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Spontaneous Neuronal Activity in the Posterior Hypothalamic Region in Humans

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Abstract

Introduction—Deep brain stimulation (DBS) of the posterior hypothalamic region (PHR) is an emerging technique for the treatment of medically intractable cluster headache (CH). Few reports have analyzed single unit neuronal recordings in the human PHR. We report properties of spontaneous neuronal discharge in PHR for six patients who underwent DBS for CH

Materials and Methods—Initial target coordinates, determined by magnetic resonance imaging (MRI) stereotactic localization, were 2 mm lateral, 3 mm posterior, and 5 mm inferior to the midpoint of the anterior commissure-posterior commissure (AC-PC) line. A single microelectrode penetration was performed beginning 10 mm above the anatomic target, without systemic sedation. Single units were discriminated off line by cluster cutting in principal components space. Discharge rates, interspike intervals, bursting activity, and oscillatory activity were analyzed and compared between ventromedial thalamic and hypothalamic units.

Results—Six patients and 24 units were evaluated. Units in the PHR had a slow, regular spontaneous discharge with wide, low amplitude action potentials. The mean discharge rate of hypothalamic neurons was significantly lower (13.2 ± 12.2 ; mean $\pm$ SD) than that of medial thalamic units (28.0 ± 8.2). Oscillatory activity was not detected. Measures of bursting did not clearly distinguish medial thalamus from hypothalamus.

Conclusion—Single unit discharge rate of neurons in the posterior hypothalamic region of awake humans was 13.2 Hz and was significantly lower than medial thalamic neurons recorded dorsal to the target. The findings will be of utility for microelectrode localization of the CH target and for comparison with animal studies.

Keywords

hypothalamus; periventricular gray (PVG); electrophysiology; single unit; microelectrode; cluster headache

Introduction

Deep brain stimulation of the posterior hypothalamic region has recently been reported for treatment of cluster headache (CH) (16, 26, 29, 34) and behavioral disturbances (6, 7). The

hypothalamus, along with the peri-aqueductal gray(PAG) and periventricular gray (PVG) matters form a continuous rim of gray matter surrounding the third ventricle and cerebral aqueduct, all with similar histologic structure. Some anatomists consider the posterior border of the hypothalamus as the mamillothalamic tract (MMT)(25, 30), while others consider it to extend several mm more posterior than this (31). The region targeted for therapy of CH is 3–5 mm posterior to the MTT, and is thus referred to here as the “posterior hypothalamic region” (PHR).

A few studies have qualitatively described neuronal activity in the PHR (23, 24, 26). Only one report has analyzed single unit neuronal recordings in the human PHR(4), and animal studies are only slightly more numerous (3, 14, 19, 32). We hypothesized that neurons in this area have identifiable electrophysiological characteristics distinguishable from the surrounding regions, namely the thalamus and the red nucleus. We report the neuronal physiology of the PHR from six patients undergoing microelectrode guided DBS for CH.

Materials and Methods

Study subjects

All patients fulfilled the recently proposed guidelines for DBS therapy in CH(17) and were offered surgery after screening by a headache neurologist. Patients were consented under a protocol approved by the Institutional Review Board for study of human intra-operative microelectrode recordings (MER). Demographic information is presented in Table 1.

Target Localization

The magnetic resonance imaging (MRI) based stereotactic target localization methodology has been described previously(29). In brief, imaging sequences were (1) axial plane Gadolinium-enhanced 3D gradient echo MRI covering the entire brain at 1.5mm slices and (2) axial plane T2-weighted fast spin echo images covering the diencephalic regions at 2.0 mm slices. Images were imported into a stereotactic planning workstation (Framelink version 4.1, Medtronic-SNT), computationally fused, and reformatted to be orthogonal to the AC-PC and midsagittal planes.

The target coordinates as reported by Franzini et al (5) previously were –2 mm lateral, 3 mm posterior, and 5 mm inferior the midcommissural point. To account for possible variations in diencephalic anatomy that may affect target coordinates as measured from the commissures, the T2FSE sequence was utilized to confirm that the intended target point was located 3–5 mm posterior to the MTT and medial to the anterior border of the red nucleus, on the axial plane 5 mm inferior to the intercommissural line. The AC-PC based coordinates were modified, if needed, to ensure that the anatomic target was in a consistent relationship to the MTT and red nucleus.

The default trajectory through the brain was set at 60° from the AC-PC line in the sagittal projection and 10° from the vertical in the coronal projection (see Figure 1). Small adjustments to these angles were made when necessary to avoid traversing sulci, lateral ventricle, cortical veins and dural venous lakes.

Electrophysiological Recording

Although patients received sedation for the stereotactic frame placement and initial surgical exposure (midazolam or propofol), all systemic sedative were stopped at least 30 minutes prior to microelectrode recording and patients were awake and alert at the time of recording. One microelectrode tract recording was performed for each case. Single-unit discharge was recorded with glass-coated platinum/iridium microelectrodes, impedance 0.4–1.0 M Ω at

1000 Hz (Microprobe, Gaithersburg, MD, or FHC, Brunswick, ME). Recordings were filtered (300 Hz to 5 kHz), amplified, played on an audio monitor using the Guideline System 3000 (Frederick Haer, Inc.). Microelectrodes were advanced into the brain using manually operated microdrive (Elekta micropositioner, Elekta). Well isolated single units were digitized (20-kHz sampling rate). During recording, subjects were instructed to keep their eyes open but otherwise rest quietly. No patient experienced headache pain during the surgery.

Assignment of cell location

The location and discharge characteristics of cells along each microelectrode track were plotted on scaled drawings. There was not an abrupt, obvious change in physiology at the presumed inferior boundary of the thalamus. Cells encountered more than 5 mm above the anatomic target would be expected to be dorsal to the intercommissural line, and were thus designated as “thalamic” and those encountered within 5 mm of the anatomic target were labeled as “hypothalamic” cells.

Analysis of spontaneous activity

Digitized spike trains were imported into off-line spike sorting software (Plexon, Dallas, Texas) for discrimination of single populations of action potentials by principal component analysis. This software generated a record of spike times (subsequently reduced to millisecond accuracy) for each action potential waveform detected. The interspike intervals (ISIs) between successive spike times were used to calculate parameters of the ISI distribution, to construct autocorrelograms, and to evaluate the data stream for the occurrence of bursting or irregularity in discharge (see following text). Analyses were performed in Matlab (Natick, Massachusetts) programming environments.

Neuronal data were included in this study only if single unit action potentials could be discriminated with a high degree of certainty, and if the spontaneous activity of the neuron was recorded for 15s.

BURSTING—The data were submitted to a variety of pattern detection algorithms to assess bursting activity. Three methods for burst detection described in other studies were used here: the “L” statistic(8, 13); the “burst index” (10), defined as the mean ISI divided by the modal value; and the Poisson “surprise” method of Legendy and Salcman (15, 35). In this latter method, bursts in the discharge stream were defined as segments of data with a Poisson surprise value of >5 . The minimum number of spikes that can constitute a burst in this method was four. The resulting data were tabulated as the proportion of ISIs within bursts compared with the total number of ISIs in the entire data stream.

OSCILLATORY ACTIVITY—We utilized the “spike shuffling” method(22) to eliminate the artifactual autocorrelations that arise from the neuronal refractory period. This allowed detection of potential high frequency oscillations in the neuronal data, which would otherwise be obscured by the artifactual autocorrelation. First, neuronal spike times were represented as a delta function with bin resolution of 1 ms (a value of zero in a bin meant no spike occurred, and a value of 1 meant a spike occurred in that bin). A Fast Fourier Transform (FFT) was performed on the delta function, using 2048 points in the frequency domain. The data was smoothed using a Hanning window. The spectral resolution was 0.5 Hz. Next a “control spectrum” was generated which contained only the autocorrelation arising from the neuronal refractory period. The delta function was converted back into a sequence of ISI’s that were randomly shuffled, and converted back into a delta function. The FFT was done on the randomized delta function. This procedure was performed 100 times and the mean randomized spectrum was computed.

The real spectrum was then divided by the mean randomized spectrum to normalize it. Statistically significant peaks in the normalized spectrum were determined. To do this, the 300–500 Hz part of the spectrum was considered the control segment and its standard deviation was used as a measure of random fluctuations in the spectrum. Each frequency point between 0 and 200 Hz was then checked for deviation from the expected power, at a significance level of $p < .01$, after correction for multiple (400) comparisons.

Measurement of electrode locations

All patients underwent postoperative MRI to demonstrate the location of electrode tips, according to the published safety guidelines for performing brain MRI in patient with implanted DBS systems (9, 21). Electrode tip locations were identified in relation to the midcommissural point (Table 3). The distance of the lead posterior to the MTT at the AC-PC axial plane was also measured.

Hypothesis testing

Hypothesis testing was performed using the SPSS statistical package (SPSS, Chicago, IL). Differences in discharge parameters between thalamic and hypothalamic neurons were tested using the Mann-Whitney U test. We tested the hypothesis that spontaneous neuronal discharge rates correlate with distance from the hypothalamic target using Spearman's rho.

Results

Twenty four units from six patients were deemed suitable for analysis based on good single unit isolation with a clear neuronal refractory period and recording for a minimum of 15 seconds (mean = 43.2 sec). Two additional surgical patients did not contribute data to this study since the presence of a strong pulsation artifact (loss of single unit isolation at a regular phase of the cardiac cycle) precluded quantitative analysis.

Structures encountered

All MER penetrations recorded a relatively cell-dense region >5 mm above target, presumed to correspond to medial thalamus based on anatomic reconstruction of the MER trajectory (Fig 1). The region within 5 mm of the target, presumed to be the PHR had more sparse, low amplitude units encountered at a spatial density of 1.8 cells/mm. Over 50% of the units encountered in this region had poor unit isolation due to "pulsation artifact". The "exit" of the target region was recognized in two patients by one of the following: electrical silence >1.5 mm, suggestive of entry of the microelectrode into interpeduncular cistern (one patient), or a sudden transition to higher frequency (30–40 Hz), higher amplitude AP discharge likely to be the red nucleus(29). In 4 patients, however, recording was stopped at 2.0mm below the anatomic target, without identifying a clear lower boundary of the PHR, due to fear of vascular injury that could occur with excessive advancement of the microelectrode into the IP. [What is the "IP"?]

Single unit analysis

Summary data for all units recorded from the thalamus and hypothalamus are shown in table 2. Hypothalamic units had a lower firing rate (13.29, 0.32/41.01; mean, min/max) than thalamic units (28.09, 19.12/38.15; mean, min/max) ($P < 0.05$). Moreover, a significant positive correlation was seen between mean single unit firing rate and distance from the target (figure 2) ($r^2 = 0.568$, $P = 0.0001$), showing that frequency of neuronal discharge decreased as the target was approached.

In comparison between the thalamus and hypothalamus, 2 of 3 measures of bursting showed no significant difference (see Table 2). No oscillatory behavior was detected in either

thalamic or hypothalamic units in any frequency range, including that of the cardiac cycle. The majority of hypothalamic interspike intervals were less than 100msec (figure 3A). A raster diagram of a typical PHR unit (figure 3B) illustrates the regular discharge without evident bursting.

Electrode locations

Table 3 shows electrode tip locations as determined by postoperative MRI. All microelectrode recording were made along a trajectory directed to the ultimate electrode location. Thus the DBS leads provide an anatomic marker for the MER tracks.

Discussion

MER recording and isolation of single units are feasible in the human hypothalamic region, with no morbidity in our series. The hypothalamic neurons reported here exhibited a low spontaneous firing rate and low amplitude.[Document spike size/shape.] Cells were not oscillatory. The region is further characterized by a low density of spontaneously active units compared to subthalamic nucleus or globus pallidus, targets where neurons are routinely recorded during movement disorders surgery. We also found the isolation of single units for a prolonged period of time to be difficult secondary to pulsation artifacts, presumably due to the close proximity of the recorded structures the third ventricle, interpeduncular cistern (IPC), and basilar bifurcation. Therefore only a small number of units in this region were amenable to quantitative analysis.

Identification of nuclear borders in the PHR using MER is not as distinct as for basal ganglia structures. The thalamic-hypothalamic transition is characterized by a continuum of progressively more sparse neuronal activity and decreased firing rate. The ventral hypothalamic border may be more readily distinguished by either a cessation of activity upon entering the interpeduncular cistern or a robust increase in cell density and firing rate as the microelectrode enters the anteromedial red nucleus (figure 1A).

The mean firing rate of PHR neurons in our study is 13.2 Hz. Previous studies have reported firing rates of 24 Hz in the awake human(4), 25 Hz in the awake cat, 13 Hz in the electrographic synchronized sleeping cat(19), and 13 Hz in the anesthetized rat (3). One likely reason for this is the variation in depth of the recorded area. As seen in figure 2, mean firing rate gradually decreases as recording depth increases. Also, PHR neuronal discharge rate depends on state of arousal (14, 32) which was not consistent between various studies.

The Italian group who had previously reported on DBS for CH no longer uses MER for targeting in the PHR (G. Broggi, personal communication). The change in practice followed the report of a fatal intracranial/intraventricular hemorrhage several hours following hypothalamic DBS, from a series of six patients implanted in Belgium(26). Although not directly attributable to MER, this occurrence merits careful consideration of vascular anatomy in the PHR. We do not recommend routine MER beyond the anatomic target. Penetration of the electrode tip into the IPC carries the risk of injury to vessels traversing this region. Care should also be taken avoid medial trajectories traversing the third ventricle, which may lead to venous injury.

We did not observe any correlation between single unit firing rate and cardiac rhythmicity as previously reported (4, 26). However, oscillations in the measured amplitude of action potentials were prominent during single unit recordings as seen in Figure 1A. For many excluded neurons (not shown), the action potential amplitude was reduced to an undetectable level at regular phases of the cardiac cycle. If such units were not excluded

from analysis, we would have detected artifactual periodicity in discharge at cardiac frequency.

It is not certain that the neurons whose physiology is described here are important for the mechanism of action of DBS for CH. The gray matter of the PHR is composed in part of neurons that project within the medial forebrain bundle to the midbrain tegmentum, raphe nucleus, locus coeruleus, and the periventricular gray(33). In the same area within the PHR exist neurons that carry the receptors for neuropeptides orexin A and B(28) which have been shown to mediate the hypothalamic regulation of autonomic, neuroendocrine, and nociceptive functions(2). Recent reports have demonstrated a polymorphism in one of the orexin receptors, the hypocretin receptor 2 gene, that is associated with cluster headache(20, 27). The neurons recorded here may be those expressing orexin receptors, and thus potentially causal in the pathophysiology of CH, but this remains to be demonstrated.

In this study we recorded only neuronal action potentials, not axonal potentials. Several white matter tracts traverse the target region, including the dorsal longitudinal fasciculus(11), the fasciculus retroflexus (1), the trigeminothalamic (19), the trigeminohypothalamic(19), and the reticulohypothalamic tracts(19), any one of which could mediate the effects of DBS for CH. A recent PET study performed on CH patients after DBS therapy, however, showed activation of not only local PHR, but also the thalamus, somatosensory cortex, precuneus, anterior cingulum and the trigeminal nucleus(18). These widespread effects underscore the complexity of axonal traffic in the PHR.

Conclusion

MER recording and isolation of single units are feasible in the human PHR. Single unit discharge rate of neurons in the awake human was 13.2 Hz, which was significantly lower than medial thalamic neurons recorded dorsal to the target. There was no morbidity from microelectrode recording in this region. No oscillatory activity was detected. The findings will be of utility for microelectrode localization of the CH target and for comparison with animal studies.

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Figure 1.

Anatomic representation of the trajectory and sample neuronal recordings from deep nuclei in A) Parasagittal and B) Coronal projections. The parasagittal image is 1.5mm from midline and the coronal is 3.5mm posterior to the midcommissural point. Since the actual trajectory is oblique to both planes, the track reconstruction represents a projection onto an anatomic plane. Adapted from the Schaltenbrand and Warren human brain atlas and Kalat's Biological Psychiatry. (25) (12). Each recording is 2 seconds long. Note the apparent oscillatory change in the action potential amplitude (pulsation artifact) in several recordings. Abbreviations: A: anterior hypothalamus; DHy: dorsal hypothalamus; DM: dorsomedial nucleus; IPC: interpeduncular nucleus; MB: mammillary body; PHR: posterior hypothalamic region; RN: red nucleus; T: thalamus; V: ventricle; VMH: ventromedial hypothalamus;

Figure 2. Scatterplot of neuronal firing rate versus distance along the recording trajectory from the anatomic target, demonstrating a decrease in neuronal firing rate as the target is approached. The solid line is the best fit to the data by linear regression.

Figure 3.

A, Interspike interval histogram of a PHR neuron, bin size of 1 msec. B, Raster diagram for the same neuron. Consecutive rows (5 seconds of data per row) from bottom to top represent a continuous 60 second recording.

Table 1

Patient characteristics and preoperative medication use.

Patient	Age(yrs)/Sex	Disease Duration(yrs)	Medication (mg/day)	
			Prophylactic	Abortive
1	58/m	30	prednisone (80)	Sumatriptan (sq 6)
2	42/m	9	methadone (90)	none
3	41/m	12	prednisone (10–60), verapamil (1200), lithium(1200), frovatriptan (5)	sumatriptan (sq 6)
4	66/f	16	prednisone (60) [§] , depakote (1000)	none
5	38/m	8	Verapamil (720), melatonin (9)	Sumatriptan (sq 6)
6	52/f	20	Vicodin, prednisone (80) [†]	O ₂ sumatriptan (sq 6)

[§] A 5-day course three times/year.

[†] 5-day course only when severe attacks.

Table 2

Spontaneous discharge parameters in thalamic and hypothalamic units

	Thalamus	Hypothalamus
No. of units	4	20
Mean rate, Hz	28.09 ± 8.27	13.29 ± 12.22 <i>P</i> < 0.05 *
Mean proportion of burst discharges (Legendy method)	0.05 ± 0.02	0.25 ± 0.21 <i>P</i> = 0.044
Mean L statistic	4.75 ± 0.5	5.65 ± 1.78 <i>P</i> = 0.319
Mean burst index of normalized ISI distribution	3.79 ± 4.49	10.12 ± 14.88 <i>P</i> = 0.215

Values are means ±SD;

* indicates a value that was significantly different from that for the thalamus by Mann-Whitney U test.

Table 3

Electrode locations with respect to the midcommissural point

Case	AP Dist MTT to Lead	Lead Tip Coordinates (mm from MCP)			Approach Angle (° from vert)		
		Lat	AP	Vert	Coronal Projection	Sagittal Projection	
1	3.5	1.70	0.00	-5.20	-21.17	21.55	
2	4.7	1.30	-2.70	-4.30	-24.95	33.45	
3	5.3	1.80	-3.50	-5.40	-27.53	37.80	
4	6.0	2.90	-3.30	-5.00	-32.36	30.87	
5	4.0	2.15	-1.17	-5.10	-25.53	21.19	
6	4.0	2.23	-2.03	-4.41	-30.4	35.3	
Mean ± SD	4.6 ± 0.94	2.01 ± 0.55	-2.12 ± 1.34	4.90 ± 0.44	26.99 ± 4.02	30.03 ± 7.08	

* All measurements were made on postoperative MR images. Abbreviations: dist = distance; MCP = midcommissural point; SD = standard deviation; vert = vertical.