Hearing Research, 27 (1987) 165–176
Elsevier

HRR 00907

Development of the middle latency response in an animal model and its relation to the human response *

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(Received 10 November 1986; accepted 28 January 1987)

Although the clinical use of the middle latency response (MLR) in adults is fairly straightforward, its use is complicated by maturational changes that continue throughout the first decade of life. In order to telescope the time period of this long developmental course, we have approached the study of MLR maturation using the gerbil as an animal model. The course of MLR obtained over the temporal lobe development was characterized in the Monogolian gerbil ranging in age from 10 days to 3 months of life. The adult gerbil MLR consists of two positive peaks (A and C) at 11 and 25 ms, respectively, and a negative component (B) at 16 ms. These components emerge in a systematic fashion as a function of age. The present work supports a strong age effect of increased MLR detectability in the gerbil, similar to findings reported for humans. Wave A was infrequently detected in young animals, but when present, it occurred at adult latencies. The latency of waves B and C decreased systematically with age. The amplitude of all components increased with age, similar to findings in humans. The fact that adult-like thresholds were obtained shortly after birth indicates that when present, MLRs may be a good index of hearing threshold. Effects of stimulating across a wide range of intensities were described. The gerbil model appears appropriate for the study of development of the central auditory system function.

Development; Maturation auditory evoked potential; Middle latency response

Introduction

Clinical applications of the MLR include diagnostic testing of low frequency hearing (Mendel and Goldstein, 1969; Zerlin and Naunton, 1974; Musiek and Geurnink, 1981; Scherg and Volk, 1983; Maurizi et al., 1984; Kavanaugh et al., 1984), neurological assessment of function of the higher levels of the auditory pathway (Celesia et al., 1968; Picton et al., 1974; Goff et al., 1977; Kraus et al., 1980, 1982; Wood and Wolpaw, 1982; Özdamar et al., 1982; Kileny, 1983; Musiek et al., 1984; Scherg and Von Cramon, 1986), an objective index of cochlear implant function (Gardi, 1985) and a probe of arousal state (Kileny, 1983; Hall, 1985; Erwin and Buchwald, 1986). It is apparent, however, that special developmental considerations may be necessary to interpret MLRs in pediatric patients for diagnostic purposes. Although MLRs are consistently obtained in adults, these potentials are often not detected in children (Engel, 1971; Davis et al., 1983; Kraus et al., 1985a). This poses an obvious limitation to the clinical use of the MLR, since measures of hearing sensitivity are particularly needed for the young patient who is difficult to test behaviorally. Our previous work in human subjects ranging in age from 6 days to 20 years, revealed significant maturational effects on the detectability of the MLR throughout the first decade of life (Kraus et al., 1985a).

Because of the difficulty of adequately sampling a large human population across a 10 year age span, we have approached the study of MLR maturation by using the gerbil as a model. The

* Portions of this paper were presented at the 9th Annual Meeting of the Association for Research in Otolaryngology, 1986.

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gerbil auditory system is immature at birth and develops completely within the first few months of life. Therefore the gerbil lends itself easily to investigating age effects on the MLR and permits the study of developmental processes in a controlled environment. In this study, the course of MLR development was characterized in the gerbil.

The gerbil model

Gerbils were chosen because the pups are born neurologically and behaviorally immature and auditory system development is complete within the first few months of life. Unlike most mammals, the opening of the external auditory meatus and clearing of middle ear fluid is reported to occur largely before the onset of auditory function (Finck et al., 1972). This makes it possible to study the development of the auditory pathway largely independently of external and middle ear contributions.

Another advantage of the gerbil model is that there are existing physiologic data on the ontogeny of the cochlear microphonic (CM), compound action potential (AP), ventral cochlear nucleus (VCN) as well as anatomical data on the development of the central auditory pathway (Ryan et al., 1982; Woolf and Ryan, 1984, 1985). The gerbil has hearing sensitivity in the frequency range important for human hearing (Finck and Sofouglu, 1966; Ryan, 1976).

Previously described variability in MLRs in children have been correlated directly with age, and not with language delay or mental retardation (Kraus et al., 1985a). Because MLR variability in children does not appear to reflect qualities that are uniquely human, such as language function, but to reflect age-related variables, the use of an animal model seemed appropriate.

The present investigation addressed the following questions: (1) Does the gerbil MLR follow the same developmental course that is observed in humans (Kraus et al., 1985a)? (2) How does development affect the detectability, latency, amplitude and threshold of MLR components? and (3) What effect does stimulus intensity have on MLRs in developing animals?

Materials and Methods

Simultaneous auditory brainstem response (ABR) and MLR recordings were obtained from a total of 71 unanesthetized gerbils (*Meriones unguiculatis*). Data from 5 animals were obtained at each of the following ages: 15, 20, 25, 30, 35, 40, 50 and 60 days. Recordings were also measured in 4 animals at day 10, and in 15 adult gerbils (> 90 days). Physiologic recordings were obtained 48 h following surgical placement of electrodes. In addition, data were obtained in 2 day intervals from day 12–18. In this group, data were often obtained longitudinally.

Surgery

Electrode placement was performed under either sodium pentobarbital (7.5 mg/kg) and Innovar (0.4 ml/kg) or ketamine (300 mg/kg). Small burr holes were drilled into the skull and silver ball electrodes were placed over the dura. The wires were soldered to stainless steel screws which were attached to the skull with dental cement. The screw was used as a point of electrode attachment for physiologic recording on the day of the experiment. ABR was measured from an electrode implanted 5–8 mm posterior to bregma and the MLR was obtained from an electrode over the temporal lobe (2–3.5 mm posterior to bregma and 7–8 mm lateral to bregma). Both electrodes were referenced with respect to a site 7–10 mm anterior to bregma.

Acoustic stimulation and physiologic recording

Rarefaction clicks were generated by rectangular wave pulses (0.1 ms) and delivered monaurally to Beyer DT-48 earphones with a plastic sound tube placed at the eardrum under an operating microscope and glued into place. In those animals in which the ear canal was not fully open ($\leq$ day 16), the sound tube was positioned against the folds of the external auditory meatus. Hearing level values were based on the average ABR thresholds of 14 adult gerbils.

The EEG signal was amplified differentially with a gain of 20000, filter bandpass at 3–2000 Hz with a 6 dB/octave slope. The filter settings allowed simultaneous recording of MLR and ABR

activity. A 4 channel signal averager was triggered by the leading edge of the electric rectangular pulse of the click stimulus, and 80 ms of post-stimulus time was averaged at a rate of 50 points/ms. Each averaged response was made up of responses to 128 stimuli and was stored on a digital tape recorder to be plotted off-line.

Procedural protocol

A latency–intensity function was obtained in 10 dB steps from ABR threshold to 80 dB HL in response to click stimuli presented at 4/s. Threshold was defined as the lowest intensity yielding replicable ABR activity. Replicability of response activity was assessed with 4 successive trials at 50 dB SL. Data from these 4 trials were averaged to produce detectability, latency and amplitude values. ABR threshold was checked at the end of each experiment to ensure that there had been no change in the delivery of stimuli over time.

Data analysis

The presence or absence (detectability) of the MLR components and their amplitudes and latencies were determined without knowledge of the animal's age. The presence of a response was judged on the basis of the characteristic appearance of adult MLRs: a positive peak (A) following the ABR, a subsequent negative trough (B) and a second positive peak (C). This type of visual scoring is the manner in which evoked potentials are typically identified clinically, and recent studies (Mendel et al., 1984; Kraus et al., 1985a). Support the reliability of this procedure for evaluating MLRs. The amplitude of wave A was read from the peak of the wave to a pre-stimulus baseline. Wave B was measured from the peak of wave A to the trough of wave B. Wave C was measured from B to the peak of wave C.

A least squares non-linear curve fitting procedure was used to calculate the curve of best fit for the detectability data. The curve was the function, $y = a \tanh[(x - c)/b] + d$, where x = age in days and y = percent detectability. For comparison, the same procedure was applied to human data, described elsewhere in detail (Kraus et al., 1985a).

An analysis of variance was used to compare latency and amplitude changes across age groups. Multiple t tests were then used to compare individual age groups with adult data.

Results

Fig. 1A shows a representative MLR recorded over the temporal lobe contralateral to the stimulated ear from an adult, unanesthetized gerbil. The gerbil MLR consists of two positive components at approximately 11 and 25 ms, and a negative component at 15 ms. The ABR, evident in the first 4 ms, was used to monitor the animal's hearing and physiologic condition throughout the experiment. The maturation of the ABR is the subject of a separate study (Smith and Kraus, 1987b).

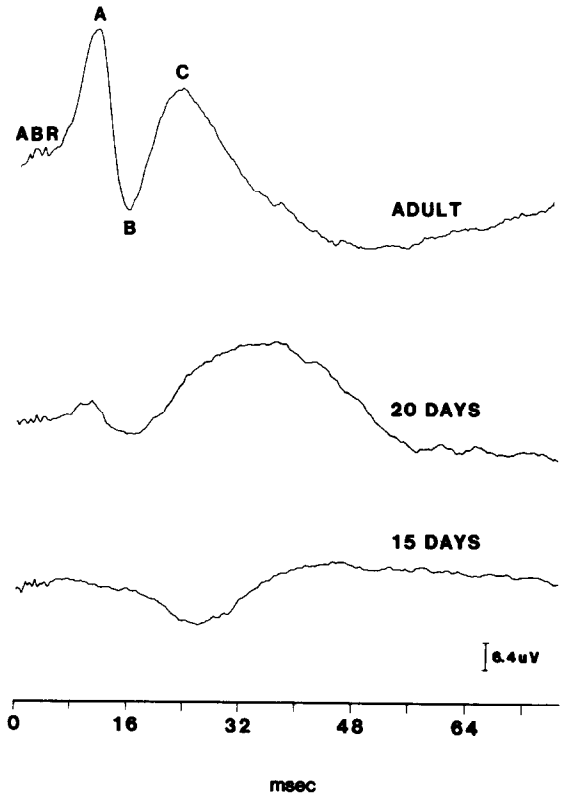

Fig. 1. Representative MLR activity observed at different ages in response to 50 dB SL click stimuli delivered at 4/s. Responses were recorded over the temporal lobe contralateral to the stimulated ear. A, adult; B, day 20; C, day 15.

Detectability

The basic developmental pattern of the emerging MLR is illustrated in Fig. 1 by representative waveforms. Wave B is the first to emerge with age, followed by wave C. Wave A is often not detected, and when present, it is small in amplitude, as is shown in the waveform obtained at 20 days. Wave A continues to have a low percent detectability and small amplitude until day 50, when it rapidly matures to assume the appearance characteristic of the adult waveform. The detectability of MLR components A, B, and C are shown in Fig. 2A for individual gerbils as a function of age. Each square represents 1 animal. The *Y*-axis represent the percentage of trials (each gerbil had 4 trials) that yielded a detectable MLR component for each animal at 50 dB SL. Evident from the figure is the absence of any response before day 14, and the trial-to-trial variability apparent among animals younger than 35 days. All components were consistently recorded in animals 50 days and older.

Fig. 2b shows analogous human data (Kraus et al., 1985b). The detectability of MLR components Na and Pa are shown for individual subjects. Similar to the animal data, there is a clear age effect on MLR detectability in humans, with subjects younger than 10 years of age showing considerable variability in comparison to older children and adults.

Fig. 3 shows the mean percent detectability of waves A, B and C as a function of age for 5 gerbils at each age tested. Evident is an increasing rate of response with age. Wave A was less frequently detected than waves B and C. In younger animals waves B and C were often detected without wave A. A least-squares curve fitting procedure

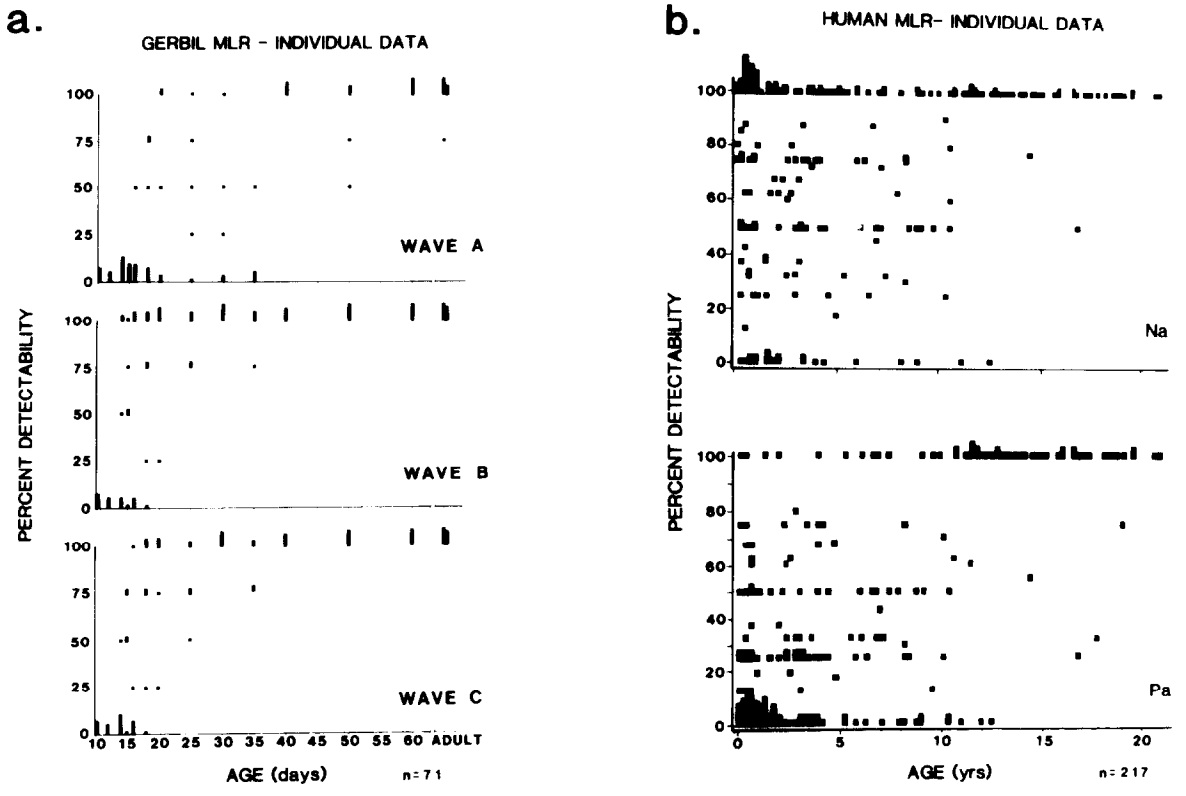

Fig. 2. Detectability of MLR components as a function of age for gerbils (a) and humans (b). Each square represents 1 subject. The *Y*-axis represents the percentage of trials that yielded a detectable MLR wave. Note that some symbols are stacked on top of each other in columns. The intended percentage value is indicated by the bottom of the column.

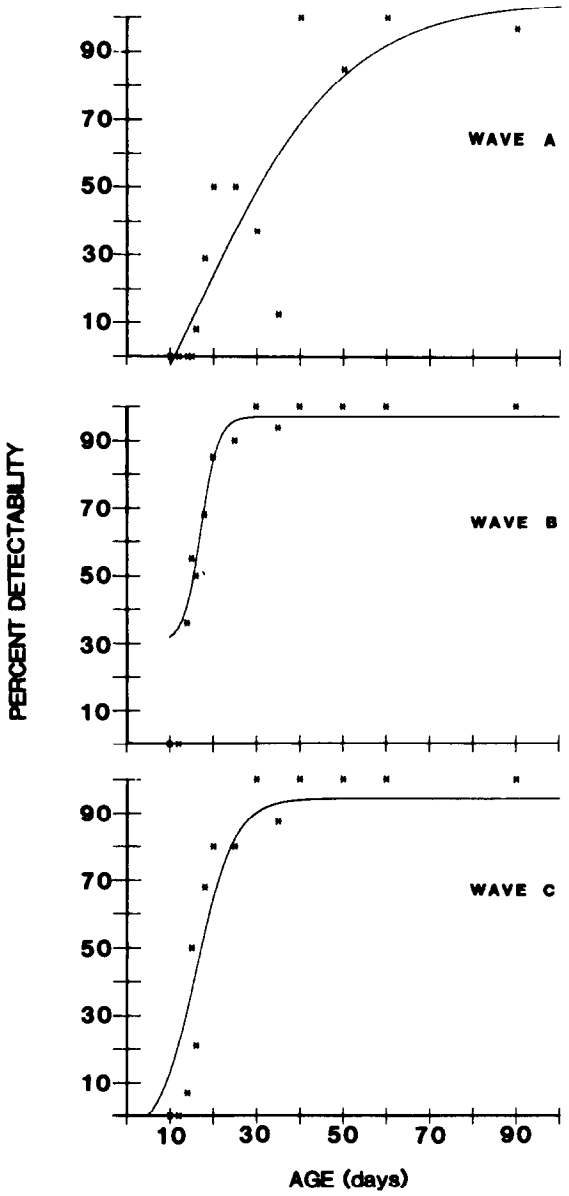

Fig. 3. Mean percent detectability of waves A, B and C as a function of age. Percent detectability was averaged across all subjects in a given age group. A least squares non-linear curve fitting procedure was used to obtain the curve of best fit.

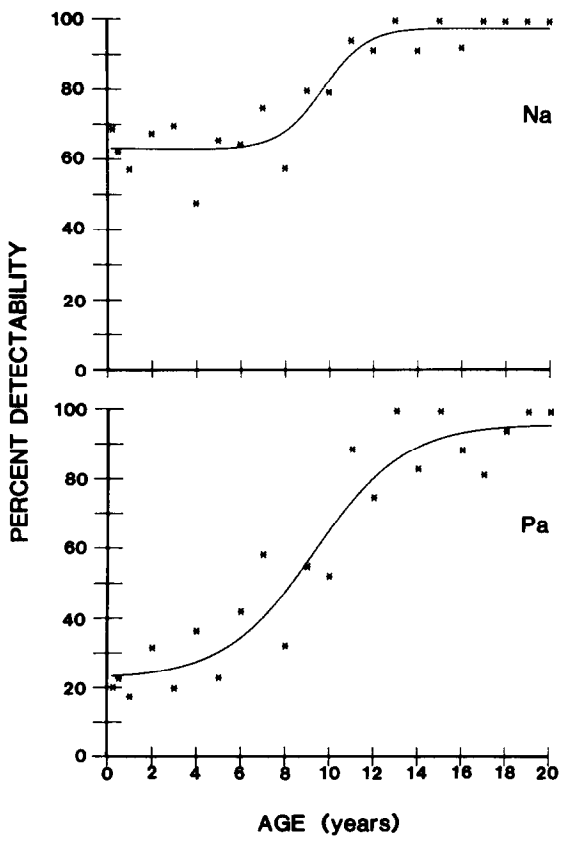

Fig. 4. Mean percent detectability of human waves Na and Pa as a function of age. Percent detectability was averaged across all subjects in a given age group. Curves of best fit were obtained with a least squares non-linear curve fitting procedure.

was used to calculate the curve of best fit for waves A, B, and C. A similar plot for human Na and Pa is shown in Fig. 4.

The gerbil MLR is less developed at birth than the human response; gerbil waves are not detected at birth whereas Na and Pa are present 60 and 20% of the time, respectively, in human neonates. The figures indicate that the detectability of gerbil waves A, B and C become adultlike by days 48, 21 and 25, respectively. Human Na and Pa detectability are adultlike by 12 and 13 years of age.

Latency, amplitude and threshold

Analysis of variance showed highly significant age effects for both latency and amplitude for all waves. The latency of MLR components in response to 50 dB SL stimuli, is shown as a function of age in Fig. 5. In animals younger than 16 days, stimulus intensity was often less than 50 dB SL because of the elevated ABR threshold. In these cases, click intensity was 100 dB HL. Latency

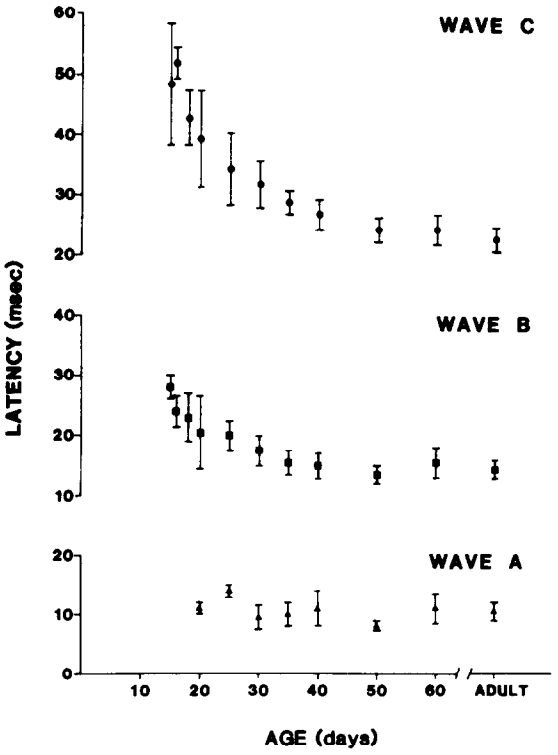

Fig. 5. Mean latencies (±1 S.D.) of MLR components as a function of age in response to 50 dB SL clicks delivered at 4/s.

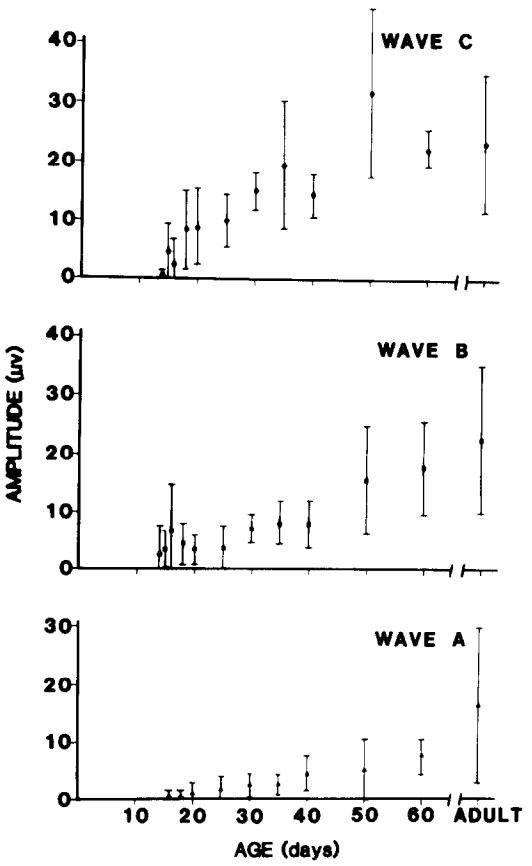

Fig. 6. Mean amplitudes (±1 S.D.) of gerbil MLR components as a function of age in response to 50 dB SL clicks delivered at 4/s.

decreased as a function of age for components B and C. Wave A was infrequently detected earlier than 40 days, but when present, was the first to attain adult latencies. Waves A and B reached adult values by days 20 and 35, respectively. At 60 days, the latency of wave C was still significantly different from the adult values.

The amplitude of each MLR component increased significantly with age, with components B and C reaching adult values by day 50. Even at 60 days old, wave A amplitude was significantly less than the adult amplitude. Figs. 6 and 7 show that wave amplitudes increase monotonically with age in the gerbil and human, respectively. In humans, similar amplitude functions were obtained with both 3 and 15 Hz highpass filter settings (Kraus et al., 1987). It must be noted, however, that stimulation rates of 4/s and 11/s were used in the gerbil and human studies, respectively.

Average thresholds of individual MLR waves are shown as a function of age in Fig. 8. Waves B and C show an orderly progression of decreased threshold with age, attaining adult values at approximately day 30. In contrast, wave A did not consistently occur at adult thresholds until day 50, although it was possible to elicit wave A in the adult threshold range as early as day 20 in some animals.

Stimulus intensity

Latency and amplitude of MLR components were measured as a function of stimulus intensity from ABR threshold to 80 dB HL. For animals of a given age, there was no change in the latency of MLR components over this range of stimulus intensities as shown in Fig. 9 for the adult group.

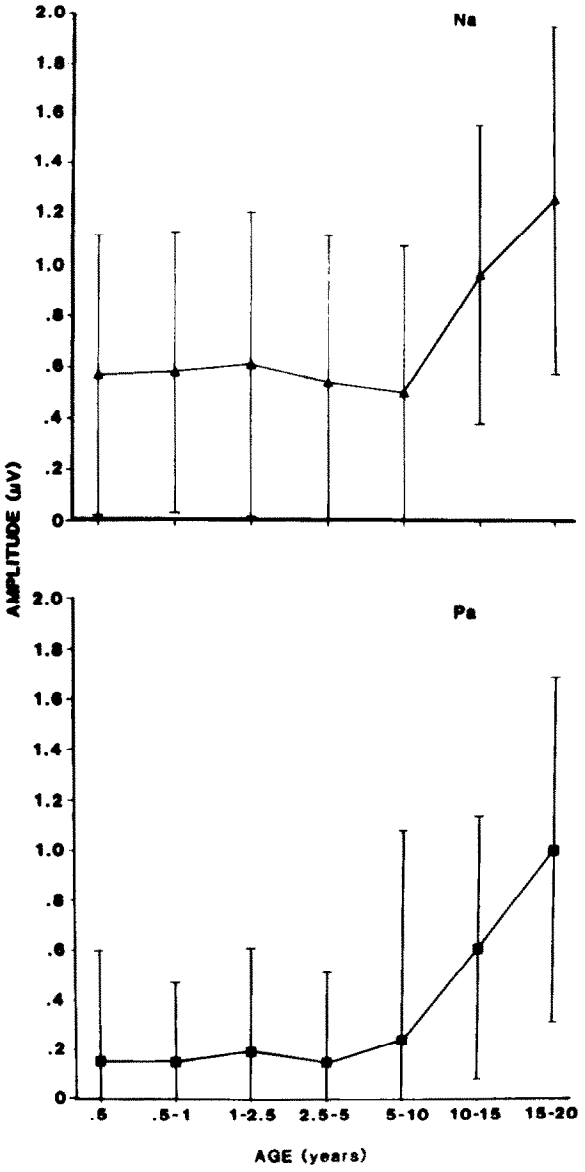

Fig. 7. Mean amplitude (±1 S.D.) of human MLR components as a function of age in response to 60 dB clicks delivered at 11/s. Filter bandpass 15–2000 Hz, 12 dB/octave.

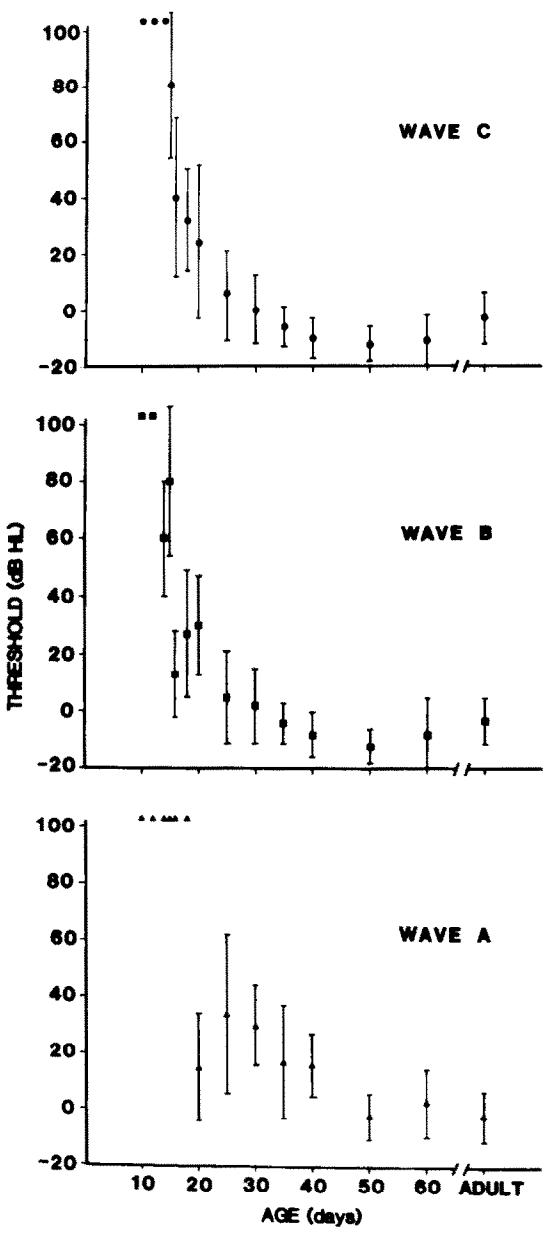

Fig. 8. Mean thresholds of MLR components (±1 S.D.) as a function of age in response to 50 dB SL clicks presented at 4/s.

There was decreased variability of latency values among subjects in a given group as the animals matured.

In adults, the amplitude of all MLR components increased with stimulus intensity up to 50 dB HL. At intensities above 50 dB HL wave A amplitude continued to grow whereas wave B and C amplitudes plateaued. Adult amplitude–intensity functions are shown in Fig. 10.

In young animals, the amplitude of wave A showed no systematic change with intensity. In animals 50 days and older the amplitude of wave

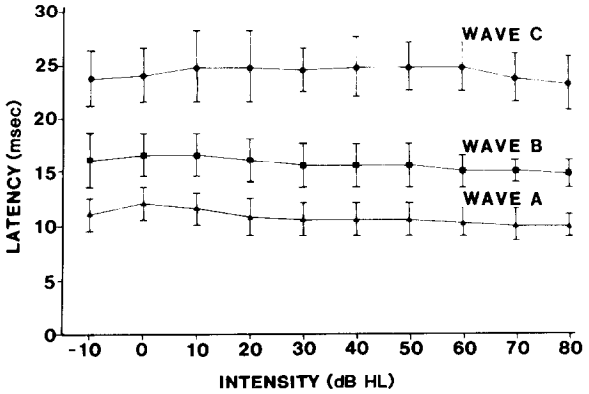

Fig. 9. Mean latencies (±1 S.D.) of MLR components as a function of stimulus intensity obtained from adult gerbils.

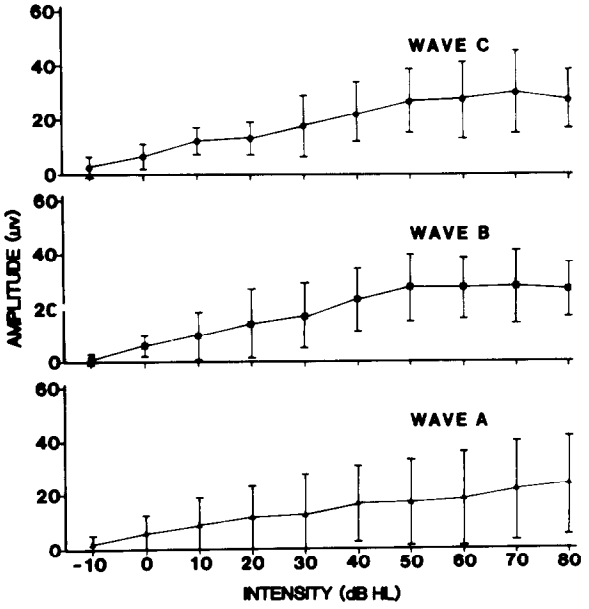

Fig. 10. Mean amplitudes (±1 S.D.) of MLR components as a function of stimulus intensity obtained from adult gerbils.

A increased with increasing stimulus levels. The absence of an intensity effect at earlier ages may be due to the variability and low amplitude of wave A at these ages. Waves B and C on the other hand, showed a systematic increase in amplitude with increases in stimulus intensity up to 50 dB HL at all ages. At high stimulus intensities (60–80 dB HL), amplitude leveled off in the adult group only. This differed significantly from findings in younger animals where MLR amplitudes sometimes decreased with increased stimulus intensity at these levels.

A summary of all statistical procedures is shown in Table I. The ages at which responses became adultlike are also indicated.

Discussion

Waveform morphology

There is little available information about MLR maturation in experimental animals. Waveforms occurring in the latency range defined by the MLR have been measured at the vertex in the anesthetized rat (Iwasa and Potsic, 1982) and the unanesthetized cat (Walsh et al., 1986a,b) with subdermal electrodes. In the rat the MLR consists of two positive peaks which become unified at approximately 30 ms with increasing age, and two negative peaks. In the cat, initial responses consist of a series of waves (two positive and two negative peaks), with the latencies of the positive waves at approximately 20 and 50 ms, respectively, In non-human primates a negative component at 7–13 ms followed by a positive component at 25–35 ms were consistently obtained in the 6-month-old orangutan and 15-month-old macaque

TABLE I
STATISTICAL ANALYSIS

	Wave A	Day adultlike	Wave B	Day adultlike	Wave C	Day adultlike
Latency × age	*	20	*	35	*	60
Amplitude × age	*	60	*	50	*	50
Latency × intensity	NS		NS		NS	
Latency × intensity × age	NS		NS		NS	
Amplitude × intensity	*		*		*	
Amplitude × intensity × age	*	60	*	60	*	50

* Significant ($p < 0.01$).
NS, not significant.

(Kraus et al. 1985b). In the gerbil, wave B emerges first, followed closely by wave C. Both waves are initially broader than the adult response. Wave A is observed only inconsistently in developing animals. The adult gerbil MLR obtained from the temporal lobe contralateral to the stimulated ear consists of two positive and one negative waveform (Kraus et al., 1987a).

Detectability

Although detectability was not been directly addressed in previous studies, the positive waveform in the rat was reported to be variable before day 24, while being more consistent thereafter (Iwasa and Potsic, 1982).

In humans, the existence of MLRs in infants and children has been the subject of much debate. Several studies have reported that MLRs are reliably obtained in children, and that waveform morphology is similar to adult responses (Mendel et al., 1977; Wolf and Goldstein, 1978, 1980; Mendelson and Salamy, 1981; McRandle et al., 1974). On the other hand, reports of the variability of MLRs in children were evident as early as 1971 (Engel, 1971) and have continued subsequently (Hirabayashi, 1979; Davis et al., 1983; Suzuki et al., 1983; Okitzu, 1984; Rotteveel et al., 1985; Kraus et al., 1985a). As is evident from a comparison of Figs. 3 and 4, the present work supports the notion of a strong age effect of increased MLR detectability which is common to both humans and gerbils. MLRs have been shown to be unpredictable in young individuals. At an early age, MLRs may be either present or entirely absent, as well as present only some of the time in a given individual.

Latency

In the gerbil, the latency of waves B and C decreased consistently as a function of age. Wave A latency matured first, followed by waves B and C, respectively. In the cat, MLR latencies followed an exponential time course with age, with earlier waves also reaching adult values before the later waves (Walsh et al., 1986a). In the rat, latency of the positive MLR component was reportedly difficult to measure in young animals, although the preceding negative trough did show a consistent trend of decreasing latency with age (Iwasa and Potsic, 1982). It is possible that the latency variability observed in the rat was caused by the anesthetic agents used in that study. A selective effect of anesthesia with respect to individual MLR components has been reported (Smith and Kraus, 1987a).

Age-related changes in MLR latency are equally equivocal in human studies, although they may be explained by the differences in stimulus and recording procedures employed in the various studies. Whereas Suzuki et al. (1984) found that MLR latencies shortened with age, Mendelson and Salamy (1981) found no significant latency changes with age. In our laboratory, age-related latency decreases were observed with 3 Hz but not with 15 Hz highpass filter settings (Kraus et al., 1987b). The present study further attests to the complexity of this issue in that one component (A) showed little age-related change in latency, whereas the later components (B and C) demonstrated the classic pattern of decreasing latency with age.

Amplitude

A significant age-related increase in the amplitude of all MLR components was found in the gerbil, similar to that observed in humans. The amplitude of waves A and B grew systematically at all ages tested, while wave C amplitude declined after day 50, although the decline was not significant. A nonmonotonic amplitude function has been observed in both the rat and the cat (Iwasa and Potsic, 1982; Walsh et al., 1986b). In the gerbil, waves B and C achieved adult amplitude values earlier than wave A, whereas in the cat, the time course of the first positive wave was earlier than for the second positive waveform.

Threshold

The ABR, an excellent measure of hearing sensitivity for frequencies above 1 kHz, falls short as a hearing measure for the lower frequencies (Picton et al., 1977; Borg, 1981; Hayes and Jerger, 1982). There has been some expectation that MLRs may provide this needed measure of hearing sensitivity. In humans, MLRs have been proposed as an index of hearing threshold in both adults (Mendel and Goldstein, 1969; Zerlin and Naun-

ton, 1974; Musiek and Geurkink, 1981; Maurizi et al., 1984; Kavanaugh et al., 1984) and children (Wolf and Goldstein, 1980; Frye-Osier et al., 1982). In the gerbil, the time course over which MLR click thresholds declined essentially followed that of the ABR throughout development. Reduction in threshold for waves B and C paralleled the increase in sensitivity for ABR wave IV. All three waves were obtained at near adult levels on day 25. Thresholds of wave A were more variable and continued to decrease until day 50. The ABR and MLR appeared to provide equally sensitive measures of threshold to click stimuli. The fact that adultlike thresholds have been obtained in both humans and experimental animals shortly after birth, indicate that when present, MLRs may be a good index of hearing threshold.

Stimulus intensity

Consistent with the findings of McGee et al. (1983) in the adult guinea pig, the present work revealed no significant latency changes with stimulus intensity. Knight et al. (1985) also found that latencies of components N17, P23, N38 and N50 recorded at the vertex in the unanesthetized rat, remained constant in response to clicks ranging from 45 to 65 dB above ABR threshold, although latencies increased at lower intensities. Human Na and Pa latency also show minimal changes with stimulus intensity (Thornton et al., 1977; Ozdamar and Kraus, 1983).

Knight et al. (1985) found increases in MLR amplitude with intensity in the rat. In the guinea pig, wave A (12 ms) amplitude increased with intensity (McGee et al., 1983). Similar to the gerbil, the amplitudes of waves B (17 ms) and C (27 ms) grew steadily over the first 50 dB and then reached a plateau. The plateau observed at high stimulus intensities, may be caused by an inhibitory process related to binaural interaction (Ozdamar et al., 1986). Such an inhibitory process was proposed based on the MLR amplitude decreases observed with binaural click stimulation, and the amplitude increases observed with monaural click stimuli when presented with contralateral white noise masking, in the guinea pig. The functions for waves B and C in the gerbil and guinea pig are similar in shape to the amplitude function for human Pa (Picton et al., 1974; Ozdamar and Kraus, 1983).

In summary, this study demonstrates in a controlled animal model that MLRs are age dependent, thereby substantiating similar observations in humans. In gerbils, the shape of the waveform changes with age. Detectability and response amplitude increase with age, while threshold and latency decrease. There are no outstanding developmental trends observed as a function of stimulus intensity. In both humans and gerbils, detectability and amplitude increase with age. In gerbils, MLR and ABR thresholds become adultlike at approximately the same time despite the difficulties in MLR detectability. Thus when present, MLRs may provide an index of threshold in young subjects. Similar to human Pa, wave A shows minimal latency changes with age. On the other hand, waves B and C are more similar to Pa with respect to their amplitude–intensity functions. Although direct correspondence between human and gerbil waveforms awaits the determination of the underlying generator sites, the development of MLRs in the gerbil and the development of MLRs in humans appear to share many similar properties. The gerbil therefore, appears to be a valuable model for the study of development of the central auditory system.

Acknowledgements

The technical contributions of Cynthia Stark and Ruth Martin are gratefully acknowledged. Supported by NIH grant no. R01 NS21150 to N.K.

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