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Midline and temporal lobe MLRs in the guinea pig originate from different generator systems: a conceptual framework for new and existing data [1]

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Summary In the guinea pig and gerbil, individual components within the MLR time frame differ in optimal recording location. Specifically, MLR components obtained from the midline differ from those obtained over the temporal lobe. In the present paper midline and temporal lobe components were shown to differ not only in scalp topography but also in response to the following experimental manipulations: intracortical injection of neural inactivating agents (lidocaine and kainic acid), temporal lobe ablation, electrolytic lesions, systemic anesthesia, stimulation rate and course of development. Since midline and temporal lobe components respond differently to experimental manipulations, it can be concluded that the midline and temporal lobe responses are mediated by different generator sources.

The particular orientation of the generators responsible for the MLR in the guinea pig and gerbil facilitates the identification of individual components. Results from simultaneous recordings of these components during experimental manipulations support the hypothesis of multiple MLR generators in laboratory animals and provide insight into the generators and developmental aspects of the MLR in humans.

Key words: Auditory evoked potentials; MLR; Generators; Auditory cortex; Scalp topography

Proposed generator sites for the middle latency response have included all structures of the lemniscal auditory pathway rostral to and including the inferior colliculus and extralemniscal auditory areas such as reticular formation. Data from humans and experimental animals point to the existence of multiple generators for individual waves in the middle latency time frame.

Humans

The suggestion that Pa is generated in the temporal lobe is derived from studies reporting a polarity reversal across the sylvian fissure (Celesia 1968; Vaughan and Ritter 1970; Cohen 1982; Wood and Wolpaw 1982a, b; Lee et al. 1984). Other studies have reported intracranial responses at the latency of Pa from widespread areas of association cortex (Chatrian et al. 1960; Ruhm et al. 1967; Lee et al. 1984). Based on the amplitude distribution of the MLR in the coronal plane, and a model developed for the late (50–300 msec) responses (Vaughan and Ritter 1970), Özdamar and Kraus (1983) proposed bilateral, vertically oriented dipole sources located in the temporal lobes as generator sources for human Pa. In this model Pa amplitude is expected to be greatest at the midline, where the activity of the 2 generators sum, in response to monaural or binaural stimulation.

Case studies of patients with cortical lesions have largely supported a temporal lobe origin for Pa. With unilateral temporal lobe lesions, Pa was attenuated or absent over the damaged temporal

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lobe, thereby supporting the hypothesis of temporal lobe dipoles (Kraus et al. 1982; Kileny et al. 1987). Similar conclusions were drawn by Scherg and Von Cramon (1986) based on a model of best fit equivalent dipoles in normal subjects and patients with confirmed cortical lesions. Absent MLRs have been reported with bilateral temporal lobe lesions (Graham et al. 1980; Özdamar and Kraus 1983).

In contrast, evidence suggesting that Pa receives contributions from structures other than the temporal lobe has been provided by studies reporting the presence of vertex Pa in patients with bilateral temporal lobe lesions (Parving et al. 1980; Rosati et al. 1982; Woods et al. 1987). Recently, we have observed a small amplitude Pa at the vertex in a patient with bilateral temporal lobe lesions. In this patient, Pa activity was absent over the temporal lobes. One hypothesis is that the midline component receives contributions from non-temporal lobe structures such as the reticular formation. The fact that this wave form was evident in this patient and not in others with similar lesions may be accounted for by the arousal state of the subject, although in no instance were EEG data available.

The 40 Hz event-related potential (ERP) is thought to reflect the superimposition of the ABR and MLR which occurs when stimuli are delivered at a rate of 40 Hz (Galambos et al. 1981). Consequently, 40 Hz ERP data may apply directly to the MLR. Because the 40 Hz response can be elicited with tactile, visual and auditory stimuli, Galambos (1982) suggested reticular formation or polymodal thalamus as generators for this response. The 40 Hz ERP has been shown to be predictably altered as a consequence of thalamic or midbrain lesions whereas the response was unaltered by temporal lobe lesions (Spydell et al. 1985).

Several studies have provided evidence that the MLR is influenced by subject state, as demonstrated by alteration in the response with anesthesia in both humans (Goff et al. 1977; Hall 1985) and experimental animals (Kiang et al. 1961; Pradhan and Galambos 1963; Teas and Kiang 1964; Celesia 1968; Buchwald et al. 1981; Hinman and Buchwald 1983; Smith and Kraus 1987a, b). An as yet unresolved issue is why sleep affects the 40 Hz ERP to a greater extent than it affects the slow ABR or MLR. Sleep does not appear to affect Pa in adults (Mendel and Goldstein 1969; Mendel 1974; Mendel and Kupperman 1974; Picton et al. 1974; Özdamar and Kraus 1983; Mosko et al. 1984; Erwin and Buchwald 1986) although it does cause significant reduction in the amplitude of the 40 Hz ERP (Galambos 1981; Brown and Shallop 1982; Klein 1983; Shallop and Osterhammel 1983; Linden 1985; Jerger et al. 1986). The above observations are consistent with the hypothesis that Pa is the product of multiple generators including auditory cortex, reticular formation and polymodal thalamus.

Experimental animals

MLR wave forms and response characteristics differ considerably with recording location. Specifically, in the cat, guinea pig and gerbil, responses within the MLR time frame obtained from the vertex appear to differ from those obtained over the temporal lobes.

On the basis of ablation experiments and correspondences between intracranial and surface recordings, cat vertex component wave A (22 msec) appears to be generated by ascending reticular formation in the midbrain and thalamus (Buchwald et al. 1981; Hinman and Buchwald 1983). Data from cortical ablation experiments and the relation between surface and depth recorded potentials suggest that cat wave 7 (12–15 msec) and guinea pig waves A (11 msec) and C (30 msec) obtained over the temporal lobe are generated primarily by auditory cortex contralateral to the stimulated ear (Celesia 1968; Kaga et al. 1980; Kraus et al. 1985; Chen and Buchwald 1986; Erwin and Buchwald 1986; Smith and Kraus 1987a).

Data from humans and experimental animals point to the existence of multiple generators in the middle latency time frame. In humans, wave Pa can be obtained from widespread areas of the cortical surface (Picton et al. 1974; Özdamar and Kraus 1983), thereby masking the possible contributions of the multiple generators which may underline the response. If Pa is in fact produced by multiple generators, then an animal model which

permits measurements of the separate contributions of these sources is ideally suited to identifying these generators.

The present work addresses the hypothesis that the midline and temporal lobe responses obtained from animal models originate from different generators. If, when midline and temporal lobe components are simultaneously obtained, they respond differently to experimental manipulations, then it can be assumed that they reflect the activity of functionally separate generator systems. The purpose of this communication is to provide functional evidence which demonstrates a dissociation between the MLR obtained from the midline and that obtained from the temporal lobe in the guinea pig and gerbil. The experimental manipulations include scalp topography, injection of neural inactivating agents into auditory cortex, temporal lobe ablation, electrolytic lesions, systemic anesthesia, stimulation rate and development. Existing data will be reviewed and discussed with respect to this concept.

Methods

General

Albino guinea pigs, weighing 300–350 g, were anesthetized with pentobarbital (15 mg/kg, i.p.) and Innovar-Vet (0.4 ml/kg, i.m.). Body temperature was maintained at 38°C. Epidural screw electrodes were implanted in the skull. For the temporal lobe and midline recordings, electrodes were placed at the midline (6 mm posterior to bregma) and over the temporal lobe contralateral to the stimulated ear (9 mm lateral to bregma). Coordinates for temporal lobe responses were obtained from previous work (Kraus et al. 1985) which showed that these components can be obtained from a 4×4 mm area over the temporal lobe and are largest in amplitude at the above coordinates. A posterior midline location was used instead of bregma because when compared, both ABR and MLR responses were larger and better defined posteriorly. Electrodes were referenced to a site over the olfactory bulbs (15 mm anterior to bregma). Comparison of this site with neck and tail references yielded little difference in MLR activity in the cat (Teas and Kiang 1964; Chen and Buchwald 1986) and guinea pig (unpublished observations).

In the gerbils, the midline electrode was implanted 5–8 mm posterior to bregma and the temporal lobe electrode 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. 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 screws were used as a point of electrode attachment for physiologic recording on the day of the experiment. Physiologic recordings were obtained 48 h following surgical placement of electrodes.

Responses were bandpass filtered (3–2000 Hz, 6 dB/octave), 80 msec of post-stimulus time was averaged with a sampling rate of 50 points/msec, and averaged responses consisted of 128 stimulus repetitions. The animal's body was restrained in an adjustable plexiglass box and the head was held stationary by a frontal anchor bolt and a custom made mandibular support device, which left the pinnae accessible. Monaural rarefaction click stimuli were delivered at a rate of 4 Hz through a Beyer DT-48 earphone and ear speculum, with an attached sound tube. The sound tube was glued into the external auditory meatus. Recordings were obtained in a sound-attenuating, electrically shielded booth. Wave latencies were measured from the midpoint of each component. Amplitudes of the MLR components were measured from the peak to the preceding negative trough or to a prestimulus baseline.

Since several of the experiments (neural inactivating agents and temporal lobe lesions) were performed on anesthetized animals, it was necessary to control for possible concurrent anesthetic/experimental effects. The effects of several anesthetic agents on the MLR have been characterized (Smith and Kraus 1987a) and consist primarily of predictable changes in wave amplitude and latency, without elimination of components. Experimental procedures were performed when systemic anesthetic effects are most stable (30 min post-sedation).

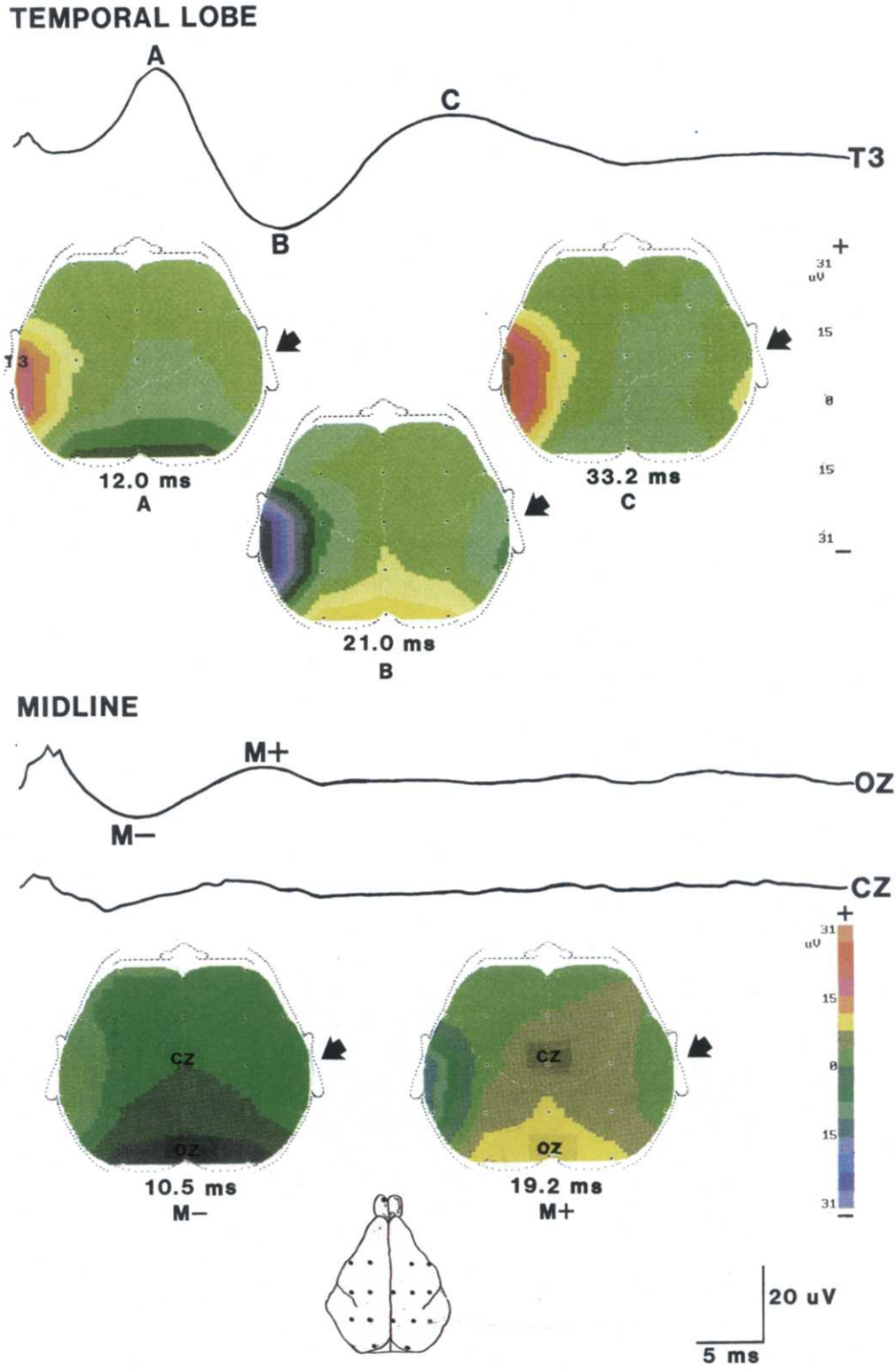

Fig. 1. A: temporal. The MLR obtained over the guinea pig temporal lobe contralateral to the stimulus ear consists of 3 components: A (12 msec), B (21 msec) and C (33.2 msec). The topographic maps illustrate the voltage measured at the latencies corresponding to each of these components. The electrode locations are shown by the schematic drawing of the guinea pig brain. Positive voltages are displayed with warm colors, negative voltages with cool colors. Notice that the amplitude of the midline components is smaller than the temporal lobe waves. B: scalp topography midline. The MLR obtained from the midline of the anesthetized guinea pig consists of a negative wave, M−, at 10.5 msec and a positive component, M+, at 19.2 msec.

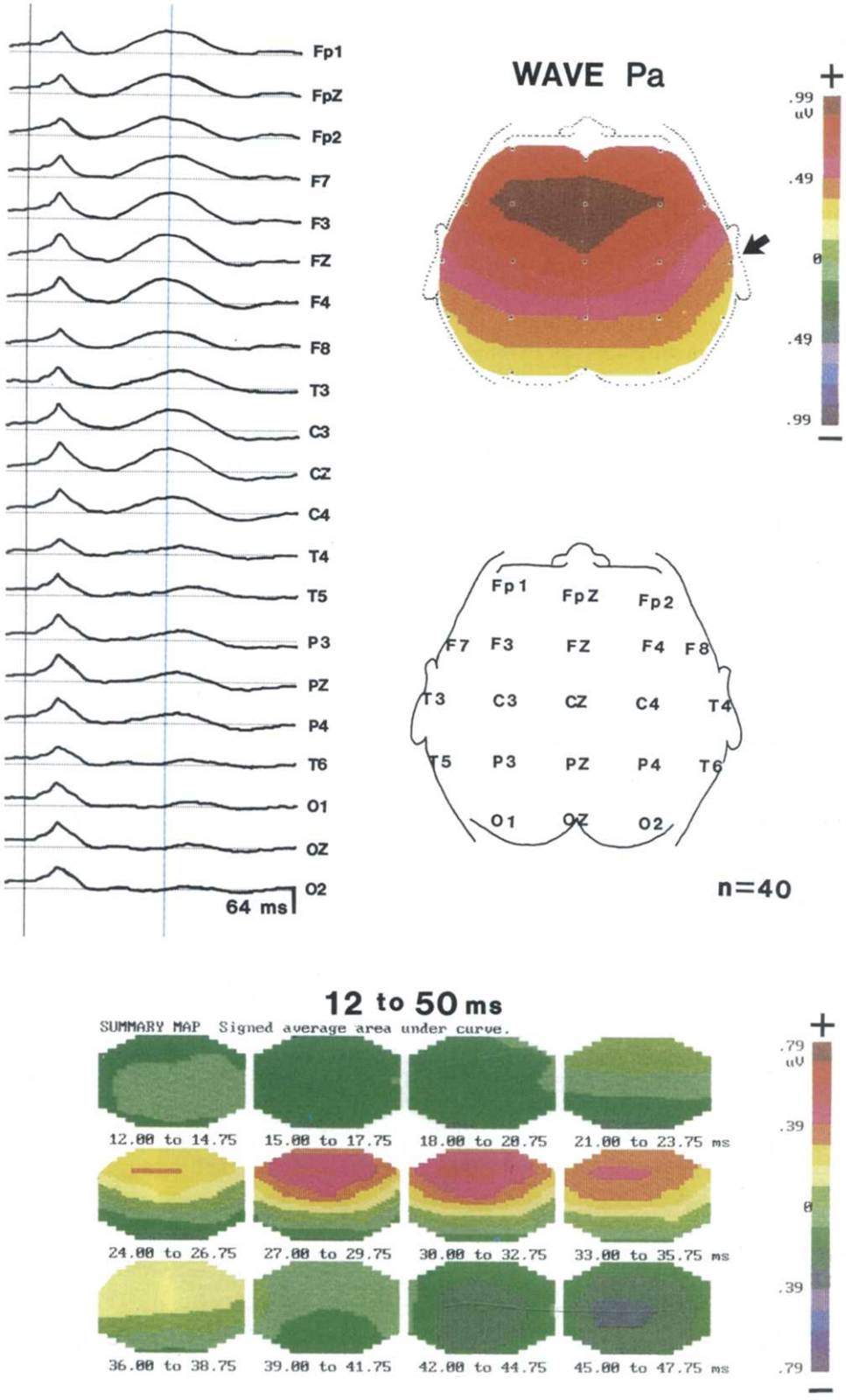

Fig. 2. Scalp topography of the human MLR (n = 40). The amplitude distribution at the latency of Pa is shown by the color map. Both the map and the individual traces shown on the left of the figure illustrate that wave amplitude is largest at the frontal and midline areas. The voltage topography evident during the MLR time frame is averaged in 2.75 msec intervals. Waves Na and Pa are visualized in the 15.0–20.75 and 27.0–35.75 msec maps, respectively.

Scalp topography

ABR and MLR activity were obtained from 6 anesthetized guinea pigs, each implanted with 16 epidural electrodes. Three different electrode arrays (2 animals each) were used. The first array mapped the entire surface of the head, analogous to the 10-20 system used in EEG electrode placement (Jasper 1958). In other animals, a grid of electrodes, spaced 2 mm apart, was positioned over 2 different locations on the cerebral hemisphere contralateral to the stimulus ear. Human data were obtained from 20 normal hearing adults using the 10-20 system. Recording filters were 30–3000 Hz for guinea pigs, 10–3000 Hz for human subjects, at 12 dB/octave and 64 msec of post-stimulus time were obtained.

Neural inactivating agents

A combination microelectrode–injection unit was advanced at a right angle to the cortical surface in 0.2 mm steps into auditory cortex and either lidocaine (1 or 2%, 30 μl) or kainic acid (10 nmol or 20 nmol in 1.0 μl Ringers, 5 μl) was deposited. Injections were made at locations at which a polarity reversal occurred for wave A. A reversal is reliably obtained with penetrations into auditory cortex gray matter at an average distance of 1.3 mm from the cortical surface (Smith and Kraus 1987a).

Baseline responses were obtained prior to the injection and provided a measure of the random fluctuation in component amplitude and latency. For each animal, means and standard deviations were computed of the baseline measures for each condition. The mean ± 2 S.D. was considered a 'normal range' for later comparisons. Following the injection, responses were obtained in 2 min intervals for 10 min and 0.5 h intervals for a period of 1 h for lidocaine and 2 h for kainic acid experiments. Ten lidocaine injections (6 animals) and 8 kainic acid injections (8 animals) were studied. Comparisons were made of the percent change from baseline [(post − pre)/(post + pre)] of the midline components at the point of maximum change in the temporal component.

Temporal lobe and electrolytic lesions

Damage to the temporal lobe was achieved by cauterization of the major cortical vasculature and mechanical disruption of the gray matter in a 6×8 mm area which included auditory cortex. Four unilateral and 2 bilateral ablations were performed.

A total of 15 electrolytic lesions were made in auditory cortex at locations at which polarity reversals occurred for wave A. Lesions were made by passing 20 μA of current for 30 sec and were confirmed histologically. MLRs from midline and temporal lobe locations were measured before and after the lesions. As with the neural inactivating agents, comparisons were made of the percent change, pre versus post lesion, of the midline and the temporal components.

Stimulation rate

Simultaneous midline and temporal lobe recordings were obtained from 15 unanesthetized gerbils at different stimulation rates (Kraus et al. 1987a). Two recordings were obtained at each of the following stimulation rates (1, 4, 10, 20 and 40 Hz) at 50 dB SL. A 2-way analysis of variance was used to compare rate effects on MLR wave forms.

Development

Simultaneous midline and temporal lobe responses were obtained from a total of 71 unanesthetized gerbils. Data were obtained at each of the following ages: 10, 12, 14, 15, 16, 18, 20, 25, 30, 35, 40, 50, 60 and > 90 days. Each age group generally consisted of 5 animals and different animals were studied in these groups. Latency and amplitude values were obtained for each animal from the average of 4 successive trials (128 stimuli each) of click stimuli presented at 50 dB SL. Analysis of variance was used to compare latency and amplitude changes with age. Data from temporal lobe but not midline responses have been previously reported (Kraus et al. 1987b).

Results

Scalp topography

The topographic maps in Fig. 1 display the spatial distribution of wave amplitude measured by electrodes distributed over both hemispheres in

the guinea pig. The 5 maps shown correspond to the latency of each wave (M −, M +, A, B and C).

Over the temporal lobe the MLR consists of waves A, B and C, with mean latencies of 15 (±1.5), 26 (±2.3) and 47 (±6.4) msec, respectively, all of which are largest over the temporal lobe contralateral to the stimulus ear. The MLR obtained from the midline consists of a negative (M −) and a positive wave (M +) with mean latencies of 14 (±1.4) and 22 (±1.9) msec, respectively. The amplitude of both waves was greatest at the more posterior electrodes. Note that the temporal lobe response is significantly greater in amplitude than the midline response. In the guinea pig, differences in wave morphology depend on electrode location, whereas components of similar latency are widely distributed in humans. This is illustrated in Fig. 2 where the scalp topography of wave amplitude is shown at the latency of Pa. The voltage topography evident during the MLR time frame (12–50 msec) is also shown.

Neural inactivating agents

The present work compares the differential effects of neural inactivating agents on the temporal lobe and midline responses. It is not our intention to describe the specific effects of these drugs, but rather to demonstrate that this manipulation produces different effects on the midline and temporal lobe MLR components. The specific effects and underlying mechanisms (excitatory vs. inhibitory, primary vs. non-primary cortex) are the subject of ongoing studies. Drug effects are complex, with some injections causing decreases and others increases in wave amplitude. However, a consistent finding was that midline and temporal lobe response amplitudes frequently varied independently. Representative wave forms illustrating a dissociation of effects for midline and temporal components with inactivating agents are shown in Fig. 3. In these examples, the midline components did not change with either drug, whereas the temporal lobe response became larger and prolonged in latency with lidocaine and grossly altered following kainic acid injection. Possibly, the increase in latency of wave A with the kainic acid is due to the loss of wave B. We speculate that the wave A

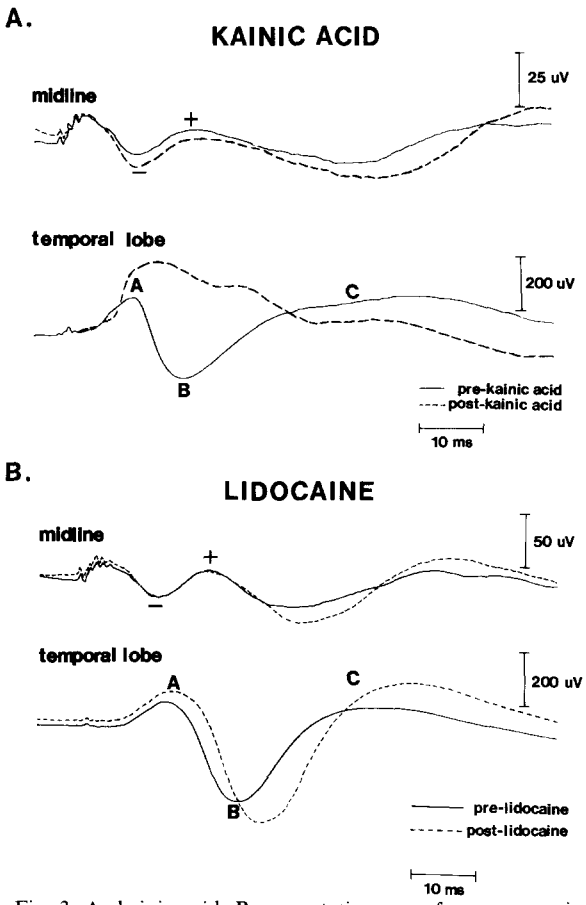

Fig. 3. A: kainic acid. Representative wave forms comparing the pre-injection with the post-injection response. The midline response showed no change whereas the temporal lobe response was grossly altered. B: lidocaine. Representative wave forms comparing the pre-injection (solid line) with the post-injection (dotted line) response. The midline component did not change whereas the temporal lobe response became larger and delayed in latency.

component in isolation has a larger amplitude and longer latency. However, the summation of wave A and the negative deflection of wave B results in a shortening of wave A latency and a diminution of wave A amplitude.

Lidocaine. Of the 10 intracranial injections of lidocaine, the amplitude of temporal waves B and C changed significantly in 6 instances and wave A changed in 4 instances. Wave M + amplitude changed in 3 instances and wave M − was unaffected.

The amplitude of all MLR components is plotted over time before and following the injection of lidocaine in 1 animal (Fig. 4). The horizontal lines in each graph define approximately a 95% confidence interval (mean ± 2 S.D.) of amplitude values over time as determined prior to the injection. Values falling outside of the pre-drug baseline range reflect significant amplitude changes. Within 10 min after lidocaine injection, this animal showed no change in the amplitude of the midline waves, whereas the temporal lobe components significantly decreased in amplitude.

Kainic acid. As with the lidocaine injections, measures of post-kainic acid injection activity were compared to the pre-injection baseline measures. Changes greater than 2 S.D. from the baseline mean were considered significant. Significant alterations in the temporal lobe MLR occurred with each of the 8 injections of kainic acid into auditory cortex. Four of the changes were amplitude increases, 2 were decreases and 2 showed an initial decrease followed by an increase. The midline positive response was significantly altered in 5 animals.

Fig. 5 illustrates the mean percent change from baseline which occurred following the injection of the drug for all waves across animals [% change = (post − pre)/(post + pre)]. Amplitude increases are represented in the upper half of the figure, decreases are shown in the lower half. The percent change in the midline response was calculated at the particular points in time which yielded the greatest change for waves A, B and C.

Changes in the amplitude of wave A were unrelated to changes in M + amplitude. Yet, on the average, M + varied in the same direction as waves B and C, perhaps indicating a common modulatory influence. Wave M − was unaffected by the drug.

Although on the average, kainic acid similarly affected M + , B and C, this was not invariant. In 3 of 8 animals, the midline response remained unaltered while the temporal lobe response changed. Figs. 6 and 7 show the time course of MLR amplitude changes following kainic acid injection. In the animal shown in Fig. 6, midline components did not vary, whereas all temporal waves were decreased in amplitude by 30 min post

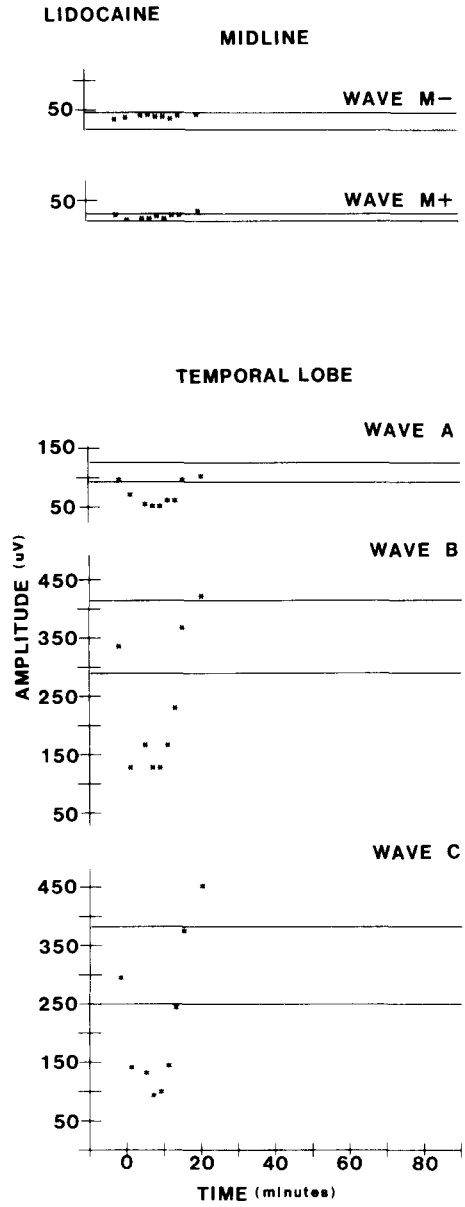

Fig. 4. Time course of MLR amplitude following lidocaine injection. The horizontal lines define a range of pre-drug amplitude variability ±2 S.D. This range of variability was obtained prior to the injection of the drug and indicates the variability over time which is expected for the animal. Values falling outside of this pre-drug baseline range are considered to reflect significant amplitude changes due to the inactivating agent. This animal showed no change in the amplitude of midline waves whereas the temporal lobe components all decreased in amplitude within the first 10 min following the injection.

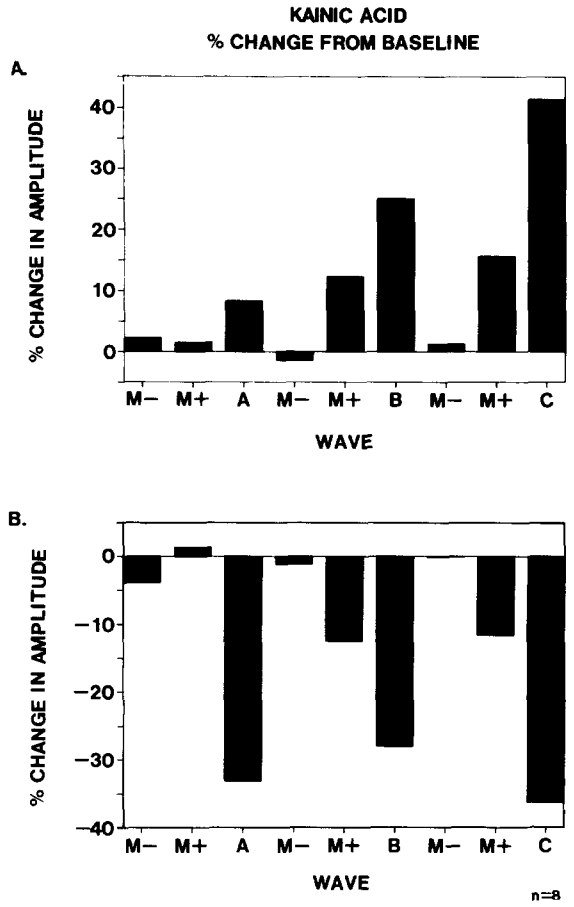

Fig. 5. Mean percent change in amplitude following kainic acid injection. Amplitude changes with respect to pre-injection baseline values are shown for all MLR waves. The percent change in the midline response was calculated at the particular point in time which yielded the greatest change for waves A, B and C. Wave M− was unaffected. On the average, M+ varied in the same direction as did waves B and C.

injection. The animal shown in Fig. 7 is an example in which M + varied together with B and C, all increasing in amplitude at about 30–60 min following the injection. The magnitude of drug injection changes was much greater (by at least a factor of 3) than any changes seen with systemic anesthesia.

Auditory cortex and electrolytic lesions

The effects of destruction of the auditory cortex on the midline and temporal response are shown in Fig. 8. Evident is that the midline response persists whereas the temporal lobe response is eliminated by this manipulation. This occurred with both unilateral and bilateral ablations of auditory cortex.

Similarly, electrolytic lesions within auditory cortex temporarily eliminated or greatly at-

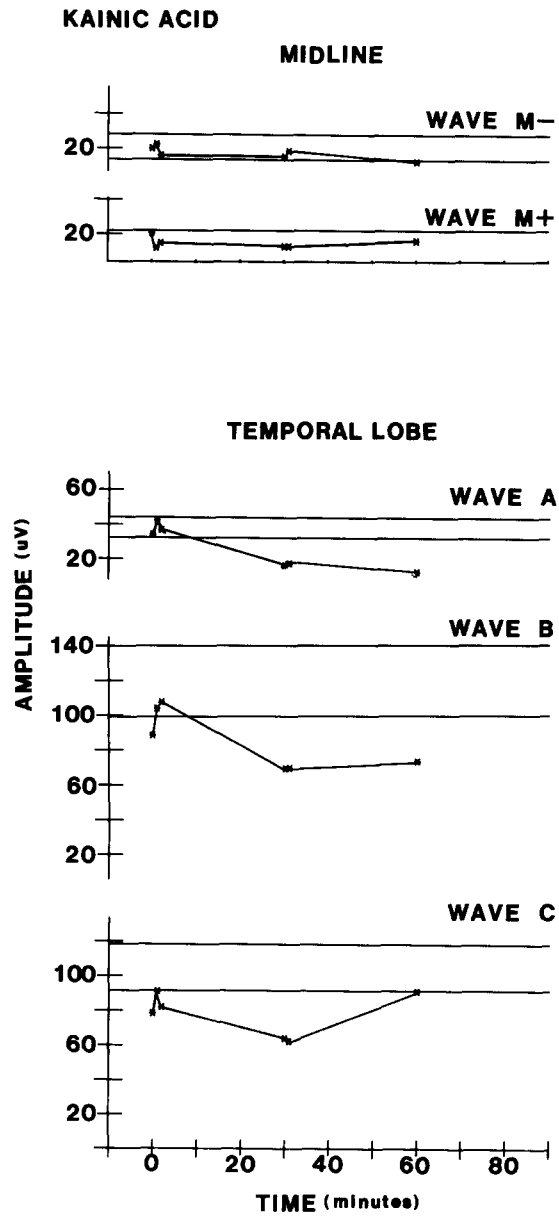

Fig. 6. Time course of MLR amplitude following kainic acid injection. Midline components did not vary whereas all temporal waves decreased in amplitude at 30 min after the injection.

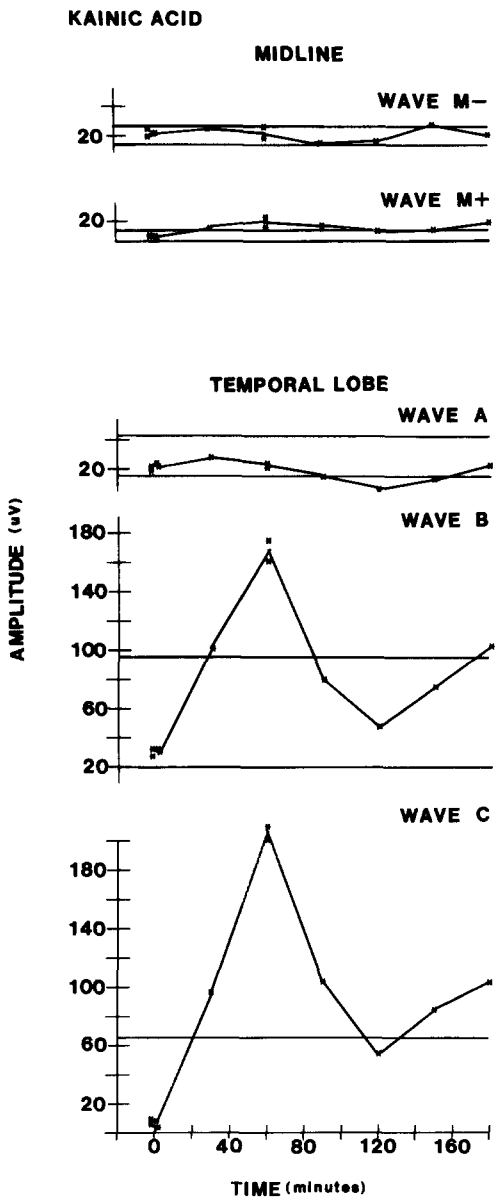

Fig. 7. Time course of MLR amplitude following kainic acid injection. This is an example in which midline M+ varied together with temporal waves B and C, all increasing in amplitude at about 1 h following the injection. Waves M− and A remained stable.

tenuated the temporal lobe response, leaving the midline response intact. The mean percent change in amplitude from pre-lesion values is shown for all waves in Fig. 8.

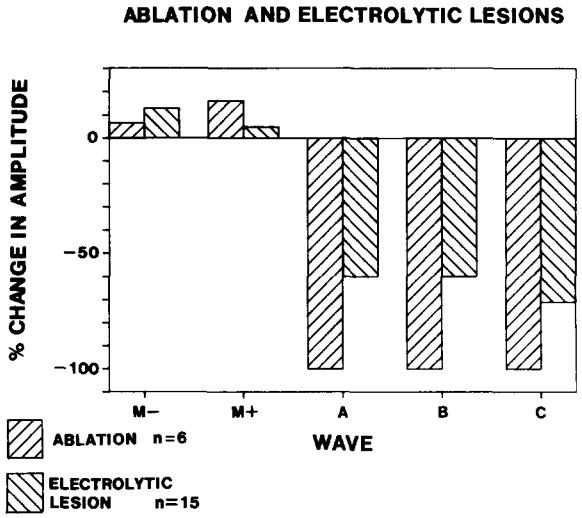

Fig. 8. Auditory cortex ablation and electrolytic lesions. The percent change in amplitude with respect to pre-manipulation baseline is shown for all waves. Ablation and electrolytic lesion values are shown with different symbols as indicated in the figure key. Midline components did not change with either manipulation whereas the amplitude of all temporal lobe components decreased radically or was eliminated entirely.

Systemic anesthesia

Both the midline and temporal lobe components can be affected by anesthetic agents, but the time course of these effects is often different. Also, changes may occur in the temporal response in the absence of midline changes. This is shown in Fig. 9 which illustrates anesthesia effects (pentobarbital and Innovar) on wave amplitude in an individual animal. No significant amplitude changes occurred in either of the midline waves while temporal wave A increased and waves B and C decreased significantly. After the initial 30 min, it was possible to maintain the animal over at least 1 h at a level at which waves A and B remained stable. Wave C continued to wax and wane and is therefore considered less reliable. The amplitude of M+ was not significantly affected by the anesthesia after the first 10 min and was actually easier to record in anesthetized animals probably because of reduced muscle noise. Although M+ does fluctuate over time, it did not change significantly during the time epochs of the experiments in which a dissociation between midline and temporal lobe components is demonstrated.

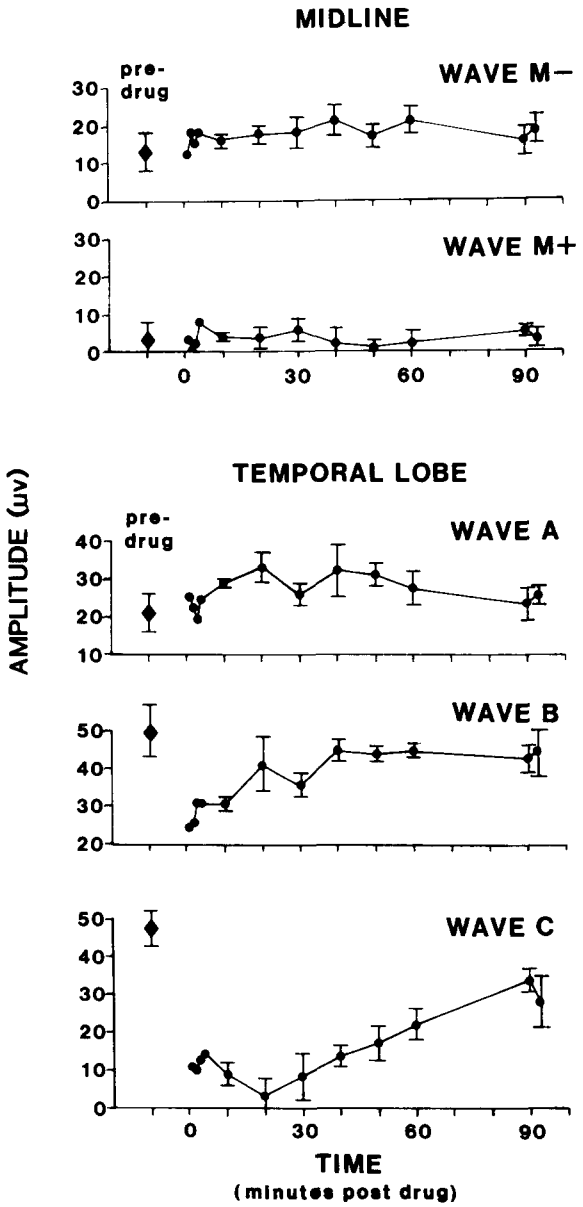

Fig. 9. Systemic anesthesia. The amplitude of all MLR components is shown in the unanesthetized (pre-drug) state and following administration of systemic anesthesia (pentobarbital and Innovar). The amplitude of the midline components did not change with the anesthetic agents whereas wave A amplitude increased significantly ($P < 0.05$) and waves B and C significantly decreased ($P < 0.05$) with the drugs.

Stimulation rate

In the gerbil, the midline and temporal lobe MLRs are differentially sensitive to rate. Amplitude-rate functions are shown for components M −, M +, A, B and C in Fig. 10, which reflects data from a representative, unanesthetized animal as rate was varied from 1 to 40 Hz. The amplitude of both midline components showed no significant

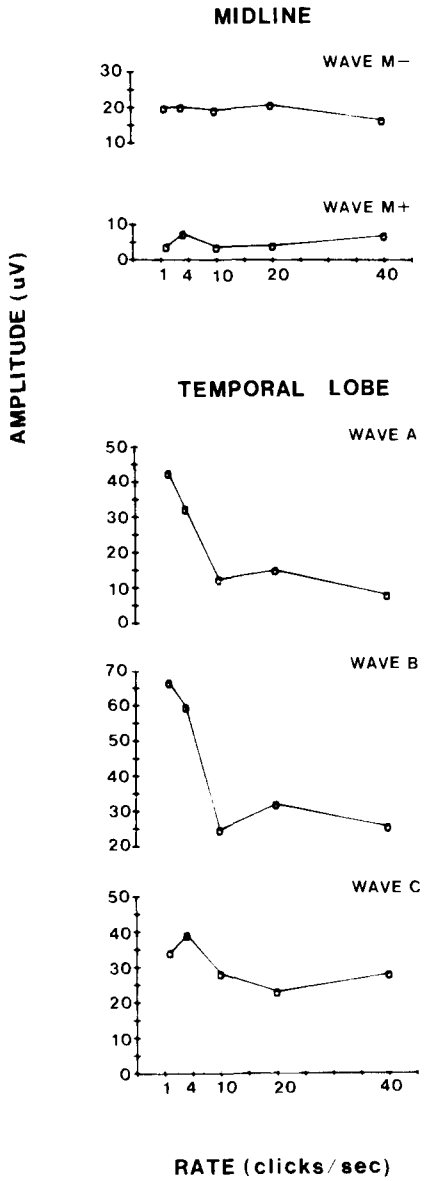

Fig. 10. Stimulation rate. MLR amplitude is shown for all MLR components for a representative animal as stimulation rate was varied from 1 to 40 Hz. The amplitude of midline components was rate resistant whereas the amplitude of temporal components decreased systematically with increasing rate of stimulation ($P < 0.01$).

change with rate. In contrast, the amplitude of each temporal lobe component decreased significantly with increased stimulation rate ($P < 0.01$).

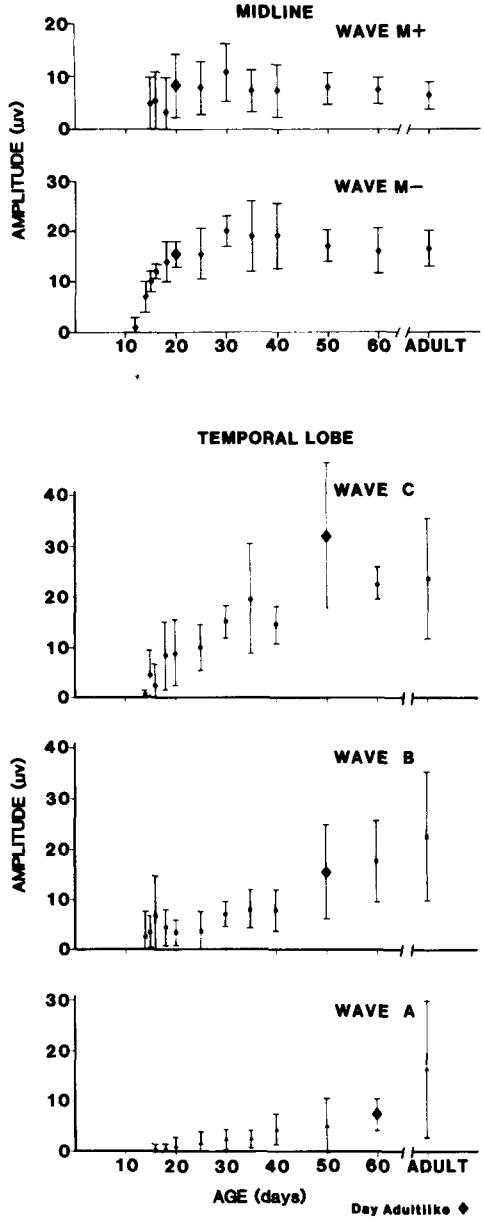

Fig. 11. Amplitude × age. MLR amplitude is shown for all MLR components as a function of age. The largest symbol in each graph represents the age at which response amplitude reached adult levels. Midline components developed earlier, with amplitude becoming adult-like on day 20 for both waves. Temporal lobe wave A became adult-like on day 60 and waves B and C reached adult values on day 50.

Development

Simultaneously obtained midline and temporal MLRs were obtained from a total of 71 unanesthetized gerbils ranging in age from 10 to

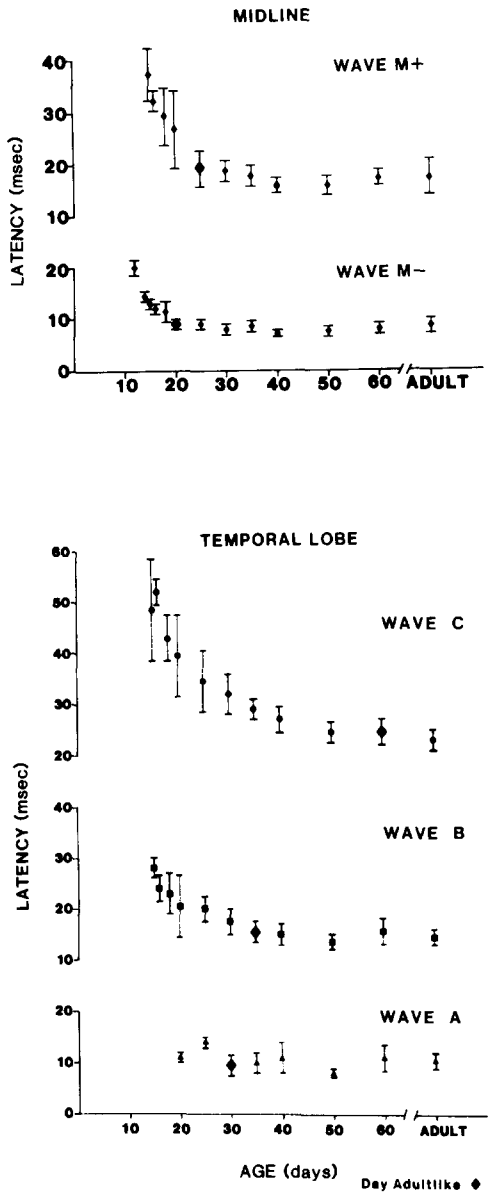

Fig. 12. Latency × age. The latency of each MLR component is shown as a function of age. The largest symbol in each graph represents the age at which latency values become adult-like for each wave. Adult-like latencies were reached on days 20, 25, 30, 35 and 60 for waves M−, M+, A, B and C, respectively.

TABLE I

Summary of effects of experimental manipulations.

Manipulation	Wave	Midline		Temporal		
		M−	M+	A	B	C
Scalp topography		largest over posterior midline		largest over contralateral temporal lobe		
Latency X (±S.D.) (n = 24)		14.0 (±1.4)	22.3 (±1.9)	15.1 (±1.5)	26.1 (±2.3)	46.5 (±6.4)
Neural inactivating agents						
Kainic acid (n = 8)						
No. with significant amplitude changes ($P < 0.05$)		0	5	7	8	8
Lidocaine (n = 10)						
No. with significant amplitude changes ($P < 0.05$)		0	2	4	6	6
Temporal lobe ablation (n = 4) unilateral (n = 2) bilateral		stable	stable	all components eliminated		
Electrolytic lesions (n = 15)		stable	stable	elimination or significant amplitude reduction of all components		
Systemic anesthesia		anesthesia effects on midline and temporal waves may follow different time courses				
Stimulation rate (n = 15)		no significant amplitude reduction with rate		$P < 0.01$ significant amplitude reduction with increasing stimulation rate	$P < 0.01$	$P < 0.01$
Development						
Day adult-like: detectability		13	24	48	21	25
Day adult-like: amplitude		20	20	60	50	50
Day adult-like: latency (not significantly different from adult, $P > 0.05$)		20	25	30	35	60
Rate × age						
Amplitude effects		NS	NS	$P < 0.01$	$P < 0.01$	$P < 0.01$

> 90 days. A general finding is that the midline waves mature earlier than the temporal lobe response. Wave M − develops earlier than the other mid-latency components and appears to follow the developmental time course of the ABR (Smith and Kraus 1987b). The amplitude of both midline waves becomes statistically adult-like on day 20. The temporal lobe responses A, B and C appear to mature later, with amplitude reaching adult values on days 60, 50 and 50, respectively. The development of amplitude is shown in Fig. 11 for all waves.

The development of latency is shown in Fig. 12 for all waves, becoming adult-like for M − , M + , A, B and C on days 20, 25, 30, 35 and 60, respectively. Although the midline waves reach adult latencies at about the same time as wave A, it must be noted that the detectability (presence or absence) of wave A is very poor (about 20%) on days 20–25. Detectability for the midline waves is 85% or better by day 13 for M − and by day 24 for M + .

The above experiments are summarized in Table I.

Discussion

Scalp topography

The present work demonstrates that the guinea pig surface MLR consists of 5 components, 2 of which have maximal amplitude at the posterior midline while 3 components are largest over the temporal lobe contralateral to the stimulus ear. The differential scalp distribution of MLR components has been described in the cat (Farley and Starr 1983) and monkey (Arezzo et al. 1975).

A component at 12–15 msec which is largest in amplitude over the temporal lobe has been described in the chloralose anesthetized and awake cat (Kaga et al. 1980; Buchwald et al. 1981; Chen and Buchwald 1986). Buchwald and colleagues also describe a positive component at 20 msec which is best recorded over the temporal lobe (Chen and Buchwald 1986). These components are likely to be analogous to waves A and C, respectively, in the awake and anesthetized guinea pig (McGee et al. 1983; Kraus et al. 1985; Smith and Kraus 1987a) and awake gerbil (Kraus et al. 1987a, b). The cat midline MLR consists of components at 17–25, 35–45, 50–75 and 150–200 msec, respectively. The earliest of these waves may correspond to the guinea pig M + response. A major difference, however, is that these components differ in their response to barbiturate anesthesia: the cat response disappears while the guinea pig M + is more resistant.

As previously demonstrated (Picton et al. 1974; Özdamar and Kraus 1983), MLR components are largest over the vertex and frontal lobes. In humans, the scalp topography of the MLR is such that component Pa is obtained from widespread areas of the cortical surface. As outlined in the Introduction, several lines of evidence point to the existence of multiple generators for the Na-Pa complex. The particular scalp topography of Pa appears to mask the contributions of the multiple generators which may underlie the response. Because of the dissimilar orientation of the dipole sources contributing to the response, what appears as a single component in humans may be individually examined in animals.

Neural inactivating agents

The strategy of local injection of neural inactivating agents such as lidocaine and kainic acid has been used to examine the contribution of specific auditory brain-stem structures (Gardi and Bledsoe 1981; Wada and Starr 1983). Topical application of the convulsants pentylenetetrazol and picrotoxin on the surface of the rat auditory cortex have resulted in increases in amplitude of waves in the MLR time frame (Borbély 1970).

Effects of intracranial injections of lidocaine and kainic acid are complex, resulting in amplitude increases, decreases and no change. The direction and magnitude of the changes are likely to be site and dosage dependent and are the topic of continuing investigation. The complexity of the results and the observation that components could vary independently provide further evidence for multiple generators. As with lesion, ablation and systemic anesthesia studies, in some instances the drugs affected the temporal lobe response with no change in midline components. Interestingly, waves M + , B and C were often observed to respond similarly to the drugs. This supports the hypothesis that M + , B and C share a modulatory influence.

Temporal lobe lesions

In the guinea pig, unilateral and bilateral temporal lobe lesions eliminated the temporal lobe response whereas the midline response remained intact. The temporal lobe response was also temporarily abolished by electrolytic lesion of the auditory cortex, leaving the midline response largely unaffected. Similarly, midline waves A, B and C in the cat were unaffected by temporal lobe ablation (Buchwald et al. 1981) while the temporal lobe response was eliminated by such a lesion (Kaga et al. 1980). Temporal lobe lesions in humans have had mixed effects with studies divided between instances in which Pa was affected (Graham et al. 1980; Kraus et al. 1982; Özdamar and Kraus 1983; Scherg and Von Cramon 1986; Kileny et al. 1987) and instances in which it remained intact (Parving et al. 1980; Woods et al. 1987). These findings support the hypothesis that

the generators of the human response are complex and not restricted only to the temporal lobe.

Systemic anesthesia

Anesthesia may affect all components of the guinea pig MLR, although the time course of these effects is often different for the midline than for the temporal lobe components. Although amplitude and latency changes may occur in the temporal lobe components, systemic anesthesia (barbiturate, chloral hydrate, ketamine) does not generally interfere with the detectability of components (Smith and Kraus 1987a). This agrees with cat data showing consistent temporal lobe components with barbiturate and chloralose anesthesia (Kaga et al. 1980; Buchwald et al. 1981). The cat midline response on the other hand has been shown to be greatly barbiturate sensitive (Buchwald et al. 1981).

In humans, wave Pa is barbiturate sensitive (Goff et al. 1977) and is not detected in patients in a barbiturate coma (Hall 1985), but is not affected by the narcotic fentanyl (Kileny 1983). The detectability of Pa is unaffected in patients sedated with chloral hydrate or diazepam (Özdamar and Kraus 1983), although more subtle drug effects were not studied.

Stimulation rate

Rate of stimulation (1–40 Hz) did not have major effects on the detectability of either the midline or temporal lobe components in the gerbil. However, there was a clear dissociation between the temporal and midline waves with respect to amplitude and rate. Whereas the amplitude of the midline response did not change with rate, the temporal response was reduced in amplitude at high rates of stimulation. A similar amplitude decrease with rate in the temporal response has been reported in the guinea pig (McGee et al. 1983). In the cat, temporal lobe wave 7 was detected at high stimulation rates (Buchwald et al. 1981; Erwin and Buchwald 1986), while midline responses A, B and C were eliminated at rates greater than 10 Hz (Buchwald et al. 1981; Erwin and Buchwald 1986). Differential rate effects for midline and temporal lobe MLR components in the guinea pig have been previously reported (Yoshida et al. 1984). However, we did not consistently observe amplitude maxima in response to 20 and 40 Hz stimulation at midline and temporal lobe sites, respectively, as reported by Yoshida and colleagues.

In humans, similar to the temporal lobe response in animals, Pa detectability is rate resistant although decreasing in amplitude with increased rate (Picton et al. 1974; McFarland et al. 1975) up to 40 Hz at which point amplitude increases due to a superimposition of the ABR and MLR waves (Galambos et al. 1981).

Development

The midline and temporal lobe responses in the gerbil have different developmental time courses with respect to detectability, latency and amplitude. In general the midline response develops earlier. A similar pattern of development with respect to midline and temporal lobe components has been observed for the late auditory evoked potentials (Kurtzberg et al. 1984).

In humans, recent studies show the detectability of the MLR to be variable in children (Engle 1971; Hirabayashi 1979; Suzuki et al. 1983; Okitzu 1984; Kraus et al. 1985). Recording filters, sleep and sedation effects have been suggested as reasons for discrepancies between these results and previous studies (Mendel et al. 1977; Mendelson and Salamy 1981; McRandle et al. 1983).

The divided opinion regarding the presence of MLRs in children may be partially explained by the multiple generator hypothesis. One cannot ignore the fact that regardless of the recording conditions, Pa is sometimes present in infants and children. This demonstrates that MLR generators are at least partially developed early in life.

Experimental animal data provide a useful framework for considering human MLR development. The course of development of the animal midline response differs from that of the temporal lobe response. The midline response is mature by day 25 whereas the temporal lobe response is not mature even by day 60. The gerbil data show that the course of development of wave A, and in particular the detectability of wave A, extends throughout the second month of life. By comparison, all other gerbil MLR components reached

adult-like detectability well within the first postnatal month. Similar to our experience with human Pa, when wave A is present it occurs at adult latencies but is not detected at adult levels until later in development. Furthermore, wave A in all likelihood is generated by the temporal lobe.

These data may help explain why the MLR is inconsistently obtained in children. Perhaps the lability of the response in humans occurs because one of the generators, presumably the temporal lobe generator, has not yet developed, although other but more variable generators may have already matured. Indeed there is evidence that myelinization of the human temporal lobe continues to develop during the first 10 years of life (Yakovlev and Lecours 1967). The systematic developmental time course of MLR development observed in humans is consistent with a maturational process which extends over this period (Kraus et al. 1985). The development of the temporal lobe generator may account for increases in detectability with age.

Conclusions

The particular orientation of the generating dipoles responsible for the MLR in the guinea pig, gerbil and cat facilitates the identification of individual generating systems. Five separate components can be identified. The components vary in their development, and in their response to stimulation rate and to various forms of trauma. It is apparent that the potentials recorded at the midline develop earlier, are affected by arousal state, and are very robust in the presence of cortical trauma. The results support the hypothesis that the midline components are generated by subcortical areas, such as reticular formation or polymodal thalamus.

The components recorded over the temporal lobe show a longer course of development, are unaffected by arousal state, and are greatly altered or eliminated by cortical trauma. The results indicate that these components are generated by the auditory cortex. In some manipulations, waves B and C vary with the M+ midline component, indicating that these 3 waves share a modulatory influence.

Investigations of human MLR indicate that Pa also receives contributions from multiple generators. How those generators correspond to the animal generators is still at issue. However, we expect that the strategy of simultaneously measuring these components during various experimental manipulations in animal models may lead to a more comprehensive understanding of the MLR generators in humans.

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