

XV. COMMUNICATIONS BIOPHYSICS*

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A. EVIDENCE FOR LOCALIZED RESPONSES TO ELECTRICAL STIMULATION IN THE COCHLEA

Woolsey and Walzl,¹ and Tunturi²⁻⁴ have demonstrated that responses can be evoked in the auditory cortex of cats and dogs by electrical stimulation of the cochlea. Since shocks to different regions of the spiral lamina mapped onto different regions of the cortex, their work also indicated that the electric stimuli acted on somewhat localized portions of the eighth-nerve endings. The cochlea was damaged considerably in order to place the stimulating electrodes near the nerve endings, hence it was not possible with this technique to study responses to acoustic and electrical stimulation of the same cochlea. Kiang and Peake⁵ demonstrated interaction of electric and acoustic stimuli in the cat, but their electrical stimulation was applied at the internal auditory meatus and there was no attempt to stimulate selectively different portions of the eighth nerve. In the work reported on here electric stimuli were delivered through fine wire electrodes placed in the cochleas of guinea pigs. The interaction of cortical responses to these intracochlear shocks and to acoustic stimuli was studied for different placements of the stimulating electrodes to determine whether or not the shocks were stimulating "locally" in the cochlea.

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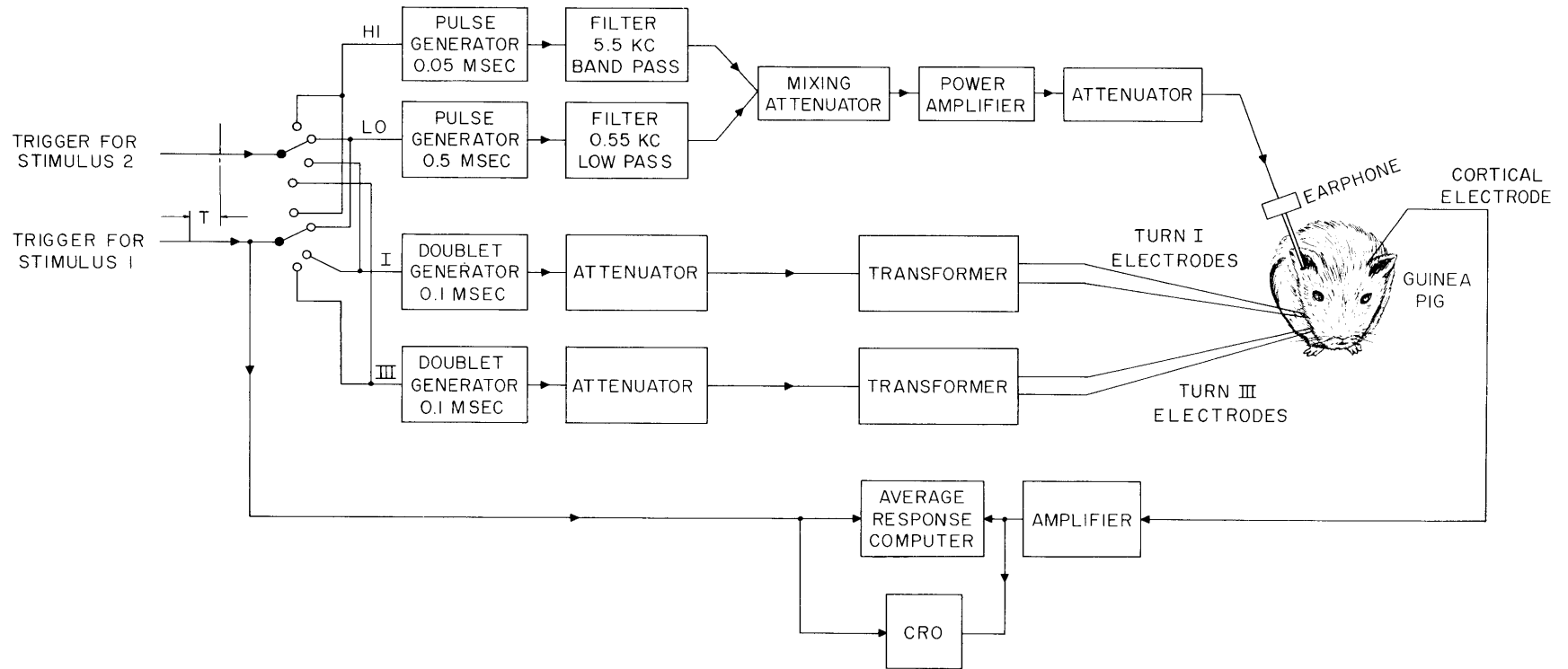


Fig. XV-1. Schematic diagram of stimulating and recording equipment. The two trigger pulses indicated on the left were repeated at a rate of 1/sec. The time delay T between the first and second pulses was variable. Each pulse triggered one of four possible stimuli. The two channels at the top, labeled HI and LO, represent the acoustic stimuli; one pulse was passed through a bandpass filter centered at 5.5 kc, and the other pulse was passed through a 550-cps lowpass filter. The electric stimuli were applied through isolation transformers to pairs of electrodes in turn I or turn III of the cochlea.

1. Methods

Young guinea pigs (200-350 grams) were anesthetized with Dial (50 mg/kg) or Nembutal (30 mg/kg) administered intraperitoneally. A small hole was drilled through the skull over the auditory area of the cortex.⁶ A wire electrode was inserted into the hole to make contact with the surface of the dura; the wire was cemented to the skull. Cortical responses were recorded between this wire and a reference electrode placed on the scalp wound. The bulla was then opened and holes were drilled in the cochlea with the aim of placing electrodes in scala tympani and scala vestibuli of turn I and/or turn III. The cochlear electrodes and their arrangement were identical with the technique that has been used extensively for recording cochlear responses.⁷ The cochlear microphonic and auditory nerve responses obtained from the intracochlear electrodes were observed in order to determine thresholds for acoustic stimuli; the polarity of the cochlear microphonic (CM) potentials was observed to determine whether the electrodes were in the proper scalae.⁷ The intracochlear electrodes were then connected for electrical stimulation, as shown schematically in Fig. XV-1. The electric stimuli were doublets made up of two adjacent 0.1-msec pulses of opposite polarity.⁸ The resulting current and voltage waveforms at the electrode terminals are shown in Fig. XV-2.

The arrangement for producing the acoustic stimuli is also indicated in Fig. XV-1. Two impulsive stimulus waveforms that had different spectral compositions were

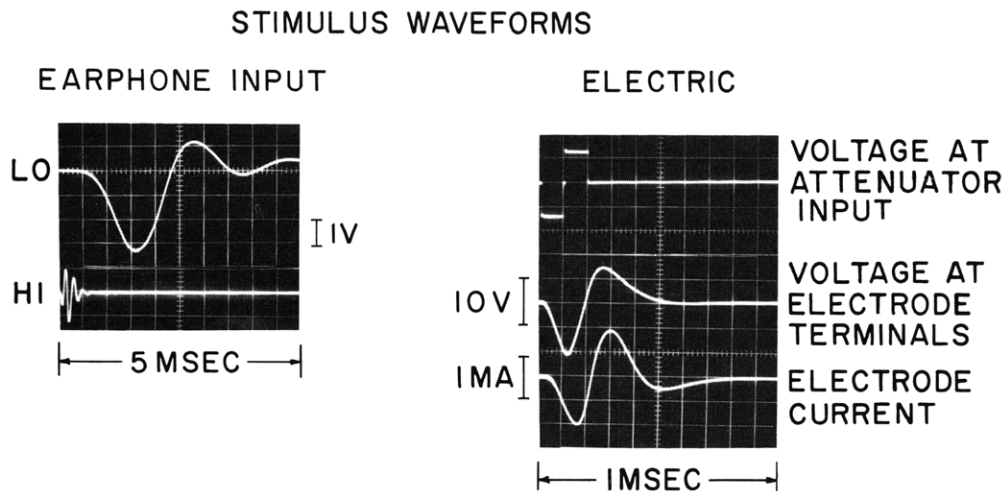


Fig. XV-2. Stimulus waveforms at 0 db. The waveforms on the left represent the input voltage to the earphone for the two acoustic stimulus configurations. The waveforms on the right represent waveforms associated with the electric stimulus. There is some variability in the amplitudes of the voltage and current at the electrodes for different electrodes, so that the amplitudes shown here are only approximate for any preparation.

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generated. These were chosen with the aim of stimulating maximally in the first turn with the high-frequency stimulus (HI) and maximally in the third turn with the low-frequency stimulus (LO). The acoustic stimulus waveforms and amplitudes are shown in Fig. XV-2.

The stimuli were presented in pairs to observe the differences in the effects of various preceding stimuli on the response to the second stimulus. The time interval T between stimuli was one of the experimental variables. The cortical responses were averaged on the ARC-1 computer.⁹

2. Results

Averaged cortical responses to acoustic clicks and to shocks applied in turn I of the cochlea are illustrated in Fig. XV-3 for several stimulus intensities. These response waveforms are typical of those seen in 20 guinea pigs. The growth of the responses to clicks with increasing intensity is similar to that seen in anesthetized cats¹⁰ and guinea pigs.⁶ However, there seem to be some consistent differences between our cortical responses and those reported by Mark.⁶ (a) The surface negative (upward) deflection (peak latency, 20-35 msec) is not as large relative to the initial surface positive (downward) deflection in our animals. (b) The variability in the response amplitude in our

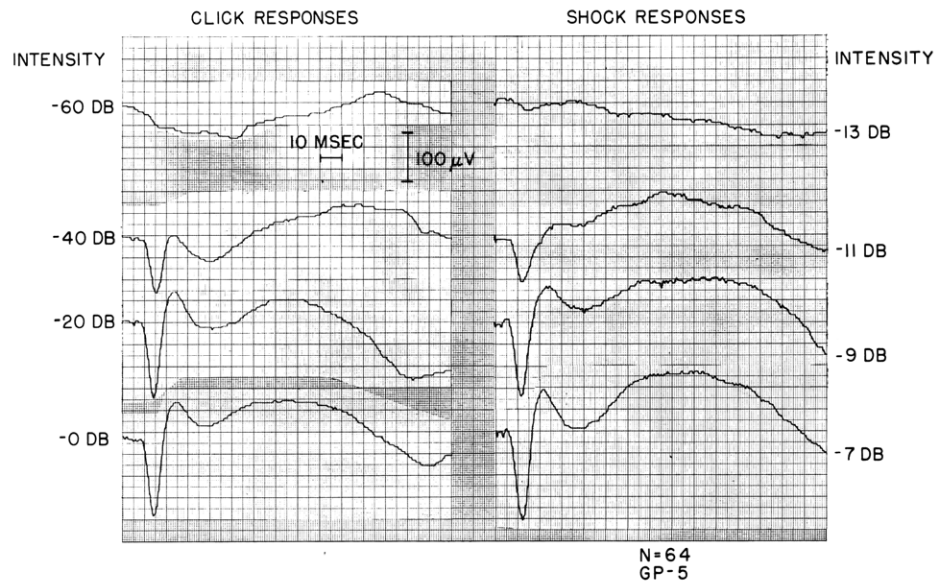


Fig. XV-3. Average cortical responses to acoustic clicks and to electric shocks applied through electrodes in scala tympani and scala vestibuli of turn I. Clicks were generated by applying 0.1-msec rectangular pulses to the earphone. Reference level (0 db): for the pulses, 4 volts; for the shocks, ~10 volts at the electrodes (see Fig. XV-2). Number of responses averaged, 64.

animals was greater and the absolute amplitude of the responses smaller than those found by Mark.⁶ Even with high-intensity stimuli (clicks or shock) that gave very large averaged responses, there were many single traces in which responses were not detectable. There was also considerable variability in the responses recorded from the cochlear electrodes, both in the auditory nerve components and the cochlear microphonic potentials. Spontaneous movements of the eardrum could be observed under the microscope. These resulted apparently from the spontaneous contractions of the middle-ear muscles which are often seen in anesthetized guinea pigs.¹² The differences in behavior of the cortical responses that we obtained and those reported by Mark are probably associated with differences in level of anesthesia. We were not able to obtain the conditions that Mark describes in which withdrawal reflexes to pinches on the feet disappeared. Our animals generally gave a strong reflex to pinches anywhere on the body. Attempts to deepen the anesthesia usually resulted in death. In several cases strong withdrawal reflexes to pinches on the feet were obtained even when the guinea pig had ceased breathing. Some animals that required artificial respiration continued to have strong withdrawal reflexes and their cortical responses were highly variable. In the few instances in which this great variability was diminished the animal died very quickly. Hence, we conclude that the large variability in cortical responses, which results partly from action of the middle-ear muscles, is very difficult to eliminate in a live guinea pig with the drugs that we used (Dial and Nembutal).

In addition to this variability from one response to the next, we also encountered considerable variability in sensitivity of the responses. Particularly in animals in which holes had been drilled and electrodes placed in the cochlea, we often found rather large changes in threshold for both acoustic and electrical stimulation. In some cases the threshold for electrical stimulation improved (that is, decreased) as much as 6 or 7 db, and it often changed 1-2 db in half an hour. Acoustic thresholds usually increased somewhat as the experiments progressed, but in some cases they decreased. Since there was so much individual variability in the cortical responses and in the averaged responses, it was difficult to obtain quantitative data for a range of stimulus conditions. The data presented in this report are the most stable that were obtained. In some cases examples are given to indicate the amount of variability encountered.

Our attempts to measure all of the interactions of HI and LO acoustic stimuli with shocks to turns I and III in the same preparation were unsuccessful. The combination of drilling 4 holes in the cochlea and stimulating electrically, along with the great variability present in the cortical response, made it difficult to obtain a preparation that gave consistent responses over a time long enough to allow any systematic measurements. The data that follow represent all of the possible combinations of the 4 stimuli, but with various combinations obtained in different animals.

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a. Interaction of Shocks to Turns I and III

Often the acoustic thresholds became very much elevated after the placing of 4 electrodes in the cochlea. In these cases it was still possible to measure responses to shocks to turns I and III. Figure XV-4 illustrates averaged responses to the 4 possible pairs of these two stimuli with $T = 50$ msec. For this condition there is little, if any, response to the second stimulus for the pairs I-I and III-III, but the second response is prominent for the pairs I-III and III-I, in agreement with the results that Tunturi^{3,4} obtained with dogs. The recovery curves shown in Fig. XV-5 indicate, however, that the shocks delivered to different turns can affect each other at shorter time intervals. The differences in interaction (between I-III and III-III combinations, for instance) are most easily observed with T between 25 and 75 msec. For this reason, most of the data presented below were taken in this range.

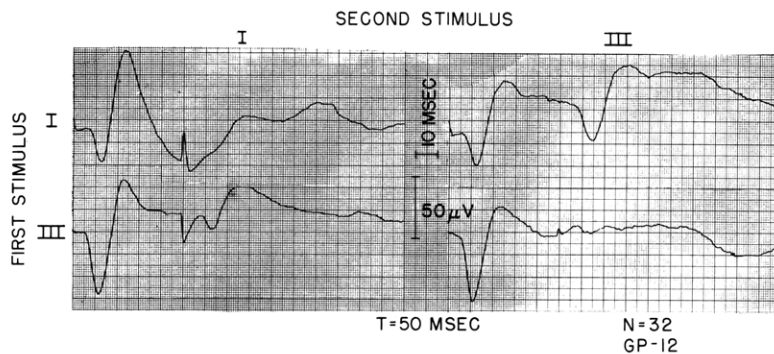


Fig. XV-4. Interaction of shocks to turn I and to turn III. $T = 50$ msec. Intensities same as indicated in Fig. XV-5. Number of responses averaged, 32.

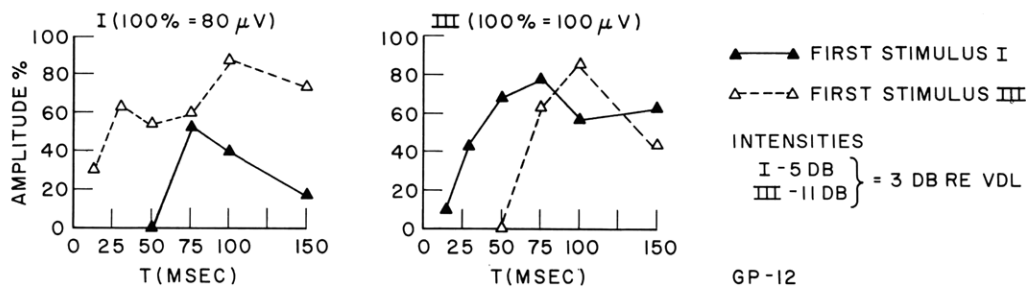


Fig. XV-5. Amplitude of response to the second stimulus vs T for shocks to turns I and III. Amplitude of responses to shocks to I are plotted on the left; to III, on the right. (In this and in Figs. XV-6 to XV-9 the response amplitudes are normalized with respect to an average of all of the amplitudes of the response to the given stimulus when it was presented first or alone.)

b. Interaction of HI and LO Acoustic Stimuli

An example of the interaction of responses to the HI and LO stimuli is shown in Fig. XV-6. The stimulus intensities and the time intervals were carefully chosen so that with a repetition of the same stimulus (stimulus pair HI-HI and LO-LO) no detectable response appears after the second stimulus, whereas with the pairs of spectrally

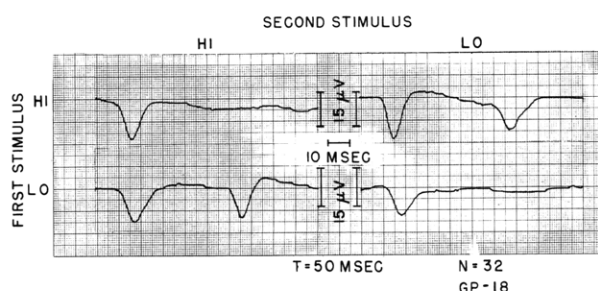


Fig. XV-6. Example of the interaction of responses to the HI and LO acoustic stimuli for $T = 50$ msec, taken from the series plotted in Fig. XV-7a. The stimulus intensities are ~ 10 db above the level at which a response waveform can be detected in an average of 32 responses (AVDL). Note that there is a slight difference in calibration of the vertical scales. Number of responses averaged, 32.

different stimuli (HI-LO and LO-HI) the response to the second stimulus is affected very little. The plots of Fig. XV-7a indicate the way in which the response amplitude for the second response depends on the interstimulus interval T and stimulus intensity; two stimulus intensities were used for each of the acoustic stimuli. The weaker stimuli (LO_w and HI_w) were approximately 10 db above AVDL and the stronger stimuli (LO_s and HI_s) were 20 db more intense. Averaged responses were taken for all 16 possible ordered pairs of stimuli. In each plot the amplitude of the response to one of the stimuli (LO_w , HI_w , LO_s , HI_s) is plotted as a function of T ; the first stimulus is the parameter. Several observations can be made from these data. (a) The low-intensity stimuli (HI_w and LO_w) interact very little with each other over the range of T examined, whereas (b) with the high-intensity stimuli (HI_s and LO_s) there is considerable reduction in the amplitude of the responses to the second stimulus. (c) With respect to the reduction of the second response, an intensity difference of 20 db can (for some conditions) outweigh the difference in spectral composition of the HI and LO stimuli. For instance, the response to HI_s is reduced more when it is preceded by LO_s than when HI_w is the first stimulus. The conclusion to be drawn from these results obtained with acoustic stimulation alone is that the degree of interaction of stimuli with different spectral distributions depends on the stimulus intensities; in order to obtain responses that have little interaction with each other (for example, HI_w and LO_w in Fig. XV-7a) very low

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intensities must be used.

Fig. XV-7b shows results obtained from another preparation. The stimulus levels used were 10 db and 50 db above VDL. These data are similar to those of Fig. XV-7a except that the curves indicate a tendency for more rapid recovery even though the strong stimuli (HI_S and LO_S) in Fig. XV-7b are 20 db more

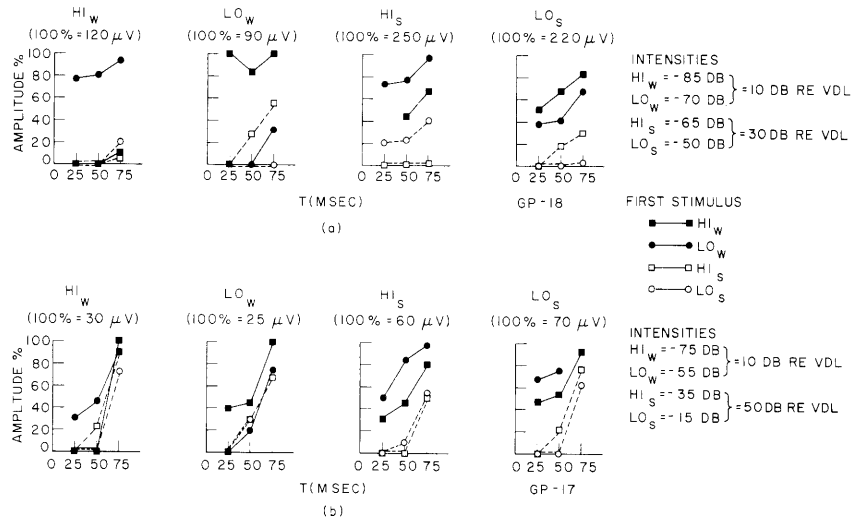


Fig. XV-7. Interaction of HI and LO stimuli at two intensity levels in two preparations. In both cases the bulla was not opened. Amplitude of the response to the second of two stimuli is plotted against the time interval T between stimuli. The stimulus is the same for all points in any one plot. The first stimulus is the parameter in each plot. (a) Weaker stimuli HI_W and LO_W are 10 db above AVDL; stronger stimuli HI_S and LO_S are 30 db above AVDL. (b) Results from another preparation in which HI_W and LO_W = 10 db, HI_S and LO_S = 50 db re AVDL.

intense (re threshold) than those in Fig. XV-7a. This difference in rate of recovery may result from a difference in the level of anesthesia in the two animals (in both cases Nembutal was used). Throughout the period in which the data for Fig. XV-7b were taken the guinea pig reacted to pinches on the feet with strong quick withdrawal reflexes. Also, there was a good deal of shivering, and the cortical responses were quite variable. (This "lightly anesthetized" state was typical of that obtained in most of our preparations.) In the case illustrated in Fig. XV-7a, the animal showed rather slow and weak reflexes to pinches on the feet and the variability in the individual responses was much less than that for the animal in Fig. XV-7b. Slower recovery of responsiveness in more deeply anesthetized animals has been previously reported by several other workers.¹¹

c. Interaction with Shocks to Turn I

Figure XV-8 shows examples of interactions obtained between HI and LO acoustic stimuli, and shocks applied between scala tympani and scala vestibuli of turn I. For the low-intensity stimuli used, a repetition of the same stimulus (HI-HI, LO-LO or I-I) produces very little response to the second stimulus. This also occurs when shock and the high-frequency stimulus are paired (HI-I or I-HI). However, the second responses are only moderately reduced when I and LO are paired.

The plots of Fig. XV-9 illustrate the interaction of these stimuli as a function of T for two sets of stimulus intensities. For the upper set, all of the stimuli are near VDL; for the lower set, the acoustic stimuli are 20 db above VDL, and the electric stimulus is 1.2 db above VDL. The stimulus intensities in any one set were chosen to give roughly the same response amplitudes to HI, LO, and shock. In all of the plots illustrated in Fig. XV-9 there is a striking similarity in the recovery curves following the HI and I stimuli, and a distinct difference between these curves and those following the LO stimuli. This similarity suggests that similar neural populations are being stimulated by the HI and I stimuli.

The data of Figs. XV-8 and XV-9 are among the most clear-cut obtained in our studies, probably as a result of the state of the preparation when these data were

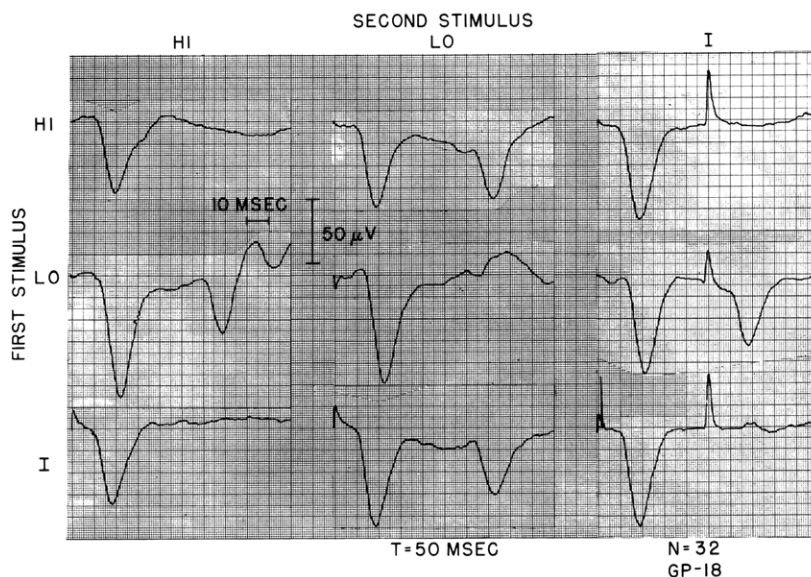


Fig. XV-8. Interaction of responses to the HI and LO acoustic stimuli and shocks to turn I for $T = 50$ msec. All of the stimulus intensities are approximately VDL. The guinea pig was being given artificial respiration and was probably in a moribund state when these data were taken. Number of responses averaged, 32.

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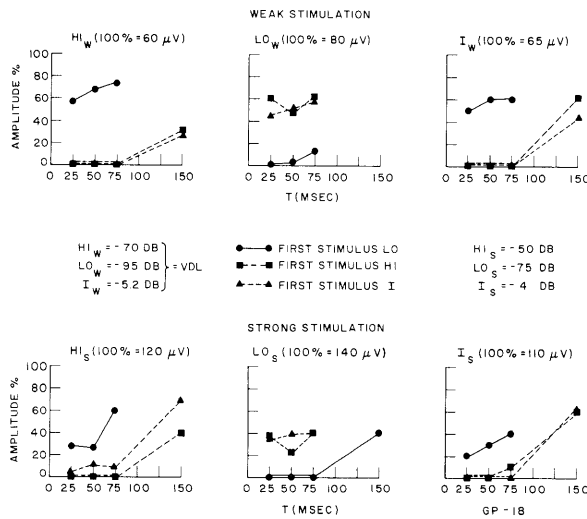


Fig. XV-9. Response amplitude for second stimulus vs T. As in Fig. XV-5, each plot gives amplitudes of responses to the stimulus indicated at the top of the plot.

obtained. There were several indications that the animal was in a moribund condition. (a) Artificial respiration was required. (b) No withdrawal reflexes could be detected. (c) The background activity from the cortical electrode was very low. (d) The cortical responses had a somewhat unusual waveform; the latencies were somewhat longer and the duration of the surface positive deflection was larger than those observed earlier from the same preparation. However,, responses from the cochlear electrodes indicated that the ear was still quite sensitive to acoustic stimuli.

d. Interaction with Shocks to Turn III

Figure XV-10 shows examples of interactions of responses to the HI and LO acoustic stimuli (both approximately 5 db above VDL) and shocks applied between scala tympani and scala vestibuli of turn III. These data were taken from an animal that was in the usual "lightly anesthetized" state, and the responses were extremely variable, as shown by the rather wide variations in the averaged responses to the first stimulus of a pair. In spite of this variability, these records clearly show that the LO acoustic stimulus interacts more with the turn III shock than the HI stimulus does. Figure XV-11 consists of plots of the response amplitude vs T which were obtained from another animal that was also in a lightly anesthetized state. The complete series was run 3 times on the same preparation. Between recording sessions the guinea pig was given additional anesthesia (Nembutal) with the hope that the variability might be reduced. There were, however, no signs that the animal ever went into a more deeply anesthetized state. In spite of the variability, the data generally indicate a much stronger interaction of LO

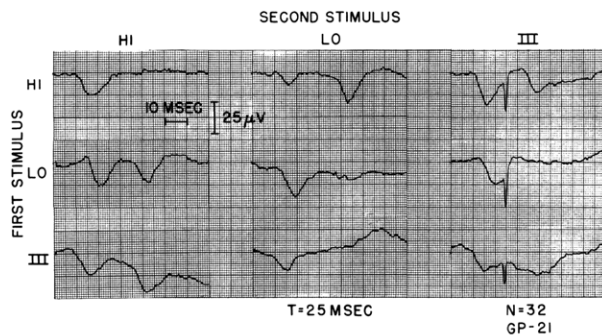


Fig. XV-10

Interaction of responses to the HI and LO acoustic stimuli and shocks to turn III for $T = 25$ msec. Acoustic stimuli, approximately 5 db above AVDL (both at -90 db); shock intensity, -5 db. Number of responses averaged, 32.

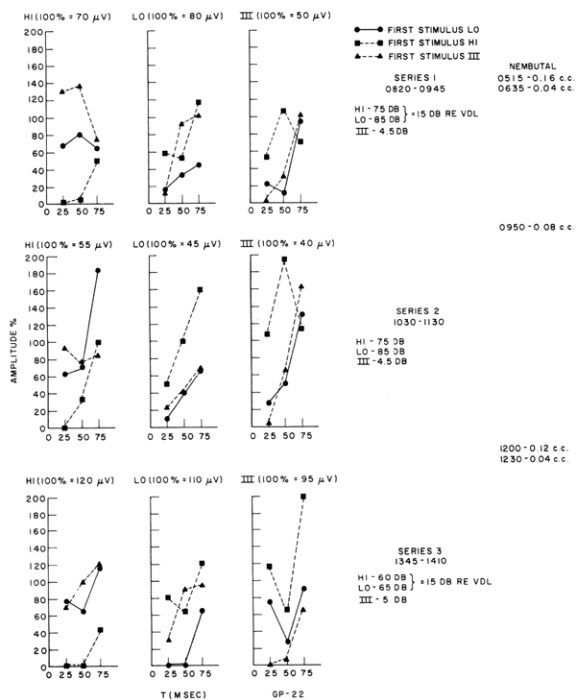


Fig. XV-11

Interaction of the HI and LO acoustic stimuli with a shock in turn III. In this preparation three series of data were taken; additional anesthesia was given between the series. The times of the series and times and doses of anesthesia are indicated. The intensities of the stimuli were the same in series 1 and 2, but they were increased in series 3 in order to maintain the response magnitudes at a reasonable level. From all signs, the animal was lightly anesthetized throughout all of these series, and there was a great deal of variability in the size of the averaged responses. In several cases the control response amplitudes varied over a range of ± 50 per cent. Because of these changing conditions, it was necessary to normalize each point with respect to the amplitude of the single averaged response taken immediately before or after, rather than averaging over all of the control response amplitudes. Amplitudes plotted are the response to the second stimulus.

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and III than of HI and III, or HI and LO, although there are a few data points that contradict this statement.

3. Conclusions

We feel that, in spite of the difficulties encountered, these data clearly indicate that it is possible for electric stimuli to act locally in the cochlea. Since this technique leaves the cochlea relatively intact, it is possible to study interactions of electric and acoustic stimuli. However, to answer more quantitative questions about this kind of stimulation (for example, how broad a section of the cochlea is stimulated?) the problem posed by the extreme variability must be solved. Two possibilities for improving the situation can be suggested. (i) The peculiar behavior of guinea pigs under anesthesia seems to be characteristic of the species. Perhaps another animal that also has its cochlea placed so that intracochlear electrodes can be inserted relatively easily would help with this problem. We have worked with chinchillas and they seem to be promising. (ii) If a technique could be developed for reducing the shock artefact in the recording channels so that the auditory nerve responses could be measured, interpretation of the action of the electric stimulus would be greatly simplified.

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B. ERRATA

In Quarterly Progress Report No. 66 (pages 306-315), in the report entitled "Some Response Characteristics of Single Units in the Cochlear Nucleus to Tone-Burst Stimulation," the last sentence of paragraph one, page 306, should read:

"In particular, for a majority of the units studied, the responses to tone-burst stimulation exhibit preferred times of firing relative to the onset of the stimulus time."

The first sentence of paragraph two, page 306, should read:

"Figure XIX-5 shows PST² histograms for eight different units in response to tone bursts."

The fourth sentence of paragraph six, page 314, should read:

"The interpeak interval and the latency decrease monotonically with increases in stimulus intensity, and increase monotonically with increases in stimulus duration or stimulus repetition rate."

R. R. Pfeiffer

