The Comparative Study of Aging and Auditory Evoked Potentials in the Mouse Model

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ABSTRACT

Objective: Presbycusis is a progressive hearing impairment associated with aging, characterized by hearing loss and a degeneration of cochlear structures. The mouse has been a useful model of presbycusis, as it displays an accelerated age-related peripheral hearing loss. The purpose of this study is compared with aging and auditory evoked potentials in the mouse.

Method: Adult male ICR mice 7, 10, 17, 23 and 27 weeks were used in this study. In order to assess age-related hearing loss (AHL), we evaluated auditory brainstem response (ABR) and auditory middle latency response (AMLR) for the evaluation of sensorineural function in peripheral auditory nerve.

Results: Hearing thresholds was significantly increased 17, 23 and 27 weeks after birthing comparing with 7 weeks in the mouse. Pa latency of AMLR was no difference for 6 weeks from 23 weeks group, Absolute latency of wave IV and interpeak latency of wave I-IV were significantly delayed for 6 weeks from 23 weeks group. The result suggests that significant changes of auditory evoked potentials from 17 weeks have taken place, age-related hearing loss (AHL) could be evaluated by the shift of hearing threshold and the increasing of ABR latency in the mouse.

KEY WORDS: Aging · Mouse model · Auditory evoked potential.

INTRODUCTION

For many people, aging is associated with a decrease in hearing sensitivity or presbyacusis. Age-related hearing loss (AHL) is the most common type of hearing impairment in humans. Many factors contribute to loss of auditory function with age. Some of these factors are disease state, genetic background, and environmental influences. Because hearing loss is very detrimental to the quality of life of the affected person and the person's loved ones, it is considered a major public health issue. Age-related hearing loss in humans is characterized primarily by an elevation of hearing thresholds, usually beginning with the high frequencies and progressing to lower frequencies. Histopathologic studies of human ears reveal that AHL is associated with the progressive degeneration of the cochlea's sensory cells and spiral ganglion cells, with the outer hair cells the most severely affected.180) AHL is extremely difficult to study experimentally in humans primarily because of confounding nongenetic factors including their frequent exposure to excessively loud noises, the presence of other ear problems, and exposure to ototoxic drugs, which also affects the viability of the sensory hair cells.

Recent reviews of the histopathology and molecular genetics of human hearing loss underscore the utility of animal models to advance the understanding of AHL in humans.94) Because of many practical benefits, including the varied degrees of hearing loss and short life span of the mouse, the mouse is a popular model of AHL.3) Hearing impaired mouse inbred strains have been very well characterized and make good models for the study of AHL.5)7)13)16)18)21) Auditory evoked potential (AEP) may be used as a hearing threshold test and a neurological screening test to assess the integrity of the peripheral auditory nerve and central auditory nervous system. These methods are based on selective recording of electrical events occurring along the auditory pathway. The graphic representation of the auditory brainstem response (ABR) and the auditory middle latency response (AMLR) includes several constant...
waves related to specific areas of the auditory pathway. The ABR is used as the determination of hearing threshold and the assessment of integrity of a peripheral auditory nerve. The AMLR is also useful in the assessment of neurological function of the higher central auditory nervous system.

The purpose of this study is compared with aging and auditory evoked potentials with hearing threshold using ABR and latency comparison using ABR and AMLR in the mouse.

MATERIALS AND METHODS

All the experimental procedures were performed in accordance with the Principles of Laboratory Animal Care (NIH publication, #80-23, revised 1996) and the Animal Care and Use Guidelines of Nambu University, Korea. Adult male ICR mice 7, 10, 17, 23 and 27 weeks (Jung-Ang Lab Animal, Seoul, Korea) were used in this study. The mouse was housed individually with a 12 h/12 h light/dark cycle with food and water ad libitum.

Auditory function tests were performed while the mouse was anaesthetized with xylazine (0.43 mg/kg) and ketamin (4.57 mg/kg) via intramuscular injection. The rectal temperature was maintained at 37 ± 0.5°C with a heating lamp during testing and recovery from anesthesia. Prior to testing, an otoscopic examination was performed on each mouse.

Peripheral and central auditory functions were determined by ABR. Two-channel recordings (GSI Audera, Viasys Healthcare Inc., USA) were obtained with needle electrodes inserted subcutaneously at the vertex, in the midline of the scalp between the external auditory canals. Reference electrodes were placed below the pinnae of the left and right ear and a ground electrode was inserted the shoulder. Electrode impedances were below 10 kohm and within 5 kohm for electrode pairs. Alternating clicks (0.1 ms duration, bandpass filter 100–3,000 Hz, rate 20.1 Hz) were delivered via insert earphones. Averages for 1000 sweeps were collected for each condition, and responses were replicated to determine reliability. The following parameters of evoked potential were evaluated; the hearing threshold, the absolute latencies of waves I, III and IV and the interpeak latencies of waves I-III, III-IV and I-IV.

Midbrain auditory pathway functions were evaluated with AMLR. Two-channel recordings (GSI Audera, Viasys Healthcare Inc., USA) were obtained with the same method of ABR. Rarefaction clicks (0.1 ms duration, bandpass filter 10–250 Hz, sweep 250, rate 9.1 Hz) were delivered via insert earphones. The parameter of evoked potential was evaluated with the absolute latencies of wave Pa.

The data was analyzed using Sigma Plot software (Systat software Inc., USA). All the data were expressed as a mean ± standard error mean. Statistical comparisons between the different treatments were performed using one-way ANOVA with a Dunnett’s multiple comparison post test. The correlation of two data sets was evaluated by Pearson correlation coefficients. P values <0.05, 0.01 and 0.001 were considered significant.

RESULTS

In this study, we performed ABR and AMLR for 5 mice group by 7, 10, 17, 23 and 27 weeks old. The mean of hearing threshold of 7, 10, 17, 23 and 27 weeks old was 18.75 dB, 40.94 dB, 46.88 dB, 56.36 dB and 73.33 dB respectively. The mean hearing threshold was significantly increased in dependent on age. The hearing threshold of 7 weeks group was normal range (Fig. 1).

We performed ABR and AMLR with 23 weeks group during 6 weeks. The hearing threshold was increased for 6 weeks from 23 weeks group. The threshold shift of...
ABR was similar for 6 weeks from 23 weeks group (Fig. 2). The Pa latency of 23 weeks group was maintained for 6 weeks (Fig. 3).

The result of latencies using ABR for 6 weeks from 23 weeks group was shown with absolute latencies wave I, III and IV and interpeak latencies wave I-III, III-IV and I-IV (Fig. 4). Absolute latency of wave I was no difference for 6 weeks from 23 weeks group. However, absolute latency of wave IV was significantly increased from 4 to 6 weeks. Interpeak latency of wave I-IV was significantly increased from 4 to 6 weeks.

**DISCUSSIONS**

Age-related alterations in auditory function were evaluated in adult male mouse involved in a long-term study on aging. We assessed mice in 7, 10, 17, 23 and 27 weeks old groups and long-term evaluation on aging for 6 weeks from 23 weeks group. The following measures of auditory function were obtained while mouse was maintained under anesthesia: (1) auditory brainstem response (ABR) for hearing sensitivity and peripheral auditory nerve function; and (2) auditory middle latency response (AMLR)
for central auditory function. The threshold shift causing AHL was significantly shown over 17 weeks groups old than 7 weeks old. ABR threshold increased 17 dB for 6 weeks from 23 weeks group. For neural function measures, there was a significant age effect for latencies of ABR. Absolute latency of wave IV and interpeak latency of wave I-IV in ABR significantly increased whereas Pa latency in AMLR did not shown age effect.

Neural function, measured by auditory evoked potentials, demonstrated that ABR and AMLR peak latency measures in the mouse of the present study were similar to previous report in animal. Torre et al(5) found that wave latency for ABR of older monkeys increased in comparing with younger monkeys. It is a same result that wave latency for AMLR was not difference with age. The decreasing of auditory function was progressive overtime in the mouse model. The research was concluded that progressive age-related changes suggest early therapeutic intervention to prevent sensory cell damage and hearing loss.11)

The mouse model for AHL research is useful. The mouse model has practical benefits, including the varied degrees of hearing loss and short life span of the mouse.8,9 It is also an ideal subject for molecular studies because of the availability of the mouse genome and the previous characterization of mutations that affect hearing.9 Hearing impaired mouse have been very well characterized and make good models for the study of AHL.5,7,13

In summary, the mouse in the current study exhibited significant age-related increase in ABR threshold and significant age-related delayed in ABR latencies. The current study was limited to use the auditory evoked potentials for AHL assessment and future studies would benefit by comprehensive assessment methods. Additionally, future studies should include measurements using a higher frequency protocol to better characterize the frequency range of the mouse. Finally, a longitudinal investigation is planned to determine whether the preservation of auditory function continues over time, particularly in the younger group of the mouse.

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REFERENCES