Characteristics of somatosensory thalamic neurons : Study on motor disease patients

Bae Hwan Lee[1], Kyung Hee Lee[1], Yong Gou Park[2], Sang Sup Chung [2], Jin Woo Chang[2]

[1]Medical Research Center, [2]Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea

요약문

시상은 체감각 정보를 처리하는데 있어서 매우 중요한 역할을 하는 부위이다. 본 연구는 운동장애 환자의 시상에서 뉴론의 활동 특성을 알아보기 위해 수행되었다. 그 결과 체감각으로서의 운동자극에 반응하는 뉴론이 essential tremor (ET) 환자의 nucleus ventralis intermedius (VIM)에서 발견되었다. ET 환자 뉴론의 평균 활동율(firing rate)은 Parkinson's disease (PD) 환자 보다 높았다. 또한 ET 환자의 VIM 에서 운동자극에 반응하는 뉴론의 평균 활동율은 PD 환자 보다 높았다. 하지만 촉각자극(touch)에 반응하는 nucleus ventralis caudalis (VC) 뉴론의 활동율은 ET 와 PD 집단간에 차가 없었다. Bursting activity 를 나타내는 뉴론은 nucleus ventralis oralis anterior (VOP)에서 ET 집단이 PD 집단보다 적었다. tremor cell 은 VIM 에서 PD 보다 ET 집단이 더 적었다. 이러한 결과는 체감각 자극에 반응하는 시상 뉴론의 특성이 운동장애의 유형에 따라 서로 다르다는 것을 시사한다.

Introduction

An essential tremor (ET) is a common movement disorder that is characterized by a postural tremor of the arms that can be accompanied by a tremor in other body parts such as the head, tongue, larynx, trunk, or legs (13). Although ET is the common movement disorder, its etiology is unclear. It is believed that ET is generated by a central oscillatory neuronal network. In addition, thalamic involvement in the oscillatory network that generates ET is suggested by neurophysiological and clinical evidence (2,3,7,12). Moreover, stereotactic lesioning or high frequency stimulation in the nucleus ventralis intermedius (Vim) and ventralis oralis posterior (Vop) of the thalamus has been shown to suppress ET effectively (15). However, the structural components involved in this network are largely unknown yet. Furthermore, there are only a few reports giving a comparison of the electrophysiological recordings of the thalamus in ET

patients and parkinsonian tremor patients (10). The purposes of this study were to investigate the characteristics of the neuronal activities of the motor thalamus (Vim and Vop) in ET patients and to compare them with those of PD patients.

Materials and Methods

Microelectrode Recording technique

The recordings of the neuronal activity were obtained in the motor thalamus of 17 PD, and 14 ET patients during microelectrode recording for the deep brain stimulation electrode implantation or lesioning procedure for two types of patients. The electrophysiological methods were similar to those previously reported (1). Briefly, the surface EMG was recorded from the contralateral wrist and leg flexors. The neuronal impulses were amplified, filtered, and fed to a window discriminator and an audio monitor. The signals were displayed on an oscilloscope and stored using a digital tape recorder for an off-line analysis. The units were selected if they were stable and well isolated. The units were recorded for at least 20 seconds (usually 60 seconds). The digitized data were transferred to a personal computer with an interface (CED 1401) for both display and analysis (Spike 2). The peristimulus time histogram was constructed and the mean firing rates were calculated. The location of the trajectory of each recorded cell was noted and the neurons were plotted on the appropriate sagittal brain map.

Analysis of data

The neurons that responded to voluntary movements were classified as voluntary (Vo) neurons, while those that responded preferentially to passive movements of a joint were classified as kinesthetic (Ki) neurons. The mean firing rate, the interspike interval (ISI), the autocorrelogram and the discharge pattern for each neuron were investigated. The ISIs allowed an evaluation of the degree of bursting of the units, following an algorithm described by Hutchison et al (11). If a unit had an index of more than 10 from the reciprocal of the modal interval divided by the mean firing rate, it was regarded as bursting. The autocorrelogram evaluated the rhythmicity and the cut-off point for the rhythmicity was 0.95. A bursting unit was classified as tremor cell if the frequency of clearly identifiable peaks on the autocorrelogram corresponded to that of tremor measured by the EMG from the arm or leg. The differences between each group were statistically evaluated using the unpaired t-test with significance level of 0.05.

Results

Comparison of mean firing rates of ET patients and PD patients

A total of 1658 units were isolated along the 54 penetrations performed in 14 ET patients and 17 PD patients (Table 1). Somatosensory cells were often found in the Vim and Vop of ET patients as in the PD patients. The Ki neurons were mainly found in the Vim (47.41 %), whereas the Vo neurons were predominant in the Vop (71.43 %) in ET patients. As reported previously, the mean firing rates of the ET patients were higher than those of the PD patients in both the Vop and Vim nuclei ($p<0.05$) (Fig. 1). In addition, the mean firing rates of the Ki neurons of the ET patients were higher than those of the PD patients in the Vim nuclei ($p<0.05$) (Fig. 2). However, the mean firing rates of the ventralis caudalis (Vc) neurons, which respond to sensory stimulation, were similar in each group (Fig. 3).

The firing pattern of Vim and Vop nuclei

An analysis of the firing patterns revealed some significant differences between the ET and PD patients for the Vo or Ki neurons. The analysis of the incidence of the bursting neurons revealed that the Vop nucleus of the ET patients had much lower number of bursting neurons (9.58%) than the PD patients (33.82 %). However, in the Vim nucleus, both groups possessed bursting neurons even though the incidence was slightly different (ET patients, 26.25 %; PD patient, 38.91 %). Tremor cells were less frequently observed in the ET patients at the Vim nuclei compared to those of the PD patients. Interestingly, tremor cells were not found in the Vop nucleus of the ET patients.

Discussion

An essential tremor is supposed to be generated within the olivocerebellar circuits. This contrasts with a resting tremor of the PD, which is probably generated in the basal ganglia loop (3). Among the most convincing clinical evidence, is the observation that an ET disappears after the lesions of the cerebellum, the pons, or the thalamus, each of which forms a part of a cerebellocortical loop (5,6,14). It has been shown that in different species, cells of the inferior olive are synchronized and that rhythmic activity is transferred through the cerebellum and the reticulospinal projection to the motoneurons (16).

However, the basic physiological mechanism of tremor genesis in PD is more complicated than that in ET. It is generally agreed that a resting tremor is produced within the basal ganglia loop, but the location and physiology of the related tremor genesis are still a matter of debate. It has recently been suggested

that a resting tremor is produced in the cerebellothalamic loop, This is because the cerebellum shows prominent hyperactivity in a tremor, and a PD tremor can be successfully treated by the placement of a lesion in the Vim nucleus of the thalamus, which is the target of the cerebellothalamic fibers (5,15). This hypothesis implies that a resting tremor should cease when the cerebellum is removed in a patient with a PD tremor. However there was a report of a continuous tremor after surgery, which contrasts with the cerebellar hypothesis for tremor genesis (2). Certainly, a single unit recording in patients during stereotactic surgery has revealed that the number of neurons with a clear relationship with a peripheral tremor varies according to the different nuclei, with the majority being found in the motor thalamus, followed by the globus pallidus internus (GPi) and the subthalamic nucleus (STN). In addition, other possibilities, such as a corticosubthalamic-internal pallidum-thalamocortical loop, may be equally likely to form an oscillating loop (3).

It is generally believed that the Vo neurons are located mainly in the pallidal-receiving area of the motor thalamus and the Ki neurons are found in the cerebellar receiving area of the thalamus (4). In this category, our results are consistent with these findings in that an increasing inhibitory input from the GPi should decrease the firing of the Vo and Ki neurons in PD patients. Moreover, it is possible that the cerebellar hyperactivity can account for the increase in the spontaneous firing rates of the Vo and Ki neurons in ET patients, as revealed using the microelectrode recording techniques of this study. Since the cerebellar projections to the thalamus are excitatory, the increased excitability of the Vim neurons might lead to increased kinesthetic feedback and contribute to the generation of a tremor (3).

The lack of a significant increase in bursting activity in the pallidal receiving areas in PD patient has been reported previously by Dostrovsky et al. (4). In addition, they suggested that bursting is unlikely to be an important factor in the etiology of a parkinsonian tremor. Interestingly, the number of tremor cells in the motor thalamus in ET patients (21/339 units, 6.19 % for Vim) in this study was much lower than those in PD patients (34/257 units, 13.23 % for Vim). These findings may be consistent with the observation in PD patients reported by Dostrovsky et al. (4). Recently, Halliday et al. (8) demonstrated no correlation between the tremor signal and the low-frequency activity recorded from the primary motor cortex in individuals with an essential tremor. They suggested that the tremor originated through the descending pathways rather than in the primary motor cortex.

In contrast, stereotactic operations in humans and the increased activity in the motor thalamus, as revealed in this study, indicate that the thalamus plays an important role in the generation of an essential

tremor. This suggests that considering the strong thalamocortical projections present, there might also be some cortical involvement (3,5,9). However, there has been no direct proof of a cerebral cortex contribution to the central oscillator that produces the essential tremor.

Conclusions

This study demonstrated the different pathophysiological mechanisms of ET and compared it with PD. This might provide a rationale for stereotactic surgery on Vim neurons in ET patients. However, the complex pathophysiological mechanisms leading to the clinical expression of an essential tremor are still unclear.

ACKNOWLEDGEMENT: This work was supported by grant No. (2000-2-20600-001-3) from the Basic Research Program of the Korea Science & Engineering Foundation.

References

1. Chang JW, Lee BH, Lee MS, Chang JH, Park YG, Chung SS (2001) Microelectrode recording-guided deep brain stimulation in patients with movement disorders (The first trial in Korea). In: Lultas-Ilinsky K, Ilinsky IA (eds) Basal Ganglia and Thalamus in Health and Movement Disorders. Kluwer Academic/Plenum Publishers, New York, pp341-347
2. Deuschl G, Wilms H, Krack P, Wurker M, Heiss WD (1999) Function of the cerebellum in parkinsonian rest tremor and Holmes' tremor. Ann Neurol 46:126-128
3. Deuschl G, Raethjen J, Lindehann M, Krack P (2001) The pathophysiology of tremor. Muscle Nerve 24:716-735
4. Dostrovsky JO, Molnar GF, Pilliar A, Hutchison WD, Davis KD, Lozano AM (2001) Neuronal activity in motor thalamus of Parkinson's disease patients, In: Lultas-Ilinsky K, Ilinsky IA (eds) Basal Ganglia and Thalamus in Health and Movement Disorders. Kluwer Academic/Plenum Publishers, New York, pp267-274
5. Duncan R, Bone I, Melville ID (1988) Essential tremor cured by infarction adjacent to the thalamus. J Neurol Neurosurg Psychiatry 51:591-592
6. Dupuis MJ, Delwaide PJ, Boucquery D, Gonsette RE (1989) Homolateral disappearance of essential tremor after cerebellar stroke. Mov Disord 4:183-187

7. Elble RJ (1996) Central mechanisms of tremor. J Clin Neurophysiol 13:133-144

8. Halliday DM, Conway BA, Farmer SF, Russell AJC, Rosenberg JR (2000) Coherence between low-frequency activation of the motor cortex and tremor in patients with essential tremor. Lancet 355:1149-1153

9. Hellwig B, Haubler S, Schelter B, Lauk M, Guschlbauer B, Timmer J, Lucking CH (2001) Tremor-correlated cortical activity in essential tremor. Lancet 357:519-523

10. Hua SE, Lenz FA, Zirch TA, Reich SG, Dougherty PM (1998) Thalamic neuronal activity correlated with essential tremor. J Neurol Neurosurg Psychiatry 64:273-276

11. Hutchinson WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE (1997) Effects of apomorphine on globus pallidus neurons in parkinsonian patients. Annals Neurol 42:767-775

12. Llnias R, Volkind RA (1973) The olivo-cerebellar system: functional properties as revealed by harmaline-induced tremor. Exp Brain Res 18:69-87

13. Louis ED (2001) Essential tremor N Eng J Med 345:887-891

14. Nagaratnam N, Kalaabail G (1997) Contralateral abolition of essential tremor following a pontine stroke. J Neurol Sci 149:195-196

15. Pahwa R, Lyons K, Koller W (2000) Surgical treatment of essential tremor. Neurology 54(Suppl 4):s39-s44

16. Wilm H, Sievers J, Deuschl G (1999) Animal models of tremor. Mov Disord 14:557-571

Table 1. Number of patients, penetration, and recorded cells in the present study.

	No. of Patients	No. of Penetration	No. of Cells
ET	14	23	878
PD	17	31	780

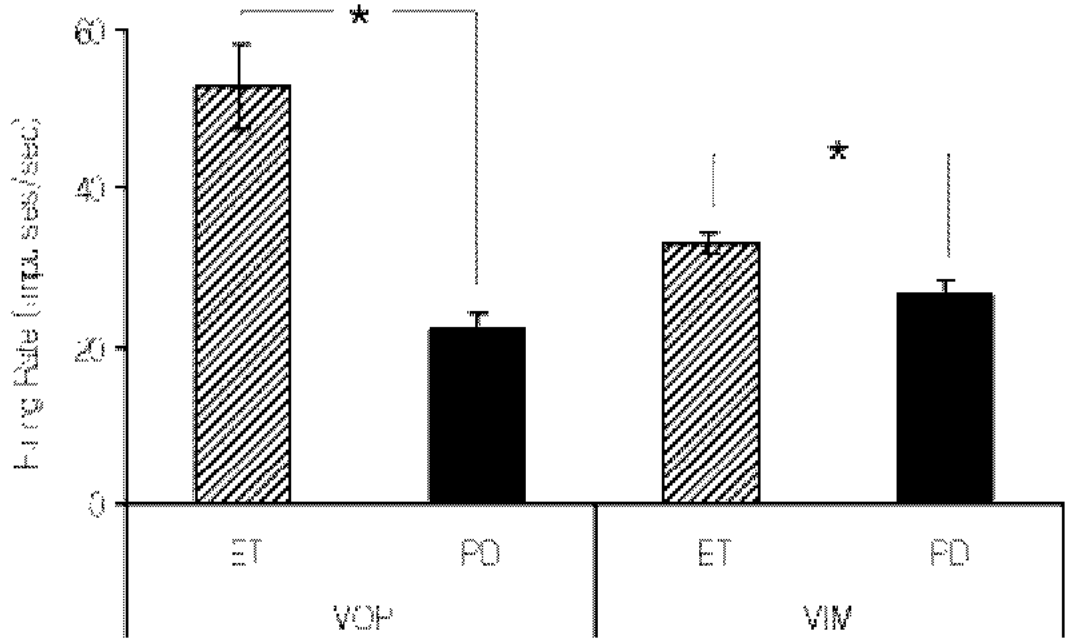

Fig. 1. Mean firing rates of the nucleus ventralis oralis posterior (VOP) and the nucleus ventralis intermediates (VIM) neurons in an essential tremor (ET) and Parkinson's disease (PD) patients. There was a significant difference between mean firing rates of the VOP and VIM neurons in ET and PD patients (*$p<0.05$).

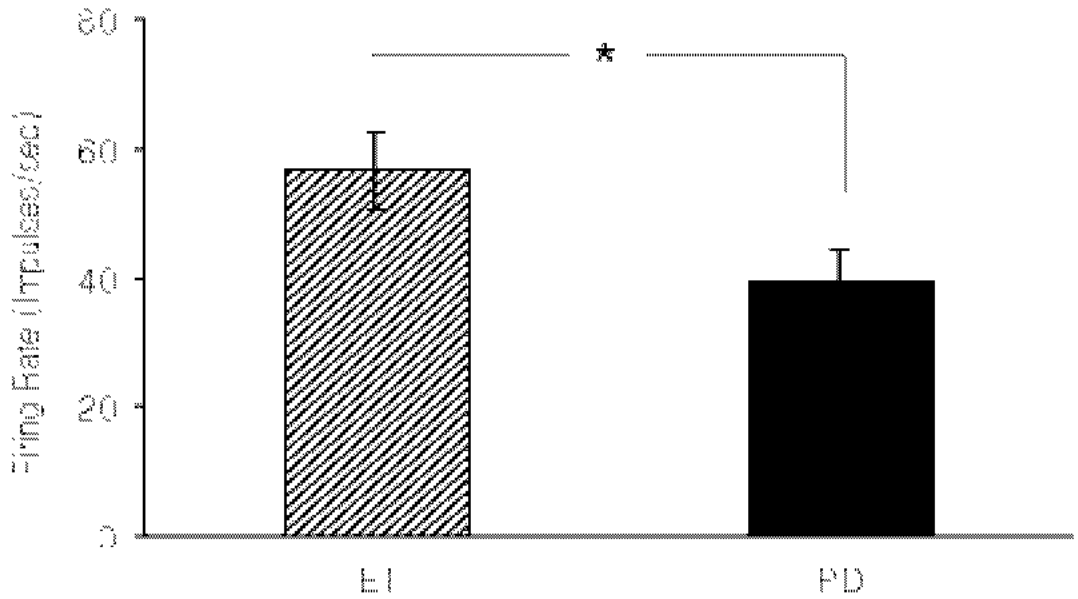

Fig. 2. Mean firing rates of the kinetic (Ki) neurons in the nucleus ventralis intermediates (VIM) of essential tremor (ET) and Parkinson's disease (PD) patients. There was significant difference between the mean firing rates of the Ki neurons in the VIM of ET and PD patients (*$p<0.05$).

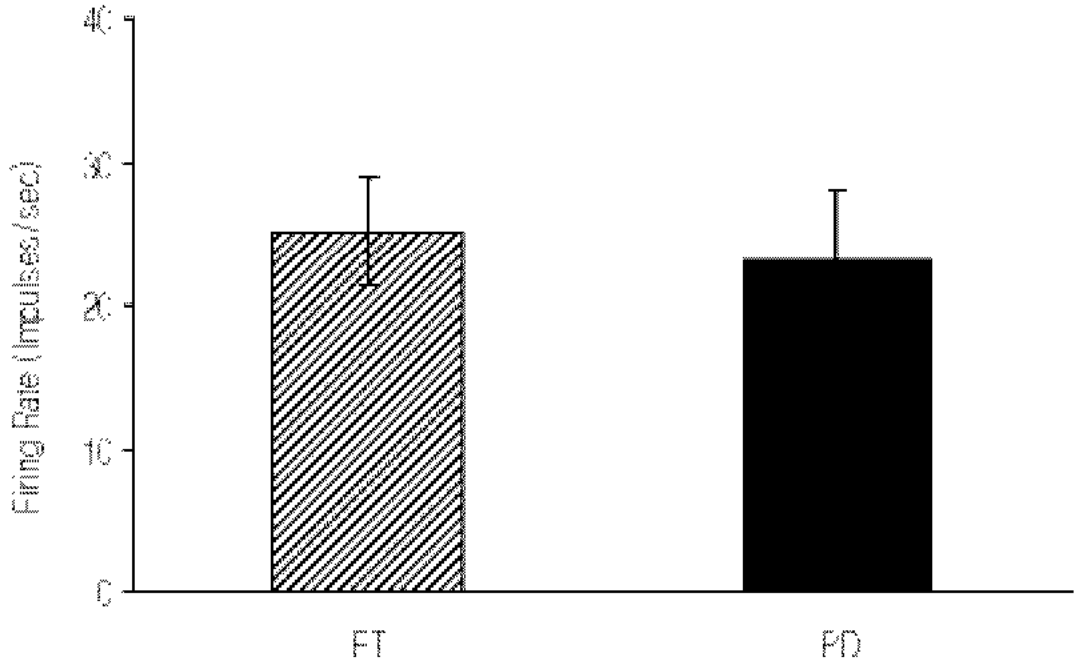

Fig. 3. Mean firing rates of the somatosensory neurons in the ventralis caudalis (VC) of essential tremor (ET) and Parkinson's disease (PD) patients. There was no significant difference between the mean firing rates of the somatosensory neurons in the VC of ET and PD patients ($p>0.05$).