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BRIEF COMMUNICATION

Discharge responses of the optic tract to flash stimuli in Parkinson's disease

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Abstract

Dopamine has a significant role in retinal processing, and it has been demonstrated that retinal dopamine content is decreased in parkinsonian patients. We measured the latency of the evoked discharges in the optic tract (OT) to flash stimuli during stereotactic pallidal neurosurgery in 25 patients with Parkinson's disease (PD) (13 women and 12 men, age 38–78 years, unified Parkinson's disease rating scale (UPDRS) Motor Score in the Off state 11–54, Hoehn and Yahr stage in the Off state 1.5–5) and investigated the effects of age at surgery, disease duration, levodopa dose, and severity of parkinsonian symptoms on the latency. OT discharges were evoked by monocular flash stimuli delivered from a flashlight with a krypton bulb with a tungsten filament. The luminance at the eye measured ~4×10^4 cd/m^2. The light wavelength of the stimulus was composed of a wide spectrum with its peak at around 800 nm or longer. The latency of OT discharges ranged 49–79 msec, and there was a significant positive correlation between the latencies of evoked activities in the OT to a flashlight and age ($r = 0.59$, $P < 0.001$, by Pearson correlation), but no correlation between the latency and the severity of parkinsonian symptoms and between the latency and duration of illness. These results indicate that the delay in visual processing and conduction at the level of the retina and the OT are substantially derived from age-related degenerative changes in the retina and visual pathway which are apparently unrelated to the striatal dopamine deficiency in PD.

Introduction

Dopamine has been detected in amacrine and interplexiform cells5 and has a significant role in retinal processing, for example, in the transmission of signals arising from a large number of photoreceptors or in the center-surround organization of retinal receptive fields.[1] Retinal dopamine content is decreased in parkinsonian patients,[2] and abnormalities in electrophysiological findings in visual functions related to dopamine deficiency in the retina or brain have been reported. The major components of visual evoked potentials (VEP) recorded with the scalp electrodes evoked by sine wave gratings or checkerboard stimuli were delayed in Parkinson's disease (PD) compared to an age-matched control group and recovered after levodopa therapy.[3,4] The prolonged VEP latency was correlated with the severity of motor impairment in PD.[5] Abnormalities of contrast sensitivity have been reported in PD patients.[5,6] In electroretinogram (ERG) in PD, a prolongation of a and b waves,[7–9] a latency recovery after levodopa therapy[8], and a decrease in b wave amplitude with flash stimuli[7–10] have been reported. Pattern ERG has revealed that PD patients have shown an attenuated medium-to-low spatial frequency ratio, and the attenuation has been correlated with the clinical stage of PD.[11]

We recorded fiber potentials in the optic tract (OT) evoked by flash lights during microrecording-guided neurosurgery targeting the internal segment of the globus pallidus (GPi) in patients with PD as a basic procedure to locate the OT lying below the ventral palldum. The OT conveys retinal signals from the retina to the lateral geniculate body. We investigated the effects of age, duration of

illness, levodopa dose, and severity of PD on the latencies of the discharge responses of the OT to the flash stimuli.

Subjects and Methods

Methods for surgical procedure and measurement of the discharge latencies have been described previously,[12] and are detailed in Data S1.

Forty-six patients with idiopathic PD underwent unilateral pallidal neurosurgery (42 ablation and four deep brain stimulation) with microrecording guidance at Shinshu University Hospital and Kakeyu Hospital between April 1998 and May 2003. In 25 patients (13 women and 12 men), the activities of the OT evoked by flash stimuli were clearly recorded during physiological mapping with a microelectrode. The age of the patients at surgery ranged from 38 to 78 years (mean 62.9 ± 8.5), disease duration from 24 to 204 months (mean 113 ± 52), Unified Parkinson's disease rating scale (UPDRS) motor score in the Off state from 11 to 54 (mean 34.7 ± 10.1), and the modified Hoehn and Yahr stage in the Off state from 1.5 to 5 (mean 3.7 ± 0.9). Ophthalmological evaluation revealed normal visual acuity with or without correction and no abnormality of either the visual field or pupil reaction, but the subjects did not undergo full ophthalmological examination by an ophthalmologist. All patients were treated with standard levodopa, 150–800 mg (mean 428 ± 168 mg), and most of them took additional doses of dopamine agonists or other antiparkinsonian medications. The study was approved by the ethics committee of Shinshu University Hospital and Kakeyu Hospital for research on human subjects according to the Helsinki declaration. All patients were fully informed on the procedure and the purpose of OT testing and gave their consent to all aspects of the study.

The OT-discharge recording system is illustrated in Figure 1. The lights in the operating room were turned off 1–2 min before the start of OT-discharge recording, and the luminance in the room was ~0.1 lx. OT-discharge responses were evoked by monocular flash stimuli delivered by a flashlight (Toshiba, TF-202, Tokyo, Japan) with a krypton bulb with a tungsten filament. The bulb was positioned at ~10 cm from and 30–45° below the patient's eyes. Light stimuli of 0.5–1.5 sec duration were delivered using a manual switch at 2–3 sec intervals, 6–12 times at each recording site. The luminance of the flashlight was strong and measured ~4×10^4 cd/m^2 using a photodiode (Hamamatsu Photonics K.K., Si PIN Photodiode S8591, Hamamatsu, Japan). The light generated a wave spectrum flash with its peak at around 800 nm or longer. Glass-coated Elgiloy microelectrodes with an impedance of 0.2–0.8 MΩ at 1000 Hz were used for single-cell and fiber recording. Fiber activity in the OT was recorded with a filter band pass of 300–10,000 Hz.

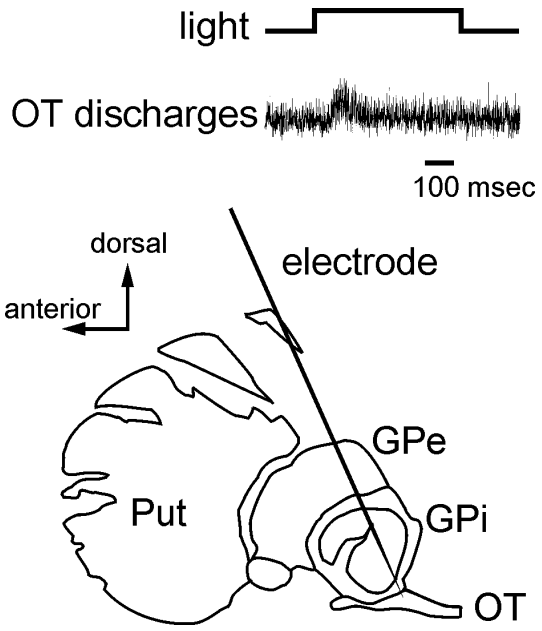

Figure 1. Diagram of the recording system of the OT discharges. A microrecording electrode was overlaid on the sagittal plane of the basal ganglia. Compound fiber discharges in the OT were recorded. Put, putamen; GPe, the external globus pallidus; GPi, the internal globus pallidus; OT, optic tract.

Linear regression analyses with Pearson correlations were performed to determine correlations between OT-discharge latencies and clinical variables, that is, age at surgery, disease duration, levodopa dose, UPDRS motor score in the OFF phase, and modified Hoehn and Yahr stage at OFF phase. We performed a backward stepwise regression analysis to determine the factors that significantly predicted OT-discharge latency. Variables were removed one by one to the model with removal at significant values of 0.15. Regression analyses were performed using a statistical software (SYSTAT version 5; SYSTAT, Inc., Evanston, IL), and a P-value <0.05 was considered to be statistically significant.

Results

The latency of OT discharges ranged 49–79 msec. The results of two-tailed Pearson correlations are presented in Table 1. Age at surgery was positively correlated with the latency of OT discharges (Fig. 2). The latency was determined using a single linear regression: Latency (msec) = 27.5 + 0.55 × Age (year) (r = 0.564, P < 0.005). The disease duration and levodopa dose were not correlated with the latency (r = 0.081, P = 0.70 and r = 0.247, P = 0.23, respectively). The variables showing severity of PD were not correlated with the latency (UPDRS motor score at OFF phase, r = 0.080, P = 0.71; Hoehn and Yahr stage at

Table 1. Bivariate analysis showing the correlations between the OT discharge latencies and clinical parameters using Pearson correlation.

	Pearson correlation	
	r	*P*
Age at surgery	0.564	<0.005
Disease duration	0.081	0.700
Levodopa dose	0.025	0.234
UPDRS PartIII (OFF)	0.080	0.706
Hoehn and Yahr stage (OFF)	0.217	0.297

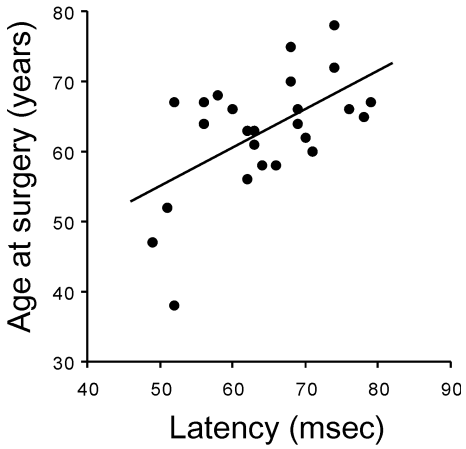

Figure 2. Scatter diagram of the latency and age at surgery.

OFF phase, $r = 0.217$, $P = 0.30$). In stepwise regression analysis, age at surgery presented only one significant predictor for the latency of OT discharges.

Discussion

Our previous study which appeared in the companion paper[12] demonstrates the presence of On- and Off-type responses in signals recorded from OT fibers in patients with PD. Most of the positive response sites at the light on event showed On-type responses, which have been derived from retinal On cells. Recording at multiple sites of the OT revealed that the latency was fairly constant under stable condition, although the latency is changeable depending on luminance and many other test conditions. Onset times of the excitatory responses at the light on event are a composite of the time for light transduction by the photoreceptors, for synaptic transmission from the photoreceptors to the ganglion cells and for conduction in the OT.

Multiple linear regression analysis revealed that age at surgery was a major determinant of the OT-discharge latency. The regression equation revealed that the latency increases linearly by 0.55 msec per year in the age range of 38–78 years. This rate is larger that of early components of VEP by flash stimuli reported by Dustman, et al.[13] or similar to that of P100 of pattern-reversal VEP reported by Allison, et al.[14] in normal subjects. The difference between the present results and those in the previous studies may be due to differences in methods or cohorts. On the other hand, the rate of increase in the OT-discharge latency with age is much smaller than the rate of increase in the latency of P3 of event-related potentials, 1–2 msec per year with age.[15] This difference in the rate of increasing latency is probably due to slowing of cognitive function with age which is included in the latency of P3.

Recently, some morphological studies using optical coherence tomography (OCT) have revealed that the thickness of the retinal nerve fiber layer is significantly decreased in patients with PD compared with normal controls.[16–18] The study using high resolution Fourier-domain OCT reported that the inner retinal layer, which is the site of amacrine cells and ganglion cells, is significantly thinner in patients with PD than in healthy subjects.[18] Contrary to these observations, no difference in retinal thickness was reported between PD patients and normal controls.[19,20] With regard to correlation between thickness of the retina and disease severity in PD, significant correlation between reduced foveal thickness and disease severity was reported,[17] while no correlation between retinal thinning and disease duration was reported.[16]

Our results showed that latency of the OT discharges did not correlate with disease duration and severity of PD in this study, suggesting that retinal degeneration does not correlate with progression of the nigrostriatal lesion in PD or that deficit of retinal dopamine does not affect the latency of the OT discharges. Only a small proportion of the ganglion cell discharges may be generated by dopamine-containing retinal cells. Prolonged latency of the cortical VEPs in severe PD patients has been reported in the literature, and our results suggest that the prolonged latency may be induced mainly by a functional abnormality in the visual cortex in PD. There may be some factors that may reduce the correlation, for instance, differences in medication history and possible ophthalmological deficits of various degrees in our patients; however, the significant correlation between latency of the OT discharges and age suggests the variance caused by such factors is not large. As the delay of the latency of the OT discharges did not correlate with the severity of PD, the rate of delayed latency of the OT discharges with age which was measured in this study could be applied to normal subjects.

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Author Contribution

All authors contributed to the manuscript equally. Dr. Takao Hashimoto – study design, patient evaluation, statistical analysis, wrote all drafts of manuscript. Dr. Satoshi Katai – assistance with surgery, patient evaluation. Dr. Tetsuya Goto – surgery, edited manuscript.

Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

