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A Behavioral Study on Electrical Stimulation of the Cochlea and Central Auditory Pathways of the Cat

GRAEME M. CLARK, J. M. NATHAR, HOWARD G. KRANZ, AND JOHANNES S. MARITZ [1]

Child Deafness Research Laboratory, Department of Otolaryngology, University of Melbourne, Melbourne 3052, Australia

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This behavioral study on cats has shown stimulus generalization for acoustic to electrical stimulation of the cochlea at frequenies from 100 to 8,000 pulse/sec. Response thresholds were determined for electrical stimulation of the apical and basal turns of the cochlea. The results show a linear increase in response threshold with rate of electrical stimulation up to a frequency of 2,000 pulse/sec. The response threshold was also lower for electrical stimulation of the basal rather than the apical electrode. Difference limen measurements for electrical stimulation of the cochlea were similar to those obtained for acoustic stimuli at 100 and 200 Hz, but were greater at higher rates of stimulation. The difference limen was also lower for electrical stimulation of the apical rather than the basal electrode. The results of this study show that electrical stimulation of the cochlea may produce a pitch sensation for rates of stimulation up to 200 pulse/sec. The results also emphasize the importance of the volley theory in the coding of low frequencies.

Introduction

This present study was undertaken to determine whether the cat can perceive a pitch sensation when the cochlea and auditory pathways are stimulated electrically. It was also designed to evaluate the relative importance of the volley and place theories in the coding of frequency, as their respective roles in pitch perception are still not clear. It was expected that the results obtained would help determine the feasibility of reproducing hearing artificially by electrical stimulation of the inner ear in man.

In the present study the ability of the cat to perceive a pitch sensation was evaluated by assessing the generalization from an acoustic to an

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electrical stimulus, thereby determining the response thresholds for different rates of electrical stimulation of the cochlea and auditory pathway, and measuring the difference limens for electrical stimulation of apical and basal cochlear electrodes. An attempt has also been made to determine the relative importance of the volley and place theories in the coding of frequency by comparing the difference limens obtained by electrical stimulation of apical and basal cochlear electrodes.

Methods

This study was performed on 21 cats. In five the results of surgery, the electrode system, and behavioral responses were satisfactory for prolonged conditioning studies. Two of these cats had electrodes in the cochlea, one had electrodes in the cochlea, lateral lemniscus, and auditory cortex, and two had electrodes in the lateral lemniscus and auditory cortex. Surgical procedures were carried out under pentobarbital sodium anesthesia (40 mg/kg, ip initially, followed by supplementary intravenous injections).

The cochlea was exposed by a ventral approach similar to the one described by Clark and Dunlop (3) for the superior olivary complex. The tympanic bulla was opened widely and the septum between the bulla and middle ear drilled away. This exposed the turns of the cochlea, the middle ear and round window, and was adequate for inserting electrodes into the modiolus and the turns of the cochlea.

Electrodes were inserted stereotactically into the lateral lemniscus using the co-ordinates of Horsley and Clarke (8) with the animal in a Trent–Wells apparatus. They were introduced into the auditory cortex under vision, after the superior temporal sulcus had been identified. An insulated ball electrode was placed on the round window to determine whether the cochlear microphonic potentials were abolished by the inner ear electrode implantations. This was found to be the case in all animals in this series.

In the cochlea a bipolar electrode was placed in the basal and another in the apical turn. These electrodes were made of 150-μ enameled stainless-steel wire (Nilstain) and were twisted for mechanical strength. The basal electrode was placed close to that region of the spiral organ (Corti) which is excited maximally by a frequency of 8 kHz and the apical electrode near the region excited by a frequency of 0.5 kHz. These locations were determined from reconstructions of the cochleas of cats as described by Schuknecht (6).

The animals were conditioned by avoidance methods using delayed conditioning techniques. The training program was usually carried out in three phases. First, the animal was conditioned to pure tones, and when the graph for correct responses reached an asymptote above the 90% level, the sound was replaced by an electrical stimulus of the same frequency, and the responses to these two types of stimuli compared. Second, the detection thresholds for different rates and types of electrical stimuli were also determined for all implanted electrodes. Third, these conditioning techniques were used to determine the difference limens for selected high and low frequency sounds. Difference limens were also measured for electrical stimulation of the various electrodes at rates of 100, 200, and 400 pulse/sec. The difference limens were determined by recording the smallest change in rate that could produce a statistically significant difference between test and spontaneous responses.

The conditioning sequence and the mode of presentation of the conditioned and unconditioned stimuli were controlled by a specially designed biological stimulating and conditioning unit (9). The electrical and acoustic stimuli were generated by a 3310A Hewlett–Packard function generator, and the signal was fed to a Rola 4 loudspeaker for sound stimulation. A Skinner type of conditioning box was used, and threshold current measurements were determined by recording the voltage across a 1.0 k ohm resistance in series with the stimulating electrode.

At the completion of the conditioning trials, the animal was anesthetized and perfused intra-arterially with normal saline solution followed by 10% formalin. The temporal bones were decalcified and both the bones and brain were embedded in low-viscosity nitrocellulose and serially sectioned. The temporal bone was stained with hematoxylin and eosin, and the brain with cresyl violet so that electrode placements and histological changes could be studied.

Results

Initially the cats were conditioned to pure tones, and their learning curves plotted. When learning was complete the tone was replaced by an electrical stimulus applied through one of the implanted electrode pairs. In all but one cat there was a rapid generalization of the conditioned response from the acoustic to the electrical stimulus. This response generalization occurred at all frequencies tested from 0.5 to 8 kHz, and the results for cat 7 can be seen in Fig. 1.

The response thresholds obtained by electrically stimulating the apical and basal cochlear electrodes at rates 100 to 5000 pulse/sec were recorded. This was done to help determine the relative importance of the place and volley theories in pitch perception, and whether electrical stimulation of the terminal auditory fibers could produce a pitch sensation. The results for cat 21 are shown in Fig. 2. These indicate that the thresholds for cochlear stimulation were lower in the basal electrode for all frequencies less than 2000 pulse/sec with the exception of those at 100 pulse/sec. Above this

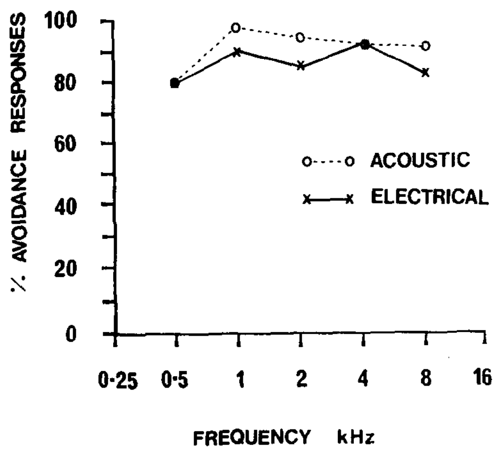

FIG. 1. Avoidance responses for acoustic and electrical stimulation of the cochlea in cat 7.

frequency the thresholds were the same. The threshold for stimulating the basal electrode at 200 pulse/sec was lower than for all other frequencies tested, and was less than when stimulating the apical electrode. The explanation for this is not immeditely obvious as the apical area of the

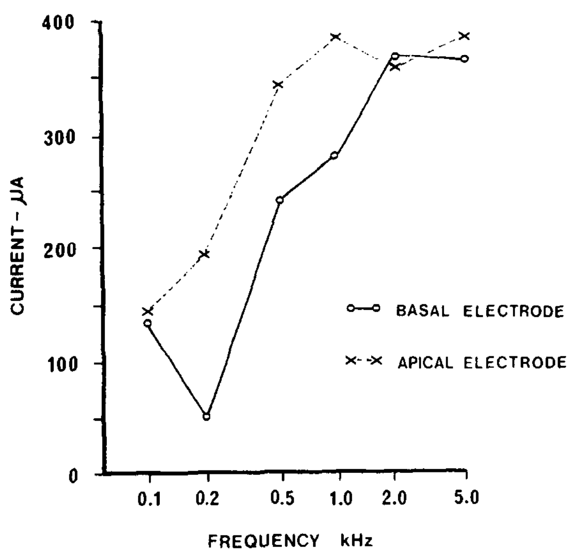

FIG. 2. Behavioral response thresholds for electrical stimulation of apical and basal cochlear electrodes in cat 21.

cochlea is thought to be stimulated selectively by low-frequency sound, and it was expected that the same would also apply to electrical stimulation of this area in a previously conditioned animal. This will be discussed further below. The graph also shows that the threshold for electrical stimulation is lower for low rates of stimulation in both electrodes up to a frequency of 1000–2000 pulse/sec.

Response thresholds were also recorded for electrical stimulation of the cochlea, lateral lemniscus, and auditory cortex at rates of 100 and 500 pulse/sec with pulse durations of 0.1 and 1 msec. The electrodes were in the apical and basal turns of the cochlea, the ventrolateral and dorsomedial portions of the ventral nucleus of the lateral lemniscus, and the anterior and posterior areas of the auditory cortex. The response thresholds shown in Table 1 are the averages for those obtained from the auditory cortex in two, the lateral lemniscus in two, and the cochlea in one cat.

The results again show a lower threshold for electrical stimulation of the basal rather than the apical cochlear electrode. There was no difference between the thresholds for stimulation of the two electrodes in the lateral lemniscus. In the auditory cortex there were lower thresholds for low rates of stimulation of the posterior rather than the anterior electrode.

In addition the thresholds in the auditory cortex were higher than those in the lateral lemniscus and the cochlea. It was also noted that the thresholds for pulses of 1 msec duration were in general higher than those with a 0.1 msec pulse width.

Difference limens obtained by electrically stimulating the apical and basal cochlear electrodes in cat 21 at rates of 100, 200, and 400 pulse/sec were recorded. This was also done to help determine the relative importance of the place and volley theories in pitch perception, and whether electrical stimulation of the terminal auditory fibers could produce a pitch sensation.

Initially difference limens for sound were measured, and the generaliza-

TABLE 1

THRESHOLD CURRENTS FOR ELECTRICAL STIMULATION OF THE COCHLEA, LATERAL LEMNISCUS AND AUDITORY CORTEX

Stimulus		Cochlea		Lateral lemniscus		Auditory cortex	
(pulse/sec)	(μ/sec)	Apical (μa)	Basal (μa)	Ventro lat (μa)	Dorso med (μa)	Ant (μa)	Post (μa)
100	0.1	250	180	260	255	340	280
100	1.0	300	200	278	255	380	300
500	0.1	250	210	260	255	340	380
500	1.0	350	280	235	260	440	440

tion to an electrical stimulus assessed. It was found this generalization was rapid for rates of electrical stimulation less than 400 pulse/sec. Data for difference limen measurements were obtained from five test sessions, and at each session the responses to 10 test stimuli were recorded. After the presentation of the 10 test stimuli the procedure was repeated without the stimuli to determine the effects of spontaneous responding. The results for electrical stimulation of the apical and basal electrodes in cat 21 are shown in Table 2.

An analysis of variance was performed on these data to compare the responses obtained from 100% and 50% changes in rate of stimulation, the apical and basal electrodes, the test and spontaneous presentations, and interactions between them.

The results of the analyses of variance can be seen in Table 3. At 100 pulse/sec the main effect C (test vs. spontaneous) and the interaction AC (100% vs. 50%; test vs. spontaneous) are significant at the 5% probability level. The results for the main effect C indicate that the means for test (6.45) and spontaneous (4.80) responses are significantly different. An alternative way of presenting this result is by working directly with the individual T–S differences. An analysis of variance based on these differences should yield a significant main effect A, which would correspond to the significant interaction AC in the first analysis. The results of the analyses for the 100, 200, and 400 pulse/sec series are shown in Table 4. Reference to the 100 pulse/sec values indicates that the main effect A is significant, and this confirms the previous results shown in Table 3.

A very interesting feature of the results in Table 4 is the residual mean square. Since the differences of original observations were taken for this analysis, the residual mean square (RMS) should have been about twice the RMS reported in Table 3. Instead the RMS (differences) was less than RMS (original observations). This phenomenon also appears in the 200- and 400-pulse/sec series. It suggests there was some correlation between the test and spontaneous results in a given pair. Possible explanations for this phenomenon will be discussed below.

The analysis of variance indicated a difference between test and spontaneous responses for the 100 pulse/sec series, but did not show whether the differences were significant for the 100% and 50% changes in rate of stimulation. For this reason Student's t-test was also required to compare the differences, and the results are shown in Table 5. These indicate that the mean T–S is significantly different from zero at A = 100%, but not at A = 50%.

The results of the analysis of variance on the 200 pulse/sec series (Table 3) show that the main effect B (apical vs. basal) was significant as well as that for the main effect C (test vs. spontaneous). The results for the main effect B indicate that the means for the apical (4.60) and

TABLE 2

BEHAVIORAL RESPONSES FROM ELECTRICAL STIMULATION OF APICAL AND BASAL COCHLEAR ELECTRODES[a]

	100 Hz											
	$\Delta f/f = 1.0$						$\Delta f/f = 0.5$					
	Apical			Basal			Apical			Basal		
	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.
Mean	7.4	3.8	3.6	7.2	4.0	3.2	5.2	4.4	0.8	6.0	7.0	−1.0
	200 Hz											
	$\Delta f/f = 1.0$						$\Delta f/f = 0.5$					
	Apical			Basal			Apical			Basal		
	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.
Mean	6.2	3.8	2.4	7.0	4.6	2.4	5.4	3.0	2.4	5.8	6.0	−0.2
	400 Hz											
	$\Delta f/f = 1.0$						$\Delta f/f = 0.5$					
	Apical			Basal			Apical			Basal		
	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.	Test	Spont.	Diff.
Mean	4.4	5.0	−0.6	5.6	4.4	1.2	4.0	4.2	−0.2	4.6	5.8	−1.2

[a] Mean: Average of five trials. Test: Test responses. Spont: Spontaneous responses. Diff: Test—spont.

basal (5.85) electrodes are significantly different. For the main effect C the means for test (6.10) and spontaneous (4.35) responses were also different. The analyses of variance on the T–S data (Table 4) show that the effects A, B, and AB are significant despite the fact that the interactions AC, BC, and ABC are not significant in Table 3.

A t test was also performed on the data from the 200 pulse/sec series (Table 5). This shows that the mean T–S is significantly different from zero for the apical and basal electrodes at the 100% change in rate of stimulus, but only for the apical electrode at the 50% change in rate.

The results of the analyses of variance for the 400 pulse/sec series show no significant effects for the data in Tables 3 and 4. It is worth observing, however, that the reduction in the RMS has had the effect of making the interaction AB nearly significant at the 5% level.

Discussion

In the present study we have shown that there is a rapid generalization of responses from sound to electrical stimulation of the auditory cortex, lateral lemniscus, and terminal auditory nerve fibers as indicated in Fig. 1. This suggests that electrical stimulation of the auditory pathways may

TABLE 3

ANALYSES OF VARIANCE ON TEST AND SPONTANEOUS DATA

		Frequencies (pulse/sec)					
		100		200		400	
Source of variation	df	SSD	F	SSD	F	SSD	F
Blocks	4	23.500	1.88	12.350	1.65	3.500	<1
A	1	0.025	<1	1.225	1	0.400	<1
B	1	7.225	2.32	15.625	8.34*	4.900	1.24
AB	1	7.225	2.32	2.025	1.08	1.600	<1
C	1	27.225	8.75*	30.625	16.35*	0.400	<1
AC	1	30.625	9.82*	4.225	2.26	2.500	<1
BC	1	3.025	<1	4.225	2.26	0.400	<1
ABC	1	1.225	<1	4.225	2.26	4.900	1.24
Residual	28	87.300		52.450		110.900	
Total	39	187.375		126.975		129.500	
Residual mean square		3.118		1.873		3.961	

[a] *Notes*: (*i*) Residual mean square = Residual SSD/Residual df.
(*ii*) $F_{1,28}$ (.95) = 4.20; thus, observed $F_{1,28}$ values greater than 4.20 indicate significant effects at the 5% level. Asterisk = P 0.05.
(*iii*) Factor A, 100% vs 50%; B, Apical vs basal; C, Test vs spontaneous.
(*iv*) df = degrees of freedom; SSD = sum of squared differences; F = F value; Blocks = days.

TABLE 4

ANALYSES OF VARIANCE ON TEST MINUS SPONTANEOUS DATA [a]

		Frequencies (pulse/sec)					
		100		200		400	
Source of variation	df	SSD	*F*	SSD	*F*	SSD	*F*
Blocks	4	21.800		8.500	1.83	2.450	
A	1	61.250	31.96*	8.450	7.30*	5.000	2.39
B	1	6.050	3.16	8.450	7.30*	0.800	<1
AB	1	2.450	1.28	8.450	7.30*	9.800	4.68
Residual	12	23.000		13.900		25.150	
Total	19	114.550		47.750		41.200	
Residual mean square		1.917		1.158		2.096	

[a] *Notes*: (*i*) See Table 3.
(*ii*) $F_{1,12}$ (.95) = 4.75; thus observed $F_{1,12}$ values greater than 4.75 indicate significant effects at the 5% level. Asterisk = $P < 0.05$.
(*iii*) See Table 3.
(*iv*) See Table 3.

produce a pitch sensation. To provide more evidence for this, however, two further series of experiments have been carried out.

In the first series of experiments the animals were conditioned to sound, and their response thresholds to electrical stimulation at different rates determined. It was considered that if there was an adequate pitch

TABLE 5

STUDENT'S *t* TEST [a]

Frequency (pulse/sec)		100%		50%	
		Apical	Basal	Apical	Basal
100	Mean (T-S)	3.6	3.2	0.8	−1.0
	t_{12}	5.81*	5.17*	1.29	−1.62
200	Mean (T-S)	2.4	2.4	2.4	−0.2
	t_{12}	4.99*	4.99*	4.99*	−0.42
400	Mean (T-S)	−0.6	1.2	−0.2	−1.2
	t_{12}	−0.93	1.85	−0.31	−1.85

[a] *Notes*: (*i*) t_{12} (.975) = 2.18; thus, for an observed t_{12} value to indicate significance at the 5% level its absolute value must exceed 2.18. This is the critical value for a two-tailed test. Asterisk = $P < 0.05$.
(*ii*) t_{12} (.95) = 1.78; this is the critical absolute value for a two-tailed test at the 10% level or a one-tailed test at the 5% level.
(*iii*) In every case t_{12} is computed as follows:
t_{12} = mean (T–S)/—(Residual mean square (T–S)/5

sensation produced by an electrical stimulus, stimulation of the apical cochlear electrode at a low rate would result in a lower response threshold than stimulation at a higher rate if the volley theory were important in the coding of low frequency. On the other hand, if the place theory were of importance, there would be little difference in response thresholds for variation in rate of stimulation. The same conclusions also apply to the coding of high frequency sound.

The results of stimulating the apical and basal cochlear electrodes at different rates can be seen in Table 1 and Fig. 2. In Table 1 the electrical stimuli were square-wave pulses of 0.1 and 1 msec duration, whereas in Fig. 2 the results were obtained with square-wave trains and therefore are not completely comparable as the current flow over time would be different.

The results in Fig. 2 show that for both apical and basal electrodes the threshold increases with rate of stimulation up to 2000 pulse/sec, at which point the threshold remains constant for higher rates of stimulation. Although an increase in threshold with rate of stimulation suggests that the volley theory is of importance in coding low frequencies, it is surprising to find the threshold lower in the basal electrode, as it is in a region of the cochlea normally responding best to high-frequency sound.

This indicates that the animal's responses may not have been due to the perception of pitch, but the generation of a nonspecific acoustic sensation created by the electrical stimulus. Results obtained by electrical stimulation of the basal end of patients' cochleas (5) and psychoacoustic studies on periodicity pitch (4), however, do show that low pitches may be perceived by stimulating the basal end of the cochlea at the appropriate rate. For this reason it is still feasible that pitch was perceived at low rates of electrical stimulation of the basal electrode by the animals in this study.

In this regard it is of particular interest that the threshold for electrical stimulation at 200 pulse/sec appeared to be the lowest obtained, and as this was close to the frequency of the sound used in the initial conditioning it is feasible that this influenced the threshold obtained with electrical stimulation. This hypothesis needs further testing, and this is being undertaken at the moment.

As the thresholds for electrical stimulation of the cochlea vary with rate and site of stimulation it is of value to compare the results with those obtained for the higher auditory centers where the neural complexity is greater, and tonotopic organization is not so precise. In the ventral nucleus of the lateral lemniscus the ventrolateral electrode was probably in a region considered to respond selectively to high frequencies, and the dorsomedial electrode in a region for low frequencies (1). Similarly the anterior cortical electrode was in a region of A1 responding to high frequencies, and the posterior electrode one responding to low frequencies (10).

The results of this comparison can be seen in Table 1. As shown there was no difference in the thresholds for different rates of electrical stimulation of the ventrolateral and dorsomedial portions of the nucleus of the lateral lemniscus. On the other hand, differences were obtained from the auditory cortex. The thresholds were greater for 500 pulse/sec rather than 100 pulse/sec and they were lower in the posterior portion of the auditory cortex for the low rates of stimulation.

As the posterior portion of the A1 area of the auditory cortex is known to respond to low frequencies the results are at variance with those obtained from the cochlea, where the threshold was lower for stimulation of the basal or high frequency portion. This difference could have been due to a greater neural density in the posterior area of the auditory cortex, or the fact that this area responded to stimulation in accordance with the volley theory and a pitch sensation was perceived.

As discussed above, it is difficult to be sure that an electrical stimulus is perceived as a pure tone, as stimulus generalization may be due to nonspecific aspects of the electrical stimulus. For this reason it was considered desirable to assess the effects of electrical stimulation by an experiment which did not involve stimulus generalization. As a result, difference limens were measured for electrical stimulation of apical and basal cochlear electrodes. It was considered that a comparison of these results with those obtained for an acoustic stimulus would help indicate the extent to which a pitch was perceived. If the difference limens for electrical stimulation of the cochlear electrodes were similar to those obtained for acoustic stimulation it would be presumptive evidence, for example, that many aspects of the pitch of a low tone were being detected.

The results of the analyses of variance (Tables 3 and 4) and *t* tests (Table 5) show that an electrical stimulus of 100 pulse/sec resulted in a difference limen of 100% for the apical and basal electrodes. A stimulus of 200 pulse/sec. gave a difference limen of 100% for the apical and basal and 50% for the apical electrode, and a stimulus of 400 pulse/sec a difference limen greater than 100% for both electrodes.

These difference limens are greater than those obtained by Shower and Biddulph (7) for acoustic stimulation in cats at 100, 200, and 400 Hz. For this reason it seems unlikely that the quality of the pitch perceived is similar for acoustic and electrical stimulation except at frequencies below 200 Hz. This is also consistent with the results of cell studies (2) where it was shown that cells in the superior olive would not follow electrical stimulation of the auditory nerve at rates greater than 200 pulse/sec.

It is also of interest to notice in Table 5 that the difference limens were significantly different for electrical stimulation of the apical and basal cochlear electrodes at rates of 200 pulse/sec. As the apical electrode was more sensitive to rates of stimulation of 200 pulse/sec, this is evidence in favour of the volley theory for low-frequency discrimination. These results also suggest that the lower response threshold for electrical stimulation of the basal rather than the apical electrode (Table 1) was not related to pitch preception alone.

The results in Table 4 are also of interest from a further point of view as they show that there is a positive correlation between the test (T) and spontaneous (S) responses for each pair of 10 stimulus presentations. This correlation is strictly between the random residuals corresponding with these results.

This positive correlation may have been due to variations in the animal's response probabilities, and fluctuations in attention would be one possible explanation. Alternatively, it is possible that a sequence of positive responses to the test stimulus could have increased the probability of response in the spontaneous group.

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