Age-Associated Changes of Flash Visual Evoked Potentials in Dogs

Tomofumi KIMOTSUKI^{1,2)}, Mitsuya YASUDA¹⁾, Satoshi TAMAHARA²⁾, Mizuki TOMIHARI²⁾, Naoaki MATSUKI²⁾ and Kenichiro ONO²⁾

¹⁾Medicinal Safety Research Laboratories, Sankyo Co., Ltd., 717 Horikoshi, Fukuroi, Shizuoka 437-0065 and ²⁾Department of Veterinary Clinical Pathobiology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan

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ABSTRACT. Age-associated changes of visual evoked potentials by flash stimulation (flash VEP) were evaluated in 53 beagle dogs aged from 1- to 15-year-old. Among the components of flash VEP consisted of 3 positive (P1, P2 and P3) and 2 negative (N1 and N2) peaks by 150 msec, the latency of P2 and the later peaks (N2 and P3) were significantly delayed with aging. Both amplitudes of the P2-N2 and N2-P3 also showed a significant correlation with aging. The flash VEP is considered to be an available and useful technique to evaluate not only for visual pathway, but also some disturbance of neurological functions, like as those reported in demented human.

KEY WORDS: age-associated change, canine, flash VEP.

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Visual evoked potentials (VEPs) indicated electrophysiological responses from retina to visual cortex is reported to be an useful technique for evaluating optic pathway [8] and also to be a sensitive indicator for dementia in human [4, 18, 22]. Visser *et al.* [21] demonstrated that the latency of the flash VEP components was delayed in the patients with dementia, especially Alzheimer's disease. The latency of the positive peak 2 (P2 :mean latency was 100 msec) and the later components were significantly delayed, although the similar results were sometimes detected in aged human. The flash VEP recorded in dogs showed 3 positive (P1, P2 and P3) and 2 negative (N1 and N2) components by 150 msec after the flash stimuli, like as those reported in human [11, 17, 19]. In addition, various age-associated pathological and/or physiological changes were commonly observed in aged dogs as well as aged human [5, 10]. Since there are few diagnostic techniques for dementia in dogs, age-associated changes of the flash VEP were evaluated using various aged beagle dogs.

Total 53 beagle dogs (25 male and 28 female) aged from 1- to 15- year-old kept in Medical Safety Research Laboratories, Sankyo Co., Ltd., were used.

The flash VEP was recorded using needle electrodes inserted in the midline of the scalp according to the method reported by Strain *et al.* [18]. Briefly, electrodes of recording, reference, and ground were placed over the midline of the nuchal crest, forehead, and vertex, respectively. Prior to recording, the dogs were instilled the mydriatic drug, including tropicamide and phenylephrine hydrochloride, and subcutaneously given atropine sulfate (0.05 mg/kg) and intramuscularly given xylazine (2–3 mg/kg) for the sedation. Then the dogs were dark-adapted at least 1 hr and the flash VEP were recorded in the dark shielded room. The

white flash stimulus was given 1/sec with the intensity of 0.6 joule using a photostimulator (SLS-3100 Photostimulator, Nihon Kohden Co., Tokyo, Japan). The xenon lamp was located about 15 cm in front of the examined eye and another eye was covered with the black cloth. The responses were recorded with signal averager (Neuropack Four Mini, Nihon Kohden Co, Tokyo, Japan). The band-pass filter was set at 1 Hz low and 1,000 Hz high. In this study, consecutive 30 responses were averaged and the latencies of flash VEP components were measured.

Quadratic regression analysis was used for statistical significance between the latency or amplitude of the components in VEP and the aging.

The flash VEP waveforms showed 3 positive and 2 negative components as reported previously [11]. Figure 1 shows typical flash VEP waveform in young (1-year-old), middle (9-year-old), and old (15-year-old) aged dogs. No remarkable difference in the latency of P1 and N1, however, the latencies of P2, N2, and also P3 were delayed in the aged dog, especially in the 15-year-old beagle dog (Table 1). Correlation between the latency or amplitude of each component in the flash VEP and the aging are shown in Figs. 2 and 3, respectively. Significant correlations were observed between the latency and the aging on P2, N2, and P3, and between the amplitude and the aging on P2-N2 and N2-P3.

The waveforms of the flash VEP in dogs were similar to those in human. From the results of our previous report [11], P1 and N1, P2 (mean latency was 53 msec), and N2 (mean latency was 81 msec) in flash VEP were referred to the retinal potentials, the potentials from retina to brainstem, and those from brainstem to visual cortex, respectively. In this study, the latency of P2 and the later peaks were significantly delayed, and the amplitudes of N2-P2 and P2-N3 were decreased with age advanced. The flash VEP was demonstrated to be a specific indicator of dementia in human, particularly on the latency of P2 [4, 18, 22], since no P2 latency delayed was detected in the patient with depres-

* CORRESPONDENCE TO: ONO, K., Department of Veterinary Clinical Pathobiology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan.

sion, confusion, and/or forgetfulness [15, 18, 22]. In addition, the amplitude of flash VEP showed more commonly in aged human [3, 23], like as shown in N2-P2 and P2-N3 of aged dogs in this study.

Many researchers demonstrated that demented human

Fig. 1. Typical waveforms of the flash VEP in young (1-year-old), middle (9-year-old), and old (15-year-old) aged dogs. The latencies of P2 and N2 were delayed in aged dog, especially in the 15-year-old beagle dog.

showed pathological and physiological changes in the brain, including amyloid deposition, reduction of biochemical enzyme activities, insufficient of cerebral blood flow, and decrease of glucose metabolism, every of which were detected in the temporal-parietal-occipital areas in the brain [9, 12–14]. Similar pathological physiological changes were also observed in aged dogs [5]. Therefore, the delay of the latency of P2 and later peaks observed in aged dogs were considered to reflect the disturbance of the potentials from retina to brainstem and behind visual pathway. The dementia patient with Alzheimer's disease also showed the delay of the P2 latency [5,23], which reflects the potentials from brainstem to visual cortex, corresponding to N2 of the flash VEP in dogs. The pathophysiological mechanism for the delay of P2 was reported that the reduction of neurotransmitter, especially cholinergic neurotransmitter, which was frequently observed in the temporal and parietal cortex and hippocampus, induced the disturbance of neuronal transmission and functions [6, 7, 16]. Neurotransmitter deficits, especially cholinergic loss, were observed in aged human and the early phase of dementia [7, 20]. The P2 delay was also induced in normal subjects by the administration with anti-cholinergic drugs [2]. Araujo *et al.* [1] demonstrated that the cholinergic system was also important in cognitive deficits in dogs. Therefore, the delay of the latency of P2 and the later peaks observed in aged dogs might be reflected the neurological disturbance with the defects of neurotransmitter. Further studies are necessary on the flash VEP in

Fig. 2. Correlation between the latency of each component in the flash VEP and the aging in dogs. Significant correlation between the latency and the aging on P2, N2, and P3 were observed.

Fig. 3. Correlation between the amplitude of each component in the flash VEP and the aging in dogs. Significant correlation between the amplitude and the aging on P2-N2 and N2-P3 were observed.

Table 1. Latency and amplitude of the components on the flash VEP waveform in dogs

age (year)	latency(msec)					amplitude(μV)			
	P1	N1	P2	N2	P3	P1-N1	N1-P2	P2-N2	N2-P3
1 (n=5)	13.8 ± 1.1	31.8 ± 0.8	51.6 ± 3.9	78.8 ± 4.7	146.8 ± 10.8	28.4 ± 14.1	25.8 ± 5.7	35.5 ± 12.6	50.7 ± 12.4
9 (n=8)	15.8 ± 3.1	30.6 ± 2.6	58.0 ± 9.3	92.5 ± 17.1	146.6 ± 16.4	26.2 ± 13.6	26.9 ± 7.9	18.7* ± 11.6	20.2** ± 9.1
15 (n=4)	13.5 ± 2.4	33.3 ± 3.9	70.5* ± 12.2	115.0** ± 13.8	188.5 ± 38.3	13.6 ± 2.2	20.2 ± 5.6	20.2 ± 4.3	22.6** ± 7.1

The values indicate mean ± SD. * and ** represent significant difference ($P < 0.05$ and $P < 0.01$, respectively) compared to the value in 1 year-old dogs by Student's *t* test.

demented dogs.

From these results, the flash VEP is considered to be an available and useful technique to evaluate not only for visual pathway, but also some disturbance of neurological functions, like as those reported in demented human.

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