

HRR 00906

Postnatal development of the auditory brainstem response (ABR) in the unanesthetized gerbil *

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(Received 3 November 1986; accepted 28 January 1987)

The auditory brainstem response (ABR) was used to study the development of 8th nerve and auditory brainstem function in 71 unanesthetized gerbils. Initial replicable responses were observed on day 14. Six vertex-positive waves and a slow negative response (SNR) were obtained in response to a 100 dB HL (re adult threshold) click stimulus on day 20. A general pattern of development characterized by decreasing threshold and wave latencies and increasing amplitudes was found. Latency changes occurred in two stages; rapid decreases in the third postnatal week, followed by a period of gradual decline toward adult latencies during the fourth and fifth weeks. Greater changes in absolute latency were observed for later waves. Development of adult-like thresholds and resistance of response detectability (presence or absence) to increasing stimulus rates occurred prior to or simultaneous with maturation of wave latencies. Increases in amplitude with age continued to adulthood for waves IV and SNR, while other waves declined in amplitude after day 20. The maturation of the ABR overlapped with the emergence and development of the auditory middle latency response (MLR). Waves B (adult latency 16 ms) and C (adult latency 25 ms) were discernable at approximately the same age that a replicable ABR was first obtained, and wave A (adult latency 14 ms) shortly thereafter. The general pattern of decreasing ABR wave thresholds and latencies with age seen in the gerbil is similar to that found in other mammals, including humans. However, the development of mature response characteristics appeared to proceed at a somewhat independent rate among the different ABR and MLR waves. The emergence of the MLR before several ABR waves suggests that development of auditory function in the gerbil may not follow a strictly sequential pattern.

ABR; MLR; Development; Auditory evoked response; Brainstem evoked response

Introduction

The auditory brainstem response (ABR), a series of short latency, volume conducted evoked potentials, provides a non-invasive measure of the development of potentials from the eighth nerve and the auditory brainstem. An increased understanding of the onset and maturation of auditory evoked potentials is important for the clinical interpretation of ABR from developing subjects, and to-

gether with depth evoked response recordings and anatomical studies, may provide information concerning the generator substrates of the ABR.

The development of the ABR has been studied in several species, including human (Hecox and Galambos, 1974; Salamy and McKean, 1976; Starr et al., 1977; Eggermont, 1983; Salamy, 1984), non-human primates (Doyle et al., 1983; Kraus et al., 1985); cat (Jewett and Romano, 1972, Mair et al., 1978; Shipley et al., 1980; Laukli and Mair, 1981, 1982; Walsh et al., 1986a-c), rat (Jewett and Romano, 1972; Tokimoto et al., 1977; Iwasa and Potsic, 1982; Church et al., 1984), mouse (Henry and Haythorn, 1978) and guinea pig (Dum, 1984). A general pattern of maturation, characterized by a decrease in ABR wave latencies and an increase in amplitude and mean sensitivity with age, is seen

* Portions of the results from this study were presented at the 9th Midwinter Research Meeting of the Association for Research in Otolaryngology, Clearwater, FL, Feb. 1986.

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in most mammals studied. Even in precocial animals such as the guinea pig, which has adult-like thresholds at birth, component latencies continue to decrease postnatally (Dum, 1984; Kraus et al., 1984). Major differences among species appear to be the degree of maturity at birth and the rate of maturation.

Several investigations have provided evidence which suggests that the development of mammalian auditory function occurs in distinct phases: an early stage, with rapid development of responses to near adult-like latencies and amplitudes, followed by a second, gradual stage with further increase in sensitivity and decrease in component latencies (Iwasa and Potsic, 1982; Eggermont, 1983; Fria and Doyle, 1984; Walsh et al., 1986a-c). It has been suggested that the rapid stage primarily reflects cochlear development, while the slower phase represents a continuation of maturation of central portions of the auditory pathway (Eggermont, 1983; Fria and Doyle, 1984).

An important consideration in the evaluation of changes in the ABR with age is the maturation of the conductive properties of the middle ear. In most altricial species the maturation of the middle ear overlaps the development of the cochlea and the emergence of cochlear and auditory brainstem potentials, thus complicating the study of auditory neuronal development. For example, Relkin et al. (1979) reported that the improvement in the threshold during functional auditory maturation in the golden hamster can largely be accounted for by development of the middle ear.

The Mongolian gerbil, an animal which has been increasingly utilized in auditory experimentation, differs from most mammals in that the clearing of mesenchymal tissue and fluid from the middle ear and the opening of the external auditory canal are reported to be largely completed prior to the onset of cochlear and auditory brainstem function (Finck et al., 1972; Woolf and Ryan, 1984). Thus, the gerbil has been proposed as a model for following the development of auditory function independent of conductive mechanisms maturation.

Most investigations of ABR development have been conducted in anesthetized animals. Several studies have reported stable ABRs in anesthetized adult animals (Bobbin et al., 1979; Cohen and

Britt, 1982), however the effects of anesthesia on developing subjects is less well understood. In the current study, evoked potentials were recorded from unanesthetized animals in order to eliminate the possibility of alteration of the ABR by direct action of anesthetic agents or secondarily through hypothermia.

The purpose of the present investigation was to study the development of the ABR in the unanesthetized gerbil from its onset to maturity and to test the theory of a two stage development pattern in the mammalian auditory system. Of particular interest was the relation between ABR development and the onset of the auditory middle latency response (MLR). A more detailed investigation of the development of the MLR is the subject of separate publications (Kraus et al., 1987a,b).

Materials and Methods

Seventy one Mongolian gerbils (*Meriones unguiculatus*) were used. All animals were born at the Michael Reese Medical Center vivarium. Electrophysiological recordings were obtained from unanesthetized subjects 48 h after surgery at 10, 12, 14, 15, 16, 18, 20, 25, 30, 35, 40, 50, 60 and 90 days after birth. There were nine animals in the adult group (> 90 days). A minimum of 3 animals was observed at each age group, with most groups consisting of 5 subjects.

Surgery

Recording electrodes were placed in developing gerbils under pentobarbital (7.5 mg/kg) and In-ovar (0.4 ml/kg) anesthesia. Adult animals were anesthetized with ketamine (300 mg/kg). Burr holes were drilled through the skull and silver ball electrodes (0.5 mm in diameter) were placed on the dura. ABR was recorded from lambda, and MLR from an electrode placed over the temporal lobe. A ground electrode was positioned in the region of the olfactory bulbs. A cephalic reference was used to minimize the distortion of the recordings from myogenic activity. The electrodes and attached wires were secured to the skull with dental cement. Small machine screws soldered to the electrode wires served as a connecting point to the amplifiers during the recording sessions.

Stimulation and recording

Broadband click stimuli (rarefaction) were generated by a 100 ms square wave and delivered through a Beyer DT-48 earphone and ear speculum with an attached sound tube. The sound tube was glued into the external auditory meatus to provide monaural stimulation. In those animals in which the pinna was not fully open (\leq day 16), the sound tube was placed against the epidermal fold covering the meatus.

Signals from the recording electrodes were amplified differentially with respect to the ground electrode and monitored on an oscilloscope. Responses were bandpass filtered (3–2000 Hz, 6 dB/octave), and summed by an averaging computer. 80 ms of post-stimulus time was averaged at a rate of 50 points/ms. Each response was the sum of 128 stimulus presentations and was recorded on a digital tape recorder for off-line analysis.

48 h after surgery, the animals were placed in a custom-made restrained box for the recording procedure. The animals were unanesthetized and awake throughout the recording sessions. Styrofoam pads were placed to restrict body movement and maintain head position. All testing was conducted in an electrically and acoustically shielded chamber.

Latency–intensity functions were obtained in 10 dB steps from ABR threshold to 80 dB SL in response to click stimuli presented at 4/s. Threshold was defined as the lowest intensity yielding any replicable ABR activity. Stimulus intensities were referenced to the average threshold for a group of 9 adult gerbils (0 dB HL). Replicability of response activity was assessed with 4 successive trials at 50 dB SL. Two recordings were also obtained at each of the following stimulation rates (1, 4, 10, 20 and 40 s⁻¹), also at 50 dB SL. For those animals in which 50 dB SL was above the limits of the stimulating equipment (100 dB HL), the replicability of the responses and the effects of stimulus rate were tested at intensities ranging from 15 to 45 dB SL.

The presence or absence (detectability) of the ABR peaks was determined without knowledge of the animals age, and was based on the characteristic appearance of an adult response. The latencies and amplitudes of individual peaks were measured

and evaluated with respect to age and rate of stimulation. Wave latencies were measured from the stimulus onset to the peak of each positive wave. The amplitude of waves I–III and V was measured from a line connecting the preceding and succeeding trough to the wave peak. Because waves III and V were inconsistently detected, the amplitude of wave IV was measured from a pre-stimulus baseline. The amplitude of a broad negative response following the positive ABR waves (SNR) was measured from its peak to the peak of wave IV.

Results

Adult response

The adult gerbil ABR consists of 6 vertex-positive waves (I–VI) and a slow negative response (SNR) occurring in the first 7 ms following stimulus onset (Fig. 1). Waves I–IV and SNR were consistently elicited at an intensity of 50 dB SL (4/s), with wave IV (3.8 ms \pm 0.2) being the most sensitive indicator of threshold. Waves V (4.8 ms \pm 0.4) and VI (5.9 ms \pm 0.4) were consistently detected only at high stimulus levels. Waves SNR (6.6 ms \pm 0.5) and IV were the largest amplitude components of the ABR. Increases in stimulus intensity from 0 to 80 dB HL produced decreases in latency and increases in amplitude for all ABR waves.

Onset of response and threshold

No replicable response was observed prior to day 12 at the highest stimulus level used (100 dB HL). A diffuse, high threshold response (2.2–2.4 ms) was obtained from 1 of 3 animals tested on day 12, 3–4 days prior to the complete opening of the external canal and pinna. Significant development of the early evoked responses occurred in the first week following its initial appearance. During this period the response remained variable in sensitivity, and was dominated by waves I and IV and a broad SNR (Fig. 1). However, with a stimulus of 100 dB HL all 6 positive waves and SNR were discernable in one animal by day 20. In contrast to the adult response, in which wave IV was the most consistently detected component at threshold, wave I was the most sensitive indicator of threshold in the developing gerbil.

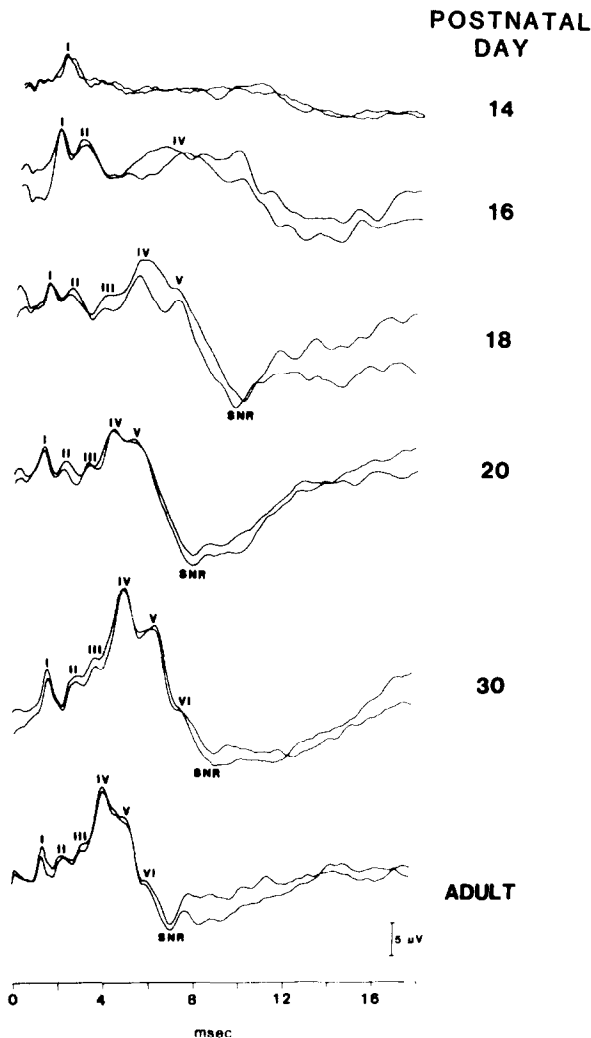


Fig. 1. Gerbil auditory brainstem response. Representative ABR waveforms illustrating the gradual emergence of peaks and attainment of adult-like latencies with age. Responses are the average of 128 presentations of a 50 dB SL or 100 dB HL click (re adult threshold) stimulus at 4/s.

Rapid decreases in threshold were observed for all waves throughout the 3rd postnatal week, particularly between days 14 and 16, a period which coincided with the completion of the opening of the pinna (Fig. 2). Threshold reduction did not occur systematically among peaks. The average group threshold for waves I and V decreased from the time the peaks first appeared, to day 18, at which time they were within 10 dB of adult thresholds. The threshold of waves II, III and

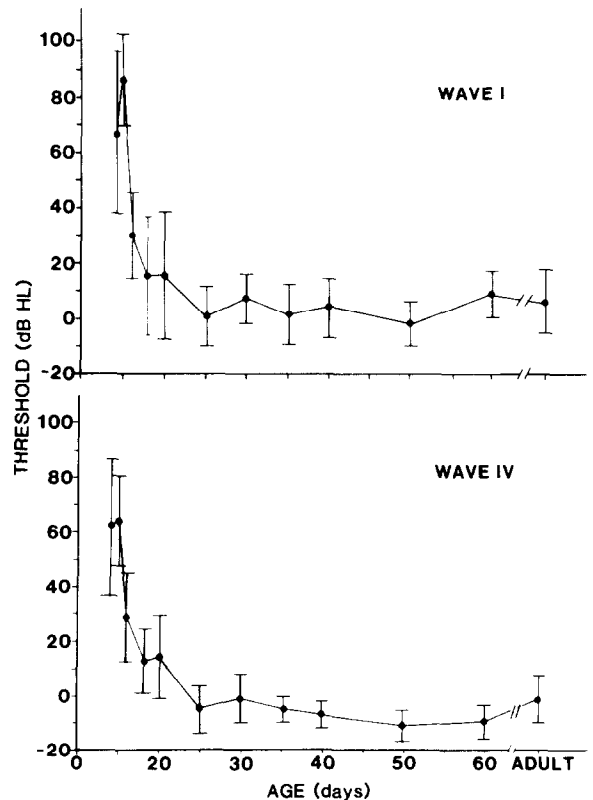


Fig. 2. Response threshold as a function of age for ABR waves I and IV. Values represent average thresholds for each age group (3–9 subjects). Vertical bars indicate ± 1 S.D.

SNR approximated adult values on day 20, while thresholds for waves IV and VI continued to decrease until 25 and 40 days after birth, respectively.

Latency

The latency of each ABR component decreased rapidly during the 3rd postnatal week (Fig. 3). This period of approximately linear latency decrease was followed by a more gradual decline throughout the 4th and 5th postnatal weeks. Variability of latency among individuals within an age group also decreased with age.

Latency changes differed among the various waves, with greater decreases in absolute latency for later waves; i.e., decrease in latency with age for later waves were greater than could be accounted for by changes in wave I latency. For example, in response to the same stimulus level

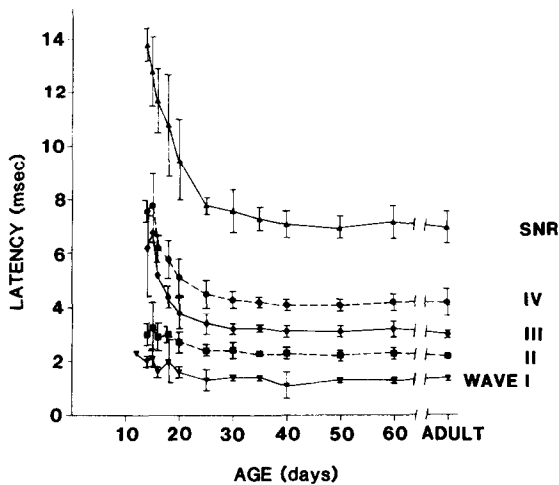


Fig. 3. Peak latency as a function of age for ABR waves I, II, III, IV and SNR. Values represent average latencies for each age group (3–9 subjects). Vertical bars indicate ± 1 S.D.

(50 dB SL) the average latency of wave SNR in adults was 2.6 ms less than on day 18. The comparable decline for wave IV was 1.1 ms, and for wave I, 0.3 ms.

The rate of latency maturation, as indicated by the length of the period in which wave latency continued to decline toward adult-like values, did not vary systematically among different ABR components. Waves I and IV were both obtained at adult-like latencies on day 25, while it was not until day 30 that waves V and SNR reached adult latencies. Latencies continued to decline through day 35 for peak II, and through day 40 for waves III and VI.

Amplitude

In response to a constant stimulus level (50 dB SL), increases in absolute amplitude as a function of age were seen for all waves through approximately day 20 (Fig. 4). With further development, changes in amplitude occurred independently among the ABR components. Wave I amplitude peaked at day 18, with only minor changes in older age groups. Decreases in amplitude were observed with continued development for waves II, III, V, and VI. Waves IV and SNR were the only ABR components which showed increased amplitude with age into the 4th and 5th postnatal

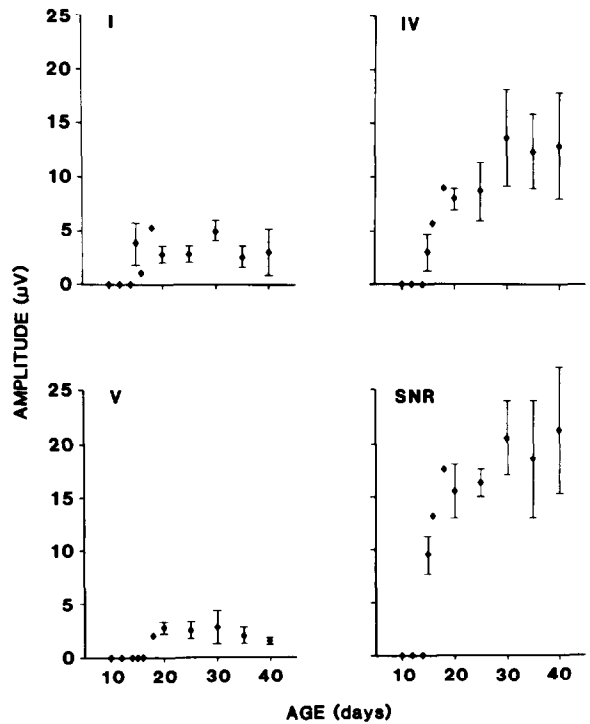


Fig. 4. Wave amplitude as a function of age for ABR waves I, IV, V and SNR. Values represent average amplitudes for each age group (3–9 subjects). Vertical bars indicate ± 1 S.D.

weeks. These waves also showed the greatest variability in amplitude within age groups.

Stimulus rate

In adult gerbils, wave latencies and amplitudes were largely resistant to stimulus rate increases,

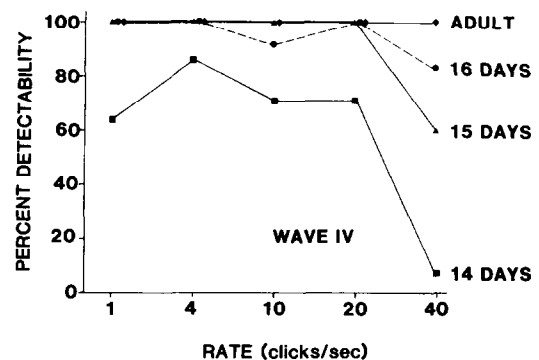


Fig. 5. Percent detectability of wave IV as a function of stimulation rate for different age groups. Values represent average percent detectability for each rate as a function of age (3–9 subjects).

with only minor changes seen at 40/s. The effects of stimulus rate on wave detectability were analyzed for developing and adult animals. Wave I was the first component to be consistently detected at all rates tested (day 14). Decreases in detectability with increased rate were seen for waves IV (Fig. 5) and SNR until days 20 and 30, respectively. Rate resistance developed prior to or simultaneous with the maturation of wave latency. Waves V and VI were not consistently detected at any stimulus rate at 50 dB SL, in any age group. It is possible that more significant rate effects on wave latencies and amplitudes would have been revealed at higher stimulation rates.

Discussion

Development of the gerbil ABR was characterized by rapid decreases in wave latency and increases in amplitude and sensitivity with age, beginning late in the 2nd postnatal week, with changes continuing through 40 days after birth. The general pattern of development is consistent with results from previous investigations with other mammals and provides support for the hypothesis of a multi-stage maturational process in as far as ABR component latencies are concerned.

A rapid development phase, with approximately linear decreases was followed by a gradual decline in latencies to adult values. This is consistent with previous studies in humans (Eggermont, 1983; Fria and Doyle, 1984; Salamy, 1984) and laboratory animals (Iwasa and Potsic, 1982; Church et al., 1984; Walsh et al., 1986a). Previous investigators have correlated the initial stage of functional development with the cellular reorganization of the cochlea and the emergence of cochlear microphonics (CM), and the gradual acquisition of adult characteristics to peripheral and central neural maturation (Eggermont, 1983; Fria and Doyle, 1984; Walsh et al., 1986a).

Response onset

The earliest occurring replicable ABR was obtained in 14 day old gerbils: 2 days after a high threshold response (possibility wave I) was obtained in 1 of 3 animal tested. This finding is in general agreement with previous investigations in this species which reported the onset of CM (Finck

et al., 1972; Woolf and Ryan, 1984), compound action potential (Finck et al., 1972; Woolf and Ryan, 1980) and neural activity in the ventral cochlear nucleus (Woolf and Ryan, 1985) between 12 and 14 days after birth.

Previous studies have reported that the Mongolian gerbil is unique in that the opening of the external canal and the clearing of the middle ear occurs largely prior to the onset of hearing (Finck et al., 1972; Woolf and Ryan, 1980). Woolf and Ryan (1985) reported that the middle ear is essentially adult-like at day 16. The complete opening of the pinna in the animals used in the current study did not occur until 15 or 16 days after birth: a period coinciding with a significant reduction in response threshold. Walsh et al. (1986a) reported that the onset of ABR could be obtained several days earlier in kittens in which the tympanic membrane had been surgically exposed as compared to intact animals. It is possible that some improvement in ABR onset and sensitivity could be achieved in the gerbil with removal of fluid and mesenchymal tissue from the middle ear or direct stimulation of the tympanic membrane.

Previous investigations have hypothesized a centripetal pattern of development for subcortical auditory structures (Pujol, 1972; Iwasa and Potsic, 1982; Ryan et al., 1982; Dum, 1984; Church et al., 1984). This conclusion is based in part on reports of sequential maturation of ABR latencies from early to later waves (Jewett and Romano, 1972; Tokimoto et al., 1977; Uziel et al., 1981; Dum, 1984; Church et al., 1984), and depth recordings which indicate that evoked potential latencies mature at progressively higher sites of the auditory pathway (Pujol, 1972). Ryan et al. (1982), using the 2-deoxyglucose autoradiographic technique to measure onset of functional activity, also concluded that central auditory function develops sequentially.

The results of the current study do not appear to support a simple pattern of sequential development of the auditory pathway, rather they indicate a somewhat independent course of development for the individual ABR waves. The emergence of components of the MLR (a response which is presumed to originate central to the brainstem), prior to the appearance of portions of the ABR

further contradicts a simple sequential development pattern.

Latency

Absolute latency decreases with age were progressively greater for later waves, however, the rate of development of adult-like characteristics did not vary systematically among the different ABR peaks. For example, wave I latency, presumably reflecting development of the end organ and neural activity of the distal portion of the 8th nerve, was the first wave to develop mature response characteristics for rate resistance (day 14), threshold (day 18), and latency (day 25). Wave IV was also obtained at adult-like latencies on day 25: 10–15 days before waves II and III reached mature latencies. The SNR, the latest component of the gerbil ABR currently under study, developed mature response characteristics earlier than several preceding waves.

Amplitude

Development changes in component amplitude occurred more independently among the ABR waves than other response characteristics. The variability in wave amplitude among subjects, which was particularly evident in younger age groups, may have obscured more systematic developmental trends.

Several waves declined in amplitude as a function of age after initial increases. The amplitude of other components continued to increase or showed no change beyond 30 days. Decreases in ABR amplitude with age were reported by Iwasa and Potsic (1982) in the rat. The authors speculated that a decrease in far-field amplitude with age may result from the increasing distance between the generating source and the recording electrode which accompanies the growth of the cortex.

Middle latency response

The development of the ABR, which began late in the second postnatal week, overlapped with the emergence and development of later auditory evoked potentials, the middle latency response (MLR), (Kraus et al., 1987a,b). MLR wave B (vertex-negative, adult latency 16 ms) and wave C (adult latency 25 ms) were initially obtained 14

and 15 days after birth, about the same age at which a replicable ABR was first recorded. The earliest MLR component (wave A, adult latency, 14 ms) was first obtained at day 20.

Reductions 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. Increases in amplitude were seen with development, however, the amplitude of MLR waves was variable at all ages. Wave C amplitude was greatest at day 50, after which it declined, similar to the pattern observed for several ABR waves, which peaked in amplitude at approximately day 20.

Wave C was obtained at adult-like latencies in gerbils older than 60 days. Wave B latency matured by day 35, an age at which 5 of the 7 ABR waves had reached adult-like values. The latency of wave A was unique among ABR and MLR waves in that it did not decrease with age. In a related study, Iwasa and Potsic (1982) described approximately simultaneous emergence of the early portion of the ABR and the MLR in the rat. They also reported only minor latency changes with age for a vertex-positive MLR wave occurring at approximately 28 ms. Whether this wave is analogous to wave A or wave C of the guinea pig MLR is unknown.

In summary, these results indicate that the as yet unknown generators of the MLR are sufficiently developed at the time of the emergence of the ABR to produce a recordable response. Only the latest component (wave C), continues to decline in latency beyond the age at which the ABR has developed. The emergence of middle latency waves prior to the appearance of portions of the ABR suggests that the gerbil MLR does not require the same degree of neural synchronization as earlier evoked responses.

Acknowledgements

The authors gratefully acknowledge the contributions of Cynthia Stark and Ruth Martin to this study. This research was supported by Research Grant NS 21150.

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