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Auditory brain-stem evoked potentials in cat after kainic acid induced neuronal loss. II. Cochlear nucleus *

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Summary Auditory brain-stem potentials (ABRs) were studied in cats for up to 6 weeks after kainic acid had been injected unilaterally into the cochlear nucleus (CN) producing extensive neuronal destruction. The ABR components were labeled by the 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, P1a and P1b. The assumed correspondence between the ABR components in cat and man is indicated by providing human Roman numeral designations in parentheses following the feline notation, e.g., P2 (III). To stimulation of the ear ipsilateral to the injection, the ABR changes consisted of a loss of components P2 (III) and P3 (IV), and an attenuation and prolongation of latency of components P4 (V) and P5 (VI). The sustained potential shift from which the components arose was not affected. Wave P1a (I) was also slightly but significantly attenuated compatible with changes of excitability of nerve VIII in the cochlea secondary to cochlear nucleus destruction. Unexpectedly, to stimulation of the ear contralateral to the injection side, waves P2 (III), P3 (IV), and P4 (V) were also attenuated and delayed in latency but to a lesser degree than to stimulation of the ear ipsilateral to the injection. Changes in binaural interaction of the ABR following cochlear nucleus lesions were similar to those produced in normal animals by introducing a temporal delay of the input to one ear. The results of the present set of studies using kainic acid to induce neuronal loss in auditory pathway when combined with prior lesion and recording experiments suggest that each of the components of the ABR requires the integrity of an anatomically diffuse system comprising a set of neurons, their axons, and the neurons on which they terminate. Disruption of any portion of the system will alter the amplitude and/or the latency of that component.

Key words: Auditory brain-stem potentials; Cochlear nucleus; Kainic acid; Neuronal loss

The cochlear nucleus is the first central station of the auditory pathway where all of the axons of nerve VIII terminate (Lorente de Nó 1933). It is a complex structure consisting of 3 separate nuclei: anteroventral (AVCN), posteroventral (PVCN) and dorsal (DCN). The anteroventral nucleus can be subdivided into 3 divisions; anterior (AVCNa), anterior posterior (AVCNap), and posterodorsal (AVCNpd) (Osen 1969). Other investigators have subdivided the cochlear nucleus into even more regions (Lorente de Nó 1933; Brawer et al. 1974). The outputs of the cochlear nucleus traverse the brain-stem to terminate widely in the auditory brain-stem nuclei (Warr 1982) including the superior olivary complex, the lateral lemniscus, the inferior colliculus, and the contralateral cochlear nucleus (Cant and Gaston 1982). How activity of the cochlear nucleus contributes to the far-field scalp-derived ABR has been analyzed using (1) recordings from near the nucleus in humans (Hashimoto et al. 1981; Møller and Jannetta 1983; Curio et al. 1987) or in animals (Achor and Starr 1980a; Legatt et al. 1986, Starr and Zaaroor 1990); (2) the effects of surgical lesions of this nucleus (Buchwald and Huang 1975; Achor and Starr 1980b); and (3) dipole models using the distribution of scalp potentials (Jewett and Williston 1971; Picton et al. 1974; Starr and Squires 1982, Scherg and Von Cramon 1985). The results indicate that two of the waves, II and III in man, and P1b and P2 in animals, are generated in the region of the cochlear nucleus. The first of these two components (P1b) is probably related to activity of nerve VIII within the cochlear nucleus (Starr and Zaaroor 1990) whereas the second component (P2) may be related to activity of the neurons of the cochlear nucleus itself (Buchwald and Huang 1975).

The lesion methods of aspiration or electrocoagulation that have been employed in prior studies are non-specific in their action since they destroy both axons and cell bodies. The experiments to be presented in this paper utilized the injection of an excitatory neurotoxic agent, kainic acid, to destroy only the neu-

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rons of the cochlear nucleus, while sparing the axons and terminals of nerve VIII (Coyle et al. 1978; Masterton et al. 1979; Rooney et al. 1988). The injections were made into different subdivisions of the nucleus in order to distinguish the relative role of neuronal activity in the different subdivisions of the cochlear nucleus for the ABR. The experiments were performed in cats studied chronically for several weeks after making the kainic acid injections to avoid the confounding acute consequences of brain lesions such as transient ischemia, edema, and local pressure.

TABLE I

Site of kainic acid injection in cochlear nucleus.

Cat	Site	Duration of study (days)
21	posterior	41
22	posterior	4
24	posterior	34
25	anterior	28
28	anterior	36
30	anterior	35

Methods

Animals

Six cats weighing 2500–3400 g, were studied. The anterior or posterior nuclear site of injection and the duration of study of these animals are contained in Table I. The results from five of the animals that survived for more than 2 weeks were analyzed further. One cat, no. 22, survived only 3 days and the data were not used because of the possible influence of acute non-specific factors.

The methods of study were identical to those reported in the previous paper (Zaaroor and Starr 1991) with the exception of the technique used to locate the cochlear nucleus for injection of kainic acid. The cat was anesthetized, placed in a stereotaxic frame, the posterior fossa exposed, a craniectomy made over one side of the posterior fossa and the dura mater opened. The lateral 1/3 of the cerebellar hemisphere was removed surgically by aspiration and bipolar coagulation, leaving the cochlear nucleus fully exposed and visible through the operating microscope. An electrode, used for both recording the potentials at its tip and for transmitting kainic acid into the brain-stem, was filled with kainic acid, 1%, and affixed to a micromanipulator and under direct vision was lowered 2–3 mm into the cochlear nucleus while presenting click stimuli. The portion of the cochlear nucleus injected, i.e., anterior

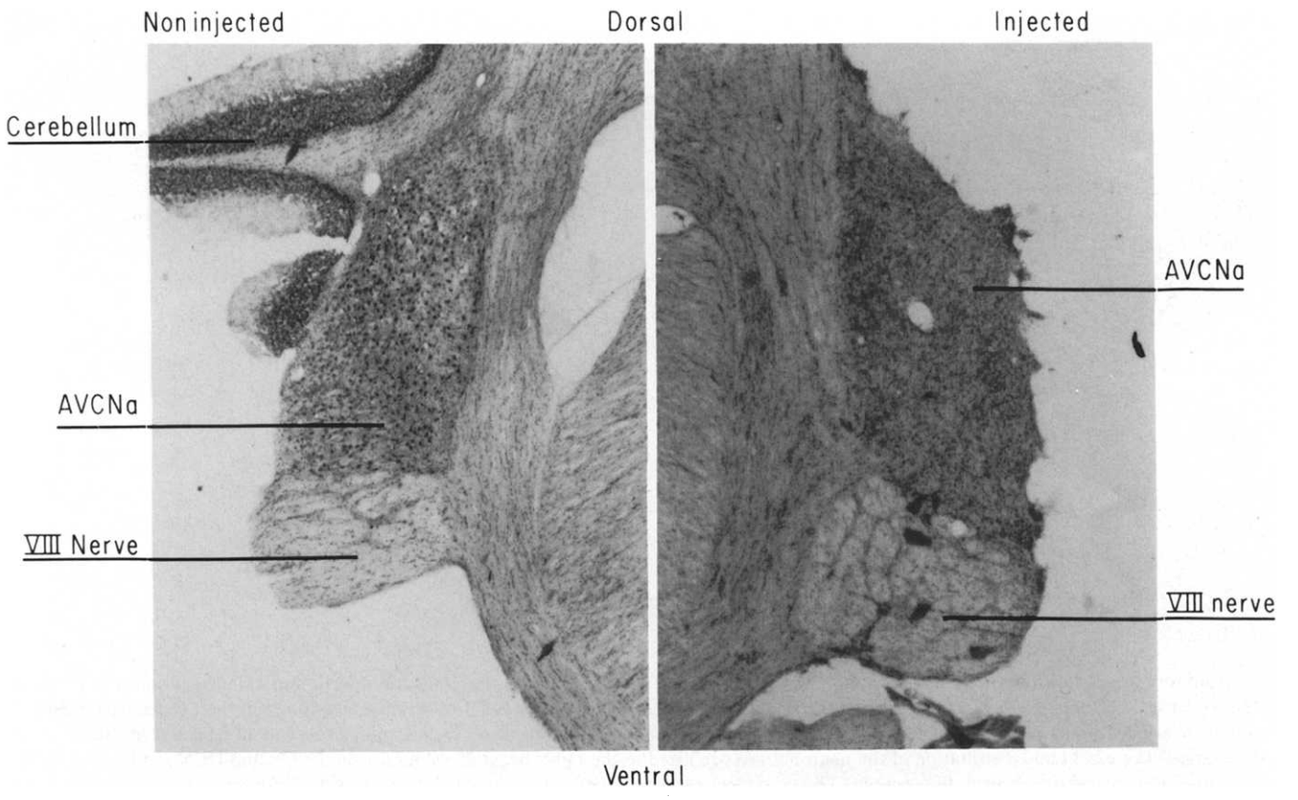

Fig. 1. Histological sections through the anterior cochlear nucleus (AVCNa) after the injection of kainic acid (right side) and from a noninjected cochlear nucleus (left side) stained with Cresyl Violet. There is a total loss of neurons after the injection with little or no change in the appearance of nerve VIII.

or posterior, was varied and is listed in Table I. Kainic acid was injected in 0.1–0.2 μl aliquot over 0.5 h to attain a total volume of 0.5 μl. Body temperature was maintained with a homeothermic blanket and infra-red lamp and the electrocardiogram monitored. As opposed to the results accompanying injection of kainic acid into the SOC (Zaaroor and Starr 1991) no heart arrhythmia developed after the injection into CN and no facial movements appeared. One cat died 4 days after the operation due to bronchopneumonia. The other 5 cats recovered without facial palsy or ataxia. They ate and drank naturally.

The methods for stimulus presentation, recording the ABR, defining the latency and amplitude of the ABR components, and statistical analyses of the results were identical to those reported in the prior paper (Zaaroor and Starr 1991). In addition, paired t tests were employed to compare the extent of attenuation of the ABR evoked from stimulation of each ear.

The extent of neural loss was defined with the aid of a camera lucida by calculating the area of the lesion and the number of neurons in this area compared to the uninjected contralateral nucleus. The count was made under high magnification (400 ×) for 3 fields in each slide containing a particular subdivision of the cochlear nucleus and then adding these values across the number of sections containing this subdivision. The posterodorsal division of the AVCN (ACVNpd) was difficult for us to distinguish preventing any tabulation of the effects of kainic acid on this subdivision. Neuronal loss was expressed as a percentage of the number of neurons on the unlesioned side. Fig. 1 contains sections through a normal and a kainic acid injected cochlear nucleus.

Results

ABR evoked from ipsilateral stimulation

There were significant changes of both latency and amplitude of many of the components of the ABR that followed the injection of kainic acid into the cochlear nucleus. After the first week the ABR stabilized and did not change throughout the remaining period of study ($P > 0.05$, ANOVA). To stimulation of the ear ipsilateral to the site of injection (Fig. 2 and Table II) there was either a loss or a marked attenuation of waves P2 (III), N2, and P3 (IV), while the later components, P4 (V) and P5 (VI), and the sustained potential shift (SPS) were attenuated to a moderate degree. The definition of the amplitude of P3 posed a problem in those animals in whom the immediately preceding marker, the peak of N2, was missing. For instance, in cats 21 and 25 (Fig. 2), there was only a sustained

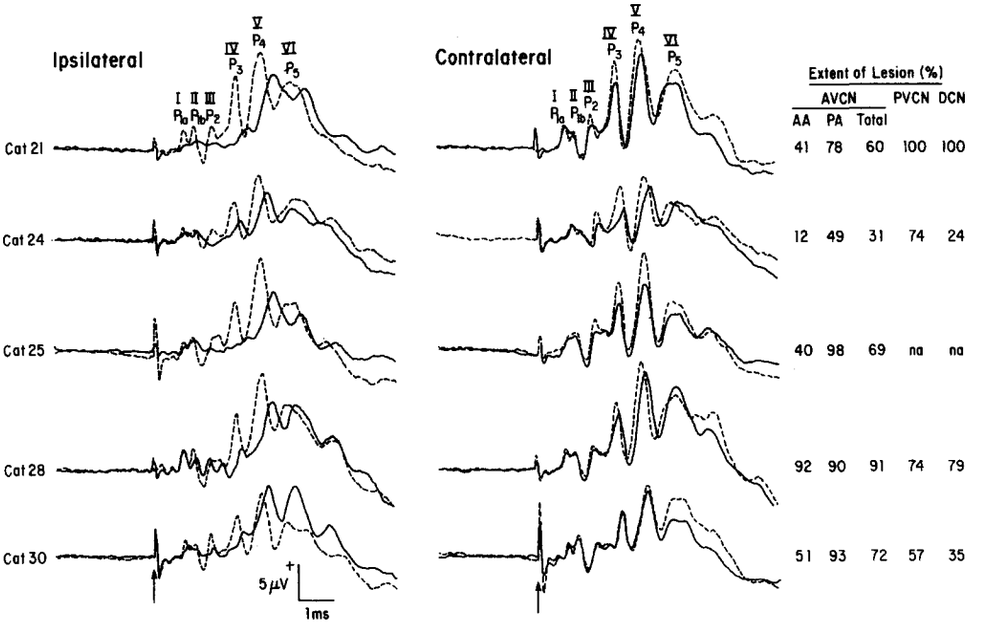

Fig. 2. Auditory brain-stem responses recorded prior (dashed line) and after (solid line) the unilateral injection of kainic acid into the cochlear nucleus of 5 cats. The components in this figure are labeled both by their polarity (P or N for positive or negative) and their sequence (1, 2, etc.) as well as by Roman numerals to show their proposed relation to the human ABR. The arrow in this and all subsequent figures refers to the time of stimulation. The extent and distribution of the neuronal loss are listed to the right. In cat 25 values for the PVCN and DCN were not available (na) because of technical problems in the sections. The vertex positive components are labeled by their polarity (P for positive) and sequence. To ipsilateral stimulation, there was a loss or marked attenuation of P2 (III) and P3 (IV) with a moderate attenuation and delay of P4 (V) and P5 (VI). P1a (I) was attenuated to a slight degree. To stimulation of the ear *contralateral* to the injection, P2 (III), P3 (IV) and P4 (V) were attenuated.

TABLE II

ABR after unilateral kainic acid injection into cochlear nucleus.

Wave	Ipsilateral stim.					Contralateral stim.				
Cat	21	24	25	28	30	21	24	25	28	30
(A) Amplitude (% decrease unless preceded by +)										
P1a (I)	71	35	53	38	33	31	+15	15	15	+6
P1b (II)	50	26	28	48	15	21	+22	20	5	+3
N1	68	15	56	62	62	19	+14	12	22	7
P2 (III)	92	100	100	33	80	45	38	27	26	12
N2	100	100	100	65	36	61	70	96	43	54
P3 (IV)	100	54	100	53	44	63	52	43	28	6
N3	97	50	95	88	99	68	48	36	15	+6
P4 (V)	35	21	48	33	34	42	21	34	5	+18
N4	58	39	50	50	57	37	20	38	13	2
P5 (VI)	66	10	59	+10	15	+26	+11	28	+55	+55
SPS	10	15	26	22	+48	14	15	33	2	18
(B) Latency (decrease in msec unless preceded by +)										
P1a (I)	0.01	0.11	0.05	0.03	0.03	0.04	0.05	0.03	0.01	0.03
P1b (II)	0.11	0.07	0.06	0.09	0.05	0.01	0.05	0.02	0.01	0.01
N1	0.07	0.21	0.06	0.03	0.09	0.06	0.14	0.03	0.01	0.03
P2 (III)	0.06	#	#	+0.04	0.08	0.10	0.14	0.03	0.06	0.03
N2	#	#	#	0.14	0.17	0.12	0.12	0.02	0.12	0.07
P3 (IV)	#	0.17	#	0.18	0.19	0.07	0.17	0.01	0.06	0.00
N3	0.24	0.11	0.33	0.09	0.09	0.10	0.14	0.01	0.09	0.04
P4 (V)	0.39	0.24	0.38	0.32	0.20	0.12	0.20	0.04	0.12	0.04
N4	0.65	0.23	0.53	0.38	0.20	0.13	0.20	0.04	0.14	+0.04
P5 (VI)	0.42	0.26	0.31	0.41	0.22	+0.03	0.25	0.03	0.08	0.26
(C) Neuronal loss in %										
Subdivision										
AVCN	60	31	69	91	79					
PVCN	100	74	NA	74	57					
DCN	100	24	NA	79	35					

Underlining = > 2.5 S.D. from preoperative values.
# = component absent so no measure possible.

potential shift at the time of P3, whereas in cat 24, a peak at the time of P3 is apparent without a clear preceding N2. A group analysis (ANOVA, Table III) comparing the amplitude of the ABR evoked before and after the injection of kainic acid showed the attenuation to be significant (ANOVA, $P < 0.05$) for waves P1a (I), N1, P2 (III), N2, P3 (IV), N3, P4 (V), N4. Only P1b (II) and P5 (VI) did not show any significant

TABLE III

ANOVA results

	ABR components										
	P1a I	P1b II	N1	P2 III	N2	P3 IV	N3	P4 V	N4	P5 VI	SPS
(A) Amplitude											
Ear (C/I)	–	–	–	**	–	**	**	**	**	**	–
Time(Pr/Po)	*	–	**	**	**	**	**	**	**	–	–
Interaction	*	–	*	–	–	–	–	–	–	–	–
(B) Latency											
Ear (C/I)	–	–	–	MD	MD	MD	–	**	**	–	NA
Time (Pr/Po)	–	**	*	MD	MD	MD	**	**	**	**	NA
Interaction	–	*	–	MD	MD	MD	–	**	*	*	NA

(C/I) = the ear stimulated relative to the injection site; contralateral (C) and ipsilateral (I). (Pr/Po) = the time of study relative to the injection; preceding (Pr) and post (Po).
* $P < 0.05$.
** $P < 0.01$.
– = not significant. MD = missing data because components were absent; NA = not applicable.

change. The change in the sustained potential shift among the individual cats ranged from an increase of 48% to a decrease of 33% and was not significant by ANOVA. The finding of a diminished wave I (P1a) is suggestive of an alteration in sound conduction through the auditory periphery, i.e., middle ear damage. However, since both the latency of the initial component, P1a, did not shift and the threshold at which P4 was evoked was not elevated (Fig. 3), it was unlikely that a conductive change was responsible for the change in the ABR. Even with the loss of the early components, P2 (II) and P3 (III), the later components P4 (V) and P5 (VI) were relatively preserved (cats 21, 24, 25). The possibility that the persistence of these latter components could be due to acoustic cross-over stimulating the ear contralateral to the injection site was rejected since the addition of masking noise to the contralateral ear had no effect on the ABR evoked from stimulation of the ear ipsilateral to injection (Fig. 4).

The latency of the ABR components generated in response to stimulation of the ear ipsilateral to injection showed that components P1b, N1, and N3 through P5 were prolonged (ANOVA, Table III) along with the intercomponent intervals, P5-P1a (VI–I), and P4-P1a (V–I). The interval between P1b and P1a was not changed significantly. The latencies of waves P2, N2, and P3 could not be analyzed by ANOVA as, in some of the cats (21, 25), all of these components were missing. However, the data from each cat analyzed individually showed that when these components were present, they were usually delayed (1 of 2 cats with P2; 1 of 2 cats with N2; and 3 of 3 cats with P3).

ABR evoked from contralateral stimulation

Unexpectedly the amplitudes of waves P2 (III), P3 (IV) and P4(V) of the ABR evoked by stimulation of the ear contralateral to the site of injection were significantly ($P < 0.05$) attenuated without any change in the sustained potential shift (Fig. 2; Tables II and III). The attenuation was significantly less than that evoked by stimulation of the ear ipsilateral to the injection ($P < 0.01$, paired t tests). The addition of masking noise to the ear ipsilateral to the injection site further reduced the amplitude of only wave P5 (VI; Fig. 4).

To stimulation of the ear contralateral to the site of injection, the absolute latencies of waves N1 and N3 as well as the intercomponent interval, P4-P1a (V–I), were prolonged (ANOVA). Analysis of the data from

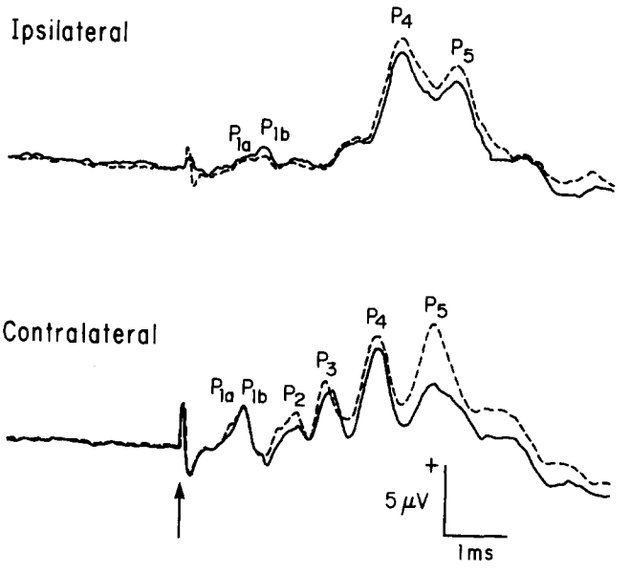

Fig. 4. The effect of the introduction of a masking noise (solid line) to the ear contralateral to that stimulated by the click on the ABR from one of the cats after kainic acid induced neuronal loss in the cochlear nucleus. Note that the ABR evoked from stimulation of the ear ipsilateral to the injection site with (solid line) and without the noise (dashed line) were quite similar. The ABR to stimulation of the ear contralateral to the lesion showed that the addition of noise to the ear ipsilateral to the injection (solid line) was associated with an attenuation of P5 (VI) compared to the ABR without noise (dashed line).

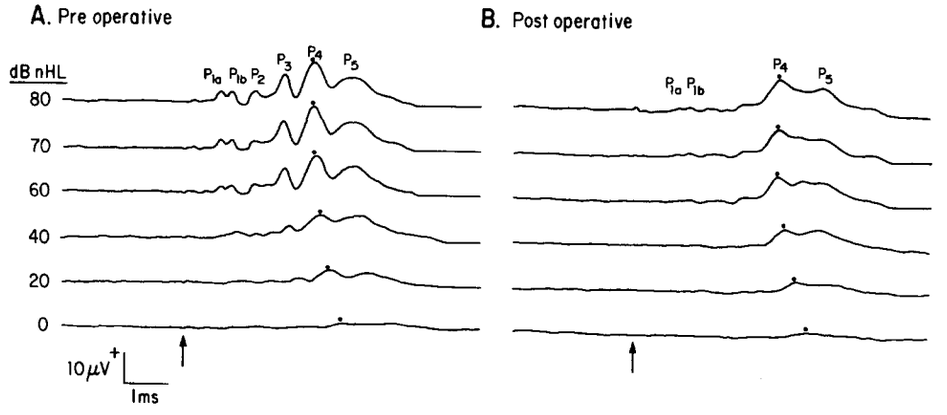

Fig. 3. The ABR to stimulation of the ear ipsilateral to the cochlear nucleus that had received kainic acid injection preoperatively (A) and several weeks postoperatively (B) at several intensity levels. The threshold of P4 (V) indicated by the black dot did not change even through the early components were attenuated following the kainic acid induced lesion.

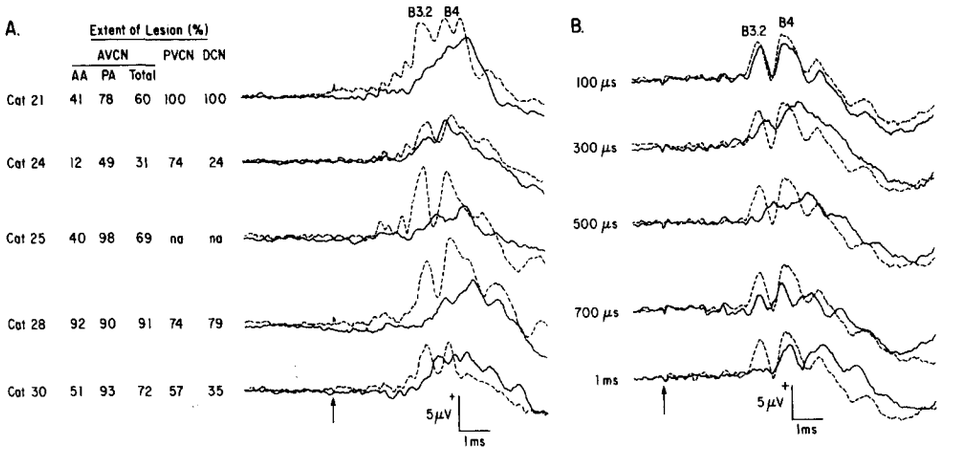

Fig. 5. Binaural interaction in the ABR before (dashed line) and after (solid line) the injection of kainic acid into the cochlear nucleus (A). In a control animal (B) the effect of delaying (solid line) the click to one ear in μsec or msec is shown in comparison to simultaneous binaural presentation. Following kainic acid induced neuronal loss in the cochlear nucleus, component B3.2 is attenuated and shifted in latency along with the sustained potential shift. Delaying the click in a control animal by 300 and 500 μsec has the same effects on binaural interaction components as in the lesioned animal without any interaural delays.

each cat individually showed that changes in the latencies of the ABR components could even be more extensive involving all components after N1 (cat 24) or N3 (cat 28).

Binaural interaction

Unilateral destruction of the cochlear nucleus affected those components of the ABR reflecting binaural processes. The initial binaural component, B3.2, was attenuated and shifted in latency with little effect on both the subsequent component, B4, and the sustained potential shift (Fig. 5A). This attenuation of B3.2 was most likely due to the alteration of the timing of inputs to binaurally sensitive auditory centers consequent upon unilateral destruction of the cochlear nucleus: the latency of P4 of the ABR evoked by stimulation of the ear ipsilateral to the injection site was delayed approximately 400 μsec compared to the P4 evoked by stimulating the contralateral ear. Normally, the introduction of a delay of the input to one ear is associated with a similar attenuation of the binaural interaction components beginning with B3.2 (see 500 μsec in Fig. 5B) comparable to that seen in the lesioned animals. Unfortunately none of the lesioned cats was studied postoperatively with time delays to assess whether the attenuated B3.2 binaural component could have been restored in amplitude if the input to the normal contralateral ear was delayed 400 μsec.

To summarize, the major consequence of kainic acid induced neuronal loss in the cochlear nucleus on the ABR to ipsilateral stimulation is a loss or marked attenuation of waves P2 (III), N2 and P3 (IV) and a moderate change in P1a (I), P4 (V), and N4; to contralateral stimulation, there was a moderate attenuation of P2 (III), P3 (IV), and P4 (V). To ipsilateral stimulation components beginning with P1b were delayed to ipsilateral stimulation whereas to contralateral stimulation the delays were less striking.

Table IV shows the extent of neural loss in the cochlear nucleus after unilateral injection of kainic acid in the 5 cats that were studied chronically from 28 to 41 days after injection. The relation between the locus and extent of the cell loss in cochlear nucleus and the extent of the change in the ABR was evaluated statistically by correlating the two measures. It was not possible to examine the relation between the extent of

TABLE IV

Neuronal loss (in %) following kainic acid injection into cochlear nucleus.

Cat	AVCN			PVCN	DCN
	AA	PA	Total		
21	41	78	60	100	100
24	12	49	31	74	24
25	40	98	69	na	na
28	92	90	91	74	79
30	51	93	79	57	35

AVCN = anteroventral cochlear nucleus; AA = anterior anterior subdivision; PA = posterior anterior subdivision; PVCN = posteroventral cochlear nucleus; DCN = dorsal cochlear nucleus; na = data not available.

the lesion and the attenuation of P2 (III) since in 3 of the 5 animals this wave was lost. The extent of loss of neurons in the posterior anterior subdivision of the AVCN (PA of the AVCN) was linearly correlated with the attenuation of waves P4 (V) and N4 evoked by stimulating the ear ipsilateral to the injection. The extent of neuronal loss in PVCN had a linear correlation with the extent of attenuation of P3 (IV) to ipsilateral stimulation and P4 (V) and N4 to contralateral stimulation. There was no linear correlation between the extent of neuronal loss in the anterior division of the AVCN (AVCNa) and the extent of attenuation of any of the waves of the ABR generated to either ipsilateral or contralateral stimulation.

Discussion

Following kainic acid induced destruction of neurons in the cochlear nucleus, waves P2 (III), N2 and P3 (IV) of the ABR evoked from stimulating the ear ipsilateral to the site of injection were either abolished or markedly attenuated, while the later components P4 (V) and P5 (VI) were only moderately attenuated and shifted in latency. This result supports Buchwald and Huang's (1975) conclusion that wave P2 (III) depends upon the integrity of the cochlear nucleus. These authors surgically transected the brain-stem in a sequential manner and when nerve VIII and cochlear nucleus remained only waves P1 and P2 persisted. Separation of the cochlear nucleus from nerve VIII resulted in the loss of P2. In our study, P3 (IV) could also be lost following the destruction of the neurons of the cochlear nucleus indicating that both P2 (III) and P3 (IV) are dependent upon the integrity of the neurons of the cochlear nucleus. Component P3 (IV) is lost following transection of the midline trapezoid body where the axons of cochlear nucleus neurons course (Buchwald and Huang 1975; Wada and Starr 1983a) or markedly attenuated (Zaaroor and Starr 1991) following the destruction of the neurons of the SOC bilaterally, the terminal site of many of the cochlear nucleus neurons. Thus, the role of the cochlear nucleus neurons and their axons in the generation of P3 (IV) is most likely secondary, via activation of other neuronal systems distant from the cochlear nucleus itself. The anatomical bases for the generation of wave P3 (IV) would therefore seem to include the neurons of the cochlear nucleus, their axons in the trapezoid body and the SOC neurons upon which they terminate. The concept that the generators of the ABR waves are either neurons or fiber tracts may be too limiting. The conclusion to be drawn from the studies noted above is that the generation of an ABR component requires the integrity of a group of neural elements comprising a set of neurons, their axons, and the neurons upon which the latter terminate.

The relative preservation of the later waves, P4 (V) and P5 (VI), even when several of the preceding components, P2, N2 and P3, were lost indicates that the appearance of wave P4 through P5 must be relatively independent of the integrity of the cell bodies of the cochlear nucleus. Even near total destruction (up to 75%) of the cells in cochlear nucleus was accompanied by only a modest attenuation of these components. The components of the ABR are obviously not sequentially dependent upon one another, a conclusion apparent from studies both in man (Stockard and Rossiter 1977) and experimental animals (Wada and Starr 1983b) in which the loss of early components of the ABR was not necessarily accompanied by the loss of later components. The retention of waves P4 and P5 in spite of the loss of earlier components indicates that the generators of P4 (V) and P5 (VI) can become almost completely active with only a fraction of the output of the cochlear nucleus. Moreover, when we examined the middle- and long-latency cerebral components (up to 256 msec in latency) in these cats, we found them to be only slightly attenuated even though portions of the ABR were absent. This finding is similar to the preservation of the N19 cerebral component of the somatosensory evoked potential recorded from the cerebral hemisphere in the presence of a neuropathy, severe enough to prevent the detection of a whole nerve action potential (Desmedt and Noël 1973).

Wave P1a (I) was significantly attenuated and wave P1b (II) was significantly delayed following the injection of kainic acid into the cochlear nucleus. These results are puzzling since both of these components are generated by nerve VIII (Sohmer and Feinmesser 1967; Starr and Zaaroor 1990). It is unlikely that kainic acid either spreads passively or was transported retrogradely along the axons of nerve VIII to the cochlea to damage the ganglion cells or the axons of nerve VIII. Rather, the responsiveness of the ganglion cells of nerve VIII in the cochlea may have been altered by a process similar to diaschisis (Von Monakow 1914) since the neurons of the cochlear nucleus upon which the nerve VIII axons terminate were destroyed. We have previously invoked a process akin to diaschisis to account for the attenuation of P2 (III), generated by the neurons of the cochlear nucleus, when their terminal cells in the SOC were destroyed (Zaaroor and Starr 1991).

The attenuation of components P2 (III), P3 (IV), and P4 (V) from stimulating the ear contralateral to the injection has several possible explanations. First, there are neurons in cochlear nucleus that are activated by both ipsilateral and contralateral stimuli (Mast 1970, 1973; Young and Brownell 1976). The anatomical basis of this contralateral effect may be by pathways

between the two cochlear nuclei (Adams and Warr 1976; Adams 1979; Cant and Gaston 1982) or by connections through intermediary brain-stem nuclei such as the SOC (Rasmussen 1960; Elveland 1977). Thus, the loss of neurons in one cochlear nucleus could alter the excitability of neurons in the contralateral cochlear nucleus and account for the changes in the ABR beginning with P2 (III). A second possibility is that SOC responsiveness is changed following neuronal destruction of one of the cochlear nuclei and accounts for the ABR changes to stimulation of the ear contralateral to the injection site. A third possibility is that kainic acid spreads either passively or by axonal transport through the brain-stem to damage the SOC ipsilateral to the side of injection. Histological examination of the SOC complex did not reveal neural loss. Moreover the finding that P4 (V) latency was prolonged to contralateral stimulation rather than being shortened or unaffected as when kainic acid had been directly injected into the SOC (Zaaroor and Starr 1991) would argue against this possibility.

Generators of the ABR

Table V summarizes the localization of the generators of the ABR waves as derived from the two current studies using kainic acid to destroy auditory brain-stem neurons (cochlear nucleus, this paper; superior olivary complex, Zaaroor and Starr 1991) and a number of other studies using both electrolytic lesions and recording methods. We have separated the structures participating in the generation of the various ABR components as either being 'essential' or 'contributory.' 'Essential' indicates that a structure is a principle generator for the component. 'Contributory' indicates that a structure's role is to maintain the normal functioning of the 'essential' generator. When the inputs to structures that are either 'essential' or 'contributory' play an unexpected role on the generation of the ABR components complex, they will be discussed. Nerve VIII is 'essential' for the generation of the earliest components, waves I (P1a) and II (P1b): the initial component (I) is associated with activity distally in the cochlea (Sohmer and Feinmesser 1967; Martin et al. 1987; Starr and Zaaroor, 1990) and the latter component (II) with nerve VIII activity proximally in the cochlear nucleus (Legatt et al. 1986; Starr and Zaaroor 1990). The cochlear nucleus ipsilateral to the tested ear is a 'contributory' structure for waves I and II since following the loss of neurons in that nucleus, wave I is attenuated and wave II is delayed in latency. The cochlear nucleus is 'essential' for the generation of wave III, labeled P2 in Buchwald and Huang's study (1975), without evidence from the present study that any one of the subdivisions plays the major role in its generation. The trapezoid body, the tract containing the axons of the cochlear nucleus, the SOC neurons upon which the cochlear nucleus neurons terminate, and the contralateral cochlear nucleus are all contributory structures for wave III since this component is attenuated following section of the trapezoid body in the midline (Wada and Starr 1983a), neuronal destruction of the SOC (Zaaroor and Starr 1991), or neuronal destruction of the contralateral cochlear nucleus (this study). Both waves IV (P3) and V (P4) are generated,

TABLE V

Generators of monaurally evoked ABR components.

Wave			
P1a	I	Essential –	ipsilateral nerve VIII within cochlea
		Contributory –	ipsilateral cochlear nucleus
P1b	II	Essential –	ipsilateral nerve VIII in cochlear nucleus
		Contributory –	ipsilateral cochlear nucleus
P2	III	Essential –	ipsilateral cochlear nucleus neurons
		Contributory –	trapezoid body superior olives contralateral cochlear nucleus
P3	IV	Essential –	bilateral superior olivary nucleus neurons particularly LSO and MNTB. Small portion (20%) persists after total bilateral loss of SOC neurons
		Contributory –	contralateral cochlear nucleus
P4	V	Essential –	bilateral superior olivary nucleus neurons particularly LSO and MNTB. Small portion (20%) persists after total bilateral loss of SOC neurons.
		Contributory –	contralateral cochlear nucleus
P5	VI	Essential –	bilateral inferior colliculi
		Contributory –	undefined
SPS	SPS	Essential –	bilateral superior olivary nuclei
		Contributory –	undefined

primarily by neurons in the MNTB and LSO divisions of both SOCs (Zaaroor and Starr 1991). A portion (approximately 20%) of both waves IV (P3) and V (P4) persists even after total destruction of the neurons of the SOC indicating that other neural systems must also be essential for these components. Since the input to the SOC is from cochlear nucleus, lesions of either this latter structure or the trapezoid body, which contains the axons of the cochlear nucleus neurons, would be expected to affect these components (Buchwald and Huang 1975; Wada and Starr 1983a). However, with midline lesions of the trapezoid body, P3 (IV) is lost whereas P4 (V) can persist relatively unchanged (Wada and Starr 1983a). Moreover, even after extensive neuronal loss of the cochlear nucleus the amplitudes of waves P3 (IV) and P4 (V) diminish to a only a modest degree. These findings indicate that the generators of components beginning with P3 (IV) can maintain their amplitude relatively independent of alterations to their input systems. The brain-stem auditory pathway does not behave as a linear system with regard to the amplitude of sequential ABR components. The cochlear nucleus contralateral to the test ear has a contributory role on the SOC's ability to generate waves P3 and P4 (IV and V). Buchwald and Huang (1975) demonstrated that the inferior colliculi are essential for the generation of P5 (VI). The sustained potential shift (SPS) from which these waves arise requires the integrity of the neurons of the SOC and, in particular, the LSO and MNTB subdivisions but is not affected by a loss of neurons of the CN.

Clinical relevance

The application of many of these conclusions to extending the diagnostic utility of the ABR in the clinic is complicated. In the clinical setting the definition of abnormalities of the ABR utilizes changes in the latencies of the components. Absolute amplitude measures are not employed in man because the number of trials usually averaged does not suffice to adequately decrease the variability contributed by background or random electrical potentials. This constraint does not apply to amplitude measures of the ABR in cat because, in this species, amplitudes are approximately 10-fold greater than in man and the variability introduced by background electrical activity can usually be satisfactorily reduced by averaging 1000 trials. The extent of the attenuations of ABR amplitude defined in our experiments in cat with neuronal loss in the CN and SOC could not have been identified as significantly abnormal in man using current averaging methods. In contrast, changes in latency of the ABR are used in man to define abnormalities. In general, latency delays are associated with brain-stem lesions ipsilateral to the ear being stimulated. In our experimental studies in cat, lesions in the region of the SOC affected latency variously from no effect, to an increase, or even a decrease (Zaaroor and Starr 1991). In man, the reliance on measures of latency rather than on amplitude of the ABR for defining an abnormality and then for localizing the site of brain-stem lesion is limiting and may contribute to discrepancies between the localization of generator sites of the ABR based on clinical material and those based on experimental studies in animals.

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