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Authors

Zaaroor, Menashe
Starr, Arnold

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Auditory brain-stem evoked potentials in cat after kainic acid induced neuronal loss. I. Superior olivary complex *

Menashe Zaaroor ** and Arnold Starr

University of California, Irvine, CA (U.S.A.)

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Summary Auditory brain-stem potentials (ABRs) were studied in cats for up to 45 days after kainic acid had been injected unilaterally or bilaterally into the superior olivary complex (SOC) to produce neuronal destruction while sparing fibers of passage and the terminals of axons of extrinsic origin connecting to SOC neurons. The components of the ABR in cat were labeled by their polarity at the vertex (P, for positive) and their order of appearance (the arabic numerals 1, 2, etc.). Component P1 can be further subdivided into 2 subcomponents labeled P1a and P1b. The correspondences we have assumed between the ABR components in cat and man are indicated by providing a Roman numeral designation for the human component in parentheses following the feline notation, e.g., P4 (V). With bilateral SOC destruction, there was a significant and marked attenuation of waves P2 (III), P3 (IV), P4 (V), P5 (VI), and the sustained potential shift (SPS) amounting to as much as 80% of preoperative values. Following unilateral SOC destruction the attenuation of many of these same ABR components, in response to stimulation of either ear, was up to 50%. No component of the ABR was totally abolished even when the SOC was lesioned 100% bilaterally. In unilaterally lesioned cats with extensive neuronal loss (> 75%) the latencies of the components beginning at P3 (IV) were delayed to stimulation of the ear ipsilateral to the injection site but not to stimulation of the ear contralateral to the injection. Binaural interaction components of the ABR were affected in proportion to the attenuation of the ABR. These results are compatible with multiple brain regions contributing to the generation of the components of the ABR beginning with P2 (III) and that components P3 (IV), P4 (V), and P5 (VI) and the sustained potential shift depend particularly on the integrity of the neurons of the SOC bilaterally. The neurons of the lateral subdivision (LSO) and the medial nucleus of the trapezoid body (MNTB) of the SOC have a major role in generating waves P3 (IV) and P4 (V).

Key words: Auditory brain-stem potential; Superior olivary complex; Kainic acid lesion; Neuronal loss

Approximately 20 years after the first description of the recording from the scalp of electrical activity originating in the brain-stem auditory pathway (Sohmer and Feinmesser 1967; Jewett and Williston 1971; Lev and Sohmer 1972) the exact origins of the various components comprising the auditory brain-stem response (ABR) are still uncertain. Several approaches have been employed to elucidate the generator sites: (1) scalp topography of each of the components assuming a dipole source for the observed fields (Picton et al. 1974; Starr and Squires 1982; Pratt et al. 1983, 1984; Scherg and Von Cramon 1985; Legatt et al. 1986a; Fullerton et al. 1987; Martin et al. 1987a,b); (2) clinico-pathological correlations in patients between the sites of brain-stem lesions and changes in the ABR (Starr and Achor 1975; Starr and Hamilton 1976; Stockard and Rossiter 1977); (3) electrophysiological recordings of nerve VIII and brain-stem activity in humans (Hashimoto et al. 1981; Møller et al. 1981) and in animals (Achor and Starr 1980a; Caird et al. 1985; Legatt et al. 1986a,b; Kano and Starr 1987; Starr and Zaaroor 1990) correlating the latency of intracranial events with the components of scalp derived ABR; (4) experimental brain lesions in animals comparing the site of destruction with changes in the ABR (Buchwald and Huang 1975; Achor and Starr 1980b; Wada and Starr 1983a,b,c).

The general conclusions derived from these studies are that, in man, the first vertex positive peak, labeled wave I, originates in the distal portion of the auditory nerve; the second peak (wave II) from the proximal portion of the nerve VIII near the brain-stem or from the cochlear nucleus; the third peak (wave III) from the brain-stem ipsilateral to the ear being stimulated, and the fourth and fifth peaks (waves IV and V) bilaterally from the brain-stem.

The homology between human and animal ABRs is complicated by the smaller dimension of the animal nerve VIII and brain-stem compared to their human counterparts (Moore 1987; Møller et al. 1988). The components of the animal ABR have therefore been labeled by their polarity at the vertex, P or N for

* Supported by Grant No. NS11876, The NIH.
** Present address: Dept. of Neurosurgery, Rambam Medical Center, Haifa, Israel.

Correspondence to: A. Starr, Dept. of Neurology, Univ. of California at Irvine, Irvine, CA 92651 (U.S.A.).
Tel: (714) 856-6088.

positive or negative, and their approximate latency in msec or their order of appearance. Wave I in humans and P1 in animals are of comparable origins deriving from activity in the distal portion of the nerve VIII. Wave II in humans and a component, labeled P1b in cat, that follows within 400 μsec of P1, is related to activity of the nerve VIII as it enters the cochlear nucleus (Starr and Zaaroor 1990). Waves V and VI in human are most likely comparable to waves P4 and P5 respectively in cat, whereas the relationship of P3 to III or IV is uncertain (Fullerton et al. 1987). In this and our subsequent paper (Zaaroor and Starr 1991) we suggest that P2, P3, P4 and P5 in cat are comparable to waves III, IV, V and VI in human and will refer to the ABR components recorded from cat in this study by both types of designation, i.e., by their polarity and sequence as well as by their assumed human ABR counterparts using Roman numerals.

Two generator sources of the ABR have been proposed: (1) axon discharges at the initial segment and fiber tract discharges (Jewett and Williston 1971; Stockard et al. 1980; Nunes 1981; Starr and Squires 1982; Wada and Starr 1983c; Legatt et al. 1986b) at changing impedance boundaries (Kimura et al. 1983; Nakanishi 1983) or at points of curvature (Deupree and Jewett 1988); and (2) neural synaptic events (Buchwald 1983). The relevance of the experimental animal work to these possibilities is complicated by the use of methods that are non-selective, i.e., aspiration of brain structures or destruction by electrolytic lesions which affect both fibers of passage and neurons. Furthermore, the studies were usually acute and liable to non-specific transient changes in brain-stem function associated with the induction of the lesion such as edema, local ischemia and pressure.

In the present studies we have selectively destroyed neurons in two of the major nuclear complexes of the auditory pathway, the superior olivary complex (SOC), this paper and the cochlear nucleus (CN), our companion paper (Zaaroor and Starr, 1991). Lesions were made in cats by injection into the nucleus of kainic acid, an excitatory neurotoxic amino acid, that irreversibly damages neurons by initiating sustained depolarization. This substance selectively destroys neurons and spares axons of passage and nerve terminals of extrinsic origin (Coyle et al. 1978; Masterton et al. 1979; Rooney et al. 1988). The ABRs of these cats were then defined for up to 7 weeks avoiding acute non-specific effects of the lesions.

Methods

Animals

Normative data were obtained from 23 adult cats (2700–3400 g), 8 of whom were successfully injected with kainic acid into the SOC. Three animals had only a needle inserted into the SOC to serve as 'controls.' Six animals were subsequently injected with kainic acid into the cochlear nucleus (CN) and are reported in the companion paper (Zaaroor and Starr, 1991). Six animals died prematurely following injection into the SOC and their experimental data could not be used. The site of injection and the duration of study of these animals are contained in Table I.

TABLE I

Site of kainic acid injection.

Cat	Lesion site	Postoperative study duration (days)
6	No injection	30
11	No injection	28
8	No injection	20
5	SOC unilateral	45
8	SOC unilateral	45
7	SOC unilateral	7
17	SOC unilateral	29
23	SOC unilateral	36
26	SOC unilateral	20
14	Bilateral SOC	7
20	Bilateral SOC	30

Operation

The animals were operated upon twice using sodium pentobarbital (35 mg/kg) as the anesthetic agent. Body temperature was maintained with a heating blanket and the electrocardiogram (ECG) was monitored. In the first operation the animal was prepared for electrophysiological study. Four small recording screws (0.045 × 0.125 inch) were implanted into the skull; one in the midline in the very anterior part of the frontal sinus; the other in the midline, 2 cm posterior to the coronal suture (referred to as 'vertex'), one each 1 cm lateral to the midline and 1 cm posterior to the coronal suture. Wires led from the screw electrodes to a connector plug affixed to the skull with dental acrylic. A hollow bar was inserted into the dental acrylic to serve as a mount to stabilize the animal's head during the chronic recording sessions. The dental acrylic was then bound to two 0.75 inch long screws inserted into the frontal sinus with their heads inverted through small key holes. The animal was given penicillin (300,000 units) and allowed to recover for 1 week before their evoked potentials were measured. The second operation took place after an interval of at least another 3 weeks. The cat was anesthetized, placed in a stereotaxic frame, the posterior portion of the skull exposed, a small craniectomy made and the dura mater opened for insertion of a microelectrode. The microelectrode served both to record the potential at its tip and to transmit kainic acid into the brain-stem. The microelectrode was constructed from the needle of a 10 μl Hamilton syringe

by coating it with siliconized glass (SMI, 1095-A) with a tip diameter of 30 μm and an impedance of 2–5 MΩ. The glass was sealed to the proximal end of the needle by dental wax and an electrical connector soldered to the needle. The microelectrode needle was attached to a microsyringe which was filled with kainic acid, 1% solution, and the entire assembly was affixed to a micromanipulator.

Operative recording and injection procedures

The electrode was lowered through the cerebellum to the region of the SOC while presenting click stimuli. The potentials to monaural clicks were amplified and displayed on an oscilloscope. The location of the SOC was identified by the appearance of a phase reversal of the potentials evoked by ipsilateral click stimulation (Galambos et al. 1959) at which point an injection was made. Kainic acid was injected in 0.1–0.2 μl aliquot over 0.5 h to attain a total volume of 0.5 μl. The initial cats studied developed a marked bradycardia within 1 min of the initial injection of kainic acid due to sinus block and escape rhythm. The arrhythmia could be prevented by prior treatment with atropine (0.04 mg/kg). In every cat, within 30 min of the injection, a unilateral myokymia of the face and vibrissae appeared. These movements persisted for approximately 3 h. Some of the animals subsequently had a facial paralysis which affected both perioral and periocular muscles that recovered within 1–2 weeks. Postoperatively some cats also showed a severe ataxia for up to 5 days with a tendency to turn the head and to fall toward the side of the injection and a transient reduction in food intake.

Acoustic signals

Monaural and binaural condensation clicks were presented to the awake cat through Sony (MDR-E225) dynamic earphones which were positioned close to the external auditory meati. The intensity of the clicks used varied up to 80 dB nHL (compared to normal hearing laboratory personnel). During surgery the clicks were transmitted through hollow ear bars from Beyer earphones at an intensity of 50 dB nHL. The stimulus rate in all conditions was 10.6/sec.

Kainic acid preparation

Kainic acid (2-carboxyl-3-carboxymethyl-4-isopropenylpyrrolidine, ICN C.N. 195264) was mixed with 0.9% sodium chloride in water to form a 1% solution. The solution was brought to pH = 6 with sodium hydroxide. A fresh solution of kainic acid was made prior to each injection.

ABR recording

The electrical activity from a pair of electrodes (vertex-frontal) was recorded. The frontal sinus was employed as the reference rather than a non-cephalic site, such as the neck, because in the awake animal, the use of a neck reference was accompanied by excessive muscle potentials. Certain of the components were attenuated using the frontal sinus reference compared to the neck reference but their detectability was unaffected. Electrical activity was amplified 100,000 times at a bandpass of 30–3000 Hz, digitized by a computer at a 20 μsec sample time for 10.24 msec analysis time consisting of a 3 msec prestimulus period and a 7.24 msec post-stimulus period. Two averages of 1000 click trials were made for every experimental condition. Those trials contaminated by high amplitude activity from muscle potentials were excluded from the average. The data were stored on disk for subsequent analysis. The averaged ABRs to stimulation of the right ear, left ear and both ears were defined.

Binaural interaction in the ABR was determined by subtracting the ABR to binaural stimulation from the sum of the ABR to right and left monaural stimulation.

Experimental procedures

Recordings were made with the cat awake in a restraining bag. The hollow bar in the head mount was attached to a frame which prevented head movements thereby maintaining the relationship between the earphones and the external auditory meati. Cats generally remained quiet throughout the recording period which lasted up to 2.5 h. The cats were studied at least 3 separate times prior to the injection of kainic acid and then daily after the injection for the first week and then biweekly for up to 45 days. The ABRs to monaural stimuli as a function of signal intensity were defined for each cat. Thereafter a single intensity was used (usually 80 dB nHL) except when there were changes in amplitude or latency of the components, and then several intensities were reexamined to define if the changes in the ABR were associated with a change in its threshold.

Data analysis

The components of the evoked potentials were marked and named according to their order of occurrence and polarity at the vertex electrode. There are 5 principle positive peaks and 4 negative peaks riding on the slow positive potential shift (Fig. 1). The initial peak, P1, consisted of 2 separate components, P1a (I) and P1b (II). N2 also could be subdivided into 2 separate peaks, but the occurrence of each of these peaks was inconsistent. Thus, latencies of the N2 components were not analyzed further and its amplitude included only the initial trough following P2. We defined the amplitude of a 'wave' of the ABR as the difference between the peaks of two adjacent components, naming the 'wave' by the latter component.

As examples, 'wave P2' was defined as the differ-

ence between N1 and P2 and 'wave N2' was defined by the difference between P2 and N2. An amplitude change of a wave defined by this method must be considered to involve both components comprising that wave, i.e., in the case of wave P2 the change could be due to alterations of either or both the N1 and P2 components. Other methods that use baseline-to-peak measures of amplitude can localize changes to that component only if the sustained potential shift remains unchanged. The method we utilized defines amplitude changes affecting components independent of changes of the sustained potential shift. The amplitude of the sustained potential shift was defined as the difference between the prestimulus baseline and the ABR, midpoint between components P4 and N4. Component peak latencies were measured and both the absolute latency and intercomponent peak-to-peak intervals defined.

Statistical analysis

The latencies and amplitudes of the ABR derived from 3 control sessions prior to the injection of kainic acid were analyzed in a 2-factor repeated measures ANOVA (ear × test number) to determine whether there were any differences over session or between ears. All 23 cats were used for this analysis. The mean and standard deviation of the latencies and amplitudes were obtained for each component of the ABR (Table II). The data from the 11 cats with control or experimental SOC lesion were further analyzed. Postoperative data were analyzed using a 2-factor repeated measurements ANOVA; side of stimulation (ipsilateral or contralateral) × the time of measurements (pre- or postoperative). The preoperative results were compared by ANOVA test to the results obtained from up to 4 postoperative times: in the first, second and third weeks postoperative as well as the last postoperative test. ANOVA were performed for each group of cats separately (the control, the unilaterally and the bilaterally lesioned group of cats). The unilateral group was also divided into two groups based on the extent of the lesion (> or < 75% neuronal destruction). P values equal to or less than 0.05 were considered significant. Post-hoc comparisons of the means were carried out

TABLE II

Normal measures of the ABR (23 cats), mean (X) and standard deviation (S.D.).

	Latency				Amplitude			
	Left ear		Right ear		Left ear		Right ear	
	X	S.D.	X	S.D.	X	S.D.	X	S.D.
Peak								
P1a (I)	0.93	±0.03	0.91	±0.03	2.06	±0.52	2.27	±0.57
P1b (II)	1.19	±0.04	1.19	±0.03	1.89	+0.74	1.48	+0.53
N1	1.48	±0.04	1.49	±0.03	3.14	±1.10	2.46	+0.86
P2 (III)	1.70	±0.04	1.70	±0.04	3.03	±0.97	3.91	±1.15
N2a	1.89	±0.05	1.86	±0.06	0.91	+0.53	1.69	±0.83
N2b	2.14	±0.09	2.13	±0.08	1.02	±0.72	1.26	±0.81
P3 (IV)	2.44	±0.05	2.46	±0.06	5.22	+1.19	5.72	±1.40
N3	2.73	±0.05	2.72	±0.06	4.77	+1.37	6.62	+1.98
P4 (V)	3.22	±0.07	3.22	±0.08	9.00	+1.53	9.93	+2.16
N4	3.65	±0.10	3.66	±0.10	6.68	+1.37	7.59	+2.18
P5 (VI)	4.16	±0.11	4.14	±0.12	2.86	+1.50	3.63	±1.38
SPS	NA		NA		7.14	±1.55	6.59	±1.77
Interpeak interval								
P5-P1a (VI–I)	3.23	±0.12	3.24	±0.11				
P4-P1a (V–I)	2.29	±0.07	2.31	±0.07				
P3-P1a (IV–I)	1.52	±0.05	1.54	±0.05				
P2-P1a (III–I)	0.77	±0.06	0.80	±0.05				
N4-P1a	2.72	±0.10	2.75	±0.10				
N3-P1a	1.80	±0.05	1.82	±0.05				
N2b-P1a	1.20	±0.09	1.23	±0.08				
N2a-P1a	0.95	±0.04	0.96	±0.06				
N1.5-P1a	0.55	±0.03	0.65	±0.03				
Amplitude ratio								
P5/P1a (VI/I)	1.43	±0.71	1.66	±0.63				
P4/P1a (V/I)	4.56	±1.14	4.55	±1.15				
P3/P1a (IV/I)	2.63	±0.70	2.60	±0.64				
P2/P1a (111/1)	1.48	±0.45	1.75	±0.44				
P1b/P1a (II/I)	0.92	±0.31	0.76	±0.23				

NA = not applicable.

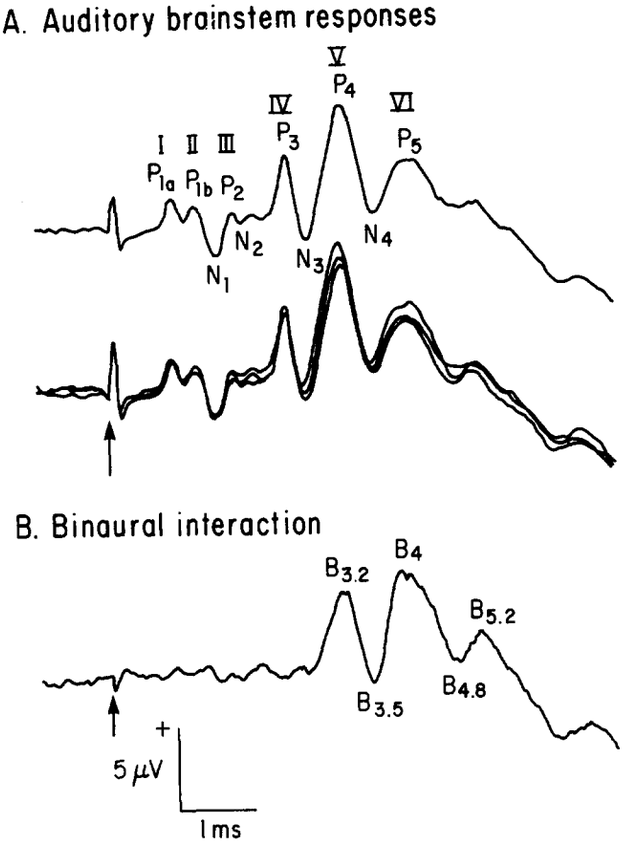

Fig. 1. The normal auditory brain-stem response (A) recorded between vertex and frontal sinus from a cat to show the replicability on 3 separate trials over a 3 week period. The grand average is plotted above. The components in this figure are labeled both by their polarity (P or N for positive or negative) and their sequence (1, 2, etc.) as well as by Roman numerals to show their proposed relationship to their human counterparts. In subsequent figures the components are only labeled by the former method. The initial component, P1, can be subdivided into 2 peaks labeled P1a (I) and P1b (II). There is a slow potential shift (SPS) that reaches a maximum in the vicinity of P4 (V) and P5 (VI). The lower portion of the figure, B, contains the ABR after the procedures for defining binaural interaction. In this and all subsequent figures the time of the click stimulus is indicated by the arrow.

using the Newman-Keuls method (Winer 1971). Correlations between the extent of the lesion in the lateral superior olive (LSO), the medial superior olive (MSO) and the medial nucleus of the trapezoid body (MNTB) subdivisions of the SOC and the postoperative change in amplitude of each wave or in latency of each component were computed. $P < 0.05$ was an indication for a significant linear correlation. The data were also analyzed for each cat individually, by comparing the pre- and postoperative values *within* each cat. Postoperative values beyond 2.5 S.D. of the preoperative mean were defined as a significant change.

Histology

At the end of the experimental sessions the animal was deeply anesthetized with sodium pentobarbital (100 mg/kg) and perfused through the heart with normal saline followed by 10% buffered formalin. The brain was removed and stored in 10% buffered formalin for 15 days. Frozen sections of the brain-stem, 30 μm in thickness, were cut and serially stained with crystal violet for cell bodies alternating with Klüver-Barrera stain or chromoxane cyanine R with crystal violet for myelin. The number of neurons in the SOC on both the injected and normal sides of the brain-stem was defined under high magnification (400 ×) by examining 3 fields in each section of each subdivision of the SOC and then adding these values across the number of sections containing that subdivision. Neuronal loss on the injected side was expressed as a percentage of the number of neurons on the unlesioned side. With the bilaterally lesioned cats the percentage of neurons lost was made comparing corresponding areas in the 3 control cats. Since the boundaries of the periolivary nuclei were difficult to define following the loss of their neurons associated with kainic acid injection, only qualitative estimates of the remaining neuronal population were made. The results of the histological analyses were used to classify the animals into subgroupings reflecting both the locus of the lesion and its extent. Fig. 2 contains a section through both a control animal and through a unilaterally lesioned animal showing the SOC with a schematic representation of the various nuclear subdivisions.

Results

Normal cats

All the components of the ABR were defined in each of the 23 cats to monaural stimulation except for waves N2a (present in 80% of trials), N2b (68%) and P5 (95%). The latencies and amplitudes of these components are contained in Table II. No significant differences between the 3 preoperative recording sessions were found for any of the waves whereas there was an overall significant difference in amplitude between right and left ear stimulation due to waves P1a, P2 and P5. Since the same earphones were always used for right and left ear stimulation, we cannot distinguish whether the observed effect reflects systematic differences in the brain-stem's responsiveness or in the earphones' characteristics.

Control cats

In 3 cats, the needle electrode was introduced into the SOC without injecting kainic acid. During the first 48 h, the ABR differed significantly ($P < 0.05$) from the preoperative recordings (Fig. 3A). In two of the animals there were both delays in latency and decreases in amplitude of all of the components consistent with a conductive change in the external or middle

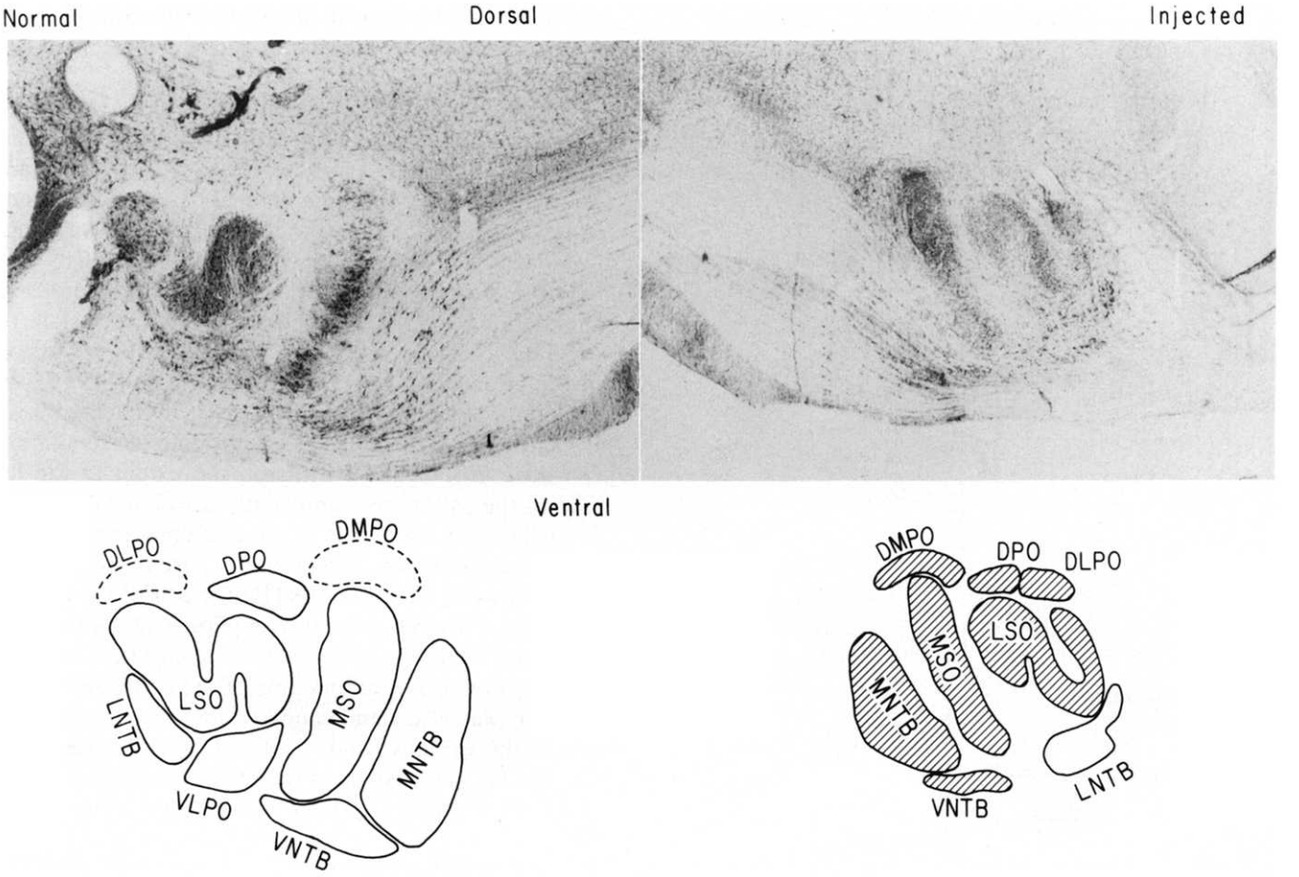

Fig. 2. Histological sections through the superior olivary complex in a normal cat (left side of figure) and one with kainic acid injected 4 weeks earlier (right side of figure). The nomenclature for the subdivisions of the complex are lateral superior olive (LSO); medial superior olive (MSO); medial nucleus of the trapezoid body (MNTB); lateral nucleus of the trapezoid body (LNTB); ventral nucleus of the trapezoid body (VNTB); periolivary nuclei including dorsolateral (DLPO), dorsal (DPO), and dorsomedial (DMPO). Note the loss of neurons and reactive gliosis (indicated by the cross-hatchings in the schematic drawing on the right) following kainic acid injection affecting all but the LNTB.

ears. The ABR in the third cat showed a delay in waves P2 through P5 without a shift in the initial component, P1a, a finding compatible with central auditory dysfunction. The ABR in the 3 control animals returned to normal in 3 days and remained constant until the animals were sacrificed up to 4 weeks later. These results indicate that in the period immediately following the use of a stereotaxic frame to guide the placement of an electrode into the region of the superior olivary complex, even without injection of kainic acid, there can be changes in both acoustic transmission through the middle ear and central auditory pathway that persist for up to 3 days. The brainstem of these cats on histological inspection was essentially normal except for a small amount of gliosis surrounding the electrode tract.

Unilateral lesions of the SOC

There were 6 animals who sustained a unilateral injection of kainic acid into the SOC that destroyed the neurons in the different subdivisions to varying degrees with dramatic effects in the ABR (Table III and Fig. 2 for the histology of animal (no. 8) with an extensive lesion and Fig. 4 for the ABR of all animals. No significant change in latency of the ABR components to either ipsilateral or contralateral stimulation was found whereas there was a significant decrease ($P < 0.05$) in amplitude (Table IV) to both ipsilateral and contralateral stimulation of waves P2 (III), P3 (IV), N3, P4 (V), and N4 and the sustained potential shift.

The extent of destruction of the SOC in these unilaterally lesioned cats varied from being almost total (cats 5, 7 and 8) to a focal damage of just one of the subdivisions of the SOC (cat 23, LSO; cat 26, MSO). The data were reanalyzed taking into account the extent and distribution of the lesions (Table III). In the 3 cats with near total destruction (> than 75%), the ABR to ipsilateral stimulation (Fig. 4) showed a significant ($P < 0.05$) lengthening of latency for waves N3, P4 (V) and N4 (Tables IV and V) with a corresponding increase in their central conduction times from P1a. To contralateral stimulation there was no shift in latency

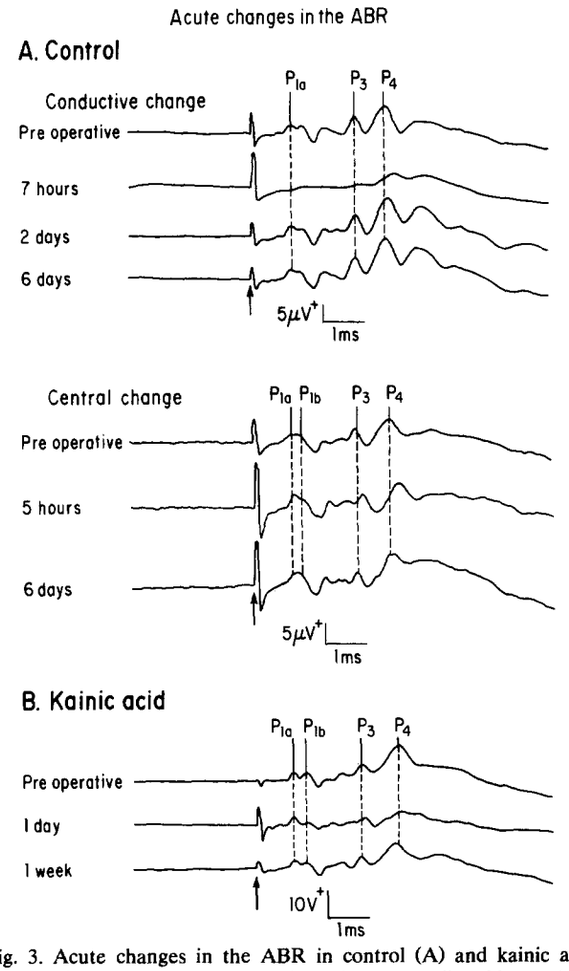

Fig. 3. Acute changes in the ABR in control (A) and kainic acid injected (B) cats. There are transient changes attributable to alterations in sound conduction through the external and/or middle ear (top panel) or to alterations in central auditory pathway conduction (middle and bottom panels).

of any of the components or of the central conduction times. For these 3 cats, the amplitude of waves P3 (IV), N3, P4 (V) and N4 and the SPS were significantly attenuated (20–60%, $P < 0.05$, Tables IV and V) to both ipsilateral and contralateral stimulation.

When the neural loss was restricted to only the MSO (45%) and a small 10% loss of MNTB (cat 26), there was no change in the latency of the ABR components to either ipsilateral or contralateral stimulation. The amplitude of components N3, P4 (V), N4 and P5 (VI) changed slightly but only to ipsilateral stimulation (see Fig. 4 and Table V). In contrast, an isolated lesion affecting 85% of LSO (cat 23) was associated with a delay in latency only to ipsilateral stimulation of P2 (III), P3 (IV), P4 (V) and N4 and an obvious attenuation of waves P3 (IV) and P4 (V) to ipsilateral stimulation and P2 (III) through P4 (V) to contralateral stimulation (Fig. 4 and Table V). Thus, an isolated lesion of the LSO had a more profound effect on the ABR than did an isolated lesion of the MSO. This conclusion is strengthened by the correlation analyses presented below.

When the change in amplitude of the ABR waves from all of the cats was correlated with the extent and distribution of the lesion in the SOC, a significant linear relationship could be defined between the extent of the lesion of LSO and the attenuation of waves P4 (V) and N4 to ipsilateral ear stimulation ($r = 0.89$ and $r = 0.90$ respectively) and P4 (V) to contralateral ear stimulation ($r = 0.83$). The extent of the lesion of MNTB was also significantly correlated with the extent of the attenuation of waves P4 (V), N4 and P5 (VI) to ipsilateral stimulation ($r = 0.94$, $r = 0.89$ and $r = 0.82$; $P < 0.05$) and with P4 (V) to contralateral stimulation ($r = 0.82$; $P < 0.05$). In contrast, the extent of the lesion of the MSO was significantly correlated ($r = 0.84$; $P < 0.05$) with the extent of the attenuation of only P5 (VI) to ipsilateral ear stimulation. These results suggest that lesions of LSO and MNTB of the SOC are related in a linear manner with the amplitude of P4 (V) and N4, whereas MSO lesions have no such linear relation to these waves. The attenuation of the sustained potential shift was also significantly related in a linear manner to the extent of the lesions of both the LSO and the MNTB subdivisions of the SOC to ipsilateral input ($r = 0.86$, $P < 0.05$; $r = 0.85$, $P < 0.05$, respectively).

Bilateral lesions of the SOC

Two cats (14 and 20) had bilateral injections of kainic acid into the SOC. The first cat (14) survived 1 week and the other cat (20) was sacrificed after 34 days. In both cats the lesions were extensive destroying nearly 100% of the neurons in SOC (Table III and Fig. 5). The ABRs postoperatively in these animals were changed with a significant increase in the latency of all components except P1a and P1b, indicative of a central auditory pathway disturbance. Group (Table IV) and individual analyses (Table VI) showed that the amplitude of the components and the slow potential shift were profoundly attenuated (approximately 70%) to stimulation of either ear except for waves P1a and N2 which were unaffected. Thus, even with almost complete bilateral destruction of the cells of the SOC, a major set of brain-stem auditory relay nuclei, no component of the ABR was totally abolished.

Binaural interaction

Binaural interaction components of the ABR consist of 3 waves and a slow potential shift (Fig. 1B). The components are labeled with the letter 'B' signifying that they are binaural and their peak latency in msec. The amplitude of the binaural interaction wave was calculated by the difference between the immediately preceding trough to the peak in question. Peaks B3.2, B3.5 and B4 were always present whereas later peaks,

TABLE III

Neuronal loss (in%) following kainic acid injection bilaterally (A) or unilaterally (B) into SOC.

Cat	SOC subdivision					
	MNTB		MSO		LSO	
	R	L	R	L	R	L
A						
14	30	80	98	80	100	100
20	64	82	99	100	100	100
B						
7		100		100		100
8		75		75		95
5		75		86		75
17		26		26		40
23		0		0		85
26		10		45		0

R = right; L = left; SOC = superior olivary complex; MNTB = medial nucleus of trapezoid body; MSO = medial superior olive; LSO = lateral superior olive.

B4.8 and B5.2, were variable (80%) and not consistently found even in the same cat. Peak B3.2 occurs at or immediately before the time of P4 (V) of the ABR and peak B4 immediately before the time of P5 (VI) of the ABR. Wave B5.2 occurs at the time of a large negative deflection that follows wave P5 (VI). Table VII contains the normative values for the latency and amplitudes of these binaural interaction components in 23 cats.

Following bilateral lesions of the SOC, binaural interaction components were abolished (Fig. 6) and only a portion (approximately 20%) of the sustained baseline shift remained. These effects were present for the duration of the postoperative period. Following unilateral SOC lesions (Fig. 6 and Table VIII), there were no changes in the latencies of any of the components, and wave B3.2 was the only component that was significantly attenuated ($P < 0.01$). Correlation analyses revealed that the extent of the lesion of the LSO was linearly related to the extent of the attenuation of B3.2. Comparison of the amplitude of binaural interaction between pre- and postoperative recordings in each cat separately revealed wave B4 to also be significantly attenuated in the two animals with the most extensive unilateral lesions (cats 5 and 8). Moreover, there was a significant linear correlation when considering all of the animals between the degree of attenuation of B4 and the extent of the lesion in the MNTB. The amplitude of the sustained potential shift from which the components of binaural interaction arose was reduced

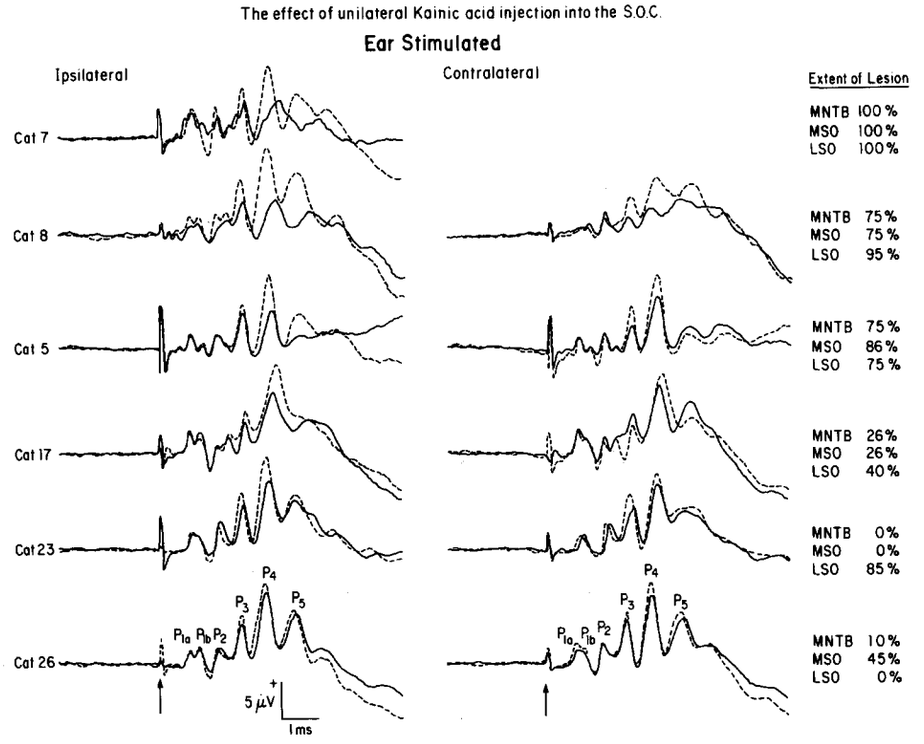

Fig. 4. The effect of unilateral injection of kainic acid on the ABR evoked by monaural stimulation and the extent of the lesion in the SOC listed to the right. The cats are arranged in order of the extent of the lesions. In this and all subsequent figures the preinjection ABRs are represented by interrupted traces and the solid traces represent the ABR up to 45 days following injection. To ipsilateral stimulation components beginning with P3 can be delayed in latency (cats 7, 8, 5) and attenuated in amplitude (all cats), whereas to contralateral stimulation there is no consistent change in latency and components beginning with P3 are attenuated in amplitude. The SPS is reduced in amplitude to ipsi- and contralateral stimulation. The contralateral ABR for cat 7 is not included because this animal had a persistent unilateral conductive loss postoperatively.

TABLE IV

ANOVA results.

	ABR components										
	P1a I	P1b II	N1	P2 III	N2	P3 IV	N3	P4 V	N4	P5 VI	SPS
(A) Unilateral lesions (all cats)											
Amplitude											
Ear (C/I)	–	*	*	–	–	–	–	–	–	–	–
Time (Pr/Po)	–	–	–	*	–	**	*	*	*	–	*
Interaction	–	–	–	–	–	–	–	–	–	–	–
Latency											
Ear (C/I)	–	–	–	–	–	–	–	–	–	–	NA
Time (Pr/Po)	–	–	–	–	–	–	–	–	–	–	NA
Interaction	–	–	–	*	–	–	–	–	–	–	NA
(B) Unilateral lesions (cats with > 75% loss of neurons)											
Amplitude											
Ear (C/I)	–	–	–	–	–	–	–	–	–	–	–
Time (Pr/Po)	–	–	–	–	–	*	*	*	*	–	*
Interaction	–	–	–	–	–	–	–	–	–	–	–
Latency											
Ear (C/I)	–	–	–	–	–	–	**	**	–	–	NA
Time (Pr/Po)	–	–	–	–	–	–	*	*	*	–	NA
Interaction	–	–	–	–	–	–	**	**	*	–	NA
(C) Bilateral lesions											
Amplitude											
Ear (R/L)	–	–	–	**	–	–	–	–	–	–	–
Time (Pr/Po)	–	–	–	**	–	*	**	**	**	*	**
Interaction	–	–	–	*	–	–	–	–	–	–	–
Latency											
Ear (R/L)	–	–	–	–	–	*	–	–	–	–	NA
Time (Pr/Po)	–	–	*	*	–	**	*	**	**	**	NA
Interaction	–	–	–	–	–	–	–	–	–	–	NA

(C/I) = for unilateral lesions, the ear stimulated relative to injection site; contralateral (C) and ipsilateral (I).
(R/L) = for bilateral lesions right (R) and left (L).
(Pr/Po) = time of study relative to injection; preceding (Pr) or post (Po).
* $P < 0.05$; ** $P < 0.01$; – = not significant.
NA = not applicable.

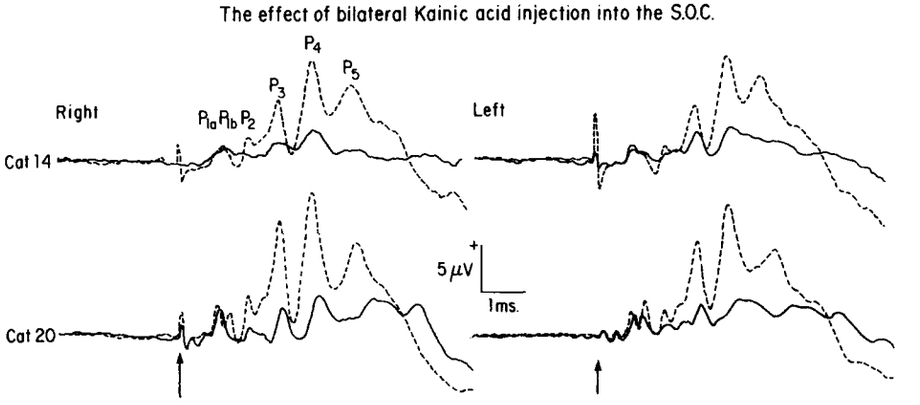

Fig. 5. The effect of bilateral injection of kainic acid into the SOC on the ABR. Note the marked attenuation of the components bilaterally beginning as early as P2 and P1b in cat 20.

TABLE V

ABR after kainic acid injection unilaterally in SOC.

Cat	Ipsilateral stim.						Contralateral stim.					
	7	8	5	17	23	26	7	8	5	17	23	26
(A) Amplitude (% decrease unless preceded by +)												
Wave												
P1a (I)	15	19	10	9	17	13	*	3	18	10	10	9
P1b (II)	7	17	20	18	14	3	*	10	9	+1	8	12
N1	62	32	33	20	23	15	*	4	30	+17	7	4
P2 (III)	56	42	14	13	16	6	*	13	13	6	30	18
N2	33	41	30	23	+20	2	*	34	+4	39	41	15
P3 (IV)	49	41	18	31	22	6	*	53	24	40	25	18
N3	40	29	5	0	15	9	*	67	36	45	24	11
P4 (V)	55	50	41	23	22	8	*	48	35	14	24	12
N4	60	56	50	20	32	9	*	44	19	12	26	15
P5 (VI)	76	59	70	+46	+10	20	*	+47	39	+170	25	24
SPS	50	63	49	27	30	11	*	51	50	6	22	6
(B) Latency (decrease in 10^1 μsec unless preceded by +)												
Wave												
P1a (I)	1	2	1	+4	1	1	*	+1	+1	2	2	0
P1b (II)	12	+1	4	+2	4	1	*	1	4	0	4	0
N1	0	7	+1	+2	4	2	*	+3	+1	2	+2	0
P2 (III)	8	8	8	2	6	5	*	2	0	+2	+2	3
N2	3	7	1	2	10	7	*	6	0	+4	+3	+2
P3 (IV)	5	12	0	+2	8	1	*	5	+1	+1	2	+2
N3	12	17	10	+6	7	2	*	4	2	+4	1	2
P4 (V)	28	7	10	+6	5	+2	*	+14	1	+2	5	0
N4	40	33	13	11	13	0	*	+20	3	+16	+1	1
P5 (VI)	57	34	1	2	+3	3	*	12	9	+2	1	+5
(C) Neuronal loss in %												
Subdivision												
MNTB	100	75	75	26	0	10						
MSO	100	75	86	26	0	45						
LSO	100	95	75	40	85	0						

* No measure taken because of conductive hearing loss.
Underlined numbers = > 2.5 S.D. from preoperative values.

TABLE VI

ABR after kainic acid injection bilaterally into SOC. A = change in amplitude (% decrease unless specified by +). B = change in latency (delay in msec unless specified by +).

Cat	Ear	ABR										
		P1a I	P1b II	N1	P2 III	N2	P3 IV	N3	P4 V	N4	P5 VI	SPS
A												
14	R	20	15	69	85	50	70	76	75	70	84	65
14	L	22	21	52	73	40	55	45	70	100	**	70
20	R	19	100	60	65	67	69	72	70	75	63	70
20	L	10	60	65	67	46	70	70	75	76	65	71
B												
14	R	0.01	0.03	+0.04	0.01	0.04	0.06	0.10	0.15	0.42	0.45	NA
14	L	0.02	0.04	0.14	0.12	0.18	0.06	0.12	0.13	*	0.43	NA
20	R	0.07	*	0.07	0.03	0.08	0.09	0.13	0.17	0.58	0.51	NA
20	L	0.03	+0.04	0.03	0.08	0.16	0.10	0.10	0.19	0.62	0.46	NA

* No data because component was absent.
** No measure taken because preceding component was absent.
Underlined numbers = > 2.5 S.D.s from preoperative values; SPS = sustained potential shift; + = decrease of latency or increase of amplitude; NA = not applicable.

TABLE VII

Normal measures of binaural interaction in the ABR (23 cats).

Component	Latency (msec)		Amplitude (μV)	
	X	S.D.	X	S.D.
B3.2	3.18	±0.11	7.06	±2.19
B3.5	3.55	±0.13	4.47	±1.75
B4	3.98	±0.11	5.16	±1.54
B4.8	4.81	±0.14	5.98	±1.82
B5.2	5.17	±0.13	1.40	±0.54
P4 (ABR)	3.22	±0.08	9.93	±2.16
P5 (ABR)	4.16	±0.11	3.63	±1.38
SPS	NA	NA	5.93	±1.88

X = mean; S.D. = standard deviation; NA = not applicable.

from 7 to 62% after unilateral injection of kainic acid into the SOC. The extent of the attenuation had a linear correlation with the extent of the lesion in the MNTB ($r = 0.94$).

Discussion

The present work shows that selective loss of neurons in the SOC is accompanied by changes in latency and amplitude of many of the components comprising the ABR. A unilateral loss of the neurons of the SOC resulted in the attenuation of up to 70% of waves P3 (IV) through P5 (VI) and the sustained potential shift in response to either ipsilateral or contralateral stimu-

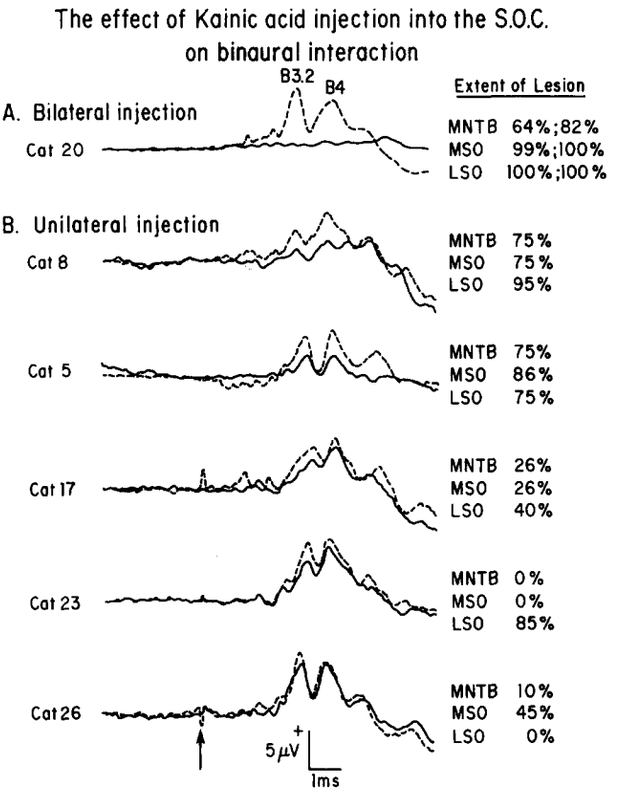

Fig. 6. The effect of kainic acid injection into the SOC on binaural interaction components of the ABR. Note the total loss of binaural interaction components and the sustained potential shift following bilateral injections and the partial changes following unilateral injection. The extent of the lesion is noted on the right.

TABLE VIII

Binaural interaction after kainic acid injection into the SOC.

Cat	B3.2	B3.5	B4	B4.8	B5.1	SPS
(A) Latency (decrease in msec)						
Unilateral						
5	0.05	0.08	0.14	*	*	
8	0.04	0.01	0.06	0.16	0.08	
17	0.12	0.12	0.03	0.03	0.06	
23	0.01	0	0.07	0.01	0.01	
26	0.07	0.02	0.04	0.06	0.10	
Bilateral						
14	*	*	*	*	*	
20	*	*	*	*	*	
(B) Amplitude (% decrease unless preceded by +)						
Unilateral						
5	9	+13	37	100	100	60
8	46	37	44	81	74	62
17	22	81	+10	14	46	15
23	37	80	21	55	60	20
26	5	+9	1	9	33	7
Bilateral						
14	100	100	100	100	100	82
20	100	100	100	100	100	82

Underlined numbers = > 2.5 S.D. from preoperative values.
* Latency measure not possible since component was absent.

lation, while with bilateral destruction, the attenuation was more extensive amounting up to 84%. Gardi and Bledsoe (1981) observed in guinea pig that immediately following unilateral injections of kainic acid to the SOC, waves P3 and P4 of the ABR were attenuated. In our experiments there was never a complete loss of any single component following total unilateral or bilateral destruction of the cells of the SOC. Thus, while the neurons of the SOC can be considered to be essential for the generation of certain portions of the ABR (waves P3 (IV), P4 (V), P5 (VI) and the sustained potential shift), these neurons are certainly not the sole generator of any particular portion of the ABR.

These results bear on 2 suggestions proposed to account for the components of the ABR: (1) that of a limited brain-stem region generating each wave (Jewett 1970; Buchwald 1983; Wada and Starr 1983c) or (2) that of multiple sites generating each wave (Achor and Starr 1980b; Kano and Starr 1986). The data from the present study are compatible with the latter proposition. Destruction of the neurons of the SOC was associated with a marked attenuation of particular portions of the ABR but never a total loss of any component. Other generator sources for the remaining portions of these attenuated ABR components (P3 (IV) through P5 (VI)) could include the system of fibers that bypass the SOCs (Merzenich and Kaas 1980) and/or the rostral auditory neurons to which they project.

Unfortunately, the results from the present experiment do not distinguish between the 2 candidate generators of the ABR: (1) axons (Kimura et al. 1983; Nakanishi 1983; Deupree and Jewett 1988) or (2) neurons (Buchwald 1983). Kainic acid while selective in destroying neurons and sparing axons passing through or near the injected site cannot be considered as solely affecting neurons and their synaptic events. The axons of those neurons destroyed by kainic acid also degenerate so that any change in the ABR associated with the use of this agent must be viewed as deriving from both the affected neurons and their axons, considered as a unit. Even with this constraint, kainic acid is a far more specific agent than the other lesion methods that had been formerly employed (aspiration, electrolysis, cooling) since kainic acid spares fibers passing through the area of injection or axon terminals originating from neurons remote from the injection site (Coyle et al. 1978; Masterton et al. 1979; Rooney et al. 1988). The use of other toxic agents, specific in their action on only the function of neurons or axons (Hall 1971; Waxman et al. 1979), might further the understanding of the role of different brain structures as contributing to the generation of the ABR.

The fortuitous occurrence of isolated lesions of the LSO or the MSO in 2 separate cats suggested that certain portions of the SOC complex contribute to the ABR differently than do other portions. In the cat with the LSO lesion (8–23) there was a significant attenuation of components P3 (IV), P4 (V) and N4 whereas in the cat with an MSO lesion (9–26) the ABR was hardly altered. Since the data are derived from only 2 cats, additional studies of other focal lesions of the SOC subdivisions are needed to verify this conclusion. However, when the changes in the ABR were considered for all of the animals using correlational statistics, similar components were affected by lesions of the LSO and MNTB (P4 (V), N4 and P5 (VI)) which differed from the pattern of components associated with the MSO lesions (only P5 (VI)). The anatomic relationships within the SOC complex may account for the similarity of effects of lesions of the MNTB and the LSO on the ABR since the output of the MNTB projects solely to the LSO (Rasmussen 1946; Glendenning et al. 1985) making the functional consequences of a lesion in either of these sites probably quite similar.

In the present study there were changes in the amplitude of the components of the ABR accompanying SOC lesions beginning as early as P2 (III) as was noted in earlier studies using electrolytic or surgical lesions in this area (Achor and Starr 1980b; Wada and Starr 1983c). The principal generator for P2 (III) is the cochlear nucleus (Buchwald and Huang 1975; Zaaroor and Starr 1991) which is distant from the site of injection in the SOC. There are 3 mechanisms that might account for how a neuronal lesion in the region of the SOC could affect the responsiveness of the cochlear nucleus and wave P2 (III) of the ABR. The first is via a change in activity of auditory feedback systems (olivocochlear bundle, middle ear muscles) that modify cochlear responsiveness (Warr 1960, 1975; Carmel and Starr 1963; Rasmussen 1964; Liberman 1989). It is unlikely that changes in these feedback systems contributed to the attenuation of P2 (III) of the ABR accompanying SOC lesions since the initial component P1a (I), which originates from nerve VIII within the cochlea, was unaffected. The second mechanism, akin to diaschisis, results in a change in function of neurons that project their axons into a lesioned area even though the neurons themselves have not been altered by the lesion (Von Monakow 1914). We have no evidence directly bearing on this possibility. A third mechanism is by direct damage to the neurons of the cochlear nucleus from spread of kainic acid either actively via axonal transport or passively by diffusion. Examination of the cochlear nucleus showed that in 2 of the cats (14 and 20) there was indeed some loss of neurons in the medial aspect of the anterior ventral cochlear nucleus compatible with the diffusion of kainic acid from the site of injection. Examination of the cochlear nucleus in the other 6 cats, however, did not show any such neuronal loss. Thus, while kainic acid may spread to the cochlear nucleus following its injection into SOC, it is unlikely to be the explanation for the attenuation of

P2 (III) since both the extent of the neuronal loss in cochlear nucleus and its probability of occurrence in the experimental animals were limited.

Results from prior experiments in which section of the fibers of the trapezoid body or midline brain-stem were made (Buchwald and Huang 1975; Wada and Starr 1983b) differ from those of the present study with respect to effects on component P3 (IV). Following midline section of the brain-stem, P3 is abolished indicating that this component requires the integrity of auditory fibers that traverse the midline. The additional conclusion that this component is generated unilaterally in the brain-stem, contralateral to the ear being stimulated, is not substantiated by the present results. Almost complete unilateral destruction of the cells of the SOC resulted in an attenuation of component P3 (IV) to stimulation of either the ipsilateral or the contralateral ear indicating that this component must be generated bilaterally by the SOC. It may be that section of the midline affects certain output systems of the SOC that cross the midline in the trapezoid body (Aitkin 1984) and contribute to the generation of P3. The conclusion from midline sectioning of the brain-stem that component P4 (V) is relatively independent of the crossing fiber systems (Wada and Starr 1983b) was extended in the present study by demonstrating that P4 (V) evoked from either ear is dependent on the integrity of the neurons of the LSO and MNTB components of the SOC.

The neurons of the SOC and especially those of the LSO and MNTB are essential for the demonstration of binaural interaction in the ABR. Bilateral lesions of the SOC were associated with the loss of binaural interaction. Unilateral lesions of the SOC only consistently affected an attenuation (up to 50%) of the initial component (B3.2) and the sustained potential shift. These findings are consistent with earlier experiments demonstrating the importance of the role of the crossing fibers of the trapezoid body and the SOCs for the generation of binaural interaction components of the ABR (Fullerton et al. 1979; Wada and Starr 1983c; Wada and Starr 1989).

Some of the alterations of the ABR following kainic acid injection into the SOC were transient, reflecting changes in both sound transmission though the outer or middle ear and/or altered central auditory pathway functions, emphasizing the need for caution in interpreting acute results (Achor and Starr 1980b) of experimental interventions.

These experiments have demonstrated that destruction of the neurons of the SOC affects the ABR components in 2 ways: the first is due to a loss of the neurons resulting in the attenuation and/or shift of latency of the components beginning at P3 (IV) and the sustained potential shift to stimulation of either ear. The second is due to indirect effects of the SOC lesions on the neurons of the cochlear nucleus that contribute to the generation of components as early as P2 (III). There was no portion of the ABR that could be considered as totally dependent on the integrity of the neurons of the SOC.

References

Achor, L.J. and Starr, A. Auditory brain-stem responses in the cat. I. Intracranial and extracranial recordings. Electroenceph. clin. Neurophysiol., 1980a, 48: 154–173.

Achor, L.J. and Starr, A. Auditory brain-stem responses in the cat. II. Effects of lesions. Electroenceph. clin. Neurophysiol., 1980b, 48: 174–190.

Aitkin, L.M., Irvine, D.R.F. and Webster, W.R. Central neural mechanisms of hearing. In: I. Darian-Smith, J.M. Brookhart, V.B. Mountcastle and S.R. Geiger (Eds.), Handbook of Physiology. Section I. The Nervous System, Vol. III. Am. Physiol. Soc., Washington, DC, 1984: 675–737.

Buchwald, J.S., Generators. In: E.J. Moore (Ed.) Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, New York, 1983, 157–193.

Buchwald, J.S. and Huang, C.-M. Far-field acoustic response: origins in the cat. Science 1975, 189: 382–384.

Caird, D., Sontheimer, D. and Klinke, R. Intra- and extracranially recorded auditory evoked potentials in the cat. I. Source location and binaural interaction. Electroenceph. clin. Neurophysiol., 1985, 61: 50–60.

Carmel, P.W. and Starr, A. Acoustic and nonacoustic factors modifying middle-ear muscle activity in waking cats. J. Neurophysiol., 1963, 26: 598–616.

Coyle, J.T., Molliver, M.E. and Kuhar, M.J. In situ injection of kainic acid: a new method for selectively lesioning neuronal cell bodies while sparing axons of passage. J. Comp. Neurol., 1978, 180: 301–324.

Deupree, D.L. and Jewett, D.L. Far-field potentials due to action potentials traversing curved nerves, reaching cut nerve ends and crossing boundaries between cylindrical volumes. Electroenceph. clin. Neurophysiol., 1988, 70: 355–362.

Fullerton, B.C. and Hosford, H.L. Effects of midline brain-stem lesions on the short latency auditory evoked responses. Soc. Neurosci. Abst., 1979, 5: 20.

Fullerton, B.C., Levine, R.A., Hosford-Dunn, H.L. and Kiang, N.Y. Comparison of cat and human brain-stem auditory evoked potentials. Electroenceph. clin. Neurophysiol., 1987, 66: 547–570.

Galambos, R., Schwartzkopff, J. and Rupert, I. Microelectrode study of superior olivary nuclei. Am. J. Physiol., 1959, 197: 527–536.

Gardi, J.N. and Bledsoe, Jr., S.C. The use of kainic acid for studying the origins of scalp-recorded auditory brain-stem responses in the guinea pig. Neurosci. Lett., 1981, 26: 143–149.

Glendenning, K.K., Hutson, H.A., Nudo, R.J. and Masterton, R.B. Acoustic chiasm. II. Anatomical basis of binaurality in lateral superior olive of cat. J. Comp. Neurol., 1985, 232: 261–285.

Hall, S.M. and Gregson, N.A. The in vivo and ultrastructural effects of injection of lysophoshatidyl choline into myelinated peripheral nerve fibers of the adult mouse. J. Cell Sci., 1971; 9: 769–789.

Hashimoto, I., Ishiyama, Y., Yoshimoto, T. and Nemoto, S. Brain-stem auditory-evoked potentials recorded directly from human brain-stem and thalamus. Brain 1981, 104: 841–859.

Jewett, D.L. Volume-conducted potentials in response to auditory stimuli as detected by averaging in the cat. Electroenceph. clin. Neurophysiol., 1970, 28: 609–618.

Jewett, D.L. and Williston, J.S. Auditory-evoked far fields averaged from the scalp of humans. Brain 1971; 94: 681–696.

Kano, Y. and Starr, A. Temporal relationship between single unit activity in superior olivary complex and scalp-derived auditory brain-stem response in guinea pig. Brain Res. 1987, 419: 262–271.

Kimura, J., Mitsudome, A., Beck, D.O., Yamada, T. and Dickins, Q.S. Field distribution of antidromically activated digital nerve potentials: model for far-field recording. Neurology 1983, 33: 1164–1169.

Legatt, A.D., Arezzo, J.C. and Vaughan, Jr., H.G. Short-latency auditory evoked potentials in the monkey. I. Wave shape and surface topography. Electroenceph. clin. Neurophysiol., 1986a, 64: 41–52.

Legatt, A.D., Arezzo, J.C. and Vaughan, Jr., H.G. Short-latency auditory evoked potentials in the monkey. II. Intracranial generators. Electroenceph. clin. Neurophysiol., 1986b, 64: 53–73.

Lev, A. and Sohmer, H. Sources of averaged neural responses recorded in animal and human subjects during cochlear audiometry (electro-cochleogram). Arch. Klin. Exp. Ohr., Nas.- u. Kehlkopf-Heilk. 1972, 201: 79–90.

Liberman, M.C. Rapid assessment of sound-evoked olivocochlear feedback: suppression of compound action potentials by contralateral sound. Hear. Res. 1989, 38: 47–56.

Martin, W.H., Jewett, D.L., Williston, J.S. and Gardi, J.N. The 3-channel Lissajous' trajectory of the auditory brain-stem response. III. Formation, analysis and reliability of planar segments in the cat. Electroenceph. clin. Neurophysiol., 1987a, 68: 333–340.

Martin, W.H., Jewett, D.L., Randolph, M.G., Williston, J.S. and Gardi, J.N. The 3-channel Lissajous' trajectory of the auditory brain-stem response. IV. Effects of electrode position in the cat. Electroenceph. clin. Neurophysiol., 1987b, 68: 341–348.

Masterton, R.B., Glendenning, K.K. and Hutson, K.A. Preservation of trapezoid body fibers after biochemical ablation of superior olives with kainic acid. Brain Res. 1979, 173: 156–159.

Merzenich, M.M. and Kaas, J. Principles of organization of sensory-perceptual system in mammals. In: J.M. Sprague and A.N. Epstein (Eds.), Progress in Psychobiology and Physiological Psychology, Vol. 9. Academic Press, New York, 1980: 1–42.

Møller, A.R., Jannetta, P., Bennett, M. and Møller, M.B. Intracranially recorded responses from the human auditory nerve: new insights into the origin of brain-stem evoked potentials (BSEPs). Electroenceph. clin. Neurophysiol., 1981, 52: 18–27.

Møller, A.R., Jannetta, P.J. and Sekhar, L.N. Contributions from the auditory nerve to the brain-stem auditory evoked potentials (BAEPs): results of intracranial recording in man. Electroenceph. clin. Neurophysiol., 1988, 71: 198–211.

Moore, J.H. The human auditory brain stem: a comparative view. Hear. Res., 1987, 29: 1–32.

Nakanishi, T. Origin of action potential recorded by fluid electrodes. Electroenceph. clin. Neurophysiol., 1983, 55: 114–115.

Nunez, P.L. Electric Fields of the Brain: the Neurophysics of EEG. Oxford University Press, New York, 1981.

Picton, T.W., Hillyard, S.A., Krausz, H.I. and Galambos, R. Human auditory evoked potentials. I. Evaluation of components. Electroenceph. clin. Neurophysiol., 1974, 36: 179–190.

Pratt, H., Har'el, Z. and Golos, E. Three-channel Lissajous' trajectory of human auditory brain-stem evoked potentials. Electroenceph. clin. Neurophysiol., 1983, 56: 682–688.

Pratt, H., Har'el, Z. and Golos, E. Geometrical analysis of human three-channel Lissajous' trajectory of auditory brain-stem evoked potentials. Electroenceph. clin. Neurophysiol., 1984, 58: 83–88.

Rasmussen, G.L. The olivary peduncle and other fiber projections of the superior olivary complex. J. Comp. Neurol., 1946, 84: 141–219.

Rasmussen, G.L. Anatomic relationships of the ascending and descending auditory systems. In: W.S. Field and B.R. Alford (Eds.), Neurological Aspects of Auditory and Vestibular Disorders. Thomas, Springfield, IL, 1964, 1–19.

Rooney, B.J., Kavanagh, G.L. and Kelly, J.B. Preservation of fibers of passage following kainic acid lesions of the superior olivary complex in the ferret. An HRP analysis. Abstracts Society for Neuroscience. 18th annual meeting Toronto, Ont., 1988: 201.9.

Scherg, M. and Von Cramon, D. A new interpretation of the generators of BAEP waves I–IV: results of a spatio-temporal dipole model. Electroenceph. clin. Neurophysiol., 1985, 62: 290–299.

Sohmer, H. and Feinmesser, M. Cochlear action potentials recorded from the external ear in man. Ann. Otol. (St. Louis), 1967, 76: 427–436.

Starr, A. and Achor, L.J. Auditory brain-stem responses in neurological disease. Arch. Neurol., 1975, 32: 761–768.

Starr, A. and Hamilton, A.E. Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brain-stem responses. Electoenceph. clin. Neurophysiol., 1976, 41: 595–608.

Starr, A. and Squires, K., Distribution of auditory brain-stem potentials over the scalp and nasopharynx in humans. Ann. NY Acad. Sci., 1982, 388: 427–442.

Starr, A. and Zaaroor, M. Eighth nerve contributions to cat auditory brain-stem responses (ABR). Hear. Res., 1990. in press.

Stockard, J.J. and Rossiter, V.S. Clinical and pathologic correlates of brain-stem auditory response abnormalities. Neurology, 1977, 27: 316–325.

Stockard, J.J., Stockard, J.E. and Sharbrough, F.W. Brainstem and auditory evoked potentials in neurology: methodology, interpretation, clinical evaluation. In: M.J. Aminoff (Ed.), Electrodiagnosis in Clinical Neurology. Churchill-Livingstone, Edinburgh 1980: 370–413.

Von Monakow, C. Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde. Bergmann, Wiesbaden, 1914.

Wada, S.-I. and Starr, A. Generation of auditory brain stem responses (ABRs). I. Effects of injection of local anesthetic (procaine HCl) into the trapezoid body of guinea pigs and cat. Electroenceph. clin. Neurophysiol., 1983a, 56: 326–339.

Wada, S.-I. and Starr, A. Generation of auditory brain stem responses (ABRs). II. Effects of surgical section of the trapezoid body on the ABR in guinea pigs and cat. Electroenceph. clin. Neurophysiol., 1983b, 56: 340–351.

Wada, S.-I. and Starr, A. Generation of auditory brain stem responses (ABRs). III. Effects of lesions of the superior olive, lateral lemniscus and inferior colliculus on the ABR in guinea pig. Electroenceph. clin. Neurophysiol., 1983c, 56: 352–366.

Wada, S.-I. and Starr, A. Anatomical bases of binaural interaction in auditory brain-stem responses from guinea pig. Electroenceph. clin. Neurophysiol., 1989, 72: 535–544.

Warr, W.B. Olivocochlear and vestibular efferent neurons in the feline brain stem: their location, morphology and number determined by retrograde axonal transport and acetylcholinesterase histochemistry. J. Comp. Neurol., 1975, 161: 159–182.

Waxman, S.G., Kocsis, J.D. and Nitta, K.C. Lysophosphatidyl choline-induced focal demyelination in the rabbit corpus callosum. J. Neurol. Sci., 1979, 44: 45–53.

Winer, B.J. Statistical Principles in Experimental Design. McGraw-Hill, New York, 1971.

Zaaroor, M. and Starr, A. Auditory brain-stem evoked potentials in cat after kainic acid induced neuronal loss. II. Cochlear nucleus. Electroenceph. clin. Neurophysiol., 1991, 80: 436–445.