Neurol Sci (2007) 28:93–95
DOI 10.1007/s10072-007-0793-1

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Spontaneous neuronal activity of the posterior hypothalamus in trigeminal autonomic cephalalgias

Received: 6 November 2006 / Accepted in revised form: 12 February 2007

Abstract Microrecordings of three neurons were obtained at the target site in three patients with trigeminal autonomic cephalalgias who were implanted with deep brain stimulators in the posterior hypothalamus. Two patients had chronic cluster headache, one short unilateral neuralgiform headache with conjunctival injection and tearing. Average firing rate was around 24 spikes/s. All neurons were firing randomly, and for most of the recordings in tonic fashion. In one patient, tactile stimulation of the ophthalmic branch, contralateral to the recording site, decreased the firing rate. Neuronal activity in these patients was similar to that reported in animal studies of the posterior hypothalamus. Positioning deep brain stimulators in the posterior hypothalamus may offer a tool to better characterise the activity of this part of the brain in humans.

Key words Posterior hypothalamus • Pain • Electrophysiology

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Introduction

Recently there has been resurgence of attention in the posterior nucleus of hypothalamus (PIH) as the target for the placement of deep brain stimulation (DBS) leads [1–3] to treat trigeminal autonomic cephalalgias (TACs), such as chronic cluster headache (CCH) and short unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). Neuroimaging techniques have shown ipsilateral posterior inferior hypothalamus activation during CCH and SUNCT attacks [4, 5]. This activity may be specific in these disorders as it is not reported in other painful conditions such as migraine.

Very scanty information is available on the firing characteristics of PIH neurons in humans. Recently, high-frequency stimulation was successfully used to treat TACs by implanting stimulating leads into the PIH, ipsilateral to the side of the pain [1, 2, 6]. We thus had the opportunity to perform microrecordings in PIH, and to describe spontaneous discharge properties of hypothalamic neurons.

Methods

The study was approved by the institutional review board, and the patients gave written informed consent. The operative techniques were previously reported [1]. Patients enrolled in the study did not take prophylactic drugs for one day before the implantation and remained awake throughout the surgical session.

Continuous physiological recordings began as the microelectrode reached the presumptive coordinates of the target, and were performed by means of a *Medtronic Leadpoint* system. The response properties of the isolated neurons were obtained with the patients fully awake. In one patient tactile stimulation at the trigeminal ophthalmic branch was performed, and the firing discharge recorded.

Post-operative data analysis was performed by the Spike2 analysis package (CED, Cambridge, UK). Single unit events were discriminated, and confirmed to arise from a single neuron,

using template-matching spike sorting software. The firing rate was calculated by dividing the total number of the isolated spikes by the length of the recording. Properties of the firing pattern were inspected by plotting inter-spike interval histograms (ISIH; 5 ms bin width and lag up to 100 ms). Autocorrelograms (5 ms bin width and lags up to 1000 ms) were plotted to evaluate the rhythmicity of the spike trains.

Results

Three patients were enrolled in the study. They all tolerated well the recording procedures and improved following the surgical implant with no relevant side effects. At the time of surgery patient 1 was aged 43, with 10 years of CCH, and pain in the left side; patient 2 was aged 47, with three years of CCH, and pain in the right side; patient 3 was 66, with 14 years of SUNCT, and pain in the right side.

Three PIH cells were recorded (one in each patient); their location was confirmed by post-implant MRI. Figure 1a displays segments of the raw electrophysiological traces. The average firing rate was around 24 spikes/s. All neurons generated for most of the recordings isolated action potentials, as shown by the highest concentration of intervals in the 10–15 ms range (Fig. 1b), with 7.2% of ISI shorter than 5 ms, which reflect very high intraburst frequencies. Autocorrelograms of two cells did not display any regularity in the occurrence of peaks and troughs (Fig. 1c), which indicates a lack of periodicity of the firing discharge. Only one autocorrelogram displayed some regularity in the occurrence of peaks and troughs, with an oscillatory pattern at around 1 Hz.

In one patient, firing rate was reduced by contralateral but not by ipsilateral tactile stimulation of the ophthalmic branch.

Discussion

This paper reports the spontaneous PIH neural activity recorded in three awake patients during DBS surgery for TACs. All patients improved following the surgical procedure, suggesting that the electrodes were at a clinically effective site. These recordings are the first observation of PIH neuronal activity in patients with TACs.

Classically the posterior hypothalamus has been linked to the control of behavioural states [7]. Firing rates similar to those observed in our patients have been reported in cats during wakefulness and REM sleep, with a low proportion of high frequency discharges [8]. Thus it appears that in both humans and cats, posterior hypothalamic neurons spontaneously discharge at around 25 Hz, in tonic fashion with rare high-frequency bursts. In fact, the low-frequency oscillation

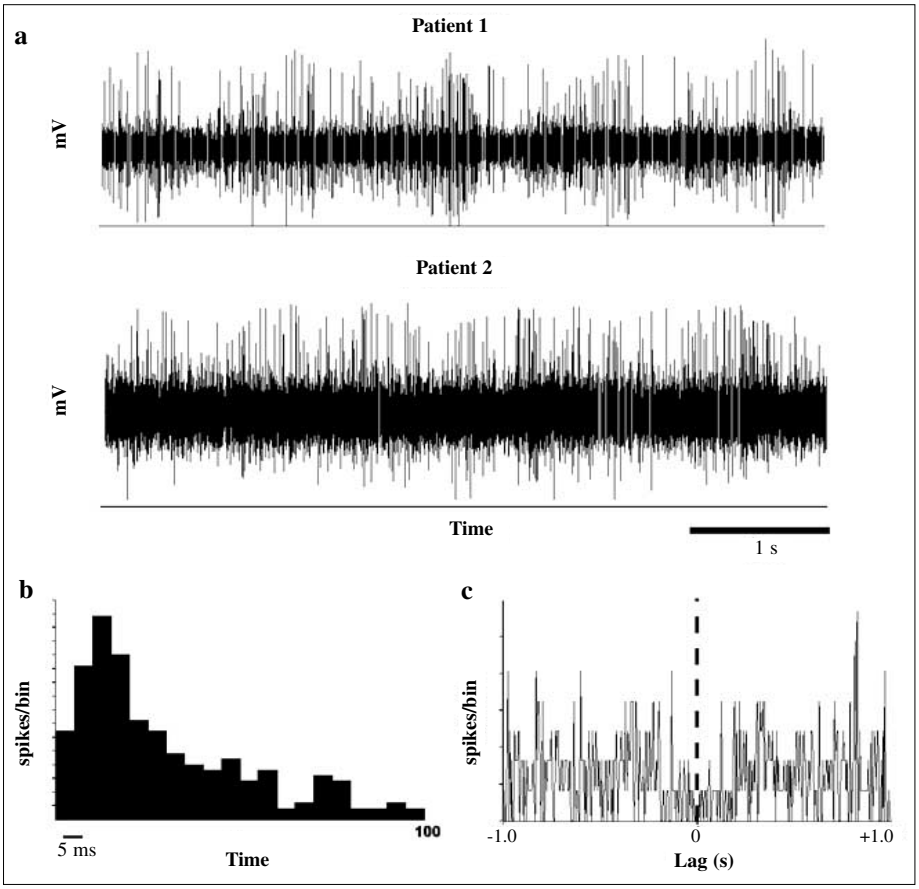

Fig. 1 Neuronal discharge pattern in PIH. **a** Raw physiological traces; **b** ISIH plotted from the cell recorded in patient 1. The highest proportion of ISI was at 10–15 ms, and the percentage of intervals shorter than 5 ms is 5.3%; **c** the autocorrelogram for the same cell as in **b** displays no regularity in the occurrence of peaks and troughs

observed in one single neuron was probably due to the proximity of the microelectrode to a vessel, in keeping with a previous observation of synchronization of the firing pattern of PIH neurons to patients' heartbeat during surgery [3].

Lesions of the posterior hypothalamus were performed by Sano to treat otherwise intractable pain [9]. Although he did not perform quantitative measurements, he reported that bilateral stimulation over the entire body evoked changes in discharge rates, and that pin prick stimulation evoked neural responses with latencies similar to those of the *C* fibres. In one of our patients, tactile stimulation of the ophthalmic branch contralateral to the recording side led to a decrease in firing rates. Altogether these observations suggest that PIH neural activity may be modulated by afferent sensory input. Experimental findings in rats show that two distinct tracts relay sensory information to the posterior hypothalamus, the trigeminohypothalamic tract that conveys nociceptive inputs from cephalic region only and the reticulohypothalamic tract which conveys sensory inputs from both cephalic and extra-cephalic regions. Interestingly, trigeminohypothalamic neurons exhibited receptive fields limited to regions contralateral to the recording site while reticulohypothalamic neurons had large and complex receptive fields extended to the whole body [10].

These findings need consideration in studies aimed to evaluate the effects of sensory stimulation on firing frequency of cells in PIH. Future implants might offer an opportunity to plan more sophisticated investigations focused on the evaluation of the firing rate, firing pattern, response to somatic, thermal and noxious stimulation in a broader number of neurons, and different pathological conditions. This may help understand the neural organisation of the posterior hypothalamus and may give clues to the pathophysiology of TACs.

Sommario *In tre pazienti affetti da nevralgia autonomica trigeminale (TACs) sono state ottenute microregistrazioni da neuroni dell'ipotalamo posteriore durante l'impianto di elettrodi di stimolazione cerebrale profonda. Due pazienti erano affetti da cefalea a grappolo cronica, uno da cefalea unilaterale neuralgiforme di breve durata e con iniezione congiuntivale e lacrimazione (SUNCT). La frequenza di scarica media era di circa 24 Hz. Tutti i neuroni avevano un'attività di scarica non ritmica e per la maggior parte delle registrazioni di tipo tonico. In un paziente la stimolazione tattile del ramo oftalmico del nervo trigemino, controlaterale al sito di registrazione, produceva un decremento della frequenza di scarica. L'attività neuronale in questi pazienti era simile a quella riportata in studi che utilizzavano modelli animali. La conoscenza dell'attività spontanea ed evocata dei neuroni localizzati nel nucleo posteriore dell'ipotalamo può fornire nuove informazioni sulla fisiopatologia delle TACs.*

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