensory input after peripheral nerve transactions (Merzenich et al. 1983a,b, 1987; Wall et al. 1986), dorsal rhizotomies (Pons et al. 1991), surgical amputation (Kelaher and Doetsch 1984; Merzenich et al. 1984; Rassmussen 1982), surgical syndactyly (Clark et al. 1988), and nerve crush with skin reinnervation (Wall et al. 1983).

Training in different behavioral paradigms has been observed to change the representation of the body in the primate sensory cortex. Behavioral training at a constant skin locus (e.g., tip of one digit, Recanzone et al. 1992) and behavioral training in which stimuli move across the skin (Jenkins et al. 1990) produced changes in the cortical representation of the body. Cortical plasticity induced by behavior can be characterized by an increased differentiation of the representation of the body part, including unusually small RFs, and by an increased area of somatic sensory representation of the body part that is involved in the behavioral paradigm (Jenkins et al. 1990; Recanzone et al. 1992). Alternatively, de-differentiation of the representation of the body can occur and is characterized by unusually large RFs and a decreased area of somatic sensory representation (Merzenich et al. 1983b; Wang et al. 1995). Reorganization of the motor cortical representation can also result from learned repetitive motor tasks (Nudo et al. 1992, 1996). It is also likely that somatic sensory disorganization is a potential outcome of excessive use, chronic pain, or nearly coincident repetitive inputs (Byl et al. 1996b; 1997; Elbert et al. 1995; Flor et al. 1997; Wang et al. 1995). The effect of these behavioral manipulations appears to depend on the age of onset and the duration of the motor behavior (Kaas 1991), as in the present data.

Thalamocortical plasticity in dystonia

In monkeys, sensory cortex has been studied in dystonia-like movements induced by repetition of a motor task involving rapid opening and closing of a manipulandum (Byl et al. 1996b, 1997). These monkeys developed hand cramps characterized by disordered motor coordination and posturing reminiscent of dystonia (Byl et al. 1996b; Hallett 1995). In these animals, representations of the hand surface are remodeled in the primary sensory cortex, area 3b (Byl et al. 1996b, 1997). The cutaneous RFs extend across multiple digits and the whole hand. This somatotopic reorganization is strikingly different from the normal representation of the hand of the adult monkey, which is defined by small, distinct, orderly, topographical RFs (Kaas 1991; Merzenich et al. 1987). The present results demonstrate that similar changes in the thalamic cutaneous representation occur in dystonia patients.

The learning hypothesis for focal hand dystonia suggests that repetitive, nearly simultaneous sensory inputs lead to a degradation of the somatic sensory representation of the hand. This mechanism may apply in patients who perform repetitive jobs (e.g., data entry clerks, musicians) under conditions of high cognitive drive (Byl et al. 1996a,b). A similar mechanism could apply to patients with generalized dystonia if the dystonic movements lead to nearly simultaneous stimulation of the afferents from different cutaneous structures or from different muscle groups. It is unclear, however, if the observed changes are merely a consequence of dystonia. Recent studies of reorganized areas of Vim demonstrate that thalamic activity leads and might drive EMG activity in dystonia, that stimulation in these areas can increase dystonia, and that lesions of these areas can decrease dystonia (Lenz et al. 1999). These findings make it unlikely that cortical changes are responsible for the alteration in thalamic activity. Thus reorganization of thalamic structures such as that reported here might contribute to dystonia.

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