Altered Peripheral and Brainstem Auditory Function in Aged Rats

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A technique for conducting free-field brainstem auditory evoked potential (BAEP) audiometry in unanesthetized, unrestrained rats revealed a non-recruiting 18 dB elevation of click threshold in aged rats. BAEPs were first recorded in young and aged rats to clicks of equal intensity (80 dB SPL). Compared to the young group, aged animals exhibited longer wave I and wave IV latencies with no difference seen in the I–IV central conduction time. The prominent negative wave (No) following wave IV was also delayed and the I–No and IV–No conduction times increased in the aged group. When BAEPs were recorded to clicks with intensities adjusted to 35 dB above individual threshold, no differences in wave I or wave IV latencies or in the I–IV central conduction time were found between groups. However, the No component was delayed and the I–No and IV–No conduction times remained prolonged in the aged group. The results suggest that in addition to changes in peripheral auditory structures, changes in the rostral auditory brainstem accompany age-related hearing loss in rats.

INTRODUCTION

Behavioral and anatomical studies indicate that the decreased auditory function accompanying senescence has peripheral and central components3,14,20,22,33 both of which can be assessed by recording the brainstem auditory evoked potential (BAEP). The BAEP is composed of a series of high-frequency positive peaks superimposed on a slower positive–negative deflection7,8,17 and has achieved widespread clinical utility since it reliably indexes abnormalities in peripheral and brainstem auditory structures6,13,31,32. Five positive peaks, designated as waves I–V, are generated primarily by sequential activity in auditory nerve, cochlear nucleus, superior olivary complex, lateral lemniscus and the input to the ventrolateral inferior colliculus1,5,11,17,19,24. It is likely that multiple generators may contribute to some of these waves5. The prominent slow negativity (No), which follows the wave IV–V complex, is considered to be generated by the inferior colliculus, particularly in the region of the central nucleus11,17,18,24.

A prolonged latency of wave I is indicative of an abnormality in peripheral auditory structures, whereas intrinsic brainstem dysfunction is indexed by the absence of components occurring after wave I or by prolongation of the latencies between these components (the interpeak interval or IPI). Thus, different patterns of abnormality in the BAEP can distinguish peripheral and brainstem dysfunction.

A prolonged wave I latency is commonly reported in elderly subjects and is largely attributable to changes in peripheral auditory structures2,15,25,28. The contribution of intrinsic brainstem dysfunction to age-related differences in the BAEP is, however, less certain. Fujikawa and Weber10 found a greater increase in wave V latency with high stimulation rates in aged individuals. However, they measured only wave V latencies and it is not clear whether their findings were due to changes in the periphery, the brainstem or both. Studies in which brainstem function was assessed by measuring BAEP interpeak intervals (brainstem conduction time) present conflicting results. Some investigations adjusted stimulus intensities for the increased thresholds of the aged pop-
ulation\textsuperscript{2,4,25}, whereas others did not\textsuperscript{15,28}. With either approach, both normal\textsuperscript{4,13} and prolonged\textsuperscript{2,25,28} conduction times have been reported for aged individuals. Thus, although aging appears to be associated with peripheral hearing loss and a corresponding increase in wave I latency, evidence of changes in auditory brainstem function in the elderly is inconclusive. Aged cats have an increased BAEP threshold; however, BAEPs to stimuli adjusted for threshold differences do not reveal significant differences in the peak latencies of waves I–V, or in interpeak intervals in aged vs young adult cats\textsuperscript{16}.

The slow negative wave occurring after the positive IV–V complex has received increasing attention with lesion studies in animals\textsuperscript{11} and depth electrode studies in humans\textsuperscript{17,18,24}, indicating a generator in the region of the inferior colliculus. However, the brainstem slow negative potential has not been systematically examined in aged human or animal populations. Since there is suggestive evidence of brainstem auditory abnormalities in aged humans, we have employed an aged rat model to test for BAEP signs of changes in auditory brainstem activity. Both fast and slow components of the BAEP were examined in unrestrained, unanesthetized young and old rats.

MATERIALS AND METHODS

**Animals**

Fischer 344 male rats were studied. The aged group consisted of 6 retired breeders with a mean age of 25 months. The young adult group consisted of 6 rats with a mean age of 8.5 months. The average life expectancy for these rats is 25 months.

**Surgical procedure**

Stainless-steel wires insulated except at the tips were placed in wells drilled in the bone over frontal cortex, (FCx: 2 mm anterior to the bregma and 2 mm lateral to the midline), at the vertex (Vx: half the distance between the bregma and lambda and just off the midline suture), over both visual cortices (VCx: at lambda, 2 mm lateral to the midline), and at 3.5 mm anterior to lambda, and 5 mm laterally on each side near the insertion of the temporalis muscle (designated ACx as it was at the rostral border of primary auditory cortex). A ground wire was inserted in the neck muscles and a stainless-steel reference screw was placed in the far frontal sinus. All wires were led to a connector which was secured to the skull with dental cement. During recording sessions a flexible cable leading to the amplifiers was inserted into the skull plug.

**Auditory apparatus**

The recording chamber consisted of a small wire-mesh cage 10 in. high and 7 in. square, located in the center of a shielded, sound attenuated, ventilated chamber fitted with a one-way window. Four speakers were mounted around the interior of the chamber equidistant from the center of the wire cage. Intensity levels were measured with a Bruel and Kjaer model 2203 sound pressure meter with an attached microphone (B & K 4144). The ambient noise was 35 dB SPL in the chamber. An additional 25 dB of white noise was introduced by a fifth speaker located above the cage. The intensity levels of the white noise and the superimposed click stimuli did not vary by more than 4 dB across measurements at any location in the recording cage.

The power spectrum of the click stimulus plus white noise background was measured with a Hewlett Packard model 5420A digital spectral analyzer at the center of the cage and at the center-points of the floor, the ceiling and each wall of the cage. Comparisons of the power spectra from each of these locations revealed that the power at any frequency in the 1 Hz to 25 kHz range did not vary by more than 4 dB across locations, except for the power measured at the floor of the cage which was 4–6 dB less than at other locations.

Free-field click stimulation was used in order to record from unanesthetized, unrestrained animals, thereby reducing the possible confounds due to repeated stress and anesthesia. This method permits frequent assessment of auditory function, and its development was of interest to us because it is particularly well suited for use in studies of the effects of behavioral state and conditioning on auditory evoked potentials.

**Recording procedure**

EEG was recorded from FCx, Vx, VCx, VCx, ACx, ACx, all referenced to the frontal sinus screw. The EEG was amplified by Grass P511K amplifiers with bandpass filter settings of 100 Hz–3 kHz.
BAEPs were obtained by averaging the responses to 1024 click stimuli with a Nicolet 1172 signal averager sampling every 30 μs over a 15 ms period. Epochs with muscle artifacts were automatically rejected.

Audiometry

BAEP audiometry was conducted on all rats using 0.1 ms click stimuli delivered at a rate of 11/s with a continuous white noise background. The BAEP threshold to the clicks was determined by collecting BAEPs (sum of 1024) at 5 dB decrements until a near-threshold level was recorded. At this point 2 dB decrements were used to find the BAEP threshold, which was defined as the lowest intensity for which there was a replicable wave IV–V complex above background noise. BAEPs were recorded for 3 further 2 dB decrements beyond apparent threshold to be certain that no consistent wave IV–V was present. BAEPs were then recorded at 2–5 dB increments until well above threshold. The value obtained with this decreasing and increasing approach was defined as threshold (T). After initial determination of the threshold, the procedure was repeated during that recording session and again on another day to check for replicability of waveform at each dB step and for replicability of threshold.

Following determination of audiometric thresholds, BAEPs were recorded to clicks at 35 dB above the individual rats' thresholds to provide data adjusted for threshold differences. This procedure was repeated on at least one other day. BAEPs were also recorded at 5, 15, 25 and 35 dB above threshold to examine for evidence of recruitment. In a separate session, BAEPs were collected at 80 dB SPL for comparison of the young and aged groups when matched for intensity.

Data analysis

Peak latencies of waves I, IV, V, and the slow negativity (No) following wave V were measured and interpeak intervals were computed from these latencies. Peak latencies were measured from stimulus onset with 0.75 ms subtracted for the air conduction time from the speakers to the center of the cage. Amplitude measures of wave IV and No were made relative to a baseline determined as the mean amplitude of the poststimulus activity during the air conduction time. Comparisons were made between young and aged groups for the BAEP-determined thresholds and for the latencies of the BAEP peaks and relevant interpeak intervals. Differences between the group means for these measures were tested for significance by non-directional (two-tailed) t-tests.

RESULTS

BAEP topography was examined initially in each rat to determine the best skull placement for rapid audiometric threshold determination. The leads over the visual cortices (VCxl and VCxr), rather than vertex (Vx), yielded the clearest and largest amplitude BAEPs in all rats, particularly with regard to waves IV and V (see Fig. 1). This may be due to the proximity of the VCx leads to the auditory brainstem. All data reported here are from the left visual cortex lead (VCxl) referenced to the far frontal sinus.

BAEP Waveforms

BAEPs were highly replicable for individual

![Fig. 1. Scalp topography of the BAEP. Exemplary BAEPs simultaneously recorded from Fx, Vx and VCx sites, referenced to far frontal sinus, in a young rat to clicks at 35 dB above threshold. S represents the time of arrival of the stimulus at the ear (stimulus onset plus 0.75 ms air conduction time). BAEPs in this and subsequent figures are the average of responses to 1024 stimuli.](image-url)
rats both within and across recording sessions (see Fig. 3). After threshold determination BAEPs were recorded to clicks at 35 dB SPL above individual threshold. These low intensities were chosen in order to minimize myogenic artifacts. The stimulus intensity means were 79.7 dB SPL for the aged group and 61.7 dB SPL for the young group. Typical BAEPs from 3 rats in each group (young, aged) are displayed in Fig. 4. The first and fourth positive peaks of the BAEP were designated as waves I and IV respectively. There was a fifth positive peak (wave V) which was most noticeable in aged rats and appeared in young rats as a shoulder on the negative-going slope of wave IV. Although BAEPs were highly reproducible in individual rats, the morphology was somewhat variable between animals, with more variability apparent in the aged group.

Following the nomenclature of Picton et al., we
have labeled the large negativity following the wave IV–V complex No. Although according to their temporally based nomenclature the No in humans is considered a middle latency component, we have included it in the description of the BAEP components because of its likely brainstem origins. The No component in this report is similar in morphology and sequential position to the negative component which has been reported to be diminished with inferior colliculus lesions in rats.

**BAEP latency and amplitude measures**

The latencies and interpeak intervals for BAEP components I, IV, V and No recorded to clicks at 35 dB above threshold were determined (see Table I). Comparisons between young and aged groups revealed no group differences for the latencies of waves I, IV, or V, nor for the I–IV or I–V interpeak intervals. The No latency for the aged group (5.94 ms, S.D. 0.23) was, however, markedly prolonged (1.19 ms difference; \( P < 0.001 \)) relative to the young group (4.75 ms, S.D. 0.23). The wave V–No interpeak interval was also significantly increased in the aged group, and consequently the wave IV–No and wave I–No interval measures were increased as well (all \( P < 0.001 \)).

Since the morphology of the fast positive peaks was variable within and between age groups, it could be argued that the peak designated as wave V in the aged group (Va) should be considered as wave IV and that wave IV latency comparisons should be made between it (Va) and wave IV in the young group (IVy). Contrasting IVy to Va reveals a significantly longer wave IV (Va) latency in aged rats relative to the young (0.55 ms difference; \( P < 0.01 \)). The analogous comparison for the wave IV–No interpeak interval between age groups is that between the wave Va–No and the wave IVy–No intervals. Use of these measures for the wave IV–No interpeak interval comparison still reveals a markedly increased interval in the aged group (0.66 ms difference; \( P < 0.001 \)).

Latency–intensity functions were determined for wave IV and No. No and wave IV latencies to clicks at 5, 15, 25 and 35 dB above threshold were measured in the aged rats, and at 5 and 35 dB above threshold in the young rats. (The data for the young group represent 5 of the 6 rats.) Increasing click intensity from 5 to 35 dB produced a significant decrease in the No latency for both the young and aged groups (\( P < 0.01 \) for all, see Table II). In the aged group the latency–intensity functions were essentially linear, indicating that the hearing loss in the aged rats was non-recruiting in the decibel range examined (see Fig. 5).

BAEPs were recorded to 80 dB SPL clicks in both young and aged rats in order to assess the contribution of the threshold differences between groups to the BAEP differences found for the aged rats. This intensity was essentially the same as the mean intensity given the aged group (mean = 79.7 dB SPL), and

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* \( P < 0.001 \).

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* Mean for 5 of 6 rats.
Fig. 5. Latency-intensity function in aged rats. The latencies of No (upper) and of wave IV (lower) are plotted as a function of increasing stimulus intensity (dB above individual threshold). Bars represent S.E.M.

about 18 dB higher than the mean intensity given the young group (mean = 61.7 dB SPL) in the 35 dB above-threshold condition.

The BAEP peak latencies and interpeak interval measures for both groups are given in Table III. Wave V was evident in only two of the 6 young rats at this higher intensity, and these values are given in parentheses in Table III. Consequently, no comparisons between young and aged groups for wave V latency or I-V and V-No interpeak intervals were made for the 80 dB SPL condition. Young rats exhibited a shorter wave I latency ($P < 0.05$) and wave IV latency ($P < 0.01$) in comparison to aged rats in the 80 dB SPL condition. However, there was no significant difference in the I-IV interval between groups.

The No latency was significantly shorter in the young group as compared to the aged group, as were the interpeak intervals I-No and IV-No ($P < 0.001$ for all) in this condition.

There were no significant differences in the amplitudes of wave IV or No between age groups in the 35 dB above-threshold condition. However, differences were apparent in the No duration, defined as the time between the falling and rising sides at the points of one-half the maximum No amplitude. Using this determination, the duration of the No wave was greater in aged than in young rats for both the 80 dB SPL and the 35 dB above-threshold conditions ($P < 0.001$; see Table IV).

**DISCUSSION**

Free-field BAEP audiometry revealed a substantial (18 dB) hearing loss to brief click stimuli in aged rats. The linear latency/intensity function for wave IV and No in the aged group coupled with normal I-IV conduction times suggests that this is largely attributable to non-recruiting peripheral dysfunction\(^27\). Whether this peripheral hearing loss is due to differences in the pinna, the middle ear or the cochlea cannot be determined with this technique.
When BAEPs were recorded to stimuli of equal intensity for each group (80 dB SPL), aged rats exhibited longer wave I and wave IV latencies without an increase in the I–IV interval, consistent with a peripheral hearing loss in the aged group.

When BAEPs were recorded to clicks adjusted for individual threshold differences wave I, IV and V latencies were virtually identical for young and aged groups, indicating that the higher intensity stimuli (18 dB increase) presented to the aged rats compensated for peripheral differences between aged and young animals. The intact central conduction times also suggest that the temporal aspects of brainstem transmission up to the auditory structures generating wave IV are not altered by advancing age, in accordance with the results reported for aged cats\textsuperscript{16}.

However, we found that whether or not threshold differences were adjusted for, and regardless of how wave IV was defined, the latency of No and the wave IV–No interval were significantly increased in the aged population. When click intensities were adjusted for individual threshold differences, aged rats exhibited a prolonged No latency and prolonged wave IV–No and V–No intervals in the presence of normal I–IV and I–V intervals relative to young rats. The effect on No latency was so large that there was no overlap of the latencies between groups, with the longest No latency in the young group (5.13 ms) being two standard deviations (S.D. = 0.23) less than the shortest No latency in the aged group (5.64 ms). In addition, the duration of No was significantly prolonged in the aged rats.

The aged rats could have had a peripheral high frequency hearing loss which effectively low-pass filtered the signal to the brainstem producing a delay in the No component, but this should have also increased the latency of the earlier positive peaks\textsuperscript{8,23} which was not observed. To further assess this possibility, BAEPs were recorded in 3 young rats to clicks low-pass filtered at 25, 15, 10, 5 and 2 kHz (6 dB/octave filter). In each rat the latencies of all BAEP components were progressively increased as the low-pass filter cut-off was lowered from 25 kHz to 2 kHz, further supporting the contention that the prolongation of the No latency is not due simply to a peripheral high frequency loss.

Clicks were presented at low intensities to reduce myogenic activity associated with the startle reflex\textsuperscript{8}, and BAEP recording was suspended during grooming or other extended periods of movement. EEG spectral analysis revealed no differences in the amount of muscle activity between young and aged groups. However, the possibility exists that the difference in the No component in the aged group might be due to a myogenic potential from a delayed startle reflex in the aged rats. To examine this issue we compared the BAEP recorded at the VCx lead to that recorded at the ACx leads, which were near the insertion of the temporalis muscle. The amplitude of the No component recorded at ACx was less than 25% of that at VCx, and there was no difference in the amplitude at ACx between young and aged groups. This argues against a myogenic source for the No latency difference in aged rats.

Depth recording studies in humans and rats suggest that our findings of a delayed latency and an increased duration of the No wave in aged rats may represent changes in activity in the inferior colliculus (IC), particularly in the region of the central nucleus\textsuperscript{11,17,18,24}. Funai and Funasaka\textsuperscript{11} conclude from their depth recording and lesion effects that the slow negativity following wave IV–V originates in the central nucleus of the IC in rats. Depth recordings in humans have shown a negativity following wave V which may be analogous to the No wave reported here and which appears to be generated by the IC\textsuperscript{17,18,24}. Thus, the differences in the No wave of aged rats found in this study may reflect delayed and/or extended responses in the IC. Whether these differences are due to altered input to the IC or an altered response to normal or aberrant input cannot be determined from these data alone.

Decreases in glucose metabolism measured with \textsuperscript{[14C]}deoxyglucose\textsuperscript{30}, and in protein synthesis measured with \textsuperscript{[14C]}leucine\textsuperscript{21} have been reported in aged rat brain. Prominent decreases in activity were seen in the auditory system, particularly in the inferior colliculus. Similar decreases in glucose metabolism in the auditory system of rats have been produced by administration of the \(\beta\)-blocker propranolol\textsuperscript{29}. Furlow et al.\textsuperscript{12} reported decreased amplitudes and increased latencies for peaks I, III, IV and V of the rat BAEP following i.v. propranolol administration. Inspection of their figure illustrating the propranolol effects reveals a greatly prolonged and extended negative component similar to the No found in the aged rats of
our study. Taken together these findings suggest that
the age-related changes in the Nc component report-
ed here may be mediated by changes in adrenergic
activity in the inferior colliculus.

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