INGVARSSON, KRISTJAN

DYNAMICS OF COCHLEAR HAIR CELLS AS INFERRED FROM COCHLEAR POTENTIALS AND RESPONSES FROM AUDITORY NERVE FIBERS.

Northwestern University PH.D. 1981

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DYNAMICS OF COCHLEAR HAIR CELLS AS INFERRED FROM COCHLEAR POTENTIALS AND RESPONSES FROM AUDITORY NERVE FIBERS.

A dissertation submitted to the Graduate School in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the field of Biomedical Engineering

by

Kristjan Ingvarsson

Biomedical Engineering Center and
Auditory Physiology Laboratory,
Northwestern University
Evanston, Illinois 60201.

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To Jóna,

Trausti and Armar.

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The years at Northwestern University have been instrumental as the end of my formal education. Not only did I learn a branch of science but also discovered a facet of human nature so prevailing in this country that by now I assume it to be an integral part of American life: respect, helpfulness, thoughtfulness.

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CHAPTER 1

INTRODUCTION AND REVIEW

CHAPTER 2

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CHAPTER 3

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SYMBOLS AND ABBREVIATIONS

AP	Whole nerve action potential
AVE	Average potential, (Vsv+Vst)/2
BM	Basilar membrane
CF	Characteristic or best frequency for a single unit
CM	Cochlear microphonic potential
COCB	Crossed olivo-cochlear bundle
DAC	Digital to analog converter
dB SPL	Sound pressure level relative to 20 micropascal
DIF	Differential potential, Vsv-Vst
EP	Endocochlear potential
FTC	Frequency-threshold curve
G+	Gaussian-shaped condensation impulse of 10 ms duration.
G-	Gaussian-shaped rarefaction impulse of 10 ms duration.
IHC	Inner hair cell
LF	Low frequency
MPP	Masking period pattern
OHC	Outer hair cell
OW	Oval window
PST	Post stimulus time (histogram)
SM	Scala media
SP	Summating potentiall
SR	Spontaneous rate of firing per second
ST	Scala tympani

SV	Scala vestibuli
RW	Round window
TM	Tectorial membrane
2TS	Two tone supression

Chapter 1

INTRODUCTION AND REVIEW

1.1 Statement of the problem.

The object of this thesis is to elucidate the means by which hair cells in the cochlea are stimulated to initiate activity of the fibers in the auditory nerve. This issue is central to understanding the performance of the auditory periphery. The hair cells in the cochlea are the transducers of mechanical vibration into synaptic activity that generates action potentials in the auditory nerve. They are attached to the basilar membrane and move with it. The relation between basilar membrane movement and hair cell excitation has been studied extensively. Still there is disagreement on one of the basic issues, whether the stimulus to a hair cell in the cochlea is the displacement, the velocity, the acceleration of the basilar membrane, or some combination of these and perhaps other variables.

Many observations have puzzled auditory physiologists for decades. Some of these are described below. As sound stimulates the ear, substantial electric activity is elicited in the cochlea. The role of these stimulus-related cochlear potentials in the excitation process is unclear. The hair cells produce most of these potentials, but it is not known whether these potentials play an active part in

the mechanisms leading to auditory nerve fiber activity or if they are only a reflection of the activity of the cells as they are mechanically stimulated by the fluids and structures in the cochlea.

The problem of the relation between BM movement and hair cell excitation has not been fully resolved, because of the difficulties in measuring events taking place at the hair cell level. To infer the function of hair cells, investigators have therefore studied the responses of auditory nerve fibers, which represent the output from the cochlea, in other words, the cochlea is treated as a "black box". The relationship between sound stimuli and nerve fiber activity is a complex one, therefore, simple models do not reflect very well many of the physiological phenomena observed. Only recently has the technology advanced to the point that it is possible to record intracellular potentials from hair cells.

Inner and outer hair cells most likely have different functions, since they have differing morphology and electrical properties. How they divide their task of detecting and analyzing sound signals is largely unknown.

Inner hair cells are innervated by over 90% of the afferent auditory fibers (Spoendlin 1972), but outer hair cells play an important role in the excitation process as well (Dallos et al. 1972a). How the outer hair cells relay their influence to the nerve is unknown. Each auditory

nerve fiber responds selectively to sounds of a specific frequency. Important processing of the sound signal must therefore take place in the cochlea. Measurements of the basilar membrane movement show that this structure vibrates maximally at a certain place for a certain frequency, but this measured tuning may be less than the sharpness of tuning of the nerve fibers. Measurements of the potentials inside inner hair cells (Russel and Sellick, 1977) indicate that the sharp tuning already exists at that level. Some sort of a "second filter", has therefore been postulated to exist (Evans 1972), located somewhere between the basilar membrane and the inner hair cells, but recent accurate measurements of the BM movement indicate that it may be as sharply tuned as the auditory fibers (Khanna and Leonard, 1981). A neural network inside the cochlea has been looked for, to explain the sharp tuning of auditory fibers, but no structural evidence of such a network has been found.

The interaction between hair cells, if it exists, has been assumed to be electrical, mechanical or both. Models of this interaction have been put forward by many investigators (Duifhuis 1976, Manley 1978, Tonndorf 1974, etc.), specifically to explain sharpening. It has not been possible to directly test the validity of these theories. Tuning of the nerve fibers is not the primary concern in this study, but it is an inherent property of single fiber response and therefore of interest.

Many facts indicate that the mentioned interaction between hair cell populations exists (e.g. Zwislocki 1977, Manley 1977, 1978). Such an interaction could explain why the experiments to be reviewed in this chapter have not given clear-cut answers to the question of the relation between BM movement and nerve fiber activity: Interaction between hair cells would increase the complexity of the BM-to-nerve response relation.

One indication of interaction between hair cell populations worth mentioning before a detailed description of available data is given is the following: As mentioned, over 90% of the auditory nerve fibers innervate inner hair cells. These cells are thought to have their cilia freely moving in the fluid above the reticular lamina (e.g. Kimura 1966), thus responding to velocity rather than displacement of the basilar membrane (Dallos et al. 1972a). Experiments indicate that nerve fibers can show activity during sustained displacement of the basilar membrane, towards one of the scalae, tympani or vestibuli. This observation could be explained with interaction between inner and outer hair cells, since the OHCs have their cilia attached to the tectorial membrane and therefore should respond to displacement of the basilar membrane. How the IHCs and OHCs would communicate in such a scheme is open to speculation.

Another factor that confounds the relationship between BM movement and auditory nerve fiber activity is the

complexity of the BM mechanics. Basilar membrane movement was reported nonlinear by Rhode in 1971, at least for frequencies near the characteristic, or best frequency. The hair cells are known to have nonlinear exitation characteristics (Flock 1971). These, and other possible nonlinearities are reflected in cochlear potentials as well as in the responses of auditory nerve fibers. Treatment of the cochlear physiology by mathematical models becomes difficult due to these nonlinearities.

The present work was performed specifically to better understand the relationship between the basilar membrane movement leading to hair cell excitation and auditory fiber activity. Many experiments indicate a causal relationship between these quantities. For example, biasing the basilar membrane in one direction, i.e. towards scala vestibuli or scala tympani has been shown to influence the response of auditory fibers. In the experiments described in Chapter 3 we induce such biasing with low frequency stimuli. A sustained response in either direction of displacement will indicate a sensitivity of the auditory fibers to displacement, a response during transition of the BM movement from one scala to the other will indicate velocity sensitivity. The influence of a biasing low frequency stimulus on the response of the auditory fibers due to a tone at the characteristic frequency is also studied. Whole nerve action potentials (AP) recorded in the vicinity of the

cochlea are believed to be a reflection of the synchronized activity of many auditory fibers. The APs can therefore be used to indirectly assess the activity of single auditory nerve fibers. The APs are also studied and the results compared to the results of single fiber studies.

It is difficult to measure the displacement of the basilar membrane directly. The approach taken has therefore been to find correlates of the BM movement. Such a correlate is the cochlear microphonic, which is used in the present study instead of measuring the BM movement directly. The time of excitation of the auditory fibers is inferred from the detection of action potentials on the auditory nerve. An attempt is then made to correlate this time with the basilar membrane movement.

In the remainder of this chapter a review of published experimental data, pertinent to the subject, is presented. Chapter 2 describes methods used in the experiments performed and reported in Chapter 3. Chapter 4 contains a discussion of the experiments in view of present knowledge of cochlear physiology.

1.2 Review of present knowledge.

A favorite way to study cochlear function has been to consider the cochlea a "black box", in other words, to use

sound stimuli or efferent nerve fiber stimulation as input and record single fiber activity or other potentials on the outside of the cochlea as output, without invasion of the cochlea itself. This approach has the great advantage of an intact cochlea, thus normal function can be assumed. The characteristic responses of auditory nerve fibers to tone stimuli have been extensively studied this way. However, all conclusions about the events taking place inside the cochlea can only be indirectly inferred from such experiments.

The fact that the relation between sound and fiber activity is still not fully understood is due to the complexity of that function. It has become clear that nonlinearities are an inherent part of the system. Mathematical models incorporating such nonlinearities have been proposed (Hall 1977, Kim et al. 1980, etc.), but the site of origin in the cochlea of these nonlinearities is not known. Our experiments, like so many others, are aimed at understanding events at the cell level by recording cochlear potentials and auditory nerve activity. Therefore, the conclusions are indirect and will stand or fall when more is known about events taking place at the hair cell level.

A. Monitoring basilar membrane movement.

The experiments described in Chapter 3 rely on an assessment of the movement of the basilar membrane to low

frequency tones. This assessment was made with the aid of the cochlear microphonic. Here we describe the movement of the BM as measured by direct methods, then show how it is related to the cochlear microphonic.

A cross section of the cochlea is presented in figure 1.1. The cochlea is a coiled duct filled with perilymph. The cochlear partition, filled with endolymph, divides this duct into two scalae, called vestibuli and tympani. Within the partition one finds the organ of Corti, the sensory structure of the cochlea. The whole partition moves as sound is presented to the ear: the movement of the basilar membrane causes the hair cell cilia to be displaced and this displacement leads to auditory nerve activity, through various intermediary events. In order to correlate auditory nerve responses with basilar membrane movement it is necessary to monitor the BM movement. To do so directly is a formidable task in itself. To measure the BM movement and concurrently obtain single auditory fiber responses, as Evans and Wilson did in 1975, presents an even greater challenge.

The first experimental observation of the basilar membrane movement was done by Békésy in 1942 (figure 1.2). He discovered that the motion has the form of a travelling wave and that it is frequency dependent: High frequencies elicit travelling waves that reach only the initial segment of the cochlear partition and as frequency decreases, a

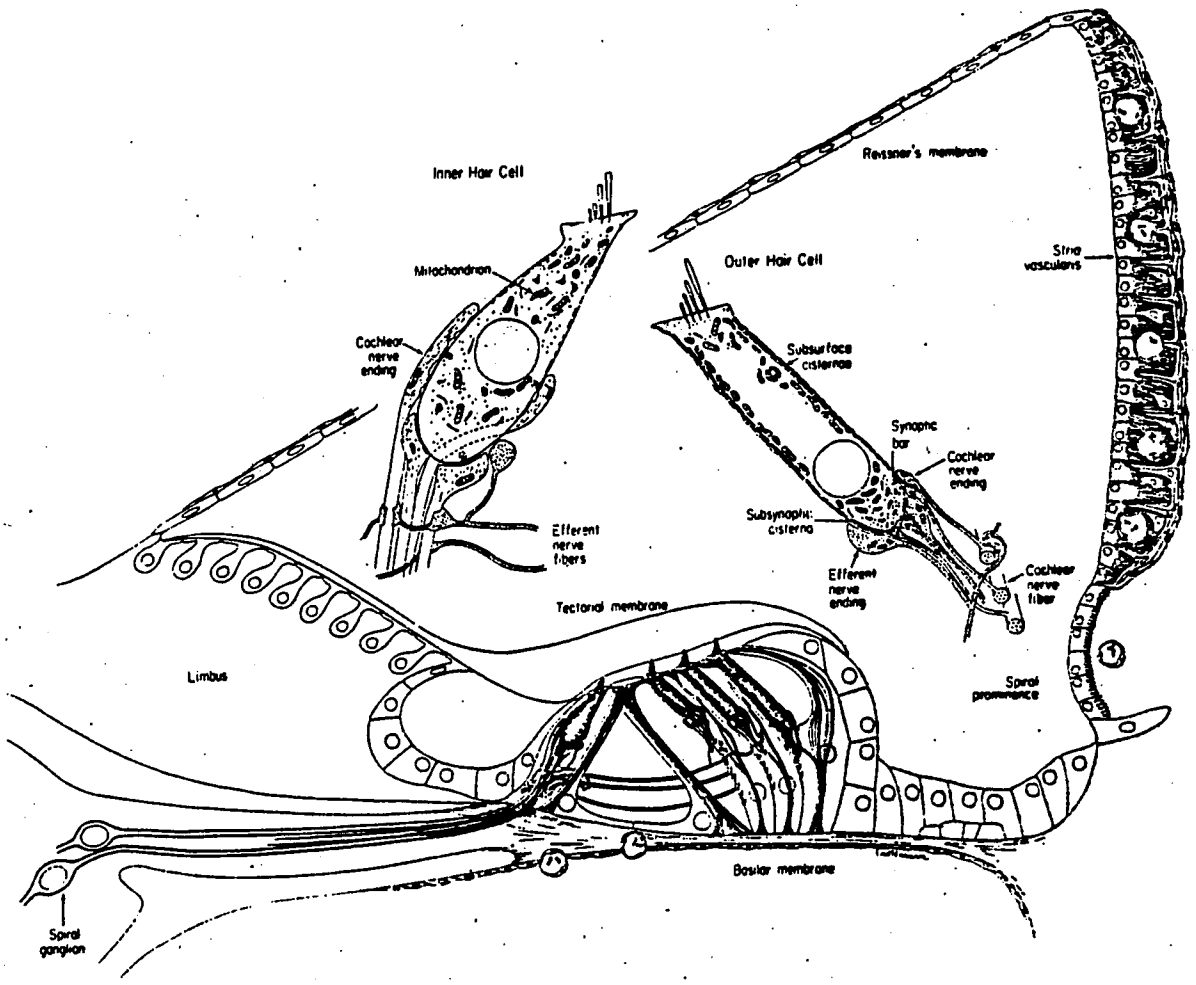

Figure 1.1 Cross section of the second turn of the guinea pig cochlea (from Smith, 1975).

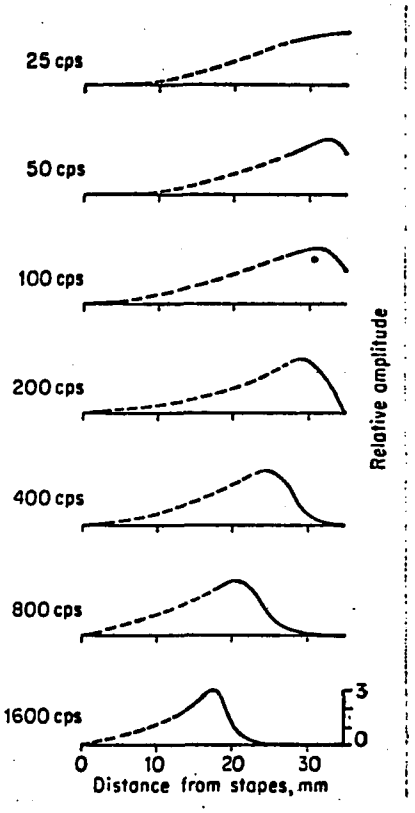

Figure 1.2 Patterns of vibration of the cochlear partition for various frequencies. (from Békésy 1960).

larger part of the partition vibrates. In order to render this movement visible with his stroboscopic technique, Békésy had to use very high sound pressure levels, on the order of 140 dB SPL (re. 20 micropascal). The travelling wave had a maximum at one point, and this maximum moved towards the apex as frequency decreased.

The precise location on the BM of the travelling wave peak as a function of frequency was measured indirectly with the aid of lesion techniques. Lurie, Davis and Hawkins (1944), exposed guinea pigs to high intensity tones and observed that the region of most damage to the cochlea was dependent on the frequency of the tone. Schuknecht (1960) made similar experiments on cats and mapped the regions of largest damage as function of exposure frequency. These experiments indicated that the frequencies are evenly distributed along the length of the partition in a more or less logarithmic fashion. Recently, Bruns (1976) mapped the cochlea of the horseshoe bat with a novel technique. Instead of damaging the organ of Corti, he induced the outer hair cell nuclei to swell by exposure to pure tones. Johnstone and Boyle (1967) measured the movement of the cochlear partition with a Mössbauer probe attached to the basilar membrane. They could thus determine the velocity of the BM and infer from it the displacement. Kohllöffel (1972) used a laser beam to measure the movement of the membrane. Capacitive probes have also been utilized to determine the movement of the partition (Wilson and

Johnstone, 1972).

Rhode (1971) used the Mössbauer technique in accurate direct measurements of basilar membrane motion. He placed the probe at the membrane where the best frequency, or frequency of largest displacement, is 7 to 8 kHz. For measurements of displacement with this method, a relatively high frequency gives better resolution, since the measured quantity is velocity. Rhode was able to detect a nonlinear movement of the membrane at frequencies near the best frequency, as seen in figure 1.3.

On the positive slope of the curve, an increase of the slope from 7 to about 24 dB per octave is noted. This slope increase becomes less apparent as higher intensity levels are used, and is practically undetectable at 90 dB SPL, indicating that a saturation occurs at higher levels. This would indicate that at lower levels, the region of maximum displacement vibrates relatively more than at higher levels, giving rise to more sensitivity of the particular region of the basilar membrane to low intensity tones of a specific frequency. The Mössbauer technique cannot be used with lower levels of sound pressure. This is unfortunate because the nonlinear behavior of the peak of the curve in figure 1.3 can lead to a relatively larger dislacement of the BM for low intensities of a stimulus of a given frequency, causing the auditory nerve fibers to be sharply tuned. Some experimental findings intimate that auditory fibers may

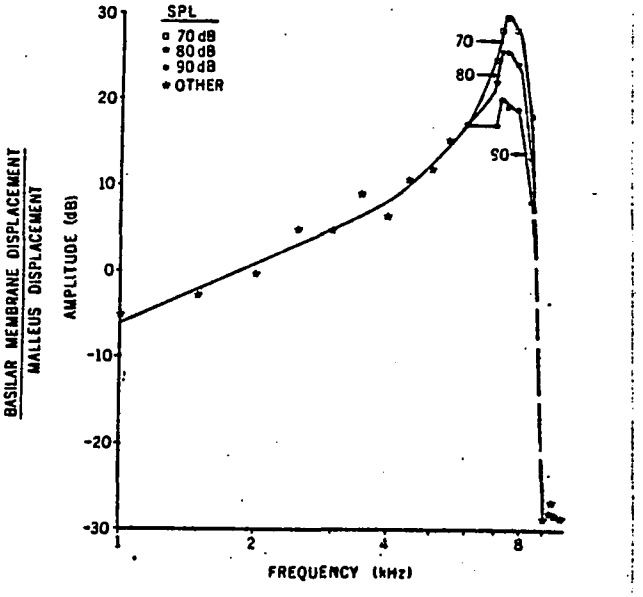

Figure 1.3 Amplitude ratio of BM displacement to that of the malleus. Note nonlinearity at the top of the curve. (From Rhode 1971).

present a sharper tuning to a specific frequency (CF) than the tuning found on the basilar membrane (Evans 1974, Robertson and Manley 1974).

A frequency selective basilar membrane does not seem to be a prerequisite for finding tuning in auditory nerve fibers. Weiss et al (1976) found no mechanical tuning to be present on a segment of the basilar membrane of the alligator lizard, but all the auditory fibers of this animal show significant tuning to a specific frequency. In mammals, however, the basilar membrane seems to have important tuning function. The sharpness of tuning has been shown to be larger than previously thought as more careful measurements are being made. Khanna and Leonard (1981) have measured high frequency slopes of BM tuning of up to 720 dB/octave, a value comparable to the tuning of single fibers.

Some information on the transient response of the basilar membrane movement exists. Rhode and Robles (1974) used the Mossbauer technique on the basilar membrane of the squirrel monkey and reported that 2 components are distinguishable in the response of the BM to click stimuli. One of them has a fast decay but the other has a longer decay; reconstruction of the BM movement from the Mössbauer data showed ringing in response to the click that did not decay exponentially. The issue of nonlinearity has been widely discussed during the last decade. It seems that

there is a nonlinearity that depends on the physiological condition of the cochlea, disappearing with less than normal state (Rhode 1973). Wilson and Johnstone (1972) did not find nonlinearities in the guinea pig, with their capacitive probe technique, nor the saturation discussed above, at any level below 110 dB SPL. It is conceivable that the physiological state of their subjects was less than optimal; hence their failure to detect nonlinearities.

B. The cochlear microphonic.

The stimulus related potential known as cochlear microphonic (CM) can be used to indirectly infer basilar membrane movement. The various experiments described below provide the data on which the correlation between BM movement and CM is based.

When a toneburst is presented to the ear, two distinct types of potential are brought about, the cochlear microphonic and the summating potential. The cochlear microphonic is an electric potential discovered by Wever and Bray (1930) generated in the cochlea as sound is delivered to it. It reminds one of the sound pressure field in front of the eardrum, as does a microphone, therefore the name. It is believed to be the aggregate response of many hair cells stimulated simultaneously. With a vibrating electrode, a device that could mechanically stimulate the cochlear structures and simultaneously record electrical activity, Bekesy showed that the cochlear microphonic is proportional to basilar membrane motion.

Tasaki, Davis and Eldredge (1954) showed that displacements of the basilar membrane result in potential changes as follows: A displacement of the BM towards SV causes the potential in SV to diminish and the potential in ST to increase. A displacement towards ST causes the polarities of these changes to reverse. Butler and Honrubia (1963) came to essentially the same conclusions.

Figure 1.4 shows that the CM as recorded from the basal turn shows strong similarities to the BM displacement curve gotten by Rhode in 1971 (figure 1.3). Even nonlinearties seen in the basilar membrane movement (figure 1.3) are seen in the cochlear microphonic data.

When a tone is presented to the cochlea, the CM appears shifted from the resting potential between SV and ST by the summating potential. Extensive studies were made by Dallos (e.g., 1973) on these potentials. These studies show that cochlear potentials change systematically with stimulus parameters (figure 1.5). The role of the SP, if any, in the excitation of auditory nerve fibers is unknown.

Dallos 1973b,1975a, Dallos et al. 1974, and Schmiedt and Zwislocki (1977) found that good agreement exists between basilar membrane movement and CM measures. The CM traces in figures 1.4 and 1.5 shows similarities to the data from direct measures of BM movement (figure 1.3). Schmiedt and Zwislocki compared mechanical measures of BM motion of Wilson and Johnstone (1972, 1975), their CM data and the data of Dallos. The agreement is excellent between these data. The general consensus is therefore that CM reflects the basilar membrane motion up to the best frequency of the location of the electrode. Figure 1.6 shows their comparative data.

In the normal cochlea, when the helicotrema is unobstructed and low frequency sounds are used, the

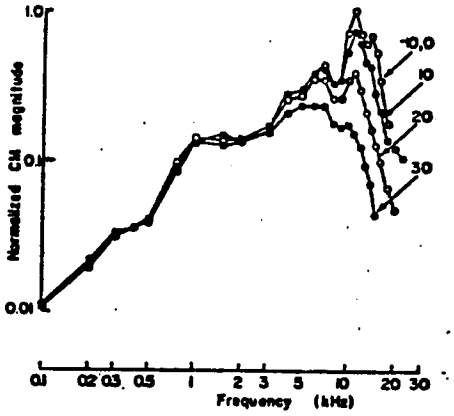

Figure 1.4 Nonlinearities in cochlear microphonic. Note similarity to basilar membrane data (figure 1.3), of the behavior of the peak for different intensities of sound. (From Dallos et al. 1974).

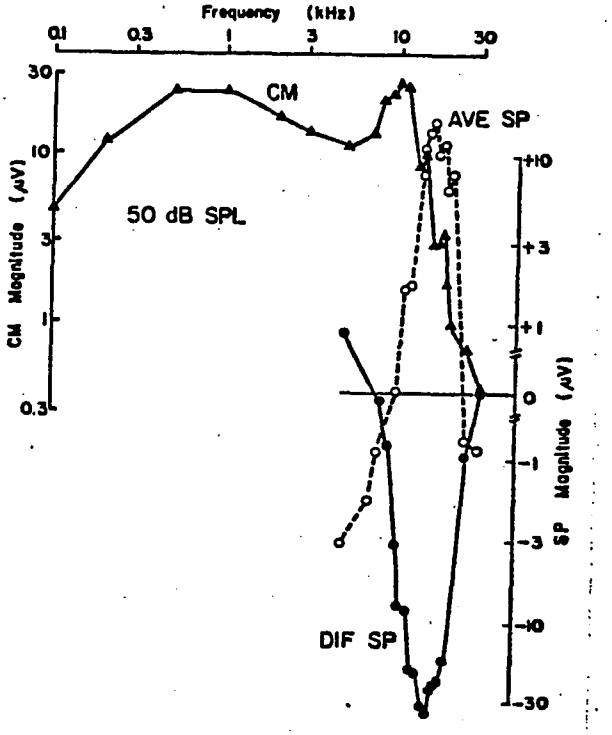

Figure 1.5 CM,DIF SP and AVE SP from first turn. DIF SP is defined as the DC potential between SV and ST; AVE SP is half the sum of the potentials in SV and ST. (From Dallos 1973b).

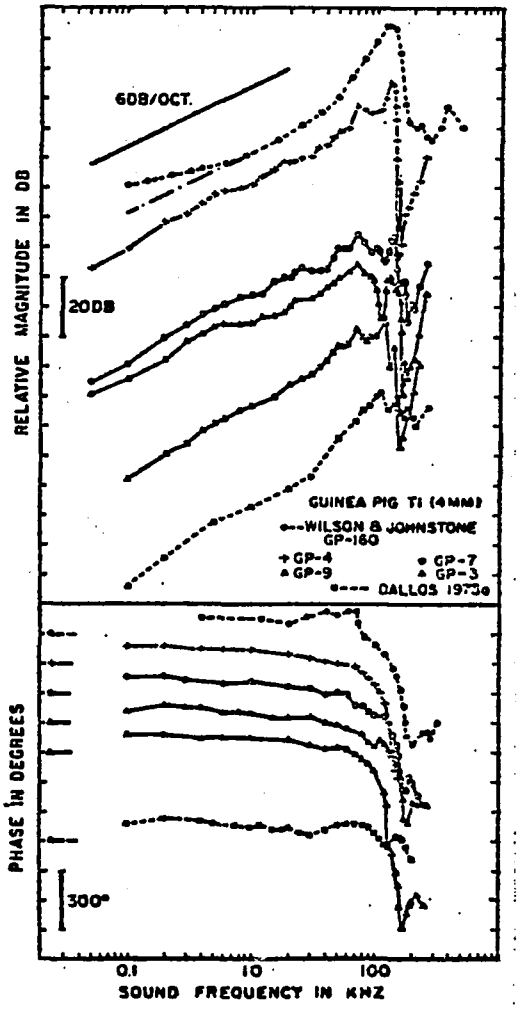

Figure 1.6 Comparison between CM and BM data. The CM data was corrected for a constant stapes displacement to be compared with the data of Wilson and Johnstone. From Schmiedt and Zwislocki 1977).

relationship between CM and sound phase is complicated. Dallos (1970) studied this relationship. Figure 1.7 shows the result of his study for the chinchilla and the guinea pig. As seen, the phase is not a well behaved function of frequency. This was interpreted not as a discrepancy of BM movement and CM generation but rather as the complex relation between sound and BM movement. The size of the helicotrema was viewed as the factor giving the large discrepancy of phase characteristic between these animals. If one wants to infer motion of the basilar membrane from the CM, one has to measure the CM for each individual animal, since for example a small interanimal variability in the size of helicotrema will affect the phase drastically, particularly between 100 and 200 Hz.

It is thus reasonably well established that the cochlear microphonic reflects basilar membrane movement. The current explanation for this observation is that outer hair cells produce most of the cochlear microphonic (Dallos and Cheatham 1976). The OHCs' cilia being attached to the tectorial membrane will modulate the ionic flow through the OHCs (Davis 1965), and produce the cochlear microphonic, as the shear between the tectorial membrane and reticular lamina occurs. By anatomical considerations, this shear is thought to be proportional to basilar membrane displacement (Rhode and Geisler 1967).

Let us examine closer the mechanisms of generation of

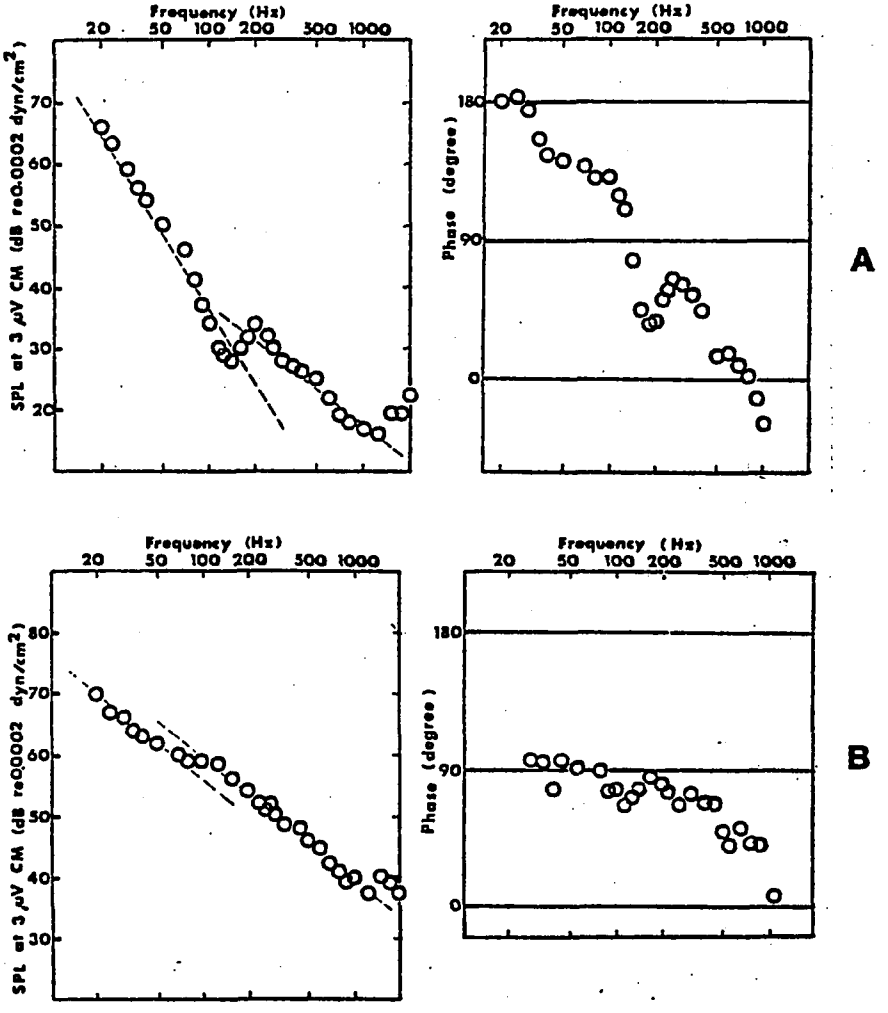

Figure 1.7 SPL needed to produce constant CM, and phase of CM for A. chinchilla and B. guinea pig (From Dallos 1970).

the cochlear microphonic and the experiments that have formed our understanding of it. A cross section of the cochlea was shown in figure 1.1. A positive potential of around 80 mV, the endocochlear potential is found inside the cochlear duct. The function of this potential is thought to be that of a driving force for current through the hair cells (Davis, 1965). The potentials in scala vesibuli and tympani as in other extracellular spaces is around 0 mV.

The EP is generated by the stria vascularis (Tasaki and Spiropoulos, 1959). All junctions between nonsensory cells surrounding the endocochlear duct have zonulae occludentes of the intermediate-to-tight type and the sensory cells and the basal cells of the stria vascularis have tight junctions (Jahnke, 1975). This provides the endocochlear duct with a high electrical resistance to SV and ST (Bekesy 1951, Honrubia and Ward 1969, Asakuma et al. 1978) if compared with the resistance between for example SV and ST. Still, the endocochlear potential is maintained at a large metabolic expense, evidenced by the fact that it disappears in seconds if the blood supply to the cochlea is cut, after which it reverses polarity and slowly disappears (Konishi, 1974).

It seems therefore that the endocochlear potential is important for the function of the cochlea. Indeed, if the EP is lowered, the activity of auditory fibers is greatly hampered (e.g. Johnstone 1980, Konishi et al. 1970). The

model put forward by Davis in 1965 has been widely accepted to explain the function of the EP. This model proposes that the EP together with the intracellular resting potential provides the potential to drive current through the apical surface of the hair cell. This current, according to Davis, depolarizes the cell, making it release neural transmitter. (This has not been directly observed in the cochlea, and the transmitter substance is still to be identified). At the same time the EP varies due to the current drain from the endocochlear duct into the hair cells. Thus cochlear microphonic is generated. There is some dispute as to which ion carries the current into the hair cell. The general consensus is that it is potassium. Konishi et al.(1976) showed that if potassium ions are not present in the endolymph, the CM is abolished. Corey and Hudspeth (1979a) find that in the bullfrog sacculus, any small cation will do, but it is interesting to note that universally the fluid surrounding sensory hair cell cilia is rich in potassium ions.

The sound-to-CM transfer is not linear, as proven by the following experiments. Nieder and Nieder (1971) determined the transfer characteristic of the generator of cochlear microphonic from modulation data. They concluded that the cochlear microphonic generator in the basal turn of the guinea pig cochlea is not linear over any appreciable range. Two amplitude minima of RW CM due to an 8 kHz tone were found per cycle of a modulating tone of 250 Hz

presented together with the 8 kHz tone. The minima of RW CM were inferred to occur in the extreme displacements of the basilar membrane toward SV and ST. Nieder and Nieder also found an hysteresis to be present in the transfer characteristic, in other words, the transfer characteristic corresponding to the ST-SV swing of the BM movement due to the 250 Hz tone differed from the transfer characteristic corresponding to the opposite swing, from SV to ST. Durrant and Dallos (1974) studied the effect of a low frequency "biasing" stimulus on the SP response to a probe tone. Effects similar to the ones observed by Nieder and Nieder on the CM were found to hold for the SP, such as modulation and hysteresis. At lower levels of the low frequency stimulus, the SP could be enhanced or depressed at different phases of the LF tone. For high intensities of the LF tone (over 90 dB SPL), the SP was generally depressed.

C. Hair cells in the organ of Corti.

Davis viewed the hair cell as a variable resistor: in one direction of bending of the cilia it would decrease the hair cell's resistance and in the other increase it. Since a current is assumed to pass through the hair cell, this current generates a potential between the inside and outside of the cell, the cochlear microphonic. Recent measures of intracellular potential of outer hair cells (Dallos, private communication, Tanaka et al. 1980) indicate that the polarity of the intracellular CM is opposite from that found

in the scala media. Together with the results of e.g. Tasaki, Davis and Eldredge, 1954, on the polarity of the potential changes when the BM is statically displaced, this would show that the OHCs are depolarized when the BM is displaced towards scala vestibuli , since the EP becomes more negative in that direction (an electrical circuit to clarify this can be seen in figure 1.9). Flock (1971) found that hyperpolarization occurs when the stereocilia are moved away from the kinocilium or basal body of a hair cell. Depolarization occurred in the other direction. The same polarities were obtained by Hudspeth and Corey (1977). They also found in the bullfrog sacculus that the depolarization caused by a mechanical stimulus of cilia gave a 3 times larger depolarization than the hyperpolarization caused by a stimulus moving the cilia in the opposite direction (away from the kinocilium). The polarity of the CM indicates that cells are depolarized when the BM is moved towards SV. Looking at the orientation of hair cells in the cochlea one concludes that movement of the BM towards SV bends the cilia outwards, towards the location of the (vestigial) basal body, therefore depolarization occurs. For the inner hair cells the relation between CM and BM movement is not as clear. Sellick and Russel (1980) have shown that inner hair cells depolarize when the basilar membrane is in the phase of maximal velocity towards SV. This is perhaps a reflection of the fact that the IHCs respond to velocity, because their cilia are not attached to the tectorial

membrane.

The relation between basilar membrane movement and hair cell polarization can be assessed indirectly from data on normal and Kanamycin treated guinea pigs (Dallos et al. 1972). In normal animals, triangular movement of the malleus induced a trapezoidal CM, reflecting a derivative relationship between movement of the malleus and BM movement. The phase was such that the SV was more positive during the positive going slope of the triangular movement of the malleus, i.e., when presumably the BM was displaced towards scala tympani. This indicates that the hair cells were hyperpolarized during the ST displacement of the BM. In kanamycin treated animals, where OHCs were missing, the responses were quite different. First, the CM was much smaller than in the normal case, a fact used to argue that OHCs produce most of the CM; secondly, only in the transitions of the triangular motion of the malleus was there a CM generated. This would indicate that the IHCs respond to the velocity of the basilar membrane. A small positive response was gotten in the negative to positive going transitions of the triangular sound field, and negative response to transitions from positive to negative slope. By the arguments of hair cell directionality and Davis' modulation theory one concludes that IHCs are depolarized in the transition ST to SV, i.e. they are sensitive to the velocity of the basilar membrane towards SV.

Recently demonstration that hair cells's potentials can also be sharply tuned to electrical stimuli has become available. Fettiplace and Crawford (1978) showed that current injection into cochlear hair cells of the terrapin will cause damped oscillations in the internal potential of the cell. These oscillations have the same frequency as the characteristic frequency for the cell when stimulated mechanically. Thus the hair cells in these animals seem to be electrically tuned. Russel and Sellick (1977) showed that IHCs in the guinea pig cochlea are sharply tuned to mechanical vibrations but mammalian cochlear hair cells have not been shown to demonstrate the ringing response to injection of current pulses.

D. Depolarization of hair cells.

Experiments indicate that depolarization of hair cells causes them to release transmitter. Here we look briefly at the mechanisms that can lead to depolarization of hair cells in the cochlea.

At least three physiological mechanisms, known to be present in the cochlea, can change the polarization of a hair cell. The bending of the cilia is one, just described; another mechanism is the effect resulting from a change in the resting potentials, specifically the EP. Such a change, if induced, will cause changed activity of the nerve cells (e.g. Konishi et al. 1970). The two methods of stimulating a hair cell - electrical and mechanical - is well demonstrated by Honrubia et al. 1976. These researchers stimulated the lateral line organ of Xenopus laevis with mechanical vibrations and also by applying extrinsic electric current. They recorded from two different afferent nerve fibers innervating the same stitch in the lateral line. The result is shown in figure 1.8.

The two cells responded similarly to the electrical stimulus, but in phase opposition when the stimulus was mechanical. Presumably this was because the two hair cells that the fibers innervated had different orientation of their cilia in the vibration field. Another important finding of Honrubia et al. was that electrical and mechanical stimuli lead to dynamically equivalent excitation

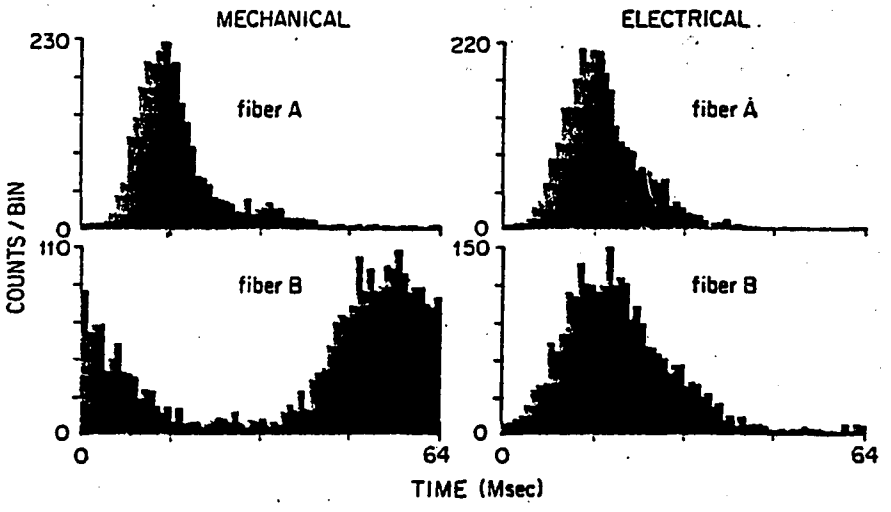

Figure 1.8 Cycle histograms from two fibers being stimulated electrically and mechanically with a 16 Hz sinusoidal stimulus. Both fibers show the same phase of activity for electrical stimulation, but opposite phase for mechanical stimulation, suggesting opposite orientation of the cilia for the two hair cells that are innervated by these fibers. (Honrubia et al. 1976).

of nerve fibers, i.e. when the amplitude of the stimulus -electrical or mechanical - was changed by equal amount of decibels, the same change of fiber discharge rate was observed. Similar results were reported by Sand et al.(1975) on the mudpuppy. They found that positive electrical intracellular stimulation increased the nerve discharges.

The third mechanism that presumably changes intracellular polarization of at least outer hair cells is the efferent activity. Galambos (1956) demonstrated that stimulation of the floor of the medulla (olivo-cochlear pathway) caused a supression of the APs evoked by a click. Fex (1959) showed that the efferent stimulation led to an augmentation of cochlear microphonic. Fex (1967) also showed that efferent stimulation caused a diminution of the endocochlear potential. Both these effects, the CM augmentation and the EP diminution were explained with Davis' (1965) scheme by the following argument: The current through OHCs was increased, because the hyperpolarization of OHCs caused by the efferent stimulation generated a greater potential difference between the exterior surface of the OHCs' cilia and the internal potential of the cells, increasing the current drain from the endolymphatic space, thus decreasing the EP and increasing the CM. Desmedt and Robertson (1975) showed that stimulation of the crossed olivo-cochlear bundle (COCB) of efferent fibers that innervate the cochlea can cause a decrease in EP by a few

mV. The authors postulate that the stimulation affects an ion channel on the base of the hair cells that leads to a hyperpolarization of the cell. This channel seems to work with small anions as evidenced by the fact that if large anions are used instead of chloride in the fluid bathing the basal end of the hair cells, the COCB stimulation does not have its normal effect on the EP.

Wiederhold and Kiang (1970) showed that stimulation of the efferent system reduced activity of single auditory fibers but did not influence the spontaneous discharges. This would indicate that the effect of efferent stimulation is presynaptic, since a postsynaptic effect would change the spontaneous rate. Geisler (1974a,b) proposed a circuit model of the organ of Corti to explain these findings, shown in figure 1.9. The circuit is based on Davis' concepts, modified to include inner and outer hair cells and an efferent effect. This model, having common current sources for inner and outer hair cells can also explain interaction between hair cell populations through the external potentials.

Brown et al. (1981) found that the inner hair cell intracellular receptor potentials are decreased by crossed olivo-cochlear bundle (COCB) stimulation; the resting membrane potential was unchanged. These researchers suggest that since the COCB primarily innervates the outer hair cells, these results may be a demonstration of the

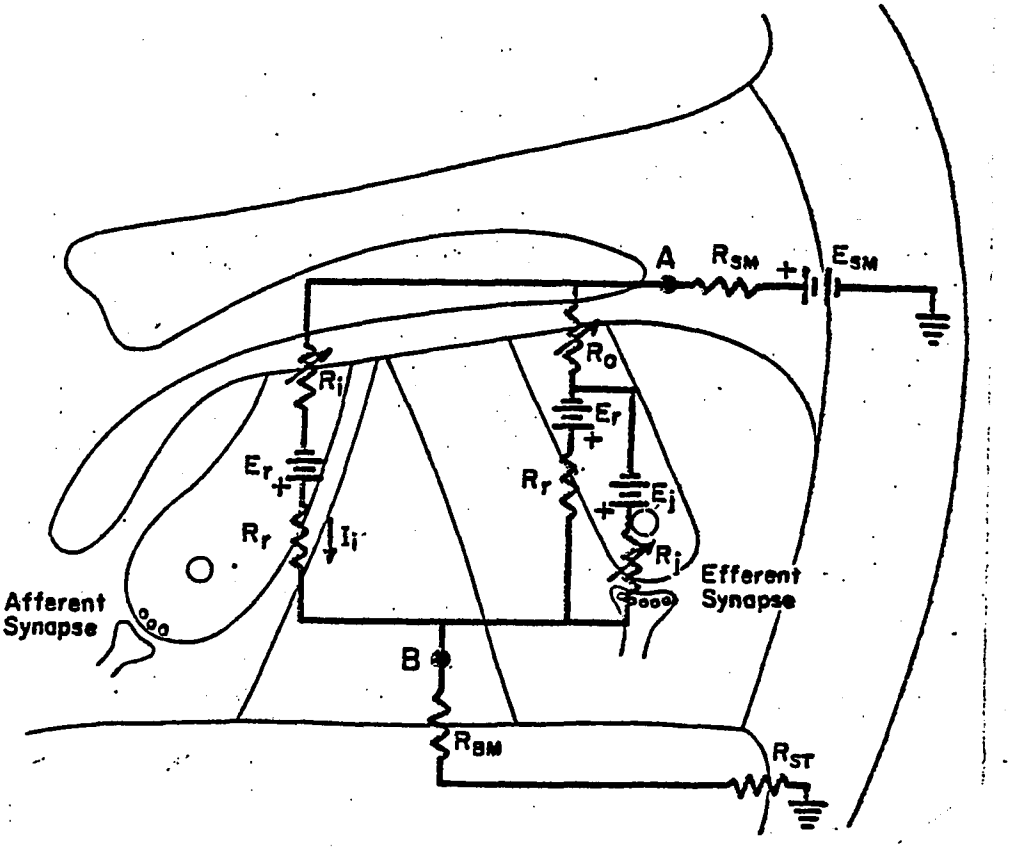

Figure 1.9 Model to explain the diminution of EP and augmentation of CM observed during CDCB stimulation. From Geisler 1974a.

interaction between outer and inner hair cells.

E. Transmitter release.

The next crucial issue is the relation between cell polarization and transmitter release. It is clear that mechanical, electrical and chemical changes in the hair cell's environment result in changes in its internal potential. Whether the polarization of the cell is the sole cause of transmitter release remains to be shown, but all evidence indicates that depolarization is one of the causes of transmitter release.

Furukawa, Ishii and Matsuura (1972) showed that there is a one-to-one correspondence between hair cell depolarization and excitatory post synaptic potentials (EPSPs) in the goldfish sacculus (inner ear). This is a demonstration that depolarization causes transmitter release. Receptor potentials at levels of only a few microvolts can elicit a response from a receptor cell, as demonstrated in experiments with the electroreceptors on fish. Lissman and Machin in 1958 showed that fields of a tenth of a microvolt per centimeter could be detected by fish. Sand et al. (1975) demonstrated, by injecting current into the hair cell of mudpuppy and recording nerve fiber activity, that there is a causal relationship between hair cell receptor potential and transmitter release. Ten times larger current injected directly into the nerve

terminal did not elicit neural activity. Sand and his colleagues viewed this as a proof that intracellular depolarization of the hair cell causes transmitter release which in turn causes activity to occur in the nerve terminal. The general consensus is therefore that depolarization is one, if not the only cause of transmitter release. The frequency-tuning curves (FTCs) of nerve fibers and isodepolarization curves found by Russell and Sellick (1978) in the intracellular potential of inner hair cells are similar. The FTC is constructed by finding the minimum intensity of sound needed to increase the firing rate by a detectable amount; the isodepolarization curves are constructed by adjusting the sound so that a certain depolarization is achieved. The similarity of these curves to each other suggests a causal relationship between depolarization and increase of firing rate.

Konishi et al. (1970) and Teas et al. (1970) showed that electrical current passed from SV to ST increased the spontaneous activity of most fibers but decreased the activity of some. The current direction that made SV more positive presumably caused depolarization of the hair cells, which caused the spontaneous activity of the nerve fibers to increase. The fact that some fibers decreased activity may show hyperpolarization to be excitatory, but more likely it is a reflection of the complex electrical pathways in the cochlear duct.

F. Single unit activity and basilar membrane motion.

Tasaki in 1954 was first to record from single auditory nerve fibers. He found that fibers were tuned to a specific frequency and also that they locked their firing to a certain phase of a low frequency stimulus, as seen in figure 1.10. This phase locking to low frequencies (under 3-4 kHz) has been reported by many others (Kiang, 1965; Rose et al. 1967; Anderson et al. 1971; Kiang and Moxon 1974). Anderson et al. found that there exists a linear relationship between frequency of a stimulus of fixed intensity and the position of the neural discharge (firing) within the stimulus cycle. The same relation was shown to hold by Geisler et al. 1974 (figure 1.11). The approximately straight lines indicate that there is a constant delay between the stimulus and the neural discharge that is independent of the frequency of the stimulus.

The transmission of signals along the cochlear partition is approximately nondispersive. Anderson et al. 1971, concluded from delay-time studies of the fiber's responses that the travel time in the cochlea was frequency independent. This is indirectly implied in Rose's et al. (1971) findings, that the shape of the stimulus is conserved in the fiber's response. Pfeiffer and Molnar (1970) studied the Fourier components of cochlear microphonic and single auditory fiber responses. They noted strong similarity between the magnitude of those components and the components

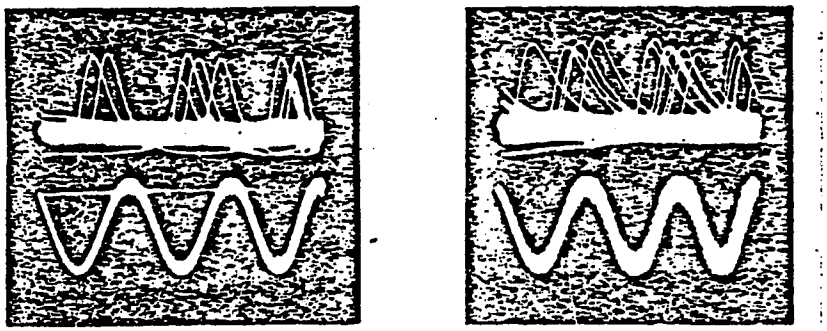

Figure 1.10 Single fiber responses. Lower trace:Vertical is the 1000 Hz stimulus as recorded with a monitoring microphone. Upper trace:Vertical is fiber activity. (From Tasaki 1954).

of CM, and concluded that it was probable that the CM was not an epiphenomenon. Since the CM is a correlate of BM movement, this similarity could be due to BM movement directly, not to the CM per se.

Dallos and Cheatham (1971) showed that the cochlear microphonic travel time displays the same independence from the frequency. Greenwood (1977) has calculated from the data of Rhode (1971) that the travel time for a signal of frequency near the best for the location in question is somewhat shorter than that for lower frequencies. On the other hand, comparison of click latency and slope measures on plots of phase of firing versus frequency such as figure 1.11 give similar results (Goldstein et al. 1971), indicating that the dispersion, if any, is small. It is therefore reasonably well established that travelling time along the cochlear partition is reflected in the response time of the fibers in a fairly simple way.

Kiang and Moxon studied the low frequency "tails" of tuning curves. They found that the phase of response of any fiber is about constant for low frequency stimuli (300 Hz), if the fiber's CF is above 8 kHz (figure 1.12).

Soon it became clear that the phase relation between the stimulus and the fiber activity is not trivial. Changing the intensity of a pure tone stimulus will change the phase of firing of the fiber by a significant amount. For a fiber with CF approximately 1400 Hz, Anderson et al.

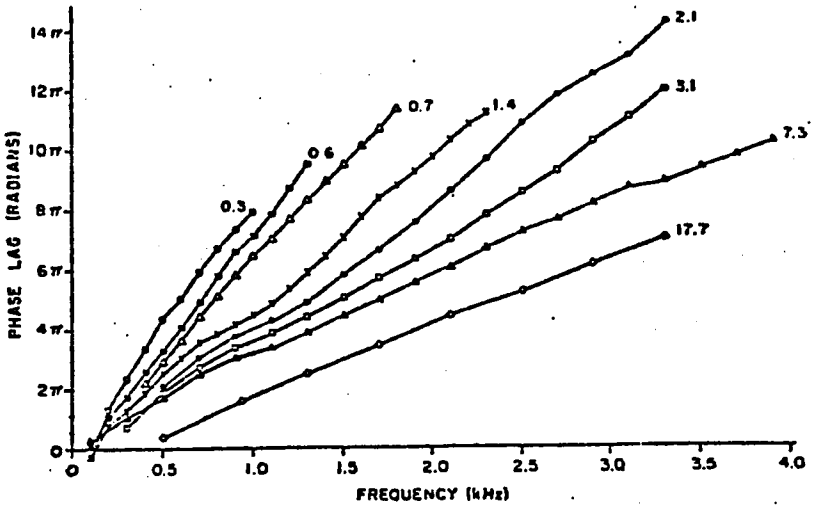

Figure 1.11 Phase lag versus stimulus frequency for eight auditory fibers. The lag is relative to sound pressure (constant SPL for each curve) in front of eardrum. CF of fibers is the parameter. From Geisler et al. 1974.

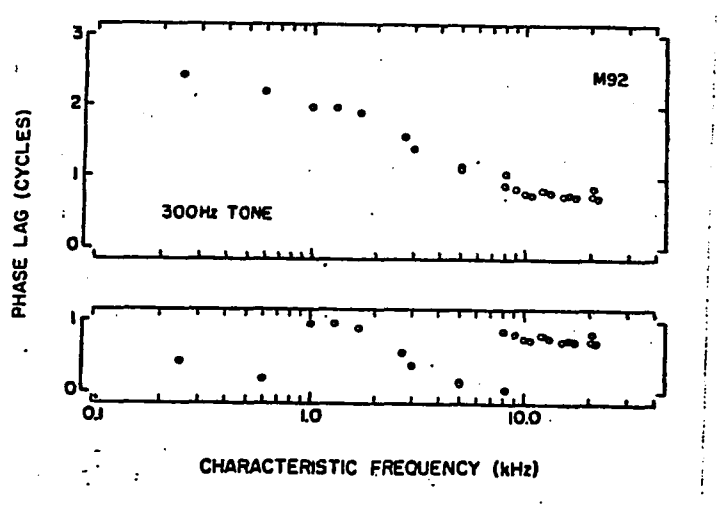

Figure 1.1.2 Phase characteristics of fibers for low frequency stimulation. Upper panel: Data from lower panel replotted shifing the points by whole cycles to form a continuous plot. Note relatively small change for fibers with CF over 8 kHz (From Kiang and Moxon 1974).

(1971) found that a 500 Hz tone will cause the fiber to fire almost 90 degrees later by increasing the intensity of the 500 Hz tone from 70 to 80 dB SPL. This is in contrast with latencies of firing observed for click stimuli, that always become shorter, or stay the same with increased intensity of the stimulus. J.B. Allen's preliminary results (Allen 1980, private communication) and also E. Relkin's results in our laboratory show the same increase in latency for higher intensity levels of the sinusoidal stimuli. Allen also shows that within a few dB of intensity increase, a large increase of latency may occur, corresponding to angles of up to 180 degrees.

It is possible that this phase jump is caused by the phenomenon of "peak splitting", commonly observed in our laboratory in the histograms of the auditory nerve activity in the chinchilla to low frequency tones: Two or more peaks appear per cycle of the LF tone, their amplitude, and to a lesser degree their position within the period vary in a nontrivial manner with stimulus intensity. Oshima et al. (1980) reported the same phenomenon in the gerbil, but did not find it in the guinea pig. Johnson (1980) found peak splitting in the responses of cochlear fibers of the cat, for frequencies lower than 450 Hz. The origin of peak splitting is unknown, and the name might be a misnomer, since it is not known whether it is one peak that splits into two or whether different mechanisms generate each peak.

As to the exact phase of movement of the BM as fiber excitation takes place, there is a conflict of views. Konishi and Nielsen (1973 and 1978) studied neural responses to stationary displacements of the basilar membrane. These researchers plugged the helicotrema with bone wax, in order to create static pressure difference between the perilymphatic scalae. They showed that this operation did not have drastic effects on the cochlear mechanics. They found that a large portion of the fibers respond to steady displacement of the basilar membrane towards scala tympani, a direction thought to inhibit both inner and outer hair cells. Fibers of low CF also showed responses during the transitions of the stimulus from one polarity to the other. Only 5% of the fibers responded to a steady displacement of the BM toward scala vestibuli.

In 1973, Zwislocki and Sokolich arrived at conclusions in general agreement with the Konishi and Nielsen study. They used low frequency trapezoidal stimuli and found that fibers could respond both to sustained displacements and to velocity of the basilar membrane towards ST. Sokolich (1977) studied responses to low frequency triangular signals. A consistent finding was that the characteristic response of a nerve fiber is dependent on the fiber's CF, but no dependency on intensity was observed. Sokolich divided the responses into 3 groups, according to the fibers' CF, and concluded that typically the fibers would respond in a fashion summarized in the following table:

BM displacement:	1<CF<2	3<CF<6	8<CF
toward SV	inh	inh	inh
toward ST	ex	ex	inh
ST to SV	ex	inh	ex
SV to ST	inh	ex	ex

These findings demonstrate well the apparent complexity of the relation between BM movement and firing of fibers.

In Kanamycin treated gerbils, Sokolich found a variety of responses. Here again an unexpected result was gotten: Fibers thought to innervate regions of the cochlea where outer hair cells had been destroyed, showed continuous firing as the BM was displaced toward scala vestibuli by the triangular stimulus, throughout a 10 ms period. This would indicate that inner hair cells might be BM displacement detectors. As in all experiments with Kanamycin-lesioned cochleas, it is difficult to separate regions of pure damage. There is always danger that the IHCs are abnormal, that the region in question has a partial complement of OHCs, or that the assessment of the best frequency at a specified region is incorrect.

The influence of a low frequency tone on the activity of a fiber due to a short tone burst at CF was studied by Romahn and Boerger (1978). They found that 7% of the fibers encountered showed different response to the burst depending on where the burst was located within the LF stimulus. 93% showed no difference in activity when the tone burst was

presented at different phases of the low frequency tone. Since this is approximately the ratio of afferents innervating IHCs and OHCs (Spoendlin 1972), the authors suggest that the responses are reflection of the existence of two different populations of nerve fibers. This result is in contrast with the results of AP experiments reviewed later. There it is demonstrated that APs are invariably influenced by low frequency tones of sufficient intensity. Unfortunately the data of Romahn and Boerger do not permit a correlation to be made between the phase of masking of the response of units due to the tone burst and the phase of basilar membrane movement, because a correlate of the BM movement such as the CM is unavailable.

The response to click stimuli has been much studied (Kiang, 1965, Pfeiffer and Kim, 1972). A latency difference in the response of the fibers is observed, depending on the polarity of the click : For rarefaction clicks, the first burst of a periodic activity comes earlier. The click response is repetitive, and the period of this activity has been shown to have the value 1/CF. Kiang et al. (1965) showed that these activity bursts interlace in time for rarefaction and condensation clicks. An explanation of this observation is that the firing takes place in a certain direction of BM movement, and therefore half a period of CF separates the rarefaction and condensation click responses (Weiss 1966). Goblick and Pfeiffer (1969) attempted to cancel the secondary peak of click histograms with a second

click, delivered a short interval of time after the first click. They found a remarkable spread in timing and intensity of the second click needed to cancel a peak, and interpreted this as evidence of nonlinearity in the response.

There is a discrepancy between the results obtained with low frequency stimulation and the physiology of cochlear hair cells as described by Flock in 1971, and Hudspeth and Corey (1977). Also, results of experiments using clicks do not agree with the ones using low frequency stimuli. Kiang et al. (1965) concluded that rarefaction moved the basilar membrane in such a direction as to increase activity of the nerve fibers. The first consequence of stimulating the cochlea with a rarefaction click is a displacement towards SV of the basilar membrane. The click experiments are therefore in consonance with the classical view of hair cell excitation and orientation of the cilia. The static and low frequency experiments give more excitation generally as the BM is displaced toward ST. The discrepancy of results could be due to the very different stimuli used. Konishi and Nielsen, and Zwislocki and Sokolich used very low frequency stimuli, whereas a click contains large energy at high frequencies. The velocity of the BM movement and possibly the absolute displacement are therefore of different magnitude for these two kinds of stimuli.

The experiments above indicate that there is a relationship between the phase of BM motion and auditory fiber resposes, although it is a complicated one. Also, the amplitude of vibration of the BM is reflected in the firing rate of the nerve fibers. This was already evident from Tasaki's study in 1954. More systematic search for the precise relationship was made by Kiang in 1965, Pfeiffer and Molnar 1970, Rose et al. 1971, Anderson et al. 1971, Geisler et al 1974, Kiang and Moxon 1974 and Palmer and Evans 1980. Kiang (1965) concluded that the rate of discharge of a single neuron being stimulated at CF "is not sufficient to specify the level of the stimulus". Fibers of same CF can have different spontaneous rates, different thresholds of firing and different input-output functions, as clearly seen in figure 1.13.

Geisler et al. (1974) concluded from the differences seen in neural and basilar membrane data that the basilar membrane displacement could not be the only input to a fiber, and that the variability seen in the neural data suggested a supressive mechanism to be present. The unknown phase relations between the sound at the tympanic membrane and the neural discharges did not permit Geisler et al. to make conclusions about the absolute phase of the BM movement when firing took place.

From the phase data of Anderson et al. (1971), Pfeiffer and Molnar (figure 3.7) and Geisler et al. (figure

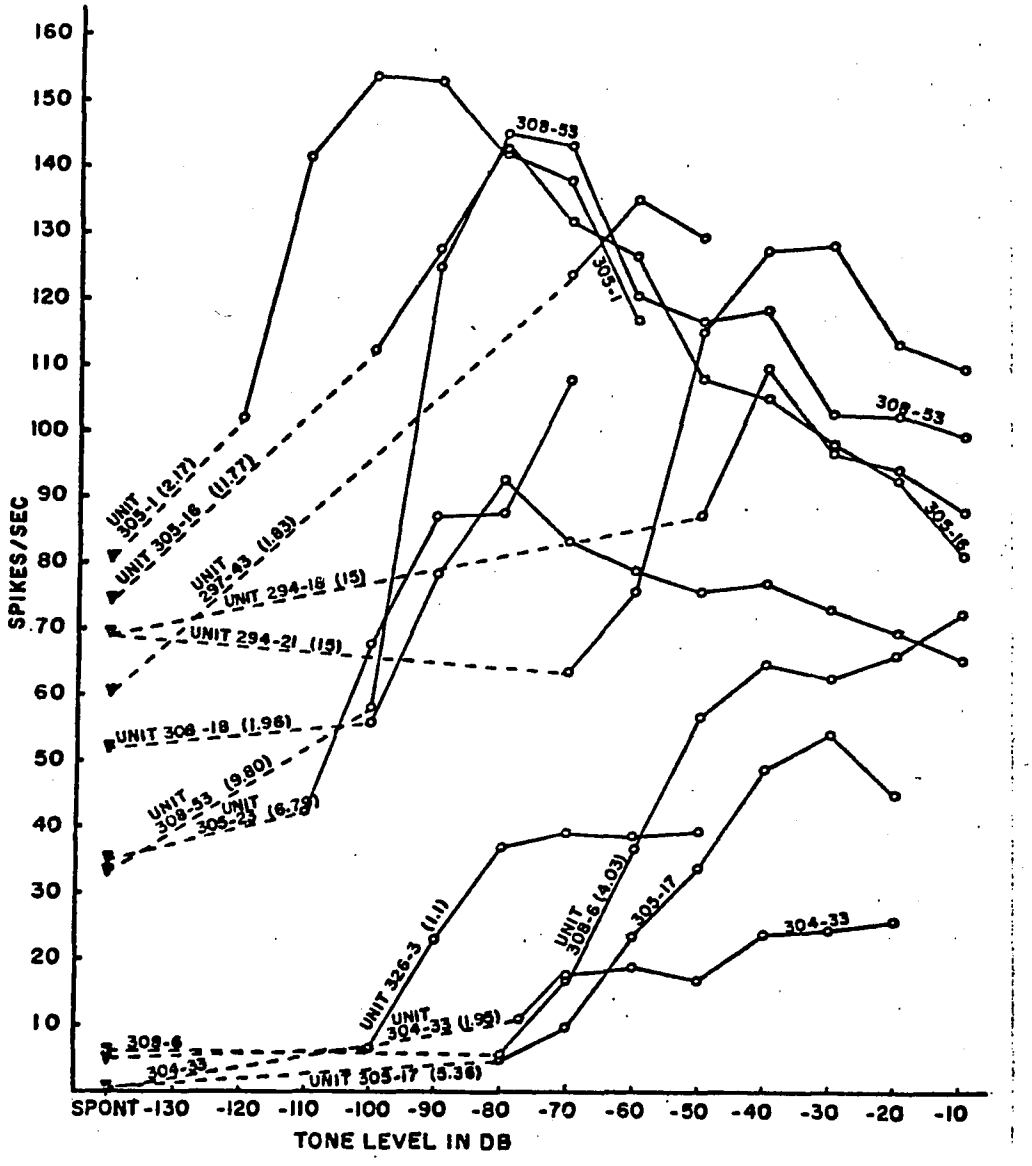

Figure 1.13 Rates of discharge of single auditory fibers plotted as function of the level of a continuous sinusoidal tone. CF's in parenthesis: Black triangles: Spontaneous rate (From Kiang 1965).

1.11) one ought to be able to extrapolate the phase of discharge to the zero-frequency and thus get the phase relation between fiber firing and sound pressure. There is, however, an unknown delay incorporated into some of these data, e.g. the data in figure 3.7. In the data in figure 1.11 the lines all seem to extrapolate and cross the vertical axis in the interval 0 to 2π. The errors in making the extrapolation are probably too large in order for one to determine this phase to a narrower interval.

G. Whole nerve action potentials

The whole nerve action potential (AP) recorded inside and in the vicinity of the cochlea is a manifestation of synchronous activity of a number of auditory fibers. Goldstein and Kiang (1958) suggested, in a theoretical model, a correlation between the AP and single fiber firing. This model is based on an assessment of the contribution from each individual nerve fiber to the AP. A probability density function P(t) is defined as the probability of a fiber firing at a certain time for a certain stimulus. This firing causes a unit response of voltage U(t) to be generated at the recording location. The effect of a large number of unit responses on the potential measured with a gross electrode was therefore postulated to be

$$V(t)=N\int_{-\infty}^{t}P(t)U(t-\tau)d\tau,$$

N being the number of fibers that have a possibility of contributing to the AP.

The validity of this formula has been demonstrated by finding the values of P and U from experimental data. P is assessed from histograms of single unit activity. This is possible because the post-stimulus histograms of fiber activity provide a good approximation of the probability function of a fiber firing given a sufficiently large amount of samples. U, the unit of contribution of a single spike

to the AP was measured directly by Kiang et al. (1976). These researchers averaged the RW waveform, using single unit activity (i.e. spikes) recorded on the auditory nerve to trigger the averager. Because the RW activity reflects responses of a group of single fibers that fire prior to the spike from one of these fibers being detected on the nerve (there is a conduction time involve before the spike is detected), the relevant average extended to times before the trigger spike was available. This was solved by having a digital delay line to include RW data that preceded the trigger spikes.

The APs elicited by clicks are similar to APs elicited by high frequency tone bursts, or by tone bursts of high intensity. Tone bursts of lower frequency and lower intensity elicit APs with larger latency. Teas, Eldredge and Davis (1962) presented clicks in the presence of noise of various frequency bands. They demonstrated that the response to the click was differentially affected by noise bands of different center frequency, indicating that the click AP was produced by a large portion of the nerve cells along the basilar membrane. By masking the basal region with high pass filtered noise, Özdamar (1975) and Özdamar and Dallos (1978) have shown a clear dependence of the AP on the frequency of a tone burst presented with the noise. Similar studies by Antoli-Candela and Kiang (1978) demonstrated a good correlation between APs and single fiber responses to click stimuli.

Another method of demonstrating the place of generation of the AP along the BM was devised by Dallos and Cheatham (1976b). They masked the AP due to a probe tone with masking tones of different frequencies. Masking tones of frequencies near the probe tone frequency were the most effective. A tuning curve (plotting the level of masker needed to reduce the AP due to the probe tone by a certain amount as a function of the frequency of the masker) shows strong similarities to a single fiber tuning curve.

These studies indicate that the AP can to a certain extent be used to infer single fibre activity. Experiments with ototoxic drugs show that the AP threshold curves - i.e. curves plotting minimum intensity needed to elicit a visible AP on an averaging computer, versus frequency - show the same kind of deviation from normal thresholds as the thresholds of single units in the same animal (Dallos et al. 1977, 1978, Johnstone et al. 1979). In the experiments described in Chapter 3, the AP was therefore used to measure indirectly the effects of a low frequency tone on the response of auditory fibers as these were stimulated by a tone burst.

Experiments on the influence of low frequency stimuli on the AP due to tone bursts have been reported. Eldredge (1976) presented clicks superimposed on "thumps" or low frequency impulses in the sound field lasting a few milliseconds. He presented the clicks on different phases

of the thump and found that when the click was presented at the time when the CM due to the thump was becoming more positive, a suppression of the AP due to the click was observed. Eldredge speculated that it could be the role of the CM to provide a suppression of fiber activity in certain phases of the stimulus. Another explanation of this phenomenon could be that the thump biased the basilar membrane, thus influencing the production of AP. For certain combinations of thump and click levels, the AP was suppressed in both phases of the CM due to the thump. This correlates well with the results of the experiments described in Chapter 3 and with the psychoacoustic data of Zwicker, reviewed below.

H. Psychoacoustic studies.

The studies of APs and single unit activity, reviewed above, that employed low frequency tones and thumps were done in an attempt to bias the basilar membrane in a certain direction so that the influence of such a bias on the normal responses of the auditory fibers could be assessed. Similar experiments have been attempted in pshychoacoustic studies.

Deatherage and Henderson (1967) showed that placing a short tone burst on different phases of a low frequency sinusoid will change the threshold of hearing the tone. They found that placing the tone on a certain phase of the

LF tone made it possible to hear the tone burst, even when presented at an intensity below the threshold for the tone burst presented alone. They named this phenomenon "sensitization". Unfortunately it is not possible to correlate the sensitization phase with the phase of BM movement in the data of Deatherage and Henderson.

Zwicker (1977a, b) attempted to infer the relation between basilar membrane movement and excitation of auditory nerve fibers in a psychoacoustic experiment. He used a probe tone of short duration to test the masking effect of a low frequency tone on this probe tone, as the probe tone was moved to different phases of the low frequency tone. Zwicker found very consistent results in these experiments. The maximum suppression, or masking, of the probe tone occurred during the rarefaction phase of the low frequency tone, and minimum masking occurred during condensation. However, for intense low frequency tones, a second maximum of masking also occurred during the condensation phase (figure 1.14).

In order to better distinguish what function of the sound stimulus provided these characteristics, Zwicker (1977b) used specially shaped low frequency maskers with distinguishable derivatives. These studies led Zwicker to several interesting conclusions. He found it possible to correlate the shape of the masking period patterns to the basilar membrane movement by using Dallos' (1970) hypothesis

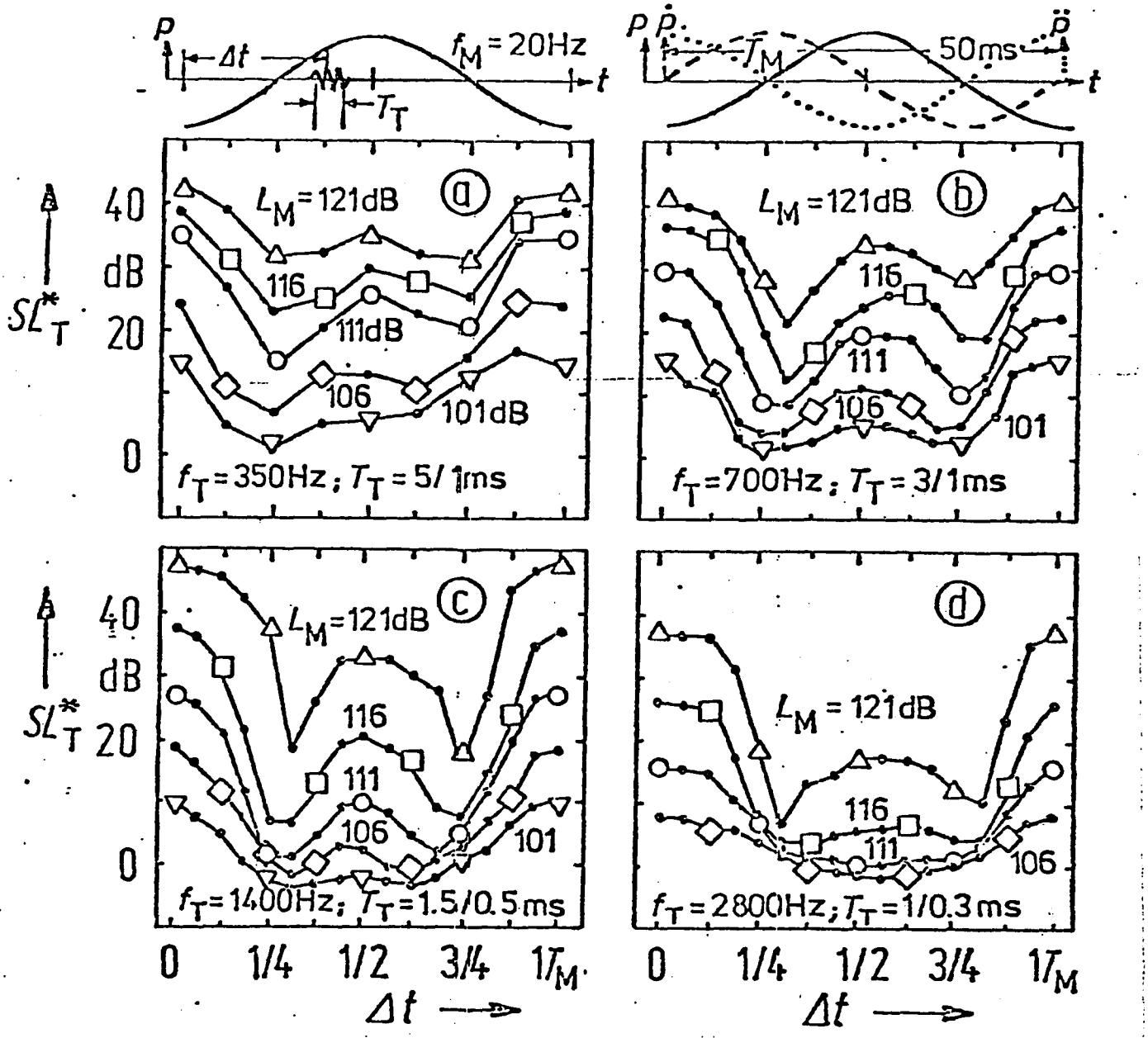

Figure 1.14 Masking-period patterns. Plotted is the level of probe tone above threshold needed to overcome the masking effect of a low frequency sinusoid. Observe the appearance of 2 masking peaks per cycle of the sinusoid for high intensity maskers. From Zwicker 1977b.

that the size of the helicotrema influences the behavior of the BM at low frequencies. This correlation indicated that masking occurred as the basilar membrane was displaced towards SV and ST, the larger of the masking peaks being found when the BM was displaced towards ST. Sensitization was also observed by Zwicker.

All the experiments described in this chapter were designed to cast light on the sound-to-neural-activity relationship. The intracellular studies must be considered the most direct measure of this relation, the psychoacoustic the most indirect. Our experiments, involving cochlear potentials and nerve activity lie somewhere in between in directness of approach.

The experiments reviewed above do not give a clear indication as to the phase of BM movement where firing takes place. The experiments described in Chapter 3 cast some light on this issue. Also, they reveal a very different pattern of response between low frequencies presented alone and the responses for low frequencies presented with a tone at the characteristic frequency.

CHAPTER 2

METHODS OF RESEARCH

Most of the techniques used in the experiments described in Chapter 3 are routinely employed in our laboratory. In a typical experiment the preparation and surgery take 2 to 3 hours. Data collection is conducted for about 10 hours after that.

2.1 Animal preparation

Choice of animal. Several reasons led us to choose the chinchilla as the main research subject. Most of the technical difficulties in recording from single auditory fibers have been worked out for this animal in our laboratory (Harris 1977). Another reason for the choice is that the chinchilla is free of middle ear infections, a common disease in guinea pigs, and trainable in psychoacoustic experiments (to correlate behavioral studies with physiological ones). Also, relatively extensive experimental data are now available on the auditory system of these animals.

Surgical procedures. Surgery is performed to insert cochlear electrodes, usually a round window electrode, prepare for insertion of a single fiber recording micropipette and prepare the animal for installing a closed sound delivery system.

The chinchillas are anesthetized with intraperitoneal injection of sodium pentobarbital (Nembutal). The initial dose of 70 mg/kg provides a deep anesthesia, lasting for about 2 hours. The dose used is such that the animal is totally relaxed, and breathes on his own. The subsequent doses of anesthetic are given to maintain the level of anesthesia, usually 15 mg/kg every 2 hours. Subcutaneous electrodes are inserted across the chest of the animal. The signal from these electrodes is amplified and connected to an oscilloscope and a loudspeaker. Heart, respiration and muscle activity are thus monitored and may be used to estimate the degree of anesthesia of the animal.

2.2 Eighth nerve approach (Harris 1977).

Tracheostomy is performed; the animal's head is fixed in a holder, and a flap of 2 by 4 cm of skin is removed from the back of the head, at the level of the lambdoid suture. The upper part of the left pinna and cartilage are cut away from the bulla, giving access to the bony external meatus. An opening is made in the ear canal ventrally to the bony external meatus opening, where the tube of the earphone for delivery of low frequency stimuli is to be inserted. The dorsal muscles that attach to the cranium are loosened from it in order to get access to the posterior part of the cranium. The supra occipital bone is partially removed in order to expose the posterior fossa, and make possible the insertion of pipette electrodes into the 8th nerve. A hole

of 2 square millimeters is then opened on the posteroventral compartment of the bulla. A teflon-insulated silver wire with its tip free from the insulation and flattened, is carefully contacted with the dorsal edge of the round window membrane. The wire is then glued to the bulla with dental cement to hold it in place. The mouthpiece of the headholder serves as the reference electrode. The animal is put in a sound insulated booth. The sound delivery system, the subcutaneous electrodes and a rectal thermometer together with a heating pad are installed. A small hole is made on the superior compartment of the bulla in order to provide pressure equalization in the middle ear, and a long thin polyethilene tube is cemented into the hole to assure normal acoustic impedance of the bulla. The sound system is calibrated for each animal, so that the sound pressure level being delivered can be related to the standard 20 micropascal (0 dB SPL). The whole nerve action potential thresholds due to tone bursts for frequencies between 500 and 20000 Hz are obtained. These thresholds are used as a reference for monitoring the state of the cochlea during the experiment. An increase in threshold of 10 dB or more is considered to indicate a deterioration of cochlear condition.

When these preparations are finished, the dura is opened and the cerebellum on the left side retracted medially about 2 mm to expose the opening of the internal meatus and the emerging eighth nerve. A pipette electrode

filled with 2 M NaCl is put in place on a hydraulic driver that is controllable from the outside of the booth. The electrode is then aimed at the dorsal part of the exposed nerve. The preparation is now ready for single auditory nerve fiber recording.

2.3 Differential electrodes (Tasaki, Davis and Legouix, 1952).

Recording with differential electrodes requires a different surgical technique. The animal is anesthetized and tracheostomy is performed. The ventral part of the bulla is exposed by ligating and cutting the external jugular vein, and removing salivary glands and musculature. The jaw is broken to expose the lateral wall of the bulla, and the external cartilagenous meatus is cut so that the sound delivery system can be installed. The ventral part of the bulla is opened to expose the cochlea. Two small holes are carefully drilled, one over scala tympani, the other over scala vestibuli of the basal turn, and a glass insulated tungsten electrode is inserted into each hole, the glass also serving as a plug for the holes to prevent perilymph from leaking out. The bulla is then closed with dental cement, and a thin polyethilene tube serving as a pressure equalizer is glued in place.

2.4 Equipment, calibration and recording techniques.

Sound system. Sinusoids were generated by a digital frequency synthesizer (Rockland 5100). The harmonic distortion of the signal was more than 70 dB below the fundamental. Click and noise generators were also available. Specially shaped stimuli, such as tone bursts with cosine envelopes, and Gaussian impulses were generated with a Digital Equipment Corporation PDP11/34 computer through a digital-to-analog converter (Analogic AN5800 series). A special circuit was used to compensate for the inherent nonlinearity that exists between the driving voltage and the sound pressure generated by a condenser microphone used as a sound source (Molnar et al. 1969). This condenser driver was used for delivery of signals of frequency higher than 300 Hz. It was connected to the bony external auditory meatus through a tube, to provide a closed system. For lower frequencies a magnetic earphone (Telephonics TDH 39) was used, connected to the ear by a steel tube, 7 mm in diameter, through the hole that was drilled on the wall of the bony external meatus. The earphone is capable of delivering higher sound pressure levels at low frequencies than the condenser driver, with significantly lower harmonic distortion. Concentric with the tube delivering sound from the condenser driver was another tube that was attached to a microphone (B&K 4134), used to monitor the sound pressure level being delivered. The maximum sound pressure level that could be obtained at each frequency was measured over the range of 100 to 20000

Hz. Any sound pressure level could then be delivered by proper attenuation of the stimulus source.

Signals recorded. The bioelectrical signals of interest are the potential of the round window electrode, of the differential electrodes and of the single fiber electrode. The reference electrode was the mouth-bar of the headholder. The signal from the round window electrode is amplified with a low level preamplifier (gain 1000) located inside the sound proofed booth, having a passband of .8 Hz to 40 kHz then led to the outside oscilloscope and averager. Two such amplifiers are used, one for each electrode, when recording with differential electrodes. The signal from the micropipette electrode is first passed through a preamplifier with a high impedance, capacitance compensated input (WPI M701), since the impedance of the micropipette electrode is of the order of 100 Megohms. After that, the signal takes a conventional route, through a low level preamplifier to the oscilloscope. The occurrence of a single fiber action potential is detected as follows: The sweep trigger level of the oscilloscope is adjusted so that action potentials (spikes) trigger a sweep. The trigger signal from the scope is used to generate .1 ms pulses that are detected and stored by a PDP-12A computer, to construct PST histograms.

For recording of signals from differential and round window electrodes an averager (Fabri-Tek instrument computer

model 1072) is used. This averager can be connected to the PDP12 computer through a digital interface, so that the computer can store the data on its digital tape for off-line analysis.

The greatest difficulty in the experiments was maintaining contact with a fiber for a time enough to obtain complete data. This required up to 15 minutes of contact. Many fibers were contacted for longer durations, but most of them faded away in less time.

Histograms. A convenient way of presenting single fiber data is to construct histograms, where the abscissa represents time and the ordinate shows the number of spikes detected within each time interval. The usefulness of histograms lies in the fact that responses of auditory fibers are random spikes, and a single sample of the spike activity due to a tone burst, for example, does not give a consistent picture, from sample to sample. One can only talk about the probability of a spike occurring in a certain interval of time, given a certain stimulus. The histogram is an excellent indicator of the probability of firing, and the greater the number of samples collected, the clearer the pattern of firing probability becomes (Goldstein and Kiang, 1958).

Averaging. The averaging technique is a very powerful

tool in recording faint bioelectric signals, and in auditory physiology some special methods are worth mentioning. The response to a stimulus A+B can differ from the sum of the responses to A and B presented individually. To analyze the influence of B upon A, an often used technique is to present A+B, then subtract from that response the response to B presented alone. This can render the response to A visible, even when B elicits a much larger response than A. This technique is used in the experiments in chapter 3 to render visible the response to a tone burst influenced by a low frequency stimulus. First both the tone burst and the LF stimulus are presented together, then the LF stimulus is presented alone and the two responses subtracted from each other.

2.5 Special stimuli.

In the experiments described in Chapter 3, the stimuli used were of somewhat unusual kind. They were synthetized by a digital computer using analytical formulae for the waveform.

Low frequency stimuli. The experiments used low frequencies in an attempt to "bias" the basilar membrane, and also to find the phase of firing of nerve fibers due to these stimuli alone. These LF stimuli were of two types, continuous sinusoids and Gaussian impulses.

The function $y=\exp(-t)^2$ is here called a Gaussian impulse, due to its similarity to the Gaussian curve in statistics. This function never becomes zero, but even for t=3, the value of the function is only .00012, or 78 dB below the value of the peak, at t=0. The Gaussian impulses were generated from this formula. The digital-to-analog converter has a 14 bit word length. At the peak of the Gaussian curve all 13 bits were set (1 bit for sign). At t=-3 and t=3 only one bit is set. Thus the transition from the end of the signal generated by the computer and the following silence is as smooth as possible. In the experiments described in Chapter 4, the Gaussian function above, with the extremes at x=-3 and x=3 was used scaled in two ways, one spanning over 10 milliseconds, with peak at 5 ms, the other spanning 20 ms, having its peak at 10 ms.

Figure 3.3 shows the voltage fed to the earphone and the resulting sound pressure in front of the eardrum of the chinchilla. Note that the sound pressure that arises from the earphone as a result of using a Gaussian impulse as driving voltage is not exactly a replica of that voltage, although the main qualities of the impulse remain the same. It was felt that attempting to generate a compensated wave for obtaining a sound field with perfect Gaussian characteristic was not worth the effort, since the results obtained with the Gaussian voltage were satisfactory, and at any rate, the cochlear microphonic was used to infer basilar membrane movement.

The sound pressure level due to the Gaussian impulses cannot be measured by the conventional method of passing the sinusoidal signal from the monitoring microphone through a narrow band filter and then measure the level of the component at the specified frequency. In the results presented in Chapter 3, the SPL of Gaussian impulses is estimated by comparing the peak of the pressure produced by the Gaussian impulse with the peak of the sound pressure produced by a sinusoid of 100 Hz.

Tone bursts of very short duration are used as "probes" on different phases of the LF stimuli. These tone bursts have to be short without excessive spectral spread. The reason for using short tone bursts is to be able to conclude that the response that they elicit is generated within a known short period of time. It is demonstrated in section 3.4 that even 4 cycles of a sine wave with a cosine envelope,

$V(t)= A(1-\cos(2\pi t/dur))\sin(2\pi Ft),\ 0<t<dur, F=4/dur$,

where F is the frequency of the sine wave, and dur is the duration of the burst, can be used as a stimulus with the capability of evoking whole nerve action potentials comparable to those elicited by longer tone bursts.

Chapter 3

DYNAMICS OF COCHLEAR HAIR CELLS

3.1 Introduction.

This chapter describes experiments designed to gain a better understanding of the relationship between basilar membrane movement and auditory nerve activity. Gross electrical activity from the cochlea, as well as responses from single auditory nerve fibers were recorded for this purpose.

The relation between BM movement and potentials at the round window is the subject of section 3.2. Section 3.3 is a report on whole-nerve action potentials elicited and influenced by low frequency tones. These LF tones were used to "bias" the basilar membrane in order to find the influence of such bias on the AP responses to tone bursts. Section 3.4 describes experiments on single fiber responses; these experiments were done to relate single fiber activity to basilar membrane movement. As before, the technique used was that of presenting tones together with low frequency "biasing" tones.

3.2 Round window electrical activity and basilar membrane movement.

It was of primary importance in this study to be able to assess the BM movement, at least for low frequency

stimuli. Unfortunately, within the confines of the present work, this movement could only be evaluated indirectly. The cochlear microphonic as measured with differential electrodes in SV and ST has been shown to be well correlated with the BM movement (Chapter I). Differential electrodes are difficult to insert in the same preparation, together with pipette electrodes for single unit recordings, because these experiments require ventral and dorsal approaches, respectively. Also, differential electrodes are invasive to the cochlea. Therefore in this section the feasibility of using a round window electrode to assess the BM movement is investigated. The question then is how well does the activity recorded by a round window electrode correlate with that measured with differential electrodes. If this correlation is good, then the RW activity may be used to estimate BM movement.

A. Low frequency sinusoids.

The electrical activity at the RW due to a sinusoidal tone is a distorted sinusoid, as described in Chapter I. It is generated by a superposition of various electrical responses, among them the cochlear microphonic. For low intensities, the CM itself is relatively free from distortion when recorded with differential electrodes. The distortion seen at the round window is caused by other sources, mainly neural. It is difficult to electrically filter neural responses from cochlear microphonic responses

without introducing an unknown phase shift in the CM. For example an AP can appear once each cycle, contributing to the fundamental component in a phase different from the CM phase. As intensity is increased the CM grows faster than the neural components. For high sound intensities the CM is the largest component of the signal. At these levels (over 80 dB SPL) the contribution of the neural components to the RW waveform is small. The phase of the CM part of the round window activity can therefore be assessed from the traces at high levels. At 80 dB SPL the positive peak is broader than the negative one. The positive and negative peaks occur at equal intervals from one-another. Using the positive peak as a phase reference gives results that are comparable to results from DIF electrode recordings. Figure 3.1 shows various waveforms of RW activity for different intensities of the sound.

The next issue is to correlate the phase of the waveform with the one obtained for differential electrodes. One chinchilla was prepared with differential electrodes in the first cochlear turn. A teflon coated silver wire was placed at the rim of the round window, by the methods described in Chapter 2. Low frequency sinusoids were then presented and the phase of the waveform at each electrode was measured relative to the phase of the voltage driving the earphone. The results are shown in figure 3.2. Note the 180 degrees difference between the DIF and the RW electrodes. It is remembered that the DIF by definition is

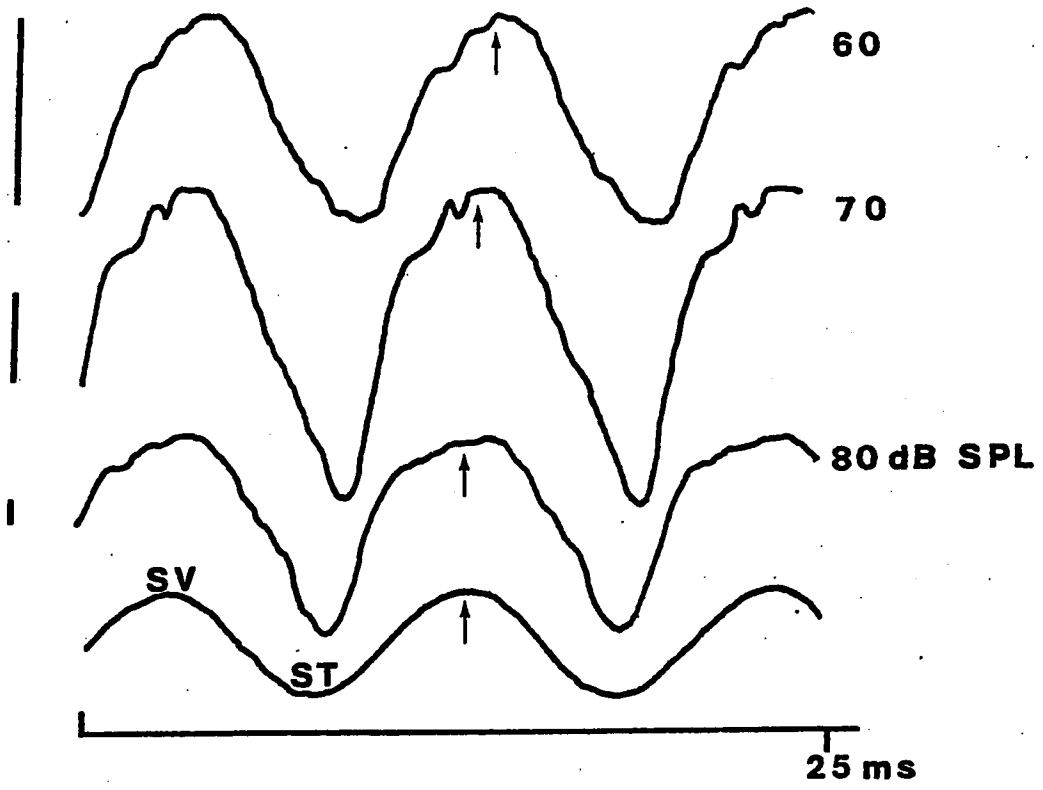

Figure 3.1. Round window electrical activity due to a 100 Hz sinusoidal continuous stimulus of 60, 70 and 80 db SPL. Arrows indicate the part of the wave used to infer the phase of the CM. D. Inferred BM motion. Bar = 60 microvolts.

the activity SV-ST; the round window activity is most like ST, therefore the 180 degree difference. From figure 3.2 one sees that the phase of the round window activity is very near that of the ST activity for frequencies between 50 and 200 Hz.

The (SV-ST) signal, which is assumed to be the best correlate of BM movement, is close to 180 degrees apart from the ST phase for the same frequencies.

The RW waveform phase, as found by the method described was therefore used as a correlate of BM movement. The relation inferred is that depicted in figure 3.1D, namely that the BM, at least in the first turn, is deflected towards scala vestibuli when the positive peak occurs on the RW waveform. The inter-animal variability of the phase at 100 Hz, as related to the voltage of the stimulus was usually within 40 degrees of the value in figure 3.1. This phase, measured for each animal, was used as a correlate of the BM movement.

In the experiments described hereafter we used 100 Hz as the low frequency stimulus. This is a somewhat unfortunate choice in the case of the chinchilla because of the steep phase change that takes place in the CM around 100 Hz (Dallos 1970a), and probably contributed to the observed variability of phase from animal to animal. The choice of 100 Hz was mainly done because it stimulates fibers of high characteristic frequency with reasonable intensity levels of

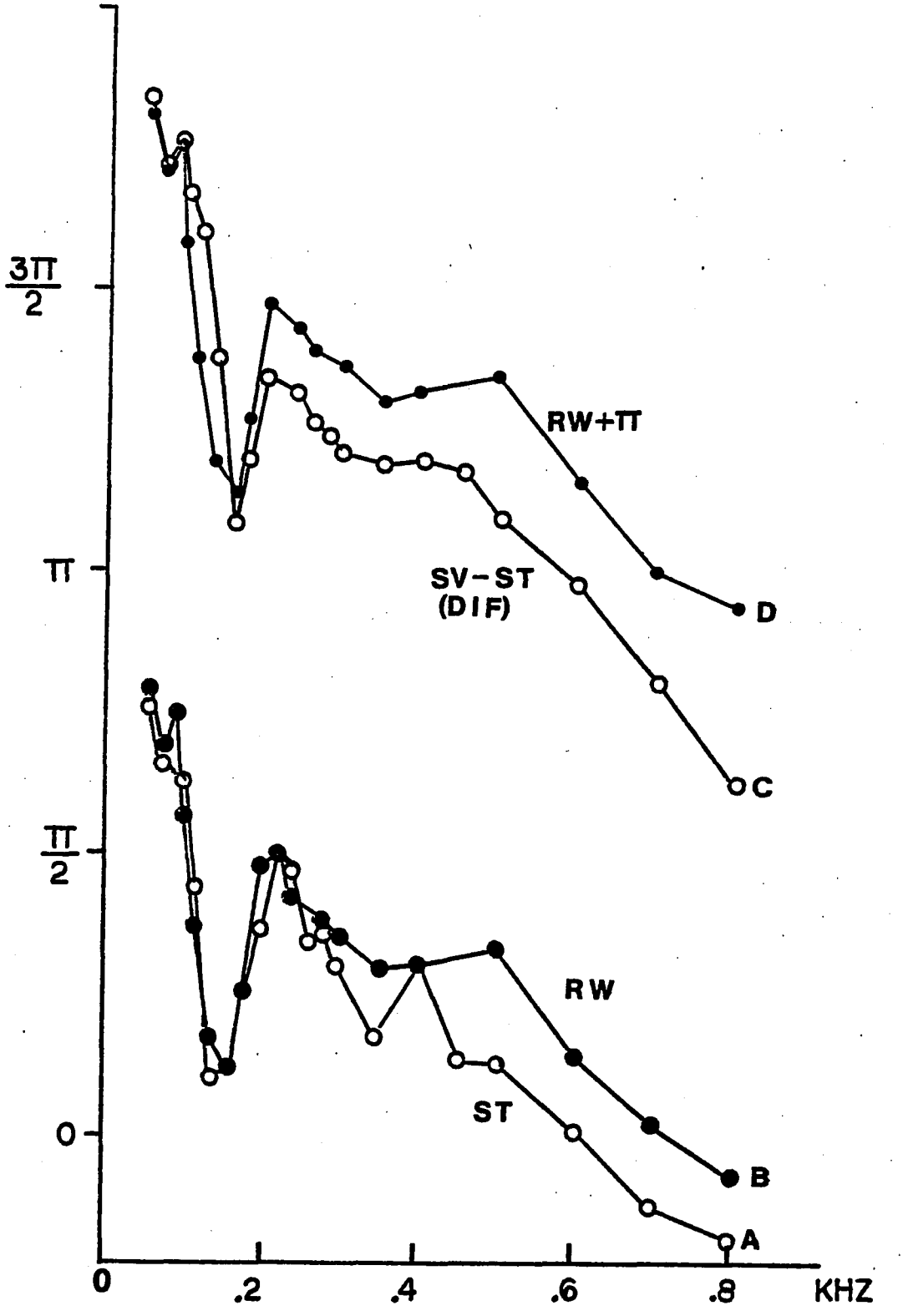

Figure 3.2 Phases of cochlear electrical activity to low frequency sinusoids. A. ST electrode; B. RW electrode; C. SV-ST (DIF). D. RW+180 degrees to compare with DIF.. Common reference: Voltage to earphone (A78).

sound, and still is many octaves below the CF of the fibers of interest.

B. Low frequency Gaussian impulses.

The main reason for using Gaussian shaped impulses is the fact that one can have large time intervals beween pulses, so that the effect of one impulse on the cochlear activity can easily be assigned to that particular pulse. This is in contrast with the use of continuous sinusoidals, where adaptation and other integrative effects make harder the interpretation of the results. Other researchers have used Gaussian shaped impulses because their derivatives are very different from one another, simplifying analysis of results (Zwicker 1977). This quality of the impulses was not explored here.

The electrical response, measured at the round window, to such stimuli is depicted in figure 3.3, for a condensation impulse, and in figure 3.4 for a rarefaction impulse of 10 ms (see Chapter 2 for explanation of parameters).

The RW trace appears to be a superposition of neural and CM activity. This can be seen by comparing it to the trace marked ANOXIC in figures 3.3 and 3.4. This trace was obtained at the end of the experiment by clamping the trachea and recording the RW activity after 10 minutes. The approximately derivative relationship between the sound and

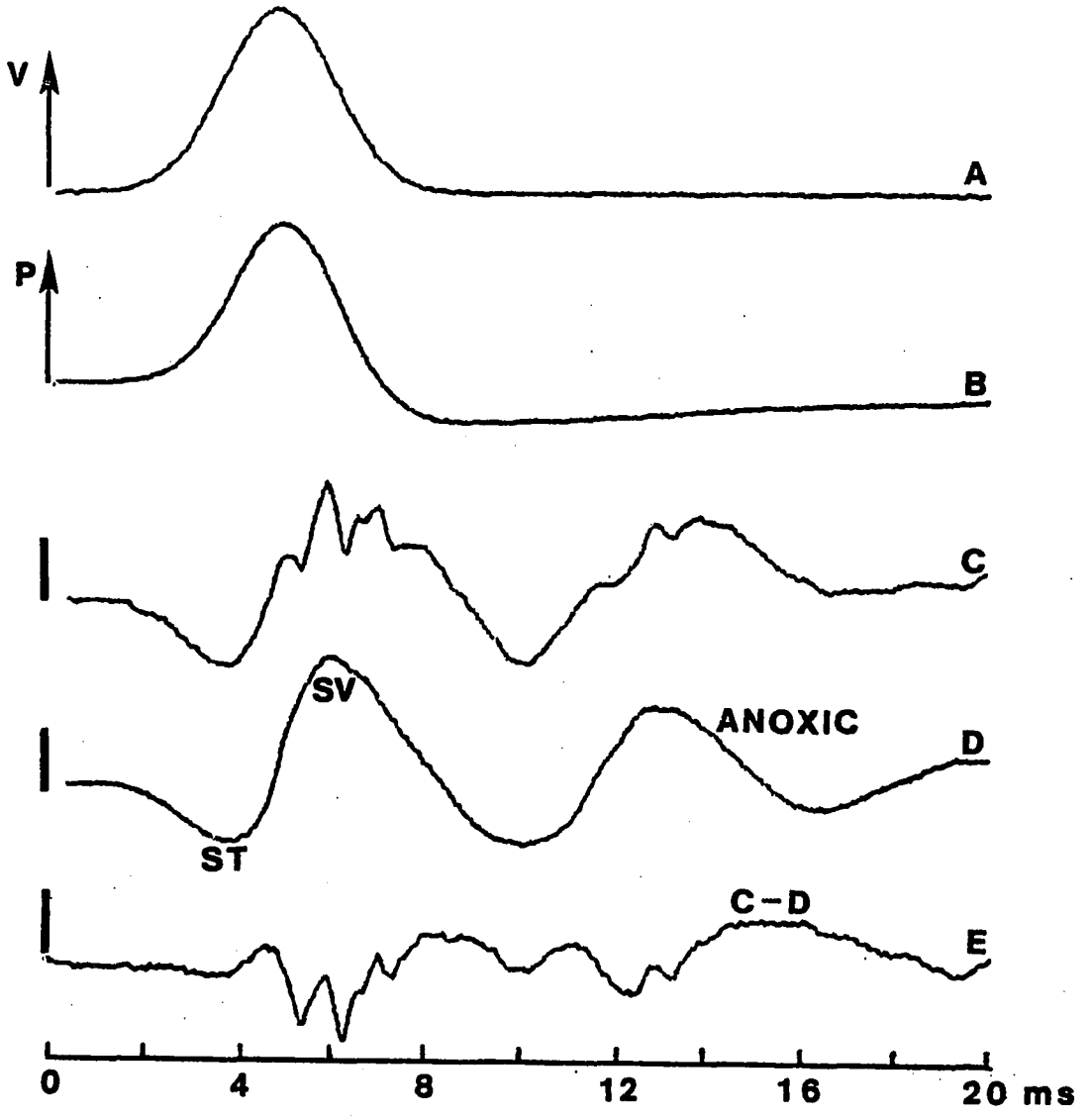

Figure 3.3 Round window electrical activity due to a Gaussian impulse. A. Voltage to earphone (condensation impulse); B. Sound pressure in front of tympanic membrane; 10 dB higher sound level was used; C. RW response; D. Same as C, for anoxic animal; E. Difference C-D. Bar= 200 microvolts (A78).

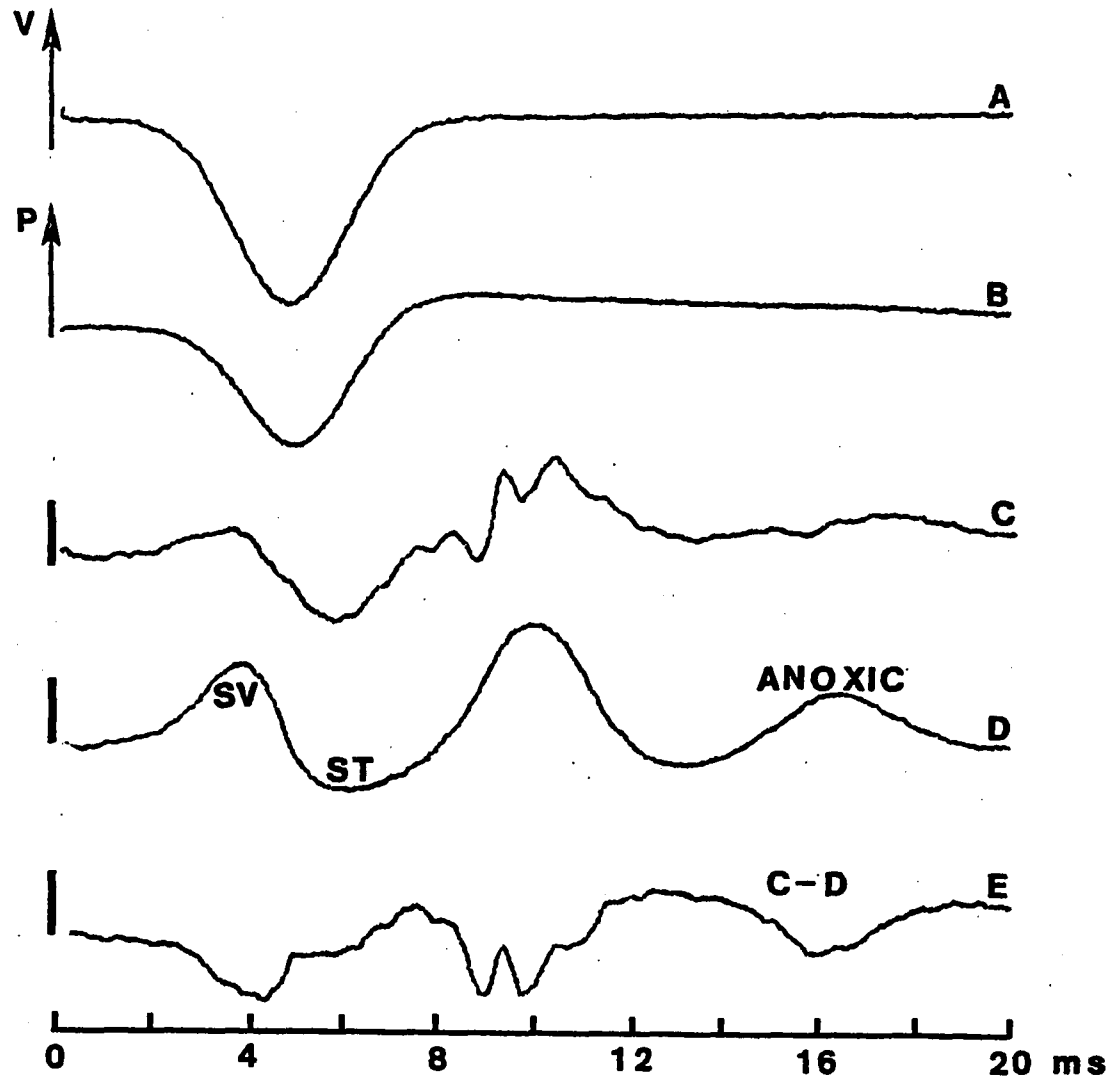

Figure 3.4 Round window electrical activity due to a Gaussian impulse. A. Voltage to earphone; B. Sound pressure in front of tympanic membrane (rarefaction impulse); C. RW response; D. Same as C, for anoxic animal, 10 dB higher sound level was used; E. Difference C-D. Bar=200 microvolts (A78).

anoxic RW activity is valid for the first 8 ms or so; after that a second and third maxima occur, at approximately 10 and 13 ms. It is not known whether this oscillation of the RW CM is a reflection of the BM movement, but as shown in subsequent sections on AP and single unit studies, these secondary peaks produce masking effects similar to the effects produced by the first and second maxima of the RW CM. In order to get records from the RW, such as in figure 3.3D and 3.4D it is necessary to work with an anoxic animal. Anoxia effectively eliminates neural activity, leaving the cochlear microphonic component unchanged in form, although smaller than in the normal animal.

C. Tone bursts superimposed on low frequency tones.

In the subsequent experiments short tone bursts are delivered to the ear, together with a low frequency tone. The goal is to place the tone burst in time such that it is delivered to the cochlea when the low frequency stimulus (LF) is driving the basilar membrane in a certain direction. Here the round window CM is used as an indirect indicator of BM movement.

A tone burst of short duration will elicit a round window response as depicted in figure 3.5. This response consists clearly of two components, the CM and the AP. Let us consider the CM. As intensity of the sound increases,

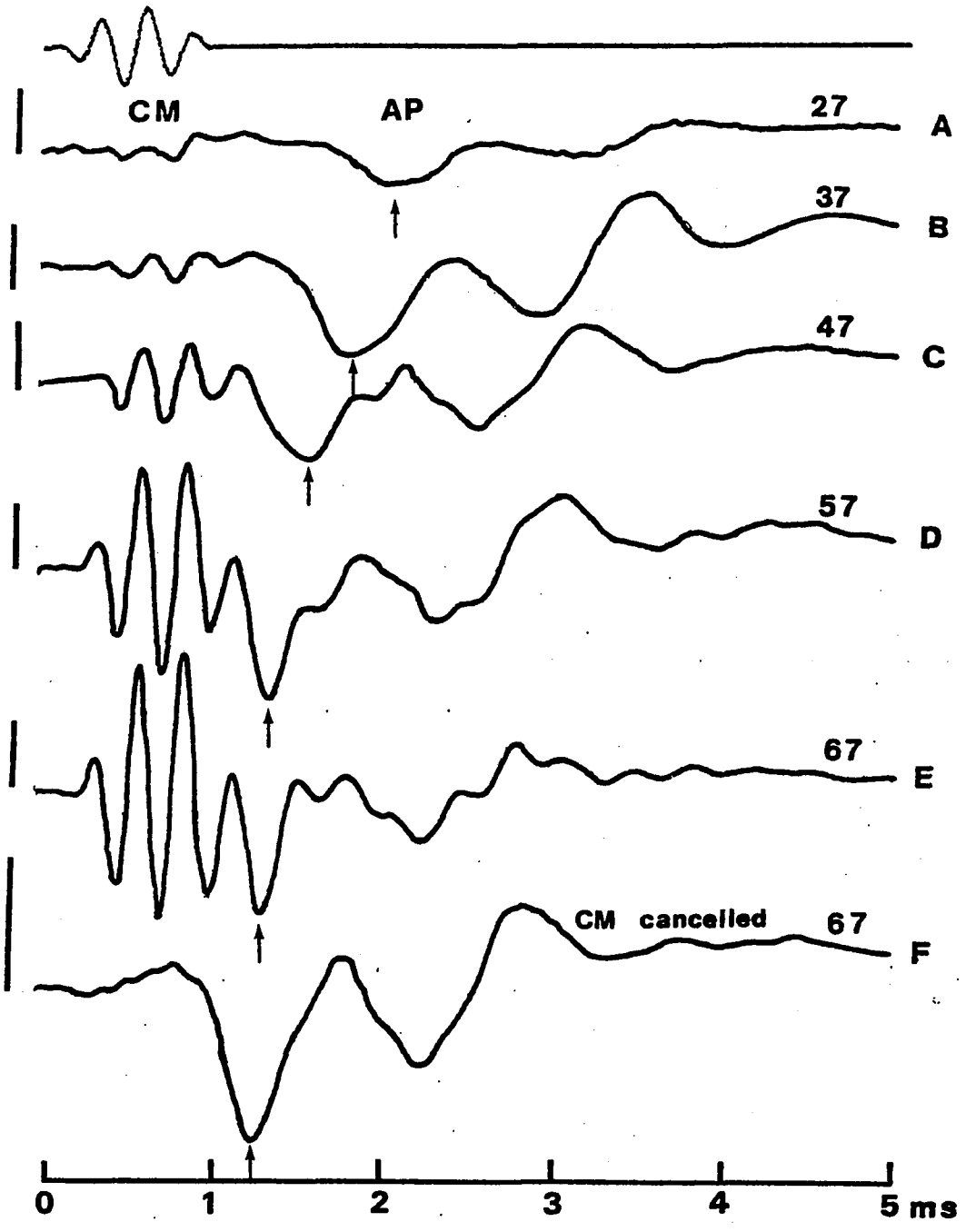

Figure 3.5 Round window responses to a tone burst of 4 kHz, 1 ms duration. Top trace: Voltage to earphone. A. to E: Round window response, 27,37,47,57,67 dB SPL; G. 67 dB SPL, but every other burst of opposite polarity to cancel CM. Bar = 50 microvolts (A78).

the CM does not change in its time of occurrence; also, for different frequencies, the time of occurrence of the CM remains unchanged. Thus, cochlear travel time is small since the RW CM is probably mostly generated by basal structures. The delay seen from the onset of the stimulus voltage is due to the propagation time from the earphone (Distance circa 4 cm, giving .13 ms delay), through the middle ear and to the place of CM generation, a total of circa .17 ms.

A tone burst can be presented simultaneously with a LF stimulus. Figure 3.6 shows the RW response to two stimuli presented together, the tone bursts occurring at different phases of the LF period. Using our assumptions on the correlation between BM movement and RW activity, we conclude that the BM is displaced approximately towards ST when for example the tone burst in figure 3.6D is delivered, and towards SV in figure 3.6E. This we believe is true for the BM movement in the base of the cochlea. The question is whether this relationship holds true as the stimulus travels on the basilar membrane, to the location where the tone burst elicits the action potential. This is important in the context of the next section, where we study the masking of the AP due to the tone burst, brought about by the LF tone.

The phase relation between the tone burst and the LF tone will hold if there is no dispersion on the basilar

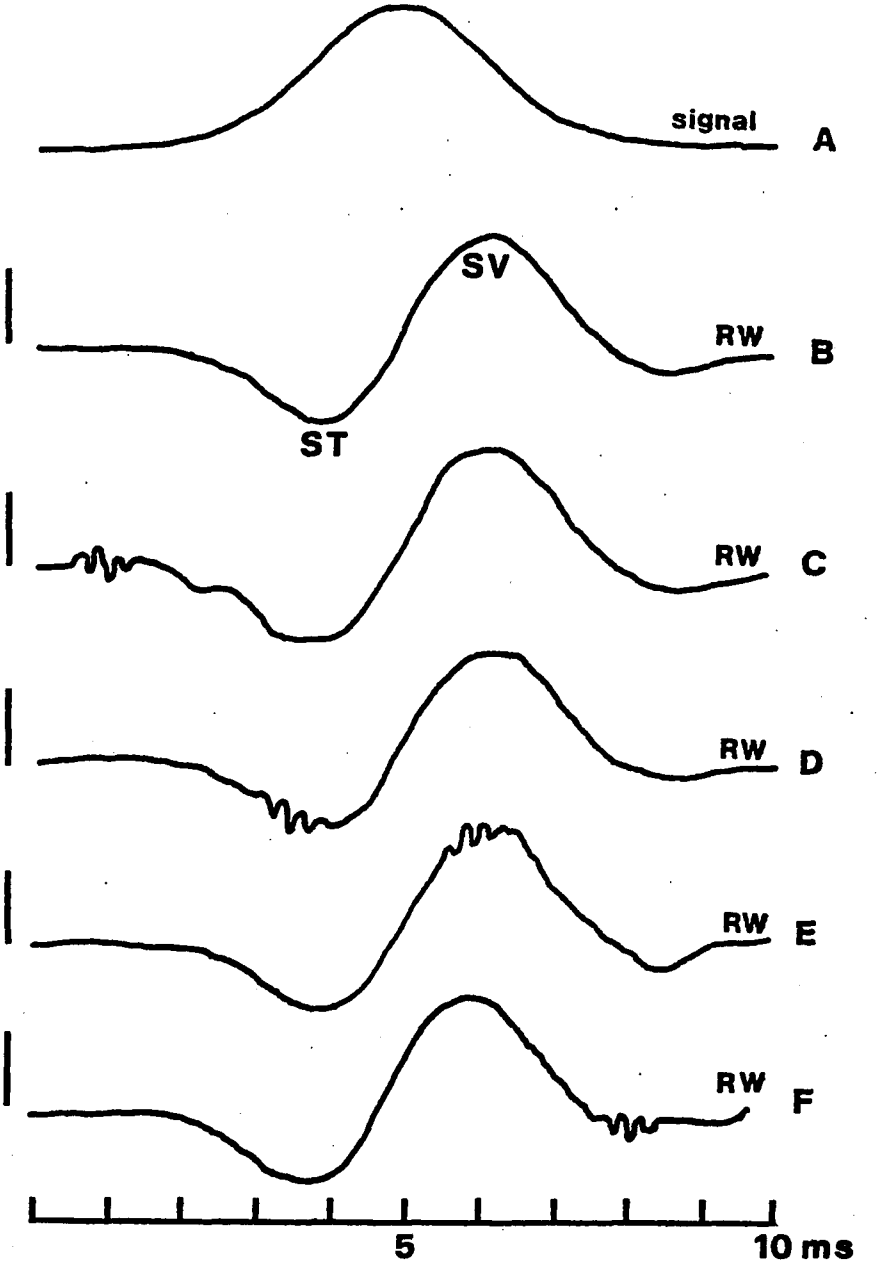

Figure 3.6 Tone burst presented with a Gaussian pulse. A. Voltage to earphone, a condensation impulse; B. Response to A alone; C. to F: Response to A and a tone burst of 4 kHz 1 ms duration starting at 0, 2.5, 5.0 and 7.0 ms, relative to the start of the toneburst voltage and to the start of the Gaussian impulse. Bar = 50 microvolts (A68).

membrane i.e. if stimuli of different frequencies travel with the same velocity. Dallos and Cheatham showed in 1971 that there is no dispersion in the cochlea, because the travel time determined from phase of cochlear microphonics seemed to be constant for all frequencies below the best frequency for the cochlear turn in question. There is some controversy as to this statement, especially for the region of CF, but for our purposes, the error in neglecting dispersion is small: A worst-case example from single unit data illustrates that dispersion is sufficiently small to be disregarded. As pointed out in Chapter 1, a figure such as 1.11 can be used to calculate the travel time, or rather, the total delay that occurs from the sound generation to the spike detection. This time delay is the slope of the curves seen in figure 1.11. As expected, this slope is of the same magnitude as the click latency of the fibers. This is true because of the approximately nondispersive qualities of the system. Figure 1.11 shows no peculiarities as the stimulus frequency approaches the CF of the fibers. For example, the curve for the fiber of CF=2.1 kHz has a slope of approximately 2.2 ms, which is comparable to click latencies for fibers of such CF. On the other hand, figure 3.7 shows a change in slope to occur as frequencies are scanned, indicating different delays for different frequencies. This change in slope is the largest reported in the literature. Note that a mere change in the phase of firing of a fiber within the cycle of the stimulus would only introduce a

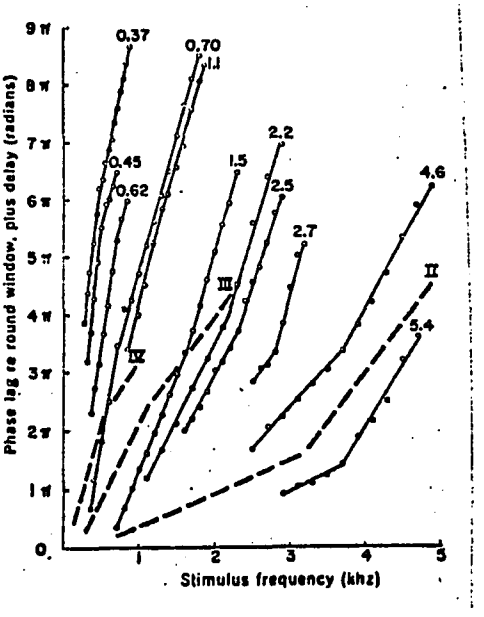

Figure 3.7 Phase of firing of fibers to tones of different frequencies. The slope of the curves is the delay between the stimulus generation and spike detection. Therefore, a slope change indicates a difference in delay. The observed changes in slope could be due to different conduction velocities for different frequencies along the basilar membrane, i.e. dispersion. From Pfeiffer and Molnar, 1970.

step, and not a change in slope in the curves. Taking the curve for the fiber of 4.6 kHz as an example, the high frequency slope is 1.2 ms, but the low frequency slope is only .6 ms. If this is due to dispersion on the basilar membrane, we can conclude that a 100 Hz stimulus arrives to the CF location 1.2 ms - .6 ms = .6 ms earlier than a 4.6 kHz stimulus. This translates into a phase discrepancy (between tone burst and LF tone) of 22 degrees, between the phase observed at the round window and the actual phase relation at the CF location.

Another argument that can be used to conclude that dispersion is negligible is the fact that the click latency of a 4 kHz fiber is in the order of 1.6 ms. At least one millisecond of this time is due to synaptic delay and neural conduction. The dispersion therefore, between what is observed at the round window and what actually occurs at the CF location has an upper limit of .6 ms.

From the observations in the preceding experiments, we conclude that a round window electrode can be used in lieu of a scala tympani electrode to infer basilar membrane motion, at least for the low frequencies considered. Further, by placing a tone burst in a certain phase of the response elicited by a LF tone, it is assumed that the burst will stay in that approximate phase relation with the LF tone to the CF location.

3.3 Whole nerve action potentials modulated by low frequency stimuli.

This section describes experiments on the influence of low frequency (LF) stimuli on whole nerve action potentials. These APs were evoked by short high frequency tone bursts presented together with LF stimuli. First we look briefly at the action potentials evoked by the low frequency tones presented alone.

A. Action potentials due to LF tones.

A continuous sinusoid having a frequency up to approximately 2000 Hz will in each cycle elicit a discrete whole nerve action potential that can be recorded from the round window or with differential electrodes. These APs are readily apparent in the round window potential for frequencies under 300 Hz, since they appear as a distortion in the sinusoidal waveform. For frequencies over 300 Hz, the AP and the CM are not easily separated and special methods such as AVE recordings, masking, or anoxia are needed to distinguish the AP from the CM. This section is a report on the action potentials elicited by sinusoids between 50 and 200 Hz and by Gaussian impulses. Of interest here is the time of occurrence of the AP as related to the cochlear microphonic. All the data are from one representative animal, where a complete set of measures was obtained.

Figures 3.3 and 3.4 provide a good example of action potentials due to a low frequency stimulus. A shows the voltage used to drive the earphone; B represents the sound field in front of the tympanic membrane; this is a condensation impulse. C and D are recordings from a round window electrode, C being from the normal anesthetized animal and D from the same animal made anoxic by clamping the trachea for 10 minutes. This method effectively abolishes the neural activity. This anoxia was induced at the end of the experiment, when all normal data had been collected. E shows the difference between C and D (D was obtained with a 10 dB higher sound level). In E, a typical N1-N2 complex is visible, the time between the N1 and N2 being around 1 ms.

Figure 3.4 shows traces similar to figure 3.3 but here the stimulus was a rarefaction impulse. As before the trace of the anoxic RW CM is used to infer BM movement.

Looking at the time where the AP occurs in the two figures, one sees that it is within the interval 1.8 to 3 milliseconds after the negative excursion of the round window cochlear microphonic. Note that in figure 3.3, a second AP appears after the second negative excursion of the RW CM.

Eldredge (1976) found similar time relation to hold between CM and AP. He used impulses of shorter duration than the ones used here.

The action potential responses to the Gaussian impulses of long duration are only detectable at high intensities of sound. Within the 25 dB range of SPL that was available, the latency of the AP did not vary much. Figure 3.8 shows traces equivalent to trace E in figure 3.4, for a series of intensities of the rarefaction impulse. As seen, the latency of the AP is nearly constant (The reason for the distorted AP in trace B is unknown). Also note that the size of the AP only increases by a factor of 2 for a 20 dB range of sound intensity.

The same observations hold for the AP generated when continuous sinusoids are used as stimuli. Figure 3.9 shows the RW electrical activity caused by a 100 Hz stimulus. B is a low pass filtered version of A, obtained by digital filtering; C is the difference between A and B, rendering the AP visible. An N1–N2 complex can be seen, although it is not as apparent as in the Gaussian impulse case. Figure 3.10 shows traces equivalent to figure 3.9 for a 200 Hz stimulus.

The latencies from the minimum of the RW CM are nearly constant, as in the case with Gaussian impulses, over the range of intensities where AP can be distinguished. For tones with period from 5 to 20 ms (200 to 50 Hz) and in the range of 60 to 90 dB SPL, the N1 appears in all cases in a range of 2.1 to 3.2 ms after the negative deviation of the RW CM.

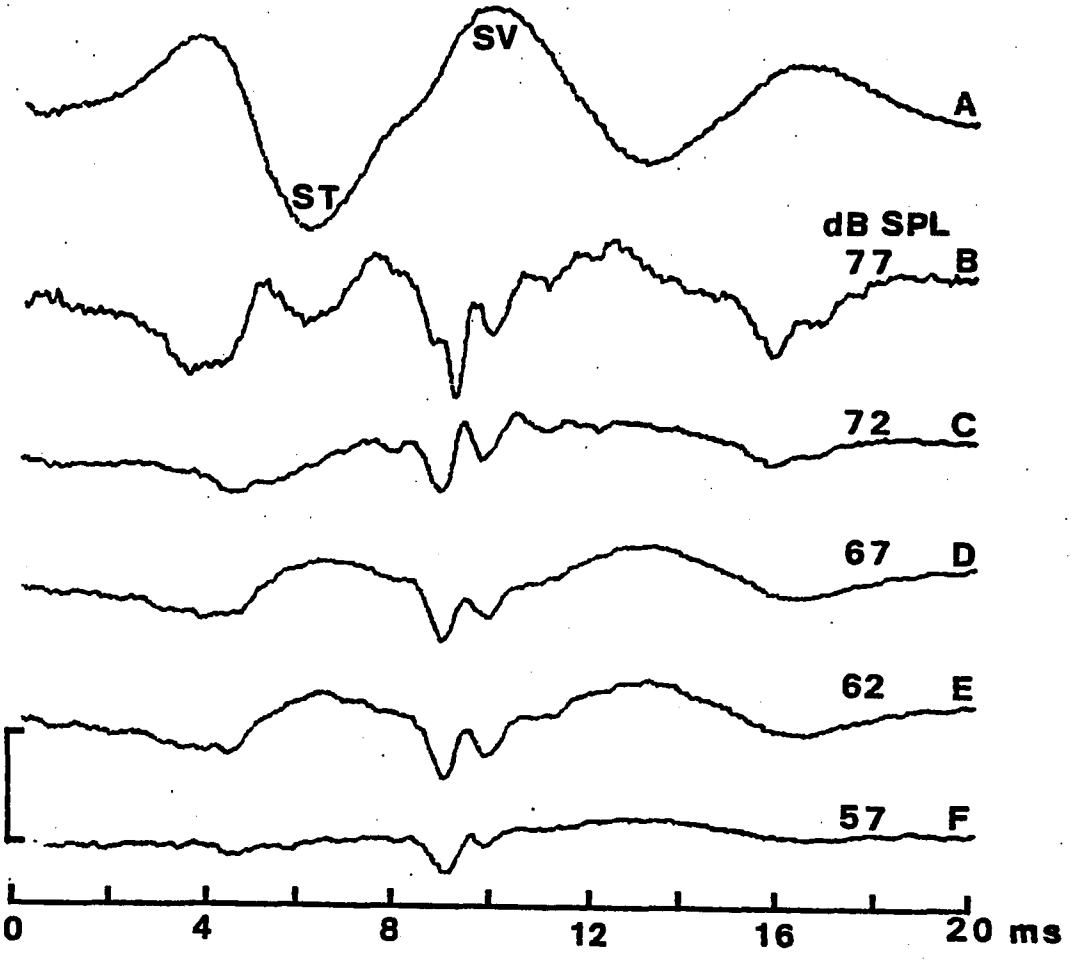

Figure 3.8 Action potentials due to a Gaussian rarefaction impulse for various intensities of the impulse, recorded from a RW electrode. A. RW CM response for phase comparison, anoxic animal: B. through F: Difference between normal and anoxic cases to render AP visible, for the peak equivalent intensities 77, 72, 67, 62 and 57 dB SPL (The peculiarity seen in the AP of trace B is of unknown origin). Bar = 200 microvolts (A78).

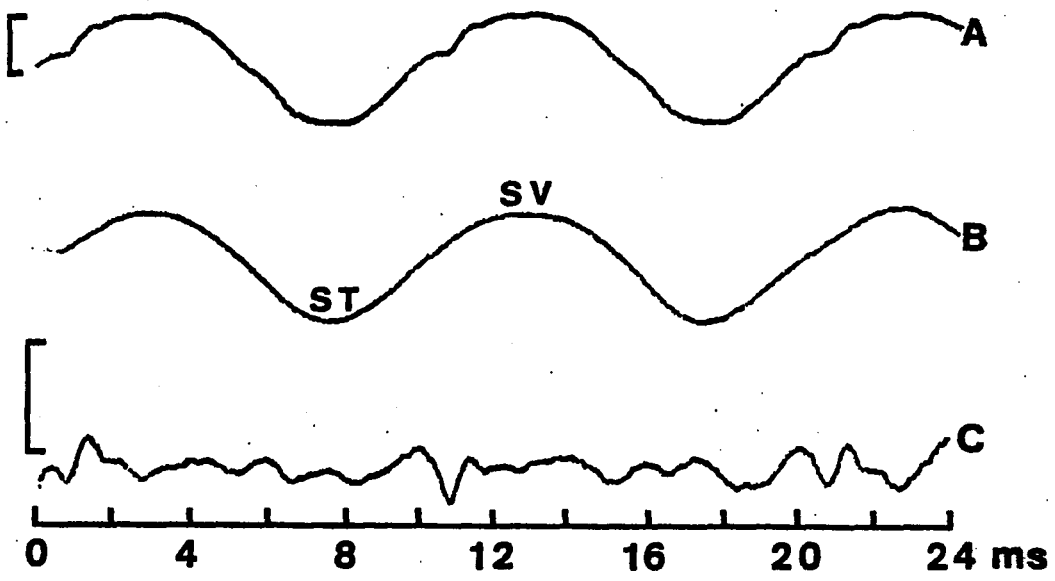

Figure 3.9 A. RW response to 100 Hz, 79 dB SPL continuous sinusoid. B. Same as A, passed through an FFT low pass filter (to simulate anoxic condition, comparable to trace D, figure 3.3); C. Difference between A and B, enhanced by a factor of 2 to render AP more visible. Bar = 200 microvolts (A78).

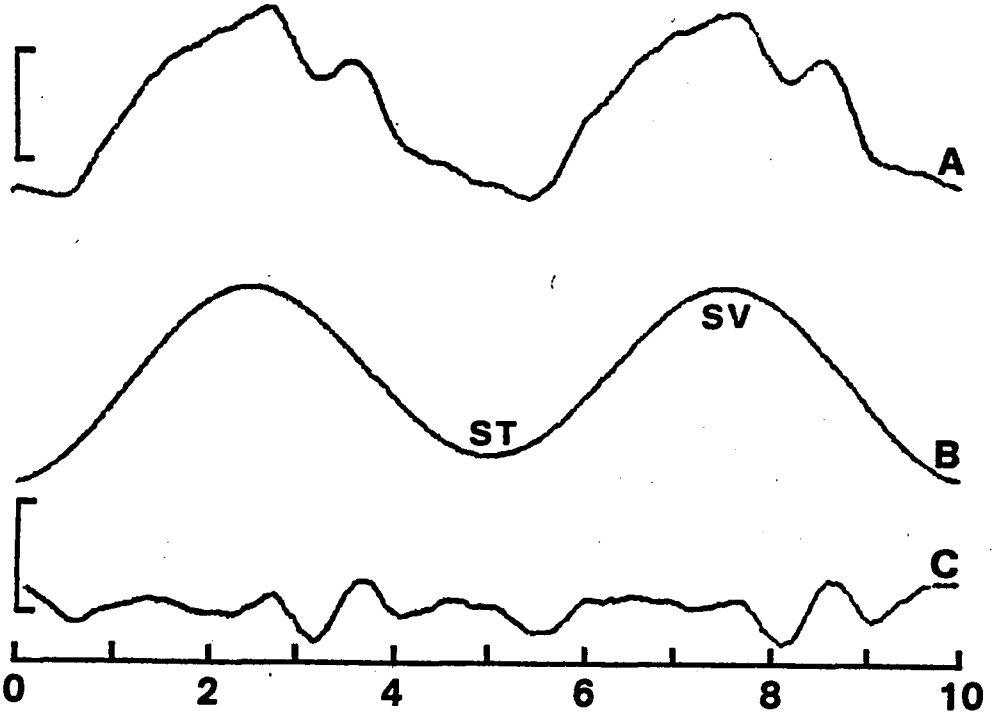

Figure 3.10 A. RW response to 200 Hz, 72 dB SPL continuous sinusoid. B. Same as A, passed through an FFT low pass filter (to simulate anoxic condidtion, comparable to trace D in figure 3.3); C. Difference between A and B, enhanced by a factor of 2 to render AP more visible. Bar = 200 microvolts.(A78).

From the experiments above on the latency of the AP we conclude that, since the latency is fairly constant over the intensity range studied, the AP must be generated predominantly by the same elements, i.e. as intensity varies, the responding population is the same. In a slightly different experiment, Eldredge (1976) came to the same conclusion. By masking the basal elements with high pass filtered noise, he was able to show that the AP is generated mostly by neurons of CF higher than 6 kHz. The Gaussian impulses used here are of lower frequency than the impulses used by Eldredge. The phase of the BM movement where excitation of auditory fibers occurs due to a LF tone cannot be assessed exactly from these data, because the CF of the fibers that contribute most to the AP is unknown. We can estimate, using the fact that the latency of fibers that possibly contribute to the AP lies in the interval 1.2 to 3.5 ms (figure 3.11), that most fibers fire in the interval from 1.4 ms before maximum ST displacement of the BM to 2.1 ms after this displacement. In other words, for low frequency stimuli, the auditory fibers fire in the general displacement of the BM towards ST.

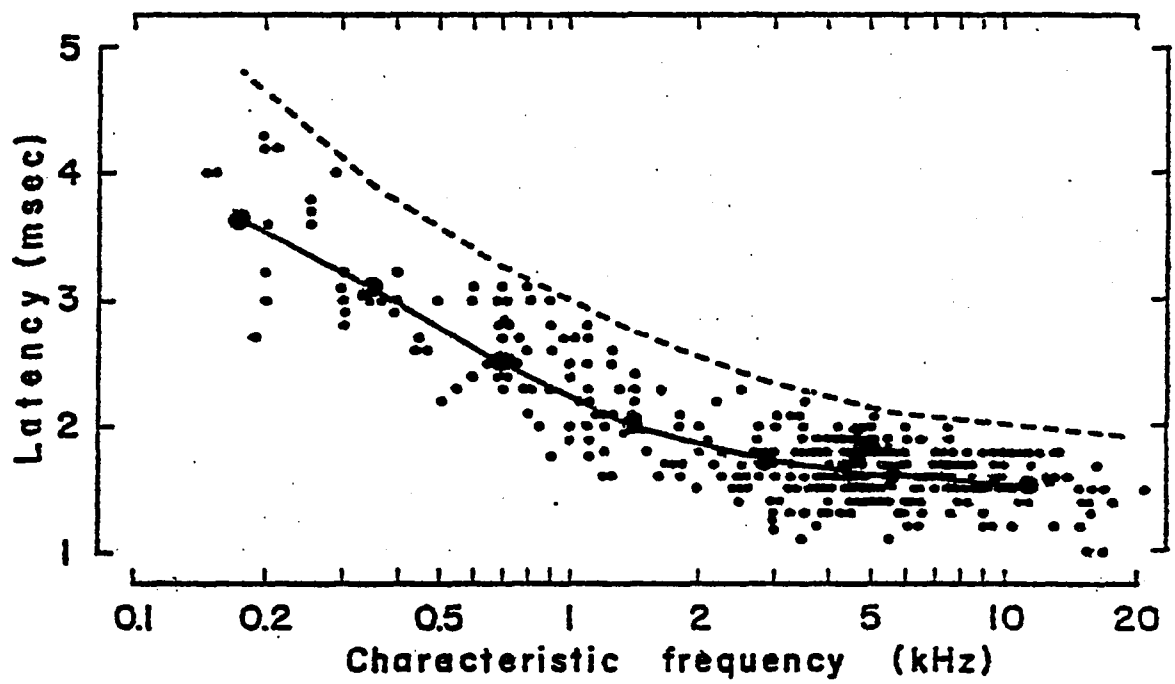

Figure 3.11 Latencies of single auditory nerve fibers of the chinchilla for rarefaction clicks. From Harris, 1977.

B. Action potentials due to tone bursts modified by LF stimuli

With the exception of the action potentials shown in figure 3.5, all the experiments described thus far have dealt with APs that are elicited by single cycles of a continuous tone or Gaussian type impulses. In the following experiments responses to the onset of tone bursts of short duration were studied, and the influence of low frequency stimuli on those responses examined. Sinusoidal 100 Hz tones and Gaussian impulses were used as LF stimuli; the tone bursts consisted of a few cycles of a tone with triangular or cosine envelope. Recordings were from RW of chinchillas (7 animals).

Figure 3.5 shows a tone burst of 4 kHz, 1 ms duration, having a cosine envelope, and the response to it for various intensity levels. The CM is always at the same location in time, although it of course increases in amplitude for higher SPLs. The AP on the other hand grows, and at the same time the N1 latency becomes shorter as intensity is increased. It is a well documented phenomenon that the AP to tone bursts behaves in this fashion (e.g. Deatherage, Eldredge, and Davis 1959). To study the influence of a low frequency stimulus on the response to a tone burst, a short burst will give a better resolution in time of the event being studied. However, the center frequency of a burst contains less of the total energy content as the burst is

shortened. Figure 3.12 shows some spectral qualities of tone bursts with cosine envelopes. A tone burst of 4 cycles, for example, has 83% of the energy within half an octave band surrounding the center frequency of the burst (trace A); the spread in frequency of the first lobe, to the frequency where the amplitude is 20 dB below the center frequency is within one octave (trace C).

More important for our purposes is to test the adequacy of using short bursts for exploring cochlear function. Figure 3.13 shows that 4 cycles of a given frequency, presented in a cosine envelope, elicits an AP with N1 latencies that depend on the center frequency of the burst. Five different frequencies were used, .5, 1, 2, 4 and 8 kHz; in all cases, the total duration was 4 cycles, making the spectral content similar, only a shift in center frequency taking place.

The latency of the N1, as function of the frequency and intensity of the burst found here is comparable to the latency of AP for longer tone bursts. The action potential thus seems to be generated entirely by the first few cycles of a tone burst. Pestalozza and Davis (1956) found a similar relationship to hold for the latency of the AP in guinea pigs. The APs due to the short length tone burst apparently do have the same characteristics as a longer tone burst in eliciting APs. Therefore short bursts, down to only 4 cycles in duration, with a cosine envelope, were used

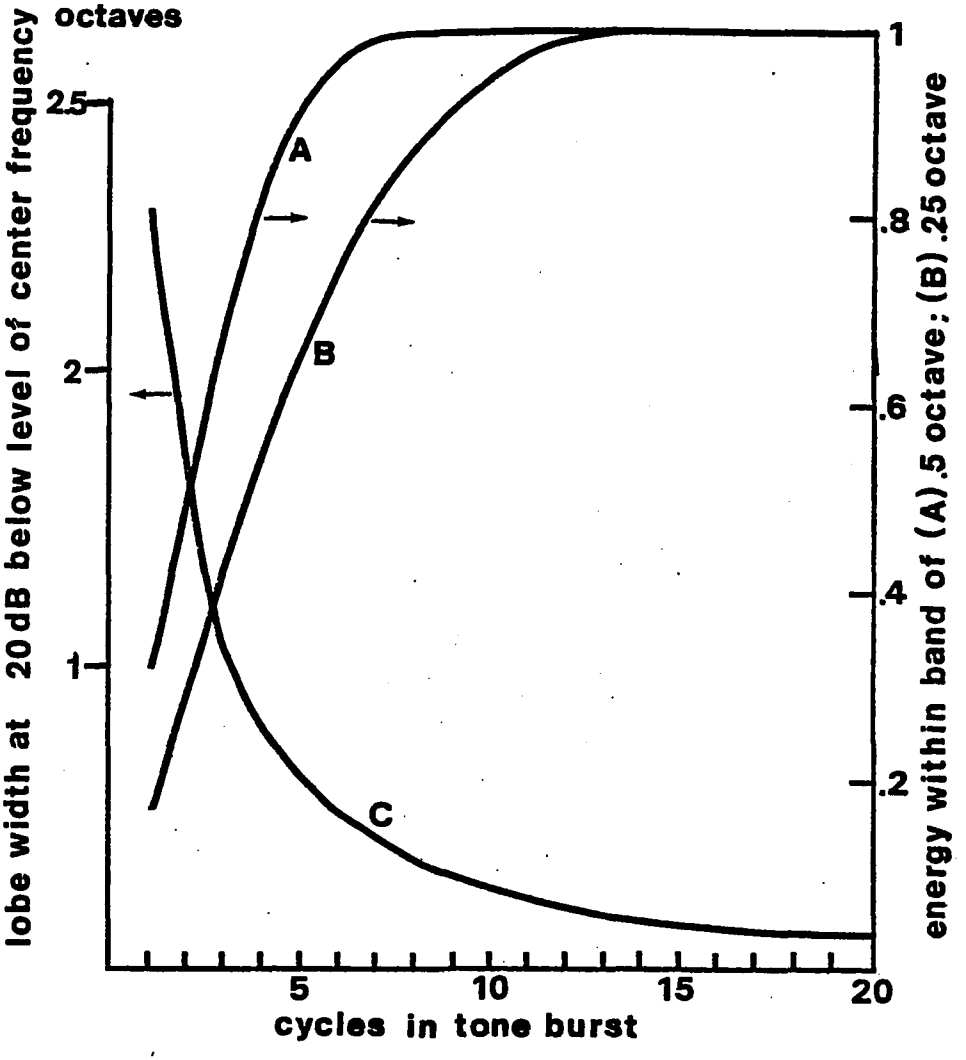

Figure 3.12 Spectral characteristics of tone bursts with cosine envelopes, calculated with fast Fourier transform. The formula used was $V(t)=(1-\cos(2\pi f/NCYC))*\sin(2\pi ft)$, where NCYC is the total number of cycles of the tonebursts. Spectral spread was defined as the frequency where the amplitude was more than 20 dB below the amplitude of f. Energy was defined as the relative energy content of the (A:1/2 and B:1/4) octave band surrounding the center frequency f. Although continuous lines are drawn, the data are valid only for integer values of cycles in tone burst.

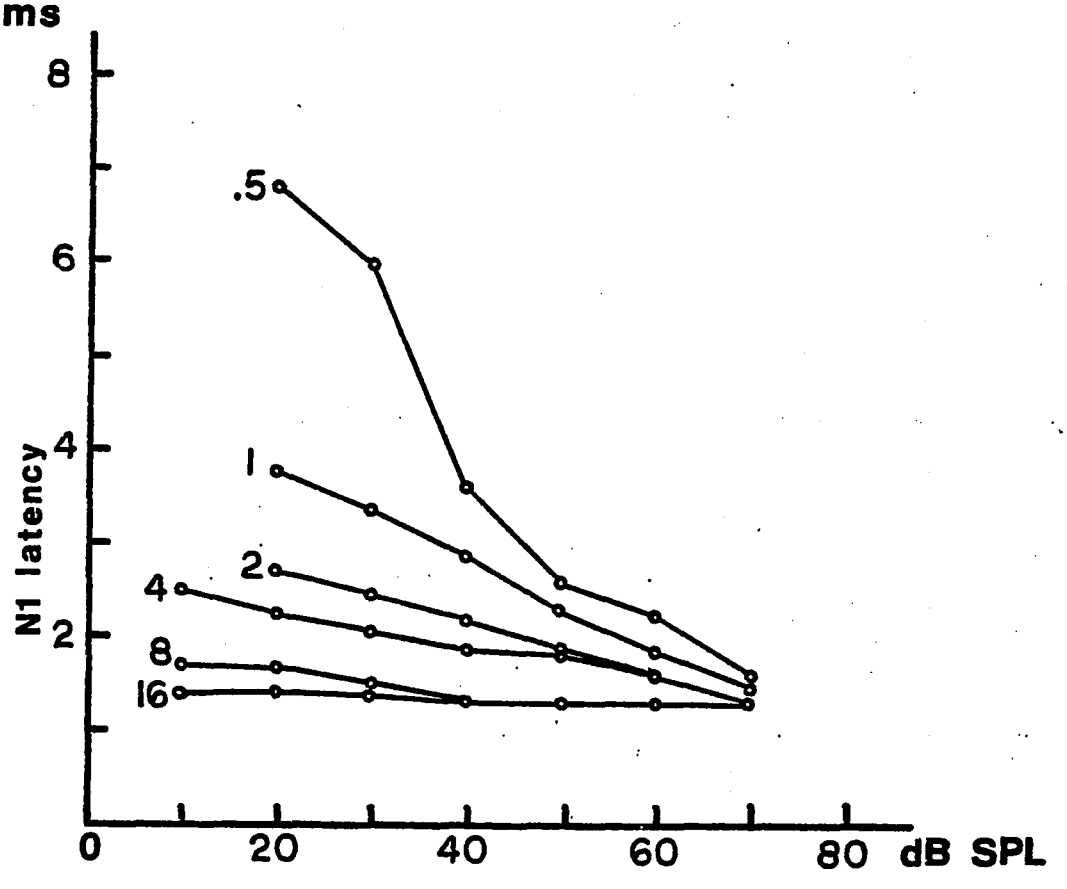

Figure 3.13 N1 latencies as function of sound pressure level. Stimulus was 4 cycles of a tone with cosine envelope. Parameter is frequency of the tone in kHz (A71).

as probe stimuli.

These tone bursts were presented together with a 100 Hz sine wave. Figure 3.14 shows that placing the burst at different phases of the 100 Hz tone has a drastic effect on the AP due to the bursts. The activity in response to the 100 Hz alone has been subtracted from all the graphs, so as to render the AP due to the tone burst visible.

The phases shown are referred to the RW CM. Thus, 90 degrees means that the burst was placed so that the center of its CM appeared on the positive maximum of the CM due to the 100 Hz tone. This corresponds to our inferred displacement of the basilar membrane towards the scala vestibuli.

The AP due to the tone burst has a latency of between one and two milliseconds. This latency does not have to be taken into account when inferring the phase of BM movement where masking takes place, since the phase is referred to the CM. In other words, we infer the masking to occur in the ST displacement of the basilar membrane because when the tone burst-elicited high frequency CM is positioned at the negative maximum of the (low frequency) RW CM due to the 100 Hz tone, masking is seen. The AP disappears completely for 270 and 315 degrees. Note that the size of the CM is almost half of the tone burst alone condition if the burst is presented in the 270 degree phase of the RW CM due to the 100 Hz. This variability of the CM was not explored; it is

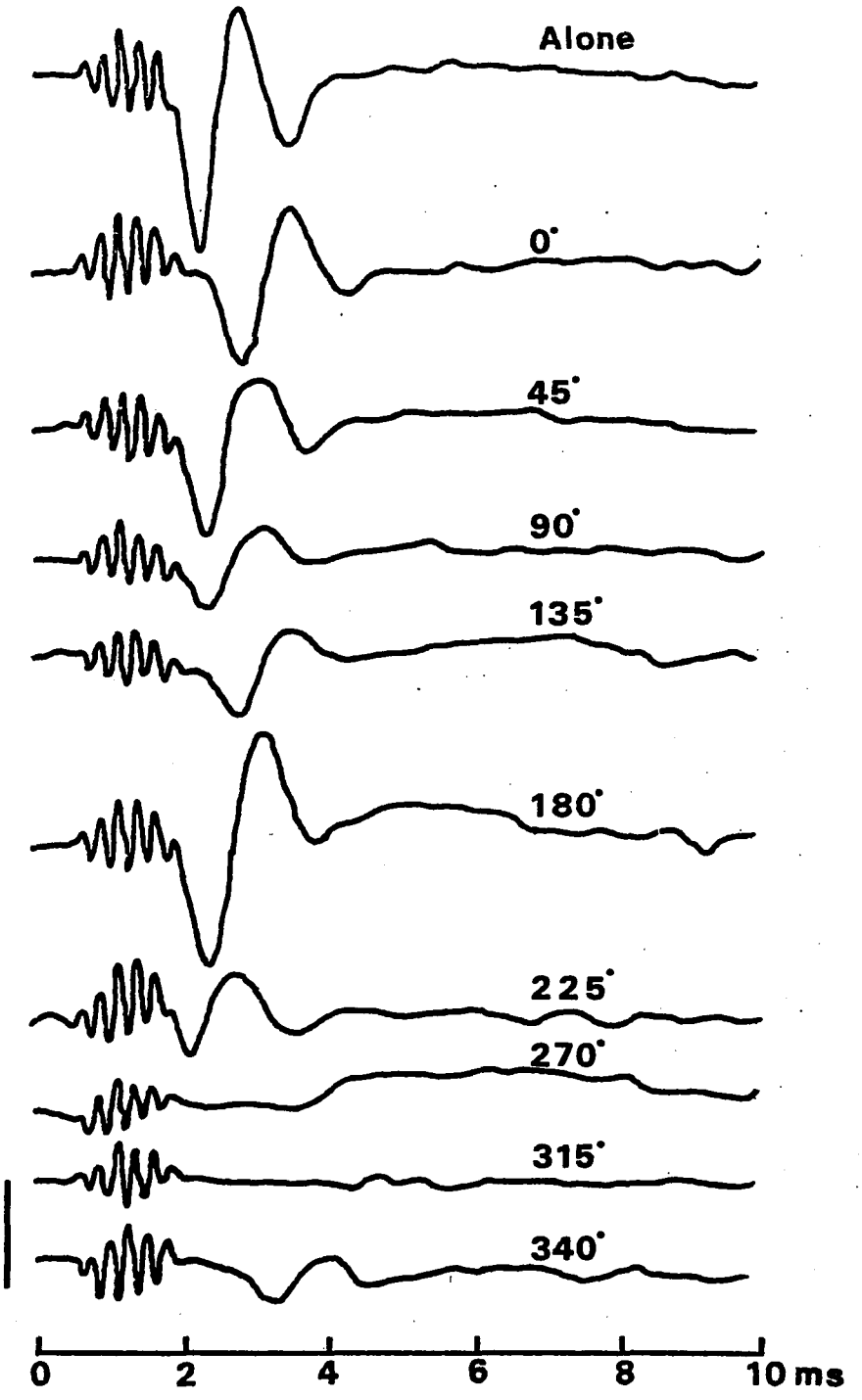

Figure 3.14 Tone bursts of 4 kHz, 45 dB SPL, 1.5 ms duration, placed at different phases of a 100 Hz continuous tone of 80 dB SPL. The phase angles shown are those of the 100 Hz RW CM where the CM due to the tone burst appears. The basilar membrane movement can be inferred from these angles, 90 degrees meaning maximum deflection towards scala vestibuli. Activity to 100 Hz alone has been subtracted from all graphs. Bar=100 microvolts (A64).

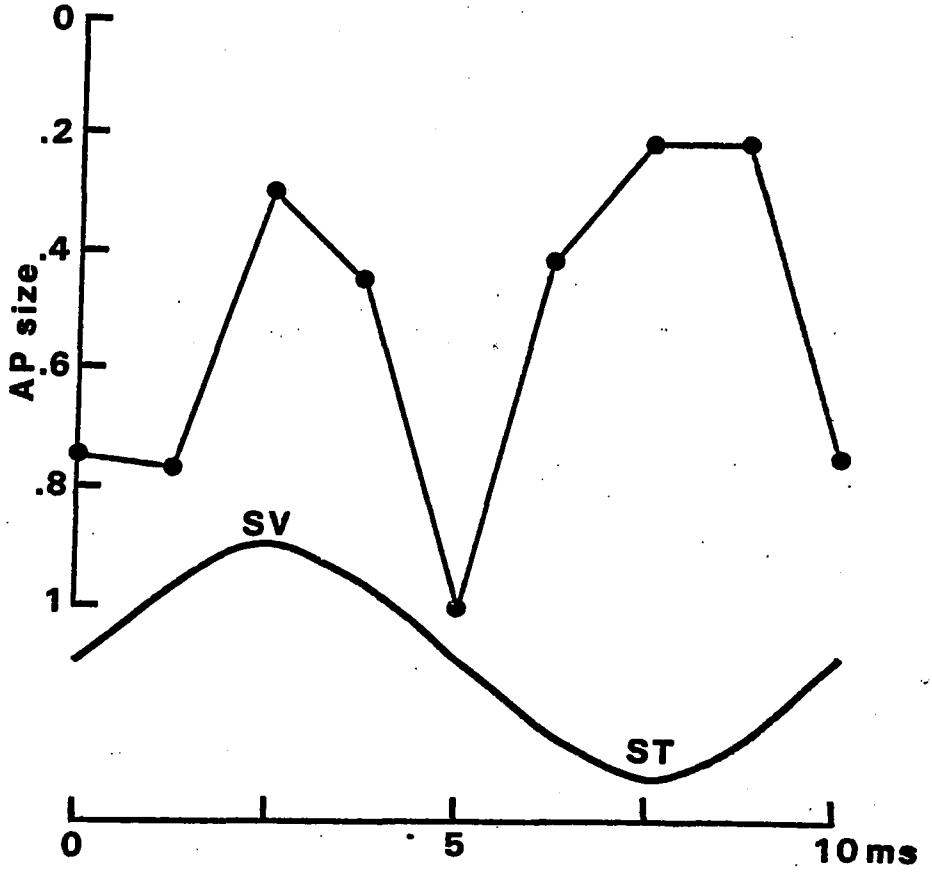

Figure 3.15 (Data replotted from fig. 3.14) Influence of a 100 Hz tone of 80 dB SPL on the size of the action potentials due to a tone burst of 4 kHz 50 dB SPL, of 1.5 ms duration, as the tone burst is presented on different phases of the 100 Hz tone. The phases are relative to the CM due to the 100 Hz tone, where the center of the CM due to the tone burst appears. Ordinate scale is relative to size of AP when tone burst is presented alone. The vertical scale is reversed for easier comparison with next figures (A64).

a manifestation of the CM interference phenomenon. When plotting the size of the AP as a function of phase (figure 3.15) it is apparent that the curve has two peaks (corresponding to minimum size of AP), one at the inferred SV and one at the inferred ST displacements. At 180 degrees the AP has almost the same size as the AP to the tone burst alone; the 100 Hz tone does not seem to mask the AP in that phase.

Returning to figure 3.14, note the change in the N1 latency, as the burst is presented in different phases of the 100 Hz signal. Very careful timing of the probe tone burst, and also the presence of the CM as a time reference in figure 3.14 rule out the possibility that the obtained latency shift be an artifact. This magnitude of latency shift is unusually large in the example shown. The latency shift depends on the intensities of the LF tone and the high frequency tone burst. Other combinations of intensities yield similar results for the amplitude of the AP, but the large latency shift is seldom observed. More commonly it is in the order of .2 ms. It is possible that the latency shift is only observed in a very narrow region of levels for the tone burst and the low frequency tone.

The latency shift was not further explored in the present study. In the literature, however, there is an interesting correlate of this phenomenon. This is the data of Zwicker (1977, fig. 14), where he shows that a very

substantial pitch increase is noticed for the probe tone in a masking-period pattern study, when the probe tone is placed in a phase of a 40 Hz tone where maximum masking occurs. Perhaps this pitch shift is produced at the cochlear level. The shorter latency that we observe for the AP at e.g. 225 degrees in figure 3.14 could be a reflection of the fact that more basal fibers respond to the stimulus. Although a causal relationship between these observations cannot be demonstrated, it is worth pointing out the qualitative agreement between these data.

Another way to quantize the effect that the low frequency has on the AP is to try to maintain the size of the AP due to the tone burst a constant, by adjusting the SPL, while placing the tone burst on different phases of the LF stimulus. Figure 3.16 shows the results of such an attempt. The intensity of the burst was increased or decreased so that the AP became of the same size as the AP elicited by the tone burst presented alone.

Note that the CM, despite changes in amplitude, does not change its location in time. The N1 latency shift is .2 ms, between 90 and 0 degrees, a more typical value than those in figure 3.14. These types of data are shown replotted in figure 3.17. Three different levels of 100 Hz were used to generate the curves shown. For lower levels of 100 Hz, masking of the tone burst occurs in the phase where the basilar membrane is inferred to be displaced towards ST.

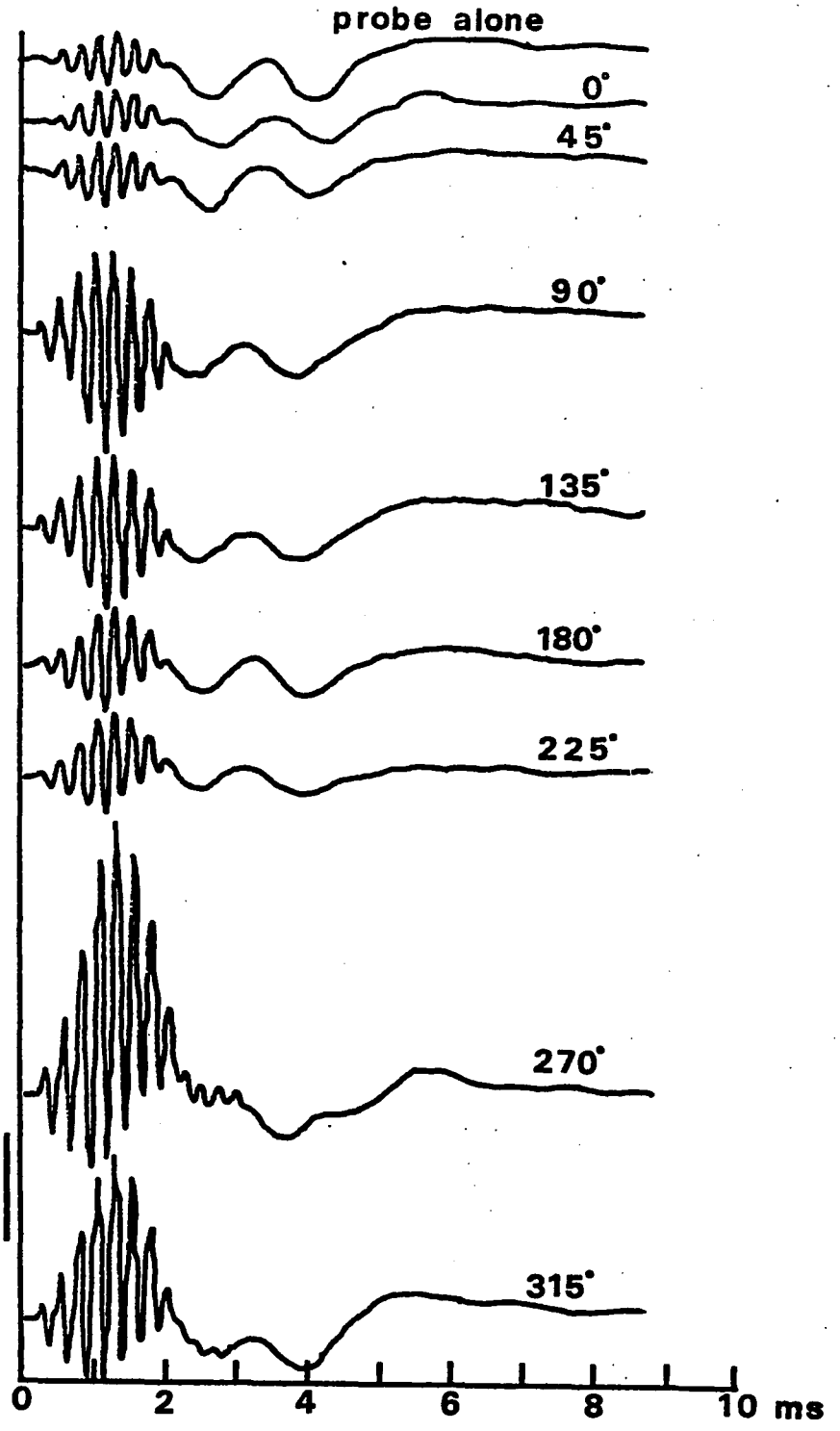

Figure 3.16 RW activity due to a tone burst of 4 kHz, 2 ms, presented together with 100 Hz, 70 dB SPL. Level of burst was adjusted so that size of AP became the same as that elicited by the tone burst alone at 50 dB SPL. Angles indicate where the center of the CM due to the tone burst appeared on the CM due to 100 Hz. Bar=100 microvolt (A66).

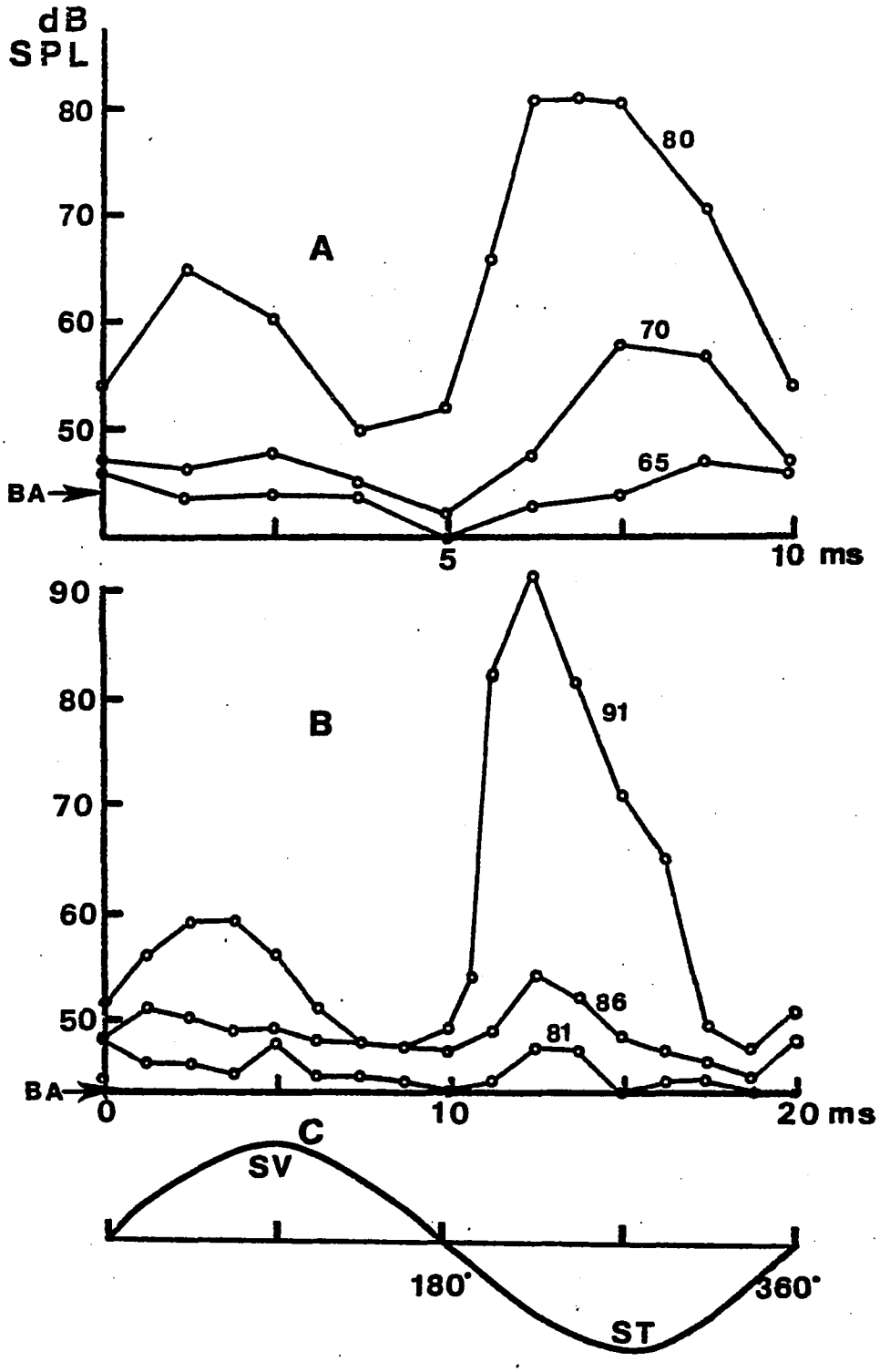

Figure 3.17 Level of tone burst needed to restore the size of the AP to the same as when the burst is presented alone. Bursts of 4 kHz, of 1 ms duration superimposed on A. 100 Hz, and B. 50 Hz. Parameter is SPL for the low frequency tone. C. Inferred BM movement. BA: Burst alone (A65, A74).

It is seen that as intensity of LF increases, two peaks of masking appear, that is to say, a secondary peak appears at 90 degrees, where the inferred displacement of the basilar membrane is towards SV. At 5 ms in curve A, a small but significant deviation of the curve towards lower SPLs is seen. This reminds one of the psychoacoustical "sensitization" that Deatherage and Henderson reported in 1967.

Equivalent curves using 50 Hz instead of 100 Hz as LF tone give similar results, as shown in figure 3.17B. Two peaks of masking appear for high level of the 50 Hz tone. The peaks occur somewhat sooner than the inferred maximum displacement of the BM towards SV and ST.

The curve in figure 3.15 depicts the size of the AP, whereas figure 3.17 depicts tone burst intensity needed to recover the AP to its size when presented without a LF tone. The curves are qualitatively similar. Both have 2 peaks, the peak corresponding to ST displacement of the BM being higher; both have their lowest point approximately in the inferred velocity phase of BM movement, from SV to ST. A more quantitative comparison between them cannot be made, since the nonlinear behavior of the AP makes such comparison unwarranted. Each of the paradigms has its own advantages. Keeping the intensity of the burst constant means that observed changes in the AP can be attributed to the LF tone; adjusting the burst's intensity to get the AP of constant

size is a method more directly comparable to the psychoacoustic "masking period pattern" paradigm of Zwicker (1976a). Emphasis was made on the latter method, that of adjusting the level of the tone burst to maintain the AP size constant, since comparisons to psychoacoustic experiments were desirable.

Note the growth of the higher masking peak in figure 3.17. For 100 Hz, the peak increases about 10 dB for a 5 dB increase in the 100 Hz level. In the 50 Hz case this does not hold, and masking in the inferred ST direction of basilar membrane movement becomes overwhelming for 50 Hz at 90 dB SPL. With an increase of only 5 dB in the level of the 50 Hz tone, one needs almost a 40 dB increase in the level of the probe tone to obtain an AP with the same size as the AP produced by the probe tone presented alone. In general this input-output relationship is very nonlinear.

When a tone burst is presented with a Gaussian impulse, changing the location in time of the tone burst relative to the impulse will have a significant effect on the AP due to the burst, as in the sinusoidal LF case just described. Maintaining the size of the AP constant by adjusting the level of the tone burst, one gets results as in figures 3.18 and 3.19. The masking seems to occur when the round window activity is either positive or negative. By comparing the graphs for positive and negative polarities of the impulse one sees that the largest peak occurs in the negative phase

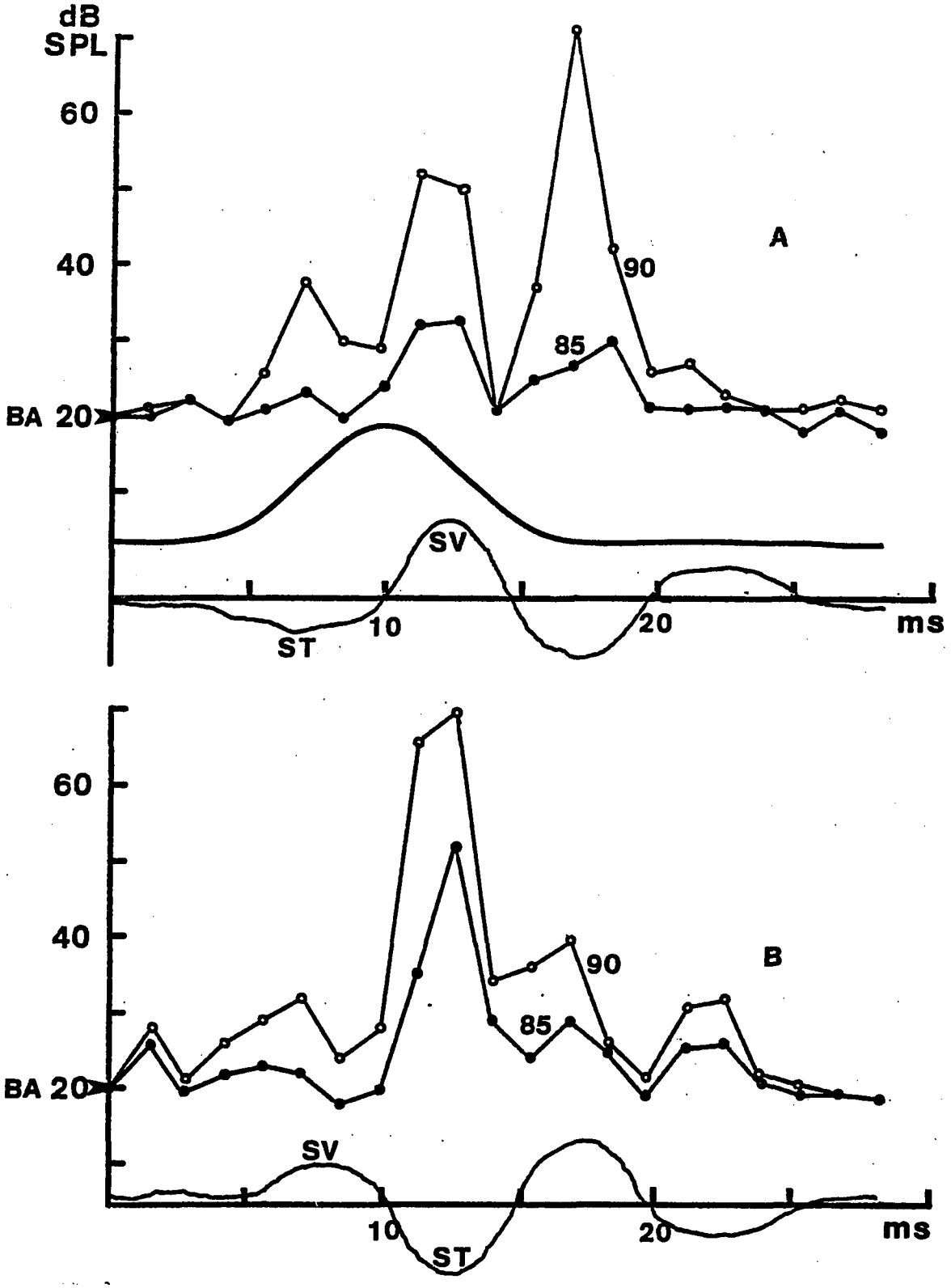

Figure 3.18 AP to tone burst presented with a 20 ms Gaussian impulse. Level of tone burst of 4 kHz, 1 ms duration needed to restore the AP due to the burst to the size of the AP when burst is presented alone at 20 dB SPL. From top: A. Response to condensation impulse, 90 and 85 dB peak equivalent SPL; Signal voltage; RW CM. B. Response to rarefaction impulse, 90 and 85 dB peak equivalent SPL. BA: Burst alone (A74).

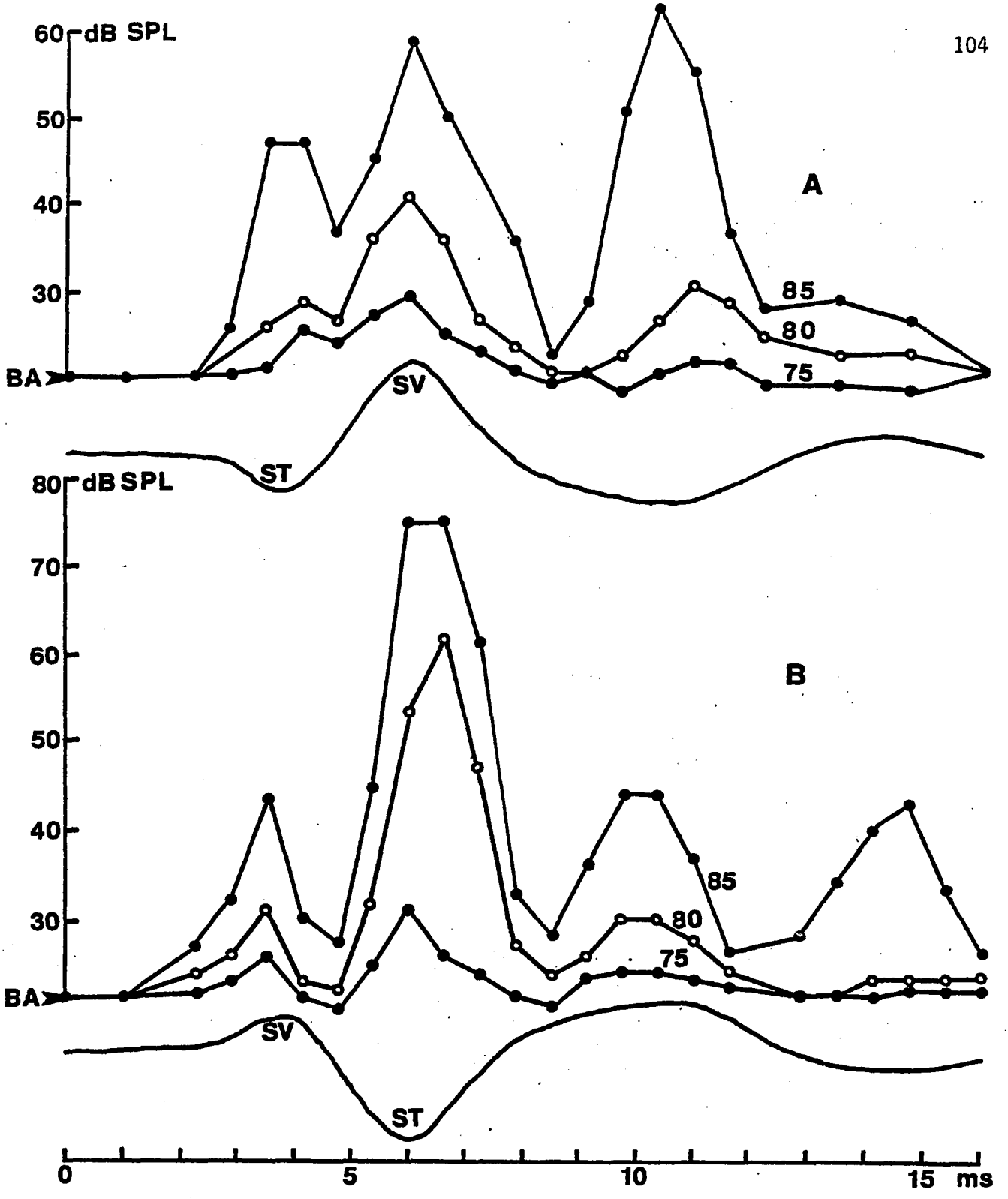

Figure 3.19 AP to tone burst presented with a 10 ms Gaussian impulse. Level of tone burst of 4 kHz, 1 ms duration needed to restore the AP due to the burst to the size of the AP when burst is presented alone at 20 dB SPL. From top: A. Response to condensation impulse, 90 and 85 dB peak equivalent SPL: RW CM. B. Response to rarefaction impulse, 85, 80 and 75 dB peak equivalent SPL. BA: Burst alone (A74).

of the RW CM, a phase we infer to indicate displacement of the basilar membrane towards scala tympani.

An interesting "integrative" effect, that distinguishes these responses from the ones due to sinusoidal tones can be observed in figures 3.18 and 3.19. It is seen that more masking is attained if the RW CM is positive before it becomes negative. In terms of basilar membrane displacement, this translates to stating that a deflection towards SV before a deflection towards ST produces more masking in the ST deflection of the basilar membrane than the masking produced by a deflection towards ST without prior deflection towards SV. This is a demonstration that the response of fibers is dependent not only on the instantaneous displacement of the BM, but also on the recent history of displacement, at least on the last two to five milliseconds.

The two types of low frequency stimuli used - sinusoids and Gaussian impulses - are radically different in nature. The continuous sinusoid will almost certainly cause adaptive mechanisms in the cochlea to affect the responses to tone bursts, whereas the Gaussian impulses are likely to influence the response to tone bursts without much adaptation.The "integrative" effect described above is perhaps the first sign of adaptation, after only a few milliseconds of stimulation: The masking due to a second deflection of the BM due to a Gaussian pulse is different

from the masking due to a first deflection.

In summary, there are two phases in the cycle of a low frequency sinusoidal stimulus where masking takes place. These phases are approximately half a cycle apart. In between these two maxima of masking there is a phase where the low frequency tone has little influence or even produces enhancement of the AP. With the aid of the RW CM and the information in Chapter I, we infer the maxima of masking to occur as the basilar membrane is displaced towards scala tympani and scala vestibuli, and the minimum influence of the LF tone on the AP due to the tone burst to occur as the BM moves from SV to ST. In the case of Gaussian impulses too, it is observed that masking takes place with displacement both towards scala tympani and vestibuli, the ST displacement giving a stronger masking. This is in qualitative agreement with the results for sinusoidal maskers. Strongest masking is obtained when the basilar membrane is displaced towards ST after having been displaced towards SV by the Gaussian impulse. This directional dependence of masking in the Gaussian impulse case is the only difference clearly demonstrable between sinusoids and Gaussian impulse masking capabilities.

3.4 Single unit responses influenced by low frequency stimuli.

It has been shown that the whole nerve action potentials due to a short tone burst can be modified by presenting a low frequency tone together with the tone burst. The observed masking pattern of the AP with its 2 peaks per cycle of the LF tone should have correlates in the response of single units. A priori, the decrease in size, or masking, of the AP due to a tone burst by a low frequency tone can have two equally likely origins. The LF tone could cause a suppression of fiber activity, diminishing the AP by inhibiting fibers from firing. The LF tone could also eliminate the AP by influencing the degree of synchrony of firing due to the tone burst. To explain, if the LF tone causes excitation of a fiber at a time near the time of arrival of the tone burst, the fiber will be insensitive to the tone burst and will not contribute to the AP as it does when the tone burst is presented alone. The two peaks in the masking pattern could be caused by either one of these mechanisms, and possibly each peak by each mechanism. Therefore, in the responses of auditory fibers it is equally likely to find 2 excitation peaks as 2 suppression peaks, at the places where masking is observed in the AP study.

In the experiments to follow it is shown that the two masking peaks per cycle of a high intensity LF stimulus observed in the AP study may be correlated with two

suppression regions in the fiber activity,per cycle of the LF stimulus.

A direct proof of this relation would involve repeating the AP experiments of section 3.3, observing responses of single units instead of whole nerve AP. This is difficult to perform due to the short time that a single fiber can be contacted. For each point on the masking diagram, a histogram would have to be constructed to study the activity of the fiber to the given timing of the tone burst on the LF tone. At least 8 points per cycle would have to be collected, to obtain a reasonably continuous curve. The single unit action potentials, or spikes, would have to be counted in each of these histograms, and this count used to assess the fiber's activity. For small samples this counting is unreliable. A given stimulus will on the other hand generate a characteristic histogram. The pattern of the histogram is well reproducible, although the total number of spikes detected may be different from histogram to histogram.

Due to these difficulties, a continuous tone at the characteristic frequency of the nerve fiber, superimposed on the LF stimulus, was used instead of tone bursts. This procedure is not equivalent to using a tone burst on various phases of the LF stimulus, since the dynamics of the response of fibers to bursts is different from the one for continuous tones. This issue is expanded in Chapter 4.

Nonetheless, the response of the fiber to the continuous CF tone is modulated by the low frequency stimulus. This modulation has two minima and two maxima per cycle, that can be correlated with the results of the whole nerve AP study described in section 3.3B.

Before we consider experiments using a LF tone together with a continuous CF tone, let us examine the response of single units to low frequency tones presented alone.

A. Low frequency stimuli presented alone.

When a low frequency tone is presented to the cochlea, whole nerve action potentials are generated. They can be detected in the RW activity superimposed on the CM as shown in section 3.3A. There it is shown that these APs occur 2.1 to 3.2 ms after the RW CM (due to the LF tone) reaches its minimum value. Subtracting the latency, it was inferred that the auditory fibers were excited from -1.4 to 2.1 ms centered around the displacement of the BM towards ST. A correlate of this finding should be found in the responses of the single auditory fibers. However, the present study shows, as the studies reviewed it Chapter 1, that the firing phase of single units is not a simple function of BM movement.

Firing phase and basilar membrane movement.

The time of excitation of the fibers as related to the BM movement can be indirectly assessed from the time of maximum activity in the histograms (tf), the time of zero crossing of the round window CM (tRWO), and the latency of the fiber (tlat) in question. The reasoning is as follows: The time tBMO is defined as the time when the basilar membrane at the location innervated by the fiber being contacted is in its upward movement, i.e. going towards SV, and crossing its resting position. The time of excitation of the nerve fiber, te, relative to tBMO is defined as the time of firing, tf, less synaptic and neural conduction time, td.

$$te=tf-td-tBMO$$

These quantities, td and tBMO were not measurable directly. To relate the basilar membrane movement to measurable quantities, the round window cochlear microphonic is used, as before. As explained in Chapter I, the RW CM is assumed to reflect the BM movement at the basal end of the cochlea. It takes a transmission time tt for a disturbance at the base to travel from the round window region to the place of innervation of the fiber. The zero crossing time of the basilar membrane, tBMO, at the location of innervation can therefore be related to the RW CM by

$$tBMO=tRWO+tt$$

thus,

$te=tf-td-tRWO-tt$

The click latency of a fiber, tlat, is made up of an acoustic delay, a travelling time on the basilar membrane and the synaptic and neural conduction time,

$tlat=tac+tt+td.$

Neglecting the acoustic delay time from the stimulating earphone to the stapes and assuming it valid to equate the travelling time of a click with the one for a sinusoidal (Goldstein et al 1971), the sum of the travelling time tt and the delay time td can be equated with the click latency of the fiber, tlat.

$tlat=td+tt$, and thus

$te=tf-tRW-tlat$

This formula can be used to assess the phase of the basilar membrane where excitation occurs.

A word about what is meant by excitation is appropriate here. The time preceding the time of detection of a spike, less the synaptic and neural delays was defined as te. The time elapsed from the onset of excitation and the start of synaptic transmission is unknown, but probably small: Corey and Hudspeth (1979b) have shown in the bull frog that less than 40 microseconds elapse from the mechanical stimulation of the cilia to depolarization of the hair cell. We estimate therefore that te is uncertain by the small time

from the appropriate BM excitatory movement to the time of synaptic transmission.

To summarize, we can estimate the motion of the BM due to the low frequency stimulus as excitation takes place, with the aid of three measurements, the RW CM, the histogram of the fiber activity due to the LF stimulus and the click latency of the fiber.

The responses of single auditory fibers to low frequency tones have considerable variation from fiber to fiber. In fact, the variability of responses does not allow a clear conclusion to be made, as to the exact phase of firing of the fiber, as related to the phase of the incoming tone. Figures 3.20 to 3.26 show histograms of the response of single auditory fibers to a 100 Hz tone. The method of collecting data to construct a histogram is discussed in Chapter 2. These figures are arranged in order of increasing fiber's characteristic frequency. The starting time of all histograms where LF sinusoids were used, is the time of positive going zero crossing of the LF voltage to the earphone. In order to relate the fiber's firing to the basilar membrane movement one has to find the time of maximum activity of the fiber, and also assess the BM movement at the place where the fiber innervates the organ of Corti. The sinusoids in the figures represent the inferred movement of the BM at the place of innervation, using the round window cochlear microphonic and the latency

of the fiber as described above.

The histograms of responses to 100 Hz tone, in figures 3.20 to 3.26, have several interesting features. First it is observed that a pattern of excitation and inhibition is brought about by the 100 Hz tone. For higher intensity of a 100 Hz tone one observes that in some instances more than one peak per cycle appears on the histogram (e.g. figure 3.21). This phenomenon has been called peak splitting. The phase of the largest peak can change with intensity as demonstrated in figure 3.24, where the peak of activity for higher levels appears later than for lower levels of the 100 Hz tone. This is in contrast to the main line of thought, that higher levels usually give shorter delays (e.g. Kiang et al, 1965).

In order to find the phase of firing of the fiber to the LF stimulus, the time of maximum activity of the fiber from histograms, for as low an intensity of the tone as possible was determined. As CF increases, higher intensities are needed to observe a response of the fiber to 100 Hz.

Figure 3.27 shows te, the time of excitation of fibers as related to BM movement, from 15 chinchillas. It is clear that a considerable spread in this time is present especially for characteristic frequencies between 2 and 5 kHz. Although the number of fibers investigated (75) is too low for a rigorous analysis there are some interesting

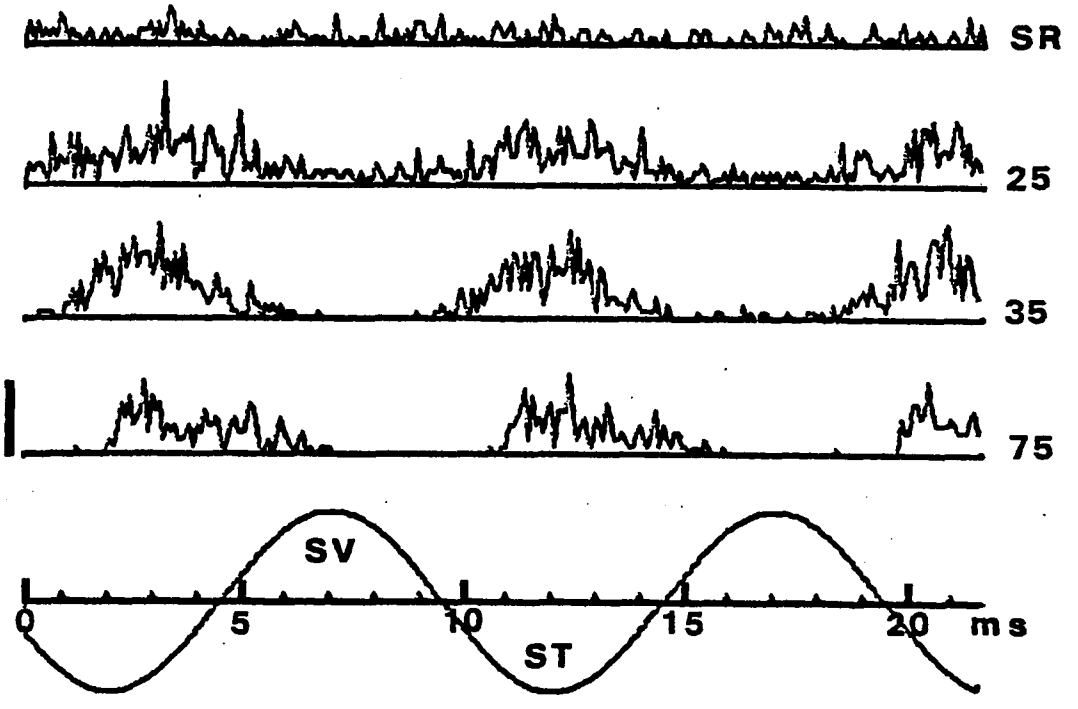

Figure 3.20 Histograms of single auditory fiber activity. Bottom trace: BM movement at the place of innervation of the fiber inferred from RW CM. shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit 85-13; CF .2 kHz; SR 68 sp/s; Lat. 3.0 ms. Bar=10 counts; N=400.

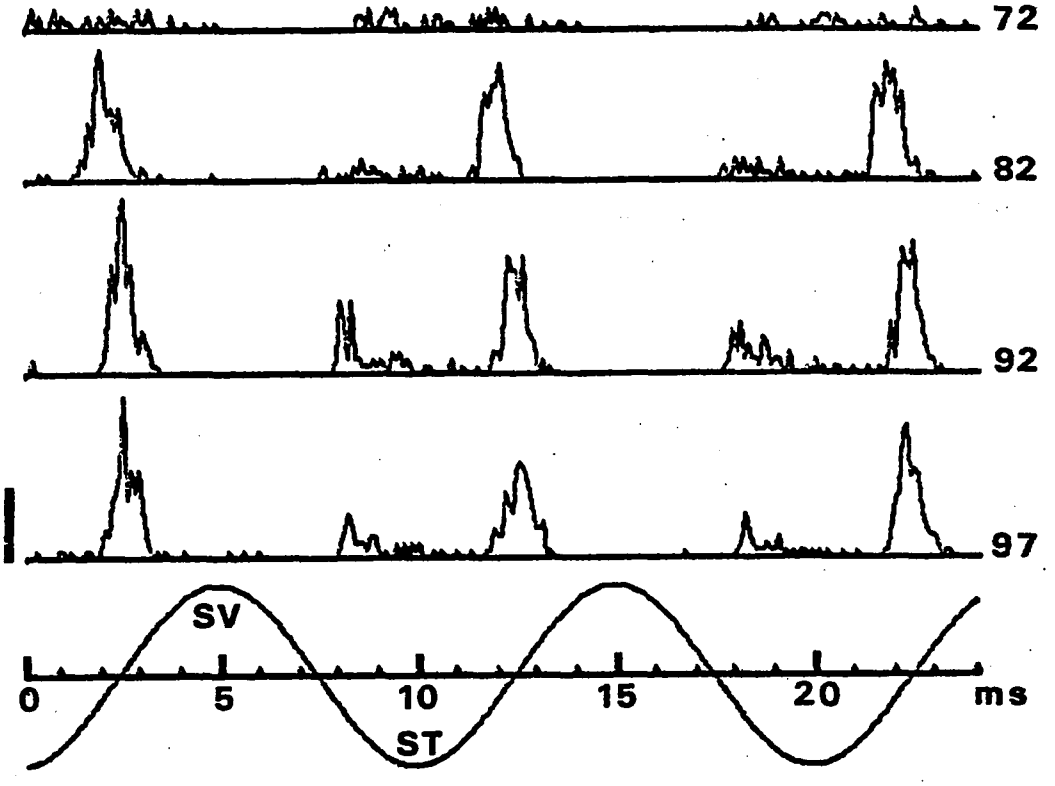

Figure 3.21 Histograms of single auditory fiber activity. Bottom trace: BM movement at the place of innervation of the fiber inferred from RW CM shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit 45-8; CF .7 kHz; SR 5 sp/s; Lat 2.4 ms. Bar=10 counts; N=400.

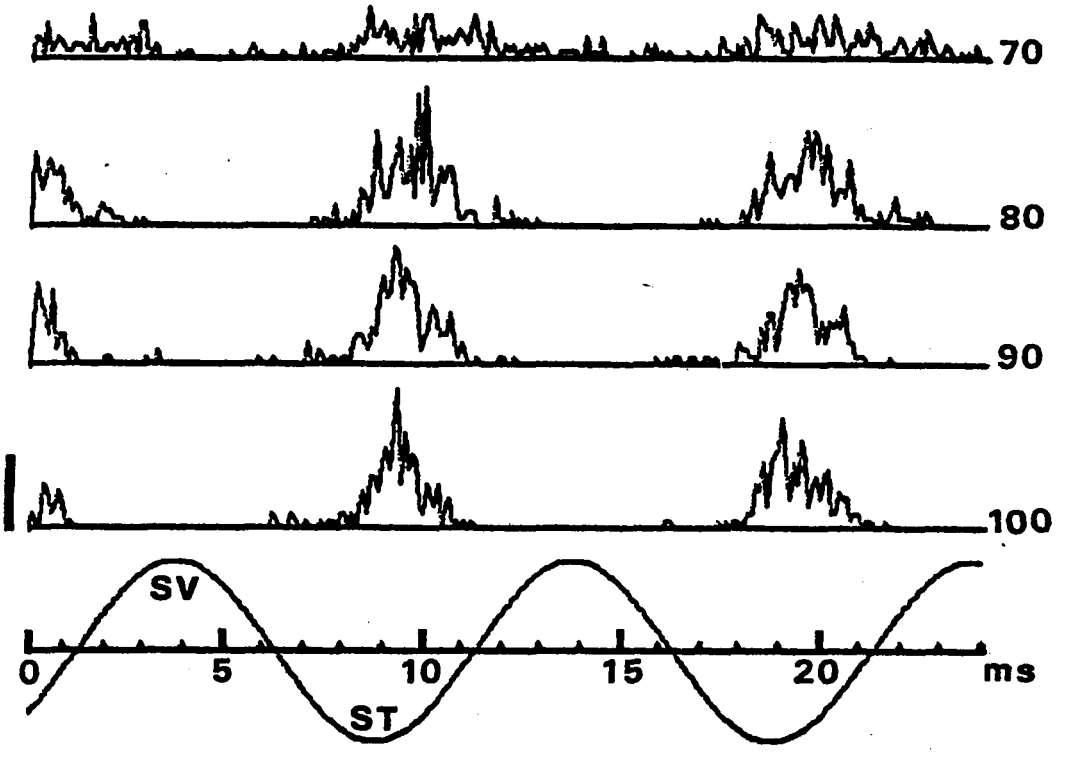

Figure 3.22 Histograms of single auditory fiber activity. Bottom trace: BM movement at the place of innervation of the fiber inferred from RW CM shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit 44-14; CF .8 kHz; SR 44 sp/s; Lat 2.2 ms. Bar=10 counts; N=400.

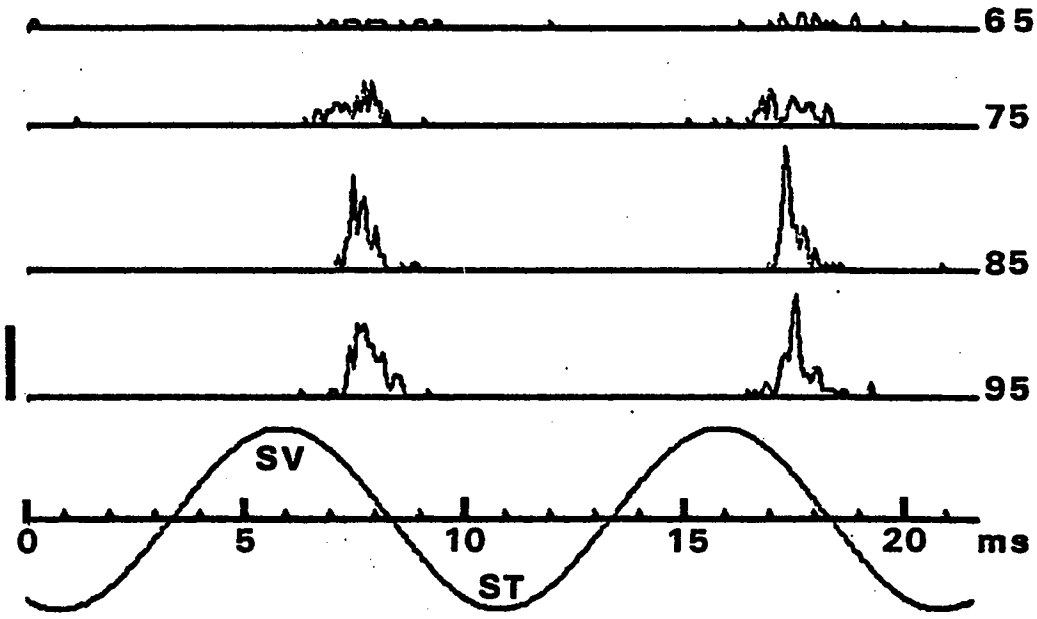

Figure 3.23 Histograms of single auditory fiber activity. Bottom trace: BM movement at the place of innervation of the fiber inferred from RW CM. shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit A84-7: CF 2.2 kHz: SR 3 sp/s: Lat. 2.2 ms. Bar=10 counts: N=400.

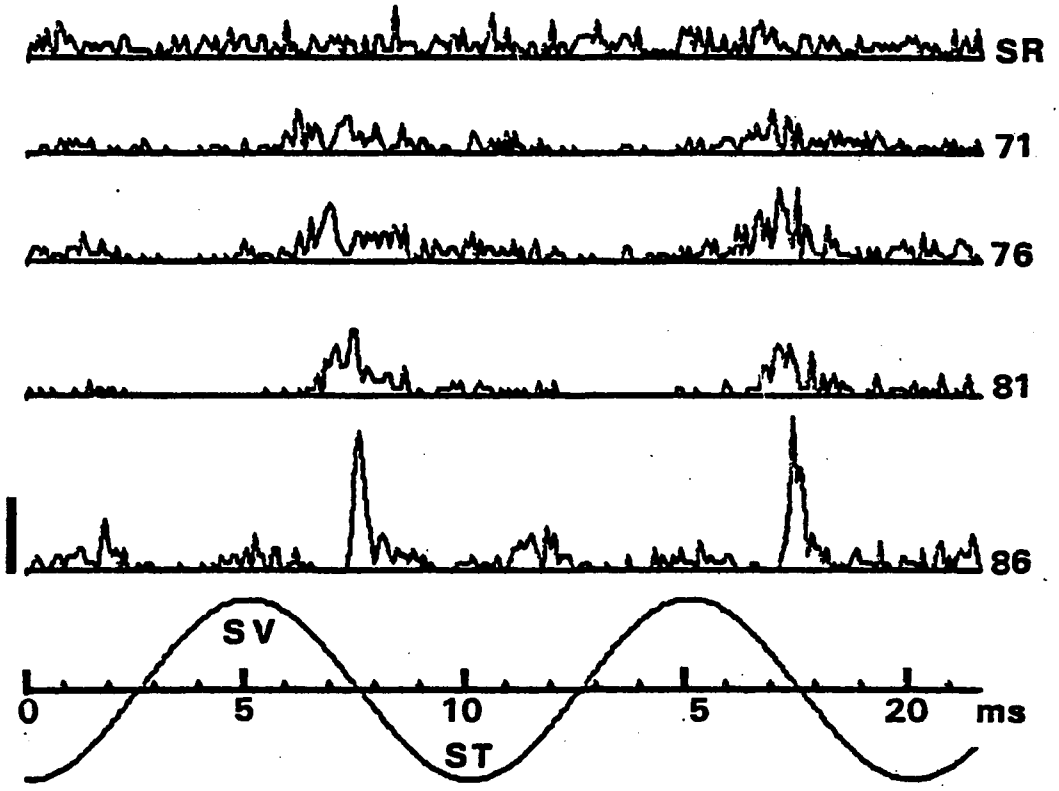

Figure 3.24 Histograms of single auditory fiber activity. Bottom trace: Inferred BM movement at the place of innervation of the fiber inferred from RW CM shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit 85-5; CF 4.5 kHz; SR 75 sp/s; Lat 1.4 ms. Bar=10 counts; N=400.

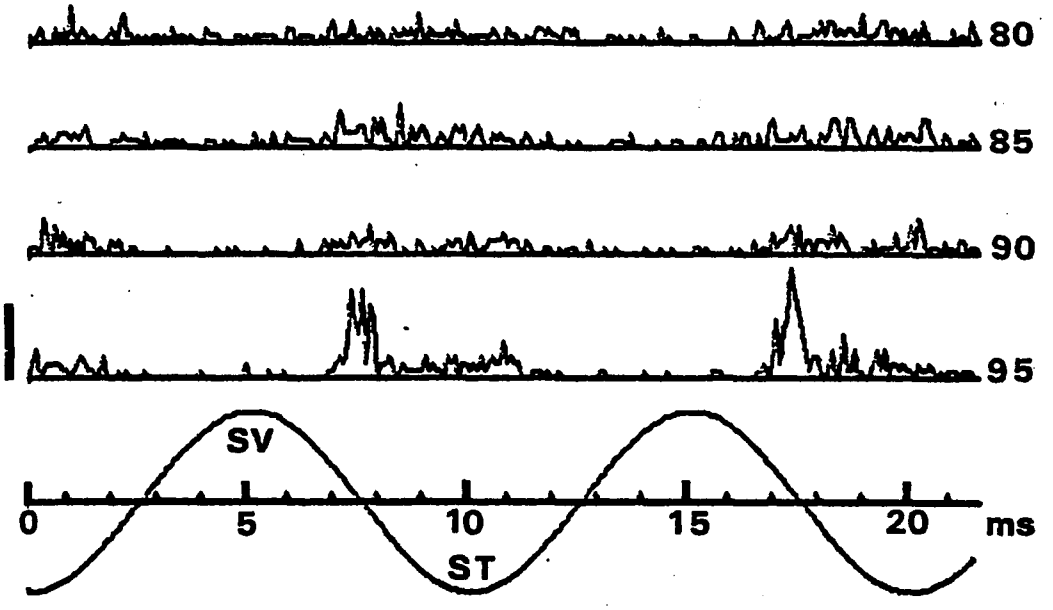

Figure 3.25 Histograms of single auditory fiber activity. Bottom trace: Inferred BM movement at the place of innervation of the fiber inferred from RW CM shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit A84-2; CF 9 kHz; SR 59 sp/s; Lat 1.5 ms. Bar=10 counts; N=400.

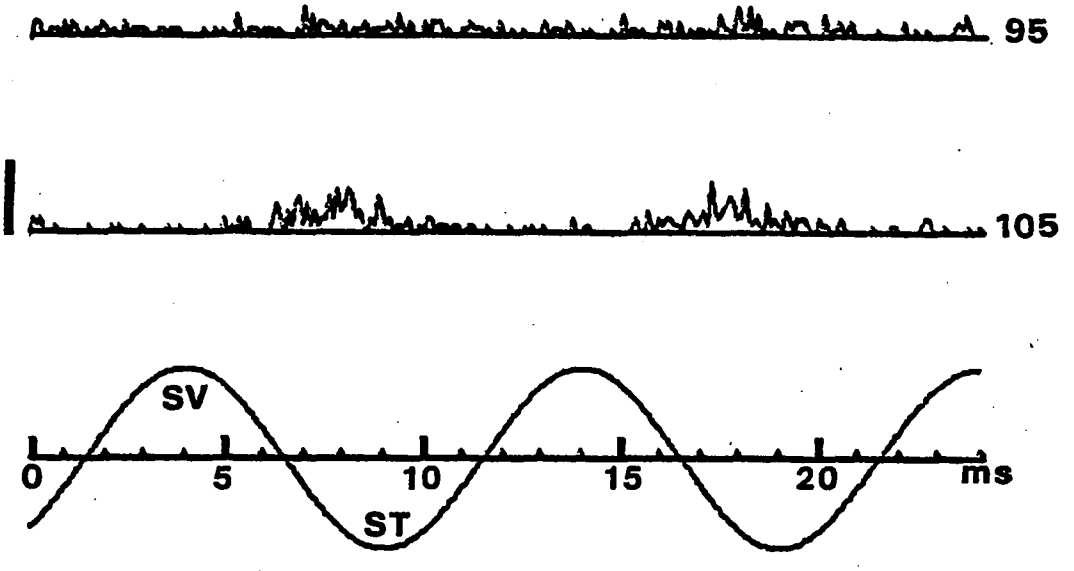

Figure 3.26 Histograms of single auditory fiber activity. Bottom trace: Inferred BM movement at the place of innervation of the fiber inferred from RW CM shifted to the right by the latency of the fiber. Parameter is level of 100 Hz tone in dB SPL. Unit A45-7; CF 20 kHz; SR 13 sp/s; Lat 1.5 ms. Bar=10 counts; N=400.

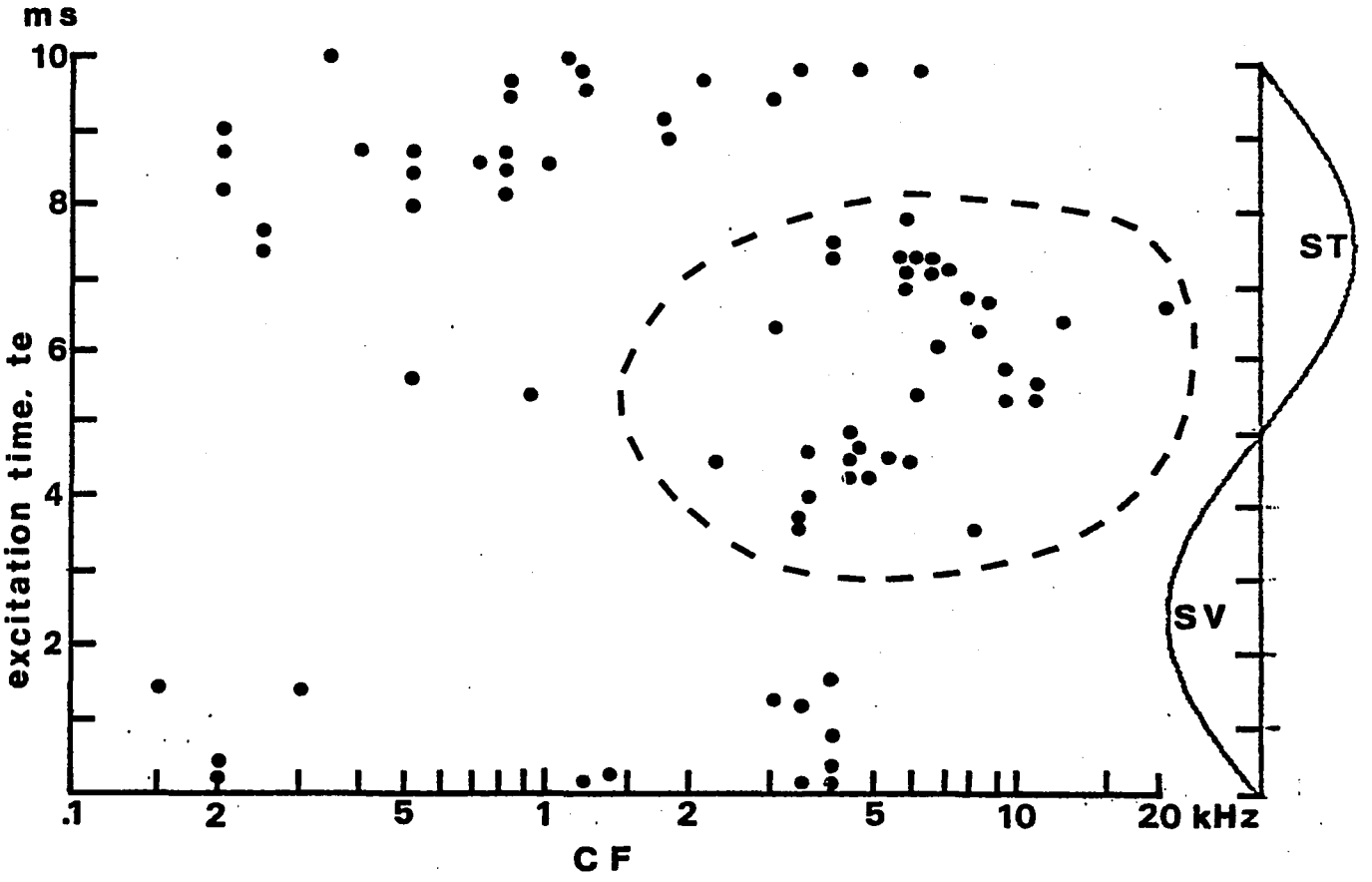

Figure 3.27 Position of maximum activity of auditory fibers within a cycle of a 100 Hz stimulus. Intensity of 100 Hz used was lowest possible to detect an activity maximum visually on a histogram. The sinusoidal represents inferred BM movement at the place of innervation of the fiber as excitation takes place. Note dichotomy of time, fibers of low CF fire around 9.6 ms (fibers with te less than 2 ms were transposed by 10 ms), fibers of high CF fire around 5.8 ms (encircled group). No fibers fired in the interval 1.7 to 3.7 ms. 75 fibers from 15 chinchillas.

features to be seen in figure 3.27. There seems to be a dichotomy of time of firing, centering around 10 ms for low frequency fibers and 6 ms for high, with an overlapping region between 3 and 5 kHz. The group of fibers encircled by the dashed line has an average excitation time of 5.9 ms, and the group outside it an average of 9.7; fibers that fired near 0 ms were transposed up by 10 ms. Observe that no fiber fired between 1.7 and 3.7 ms.

It is interesting to attempt to correlate these times to the time of occurrence of the APs in section 3.3A. There it is shown that the AP occurs at two to three milliseconds after the negative deflection of the round window CM takes place, due to the 100 Hz signal. As discussed, subtracting the latency from these figures we assessed the excitation of the fibers to occur somewhere in the interval -1.4 to 2.1 ms around the displacement of the basilar membrane towards ST. In figure 3.27 this corresponds to the interval 6.1 to 9.6 ms. In order to state that one or the other population of fibers is responsible for the AP generation, one would have to assess the time of firing of fibers to be near the average inferred AP firing time, namely around (9.6+(7.5-1.4))/2=7.85 ms. In figure 3.27, the average time of firing for fibers with CF above 6kHz is 6.1 ms; the average time of firing for low frequency fibers is around 9.7 ms. We are therfore unable to conclude which population contributes most to the observed AP due to low frequency stimuli.

The response of auditory fibers to a Gaussian impulse presented alone have similar phase characteristics as the response to 100 Hz. Figures 3.28 to 3.31 show examples of this. Fibers of CF higher than approximately 6 kHz respond weakly to a Gaussian pulse. Usually levels higher than 95 dB peak equivalent SPL are needed to evoke a response from these fibers. As in the 100 Hz study, fibers with low CF respond in a phase that is inferred to correspond to BM movement from ST to SV, and fibers with higher CF tend to respond in the opposite direction of BM movement, i.e. from SV to ST.

Comparing the single unit data in figures 3.28 to 3.31 with the data in figures 3.3 and 3.4 one can tentatively conclude that the APs seen in figures 3.3 and 3.4 are generated by predominantly low frequency fibers, because figures 3.28 to 3.31 show that fibers of CF lower than 4 kHz tend to fire in the ST to SV velocity phase of the BM movement. This conclusion is in contrast with the data of Eldredge, showing that fibers of CF higher that 6 kHz must be the main contributors to the APs. One difference here that could explain this discrepancy is that the LF impulses used by Eldredge had a cosiderably higher frequency content than our Gaussian impulses.

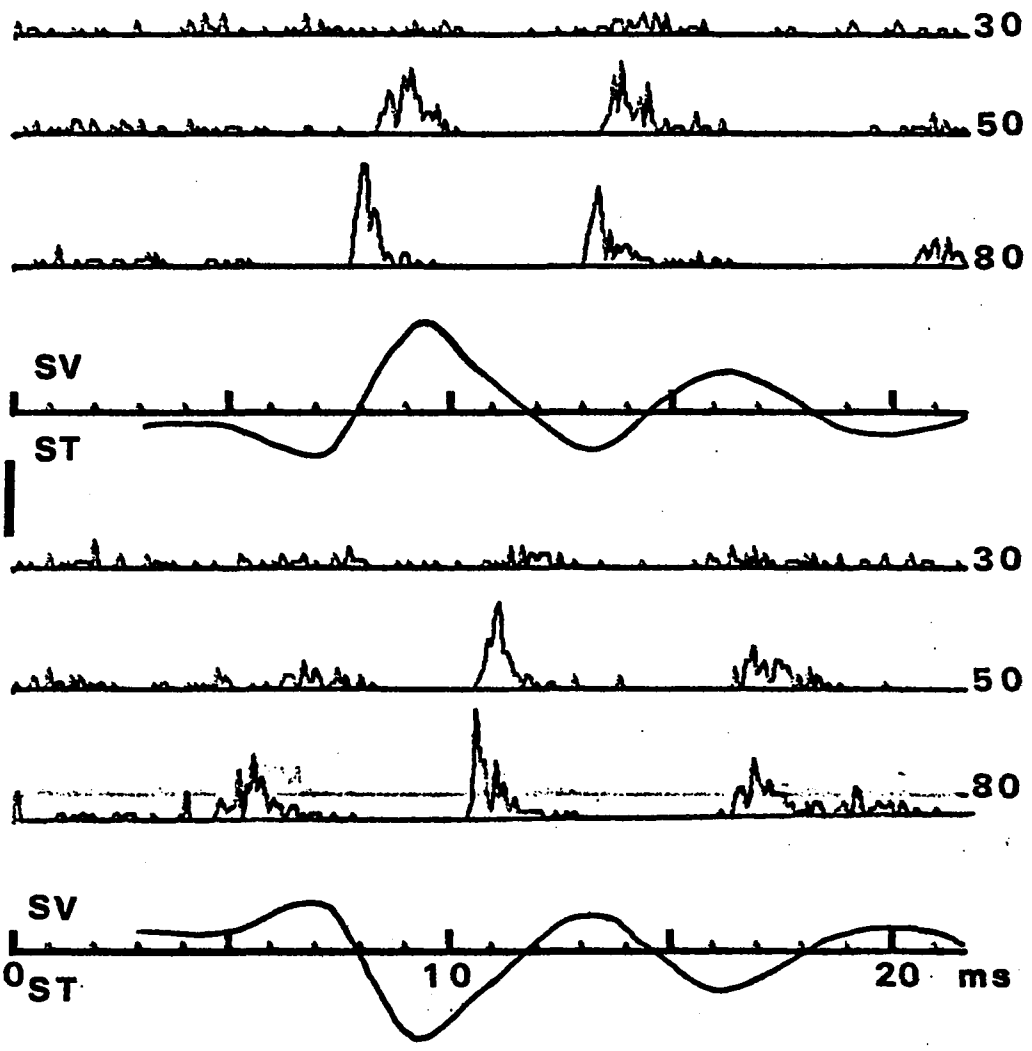

Figure 3.28 Responses of an auditory nerve fiber to Gaussian pulses. First 3 histograms are of responses to condensation impulse, last 3 for rarefaction impulse. Parameter is dB SPL of impulses (peak equivalent to sinusoidal sound). The BM movement is inferred from RW CM shifted to the right by the latency of the fiber. Unit 85-13; CF .2 kHz; SR 68 sp/s; Lat. 3.0 ms. Bar=10 counts; N=400.

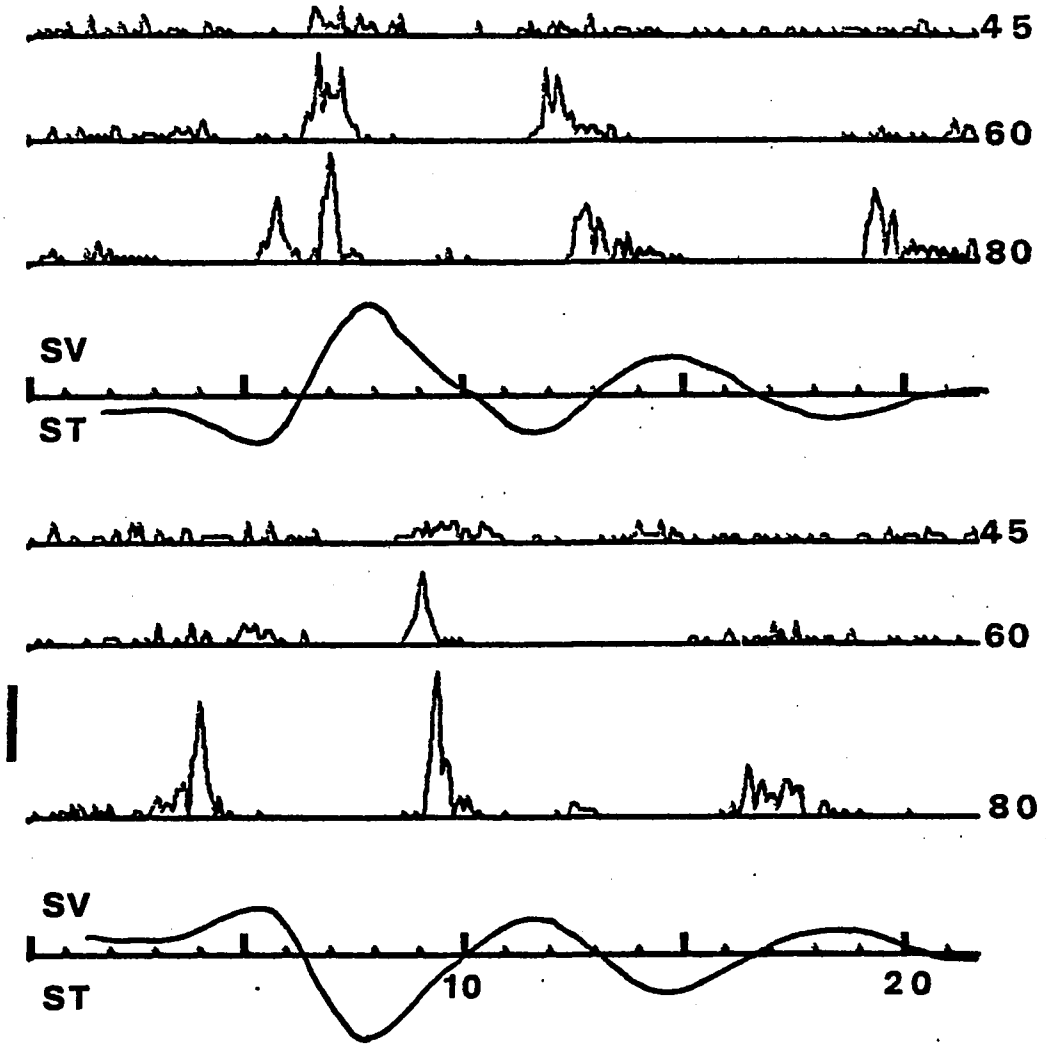

Figure 3.29 Responses of an auditory nerve fiber to Gaussian pulses. First 3 histograms are of responses to condensation impulse, last 3 for rarefaction impulse. Parameter is dB SPL of impulses (peak equivalent to sinusoidal sound). The BM movement is inferred from RW CM shifted to the right by the latency of the fiber. Unit 85-11; CF 1.0; SR 63; Lat 1.5 Bar=10 counts; N=400.

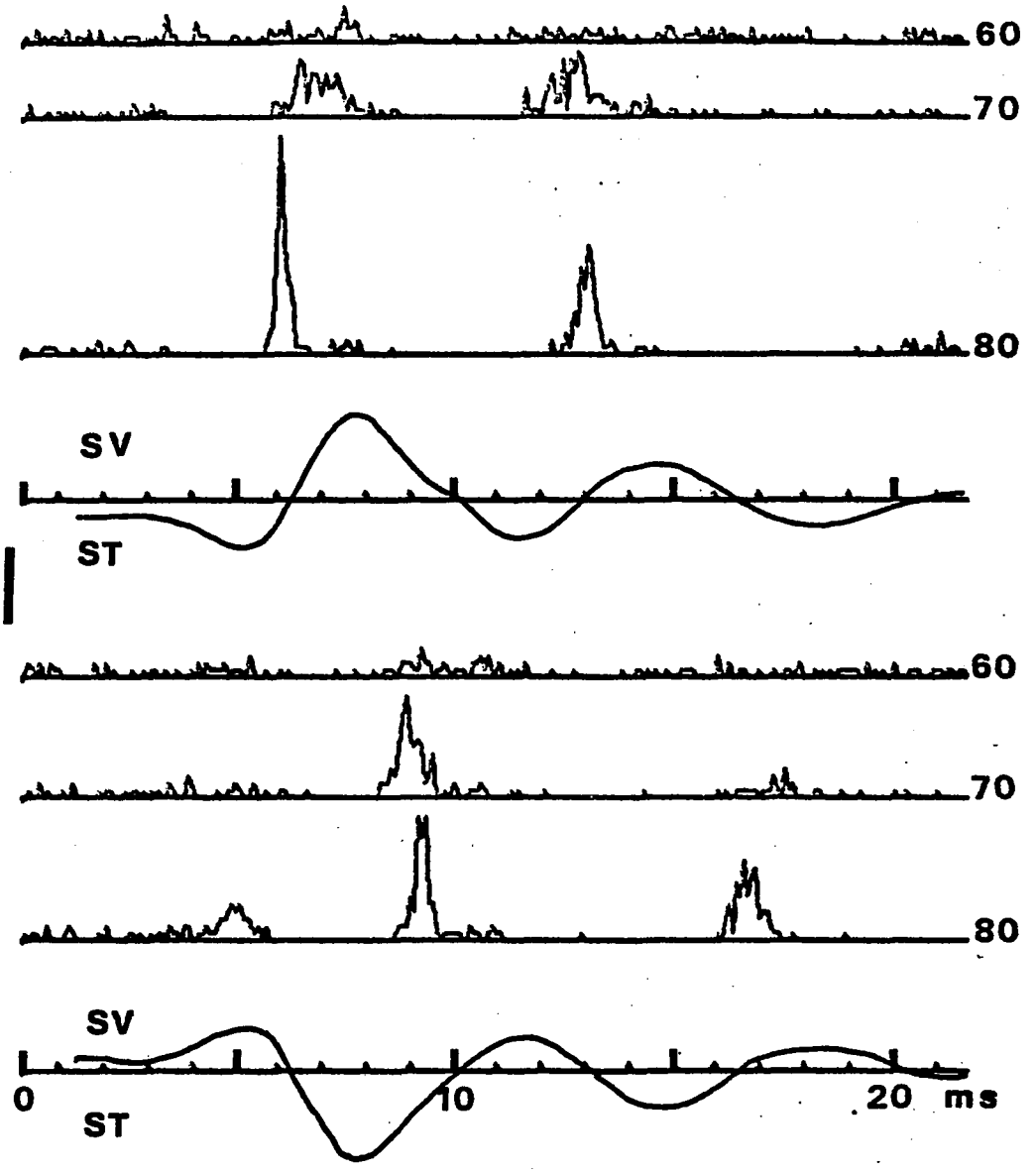

Figure 3.30 Responses of an auditory nerve fiber to Gaussian pulses. First 3 histograms are of responses to condensation impulse, last 3 for rarefaction impulse. Parameter is dB SPL of impulses (peak equivalent to sinusoidal sound). The BM movement is inferred from RW CM shifted to the right by the latency of the fiber. Unit 85-16; CF 4.0 kHz; SR 36 sp/s; Lat. 1.3 ms. Bar=10 counts; N=400.

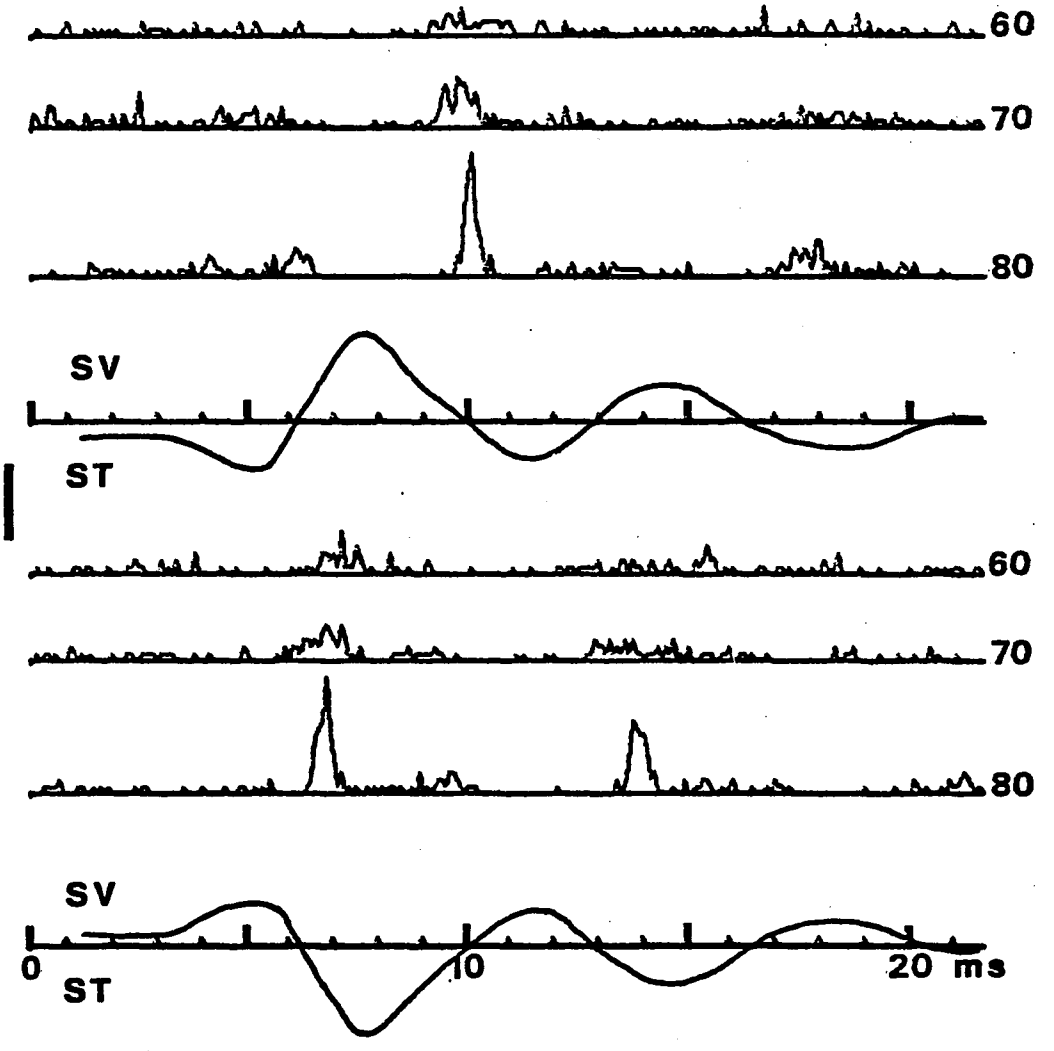

Figure 3.31 Responses of an auditory nerve fiber to Gaussian pulses. First 3 histograms are of responses to condensation impulse, last 3 for rarefaction impulse. Parameter is dB SPL of impulses (peak equivalent to sinusoidal sound). The BM movement is inferred from RW CM shifted to the right by the latency of the fiber. Unit 85-10; CF 5.5 kHz; SR 36 sp/s; Lat 1.2 ms Bar=10 counts; N=400.

B. Fiber activity in response to tones at CF together with low frequency stimuli.

When a continuous tone of 100 Hz is presented with a tone at the characteristic frequency of a fiber, the majority of auditory fibers in the chinchilla will respond in a fashion depicted in figure 3.32. The 100 Hz tone alone produces weak response in a fiber such as this, of CF=4 kHz, even at 95 db SPL (trace A). The remarkable finding is that a 100 Hz tone at 65 dB SPL, will modulate the activity of the fiber that is brought about by the CF tone (trace C). As before, it is possible to infer the basilar membrane movement as excitation takes place. It is seen that a supression of activity occurs in the inferred ST deflection of the BM. For low levels of the 100 Hz tone, the half cycle centered in the SV direction of BM deflection is not suppressive, but as the level of the CF tone is increased, a second masking region is brought about, in the phase of maximum deflection of the BM towards SV. This behavior produces two masking periods per cycle of the 100 Hz tone, one that appears for moderate levels of 100 Hz, and inferred to occur as the BM is deflected towards ST, the other appearing at the time of SV displacement of the BM, for higher levels of the 100 Hz. The two activity peaks coincide with the maximum velocity of the BM, from SV to ST and ST to SV. As intensity of 100 Hz is increased even more, one of the activity peaks may diminish. Usually it is

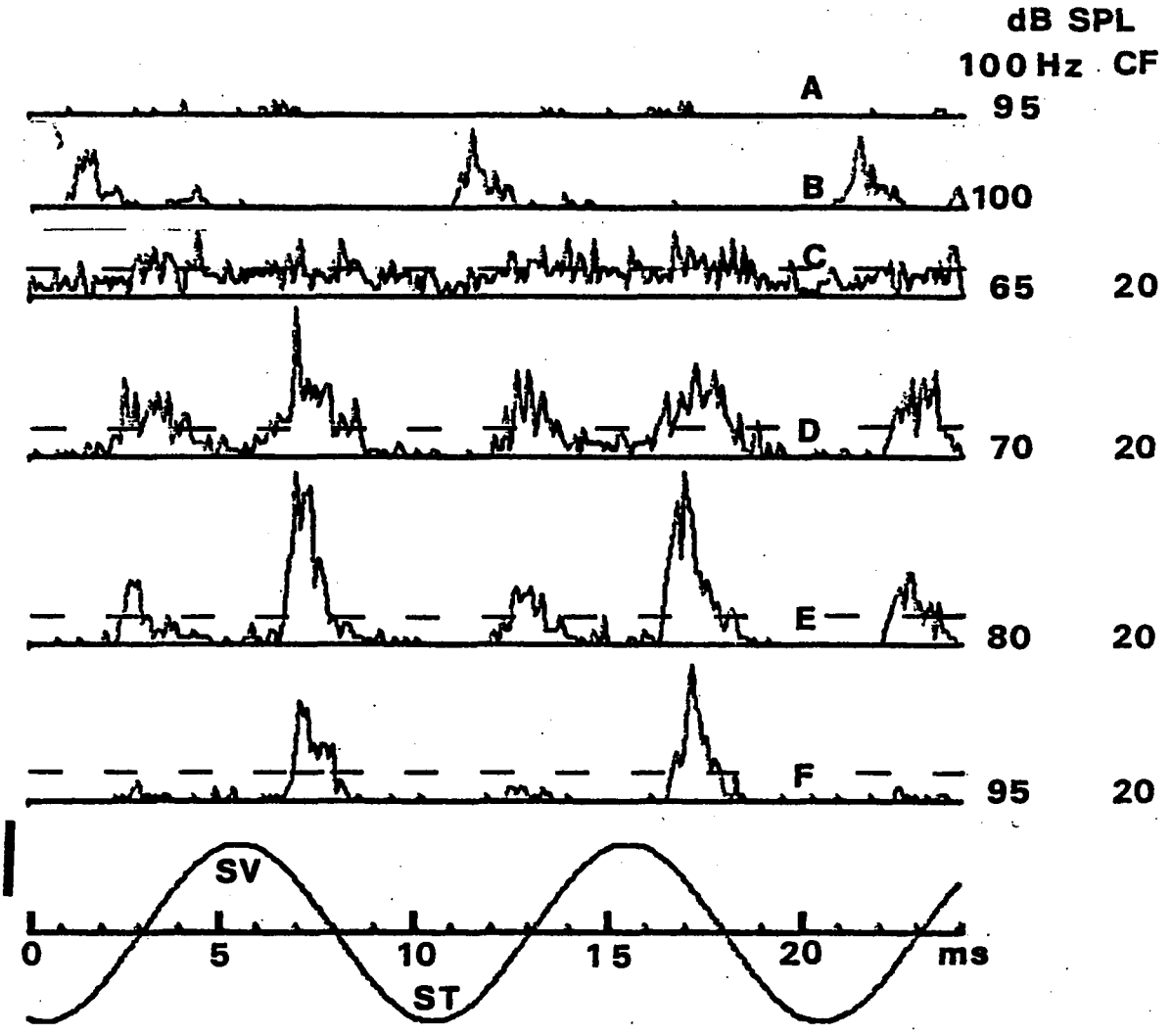

Figure 3.32 Influence of a 100 Hz tone on auditory fiber responses to a continuous tone at CF. A. 100 Hz tone alone will elicit small response, unless at high levels as in B. C to F: 100 Hz modulates the activity of the fiber due to the CF tone. Note 2 peaks of activity per cycle for high levels of the 100 Hz tone. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM and shifted to the right by the latency of the fiber. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A51-8: CF 4 kHz: SR .5 sp/s: Lat 2 ms. Bar=10 counts: N=400.

the peak that is inferred to occur as the BM moves from ST to SV that diminishes first (traces E,F).

For comparison purposes, a dashed horizontal line is drawn in each pertinent histogram, indicating the approximate activity, if the CF tone were presented alone. It is remembered that because of the variability in spike count from histogram to histogram, this line has a qualitative function only. Figure 3.33 shows data depicting the position of the two excitation peaks that almost invariably appear when a tone at CF is presented with a LF tone.

When the level of the 100 Hz tone is kept constant, decreasing the level of the continuous CF tone will have the effect of deepening the masking region in the phase of inferred deflection of the BM towards SV. This is shown in figure 3.34.

Figures 3.35 to 3.39 show that the responses of fibers of different CFs have similar characteristics of modulation. The fibers of high CF did not respond to 100 Hz when presented alone; yet the behavior of the peaks is similar to that of fibers of lower CF. Due to difficulties in maintaining good electrode contact, study of the number of spikes per histogram was not done. Therefore it is not possible to determine exactly whether the 100 Hz tone decreases or increases the average activity of the fiber. On the other hand the fact that two suppression regions are

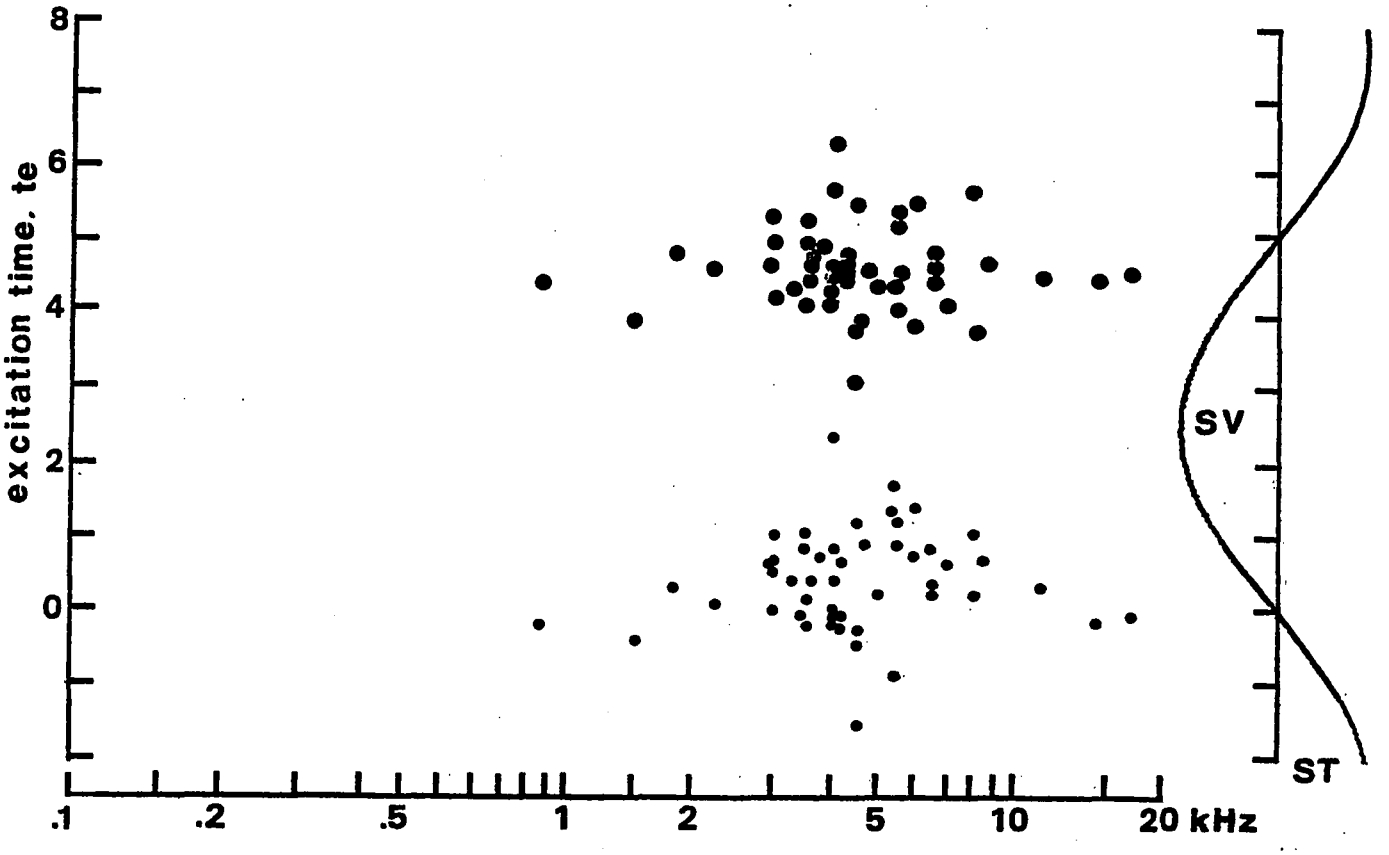

Figure 3.33 Excitation time of auditory fibers in response to a continuous tone at CF together with a 100 Hz tone. Small dots: Activity peak near inferred ST to SV velocity phase of BM movement. Large dots: Activity peak near the SV to ST velocity phase of BM movement. 49 fibers from 14 chinchillas.

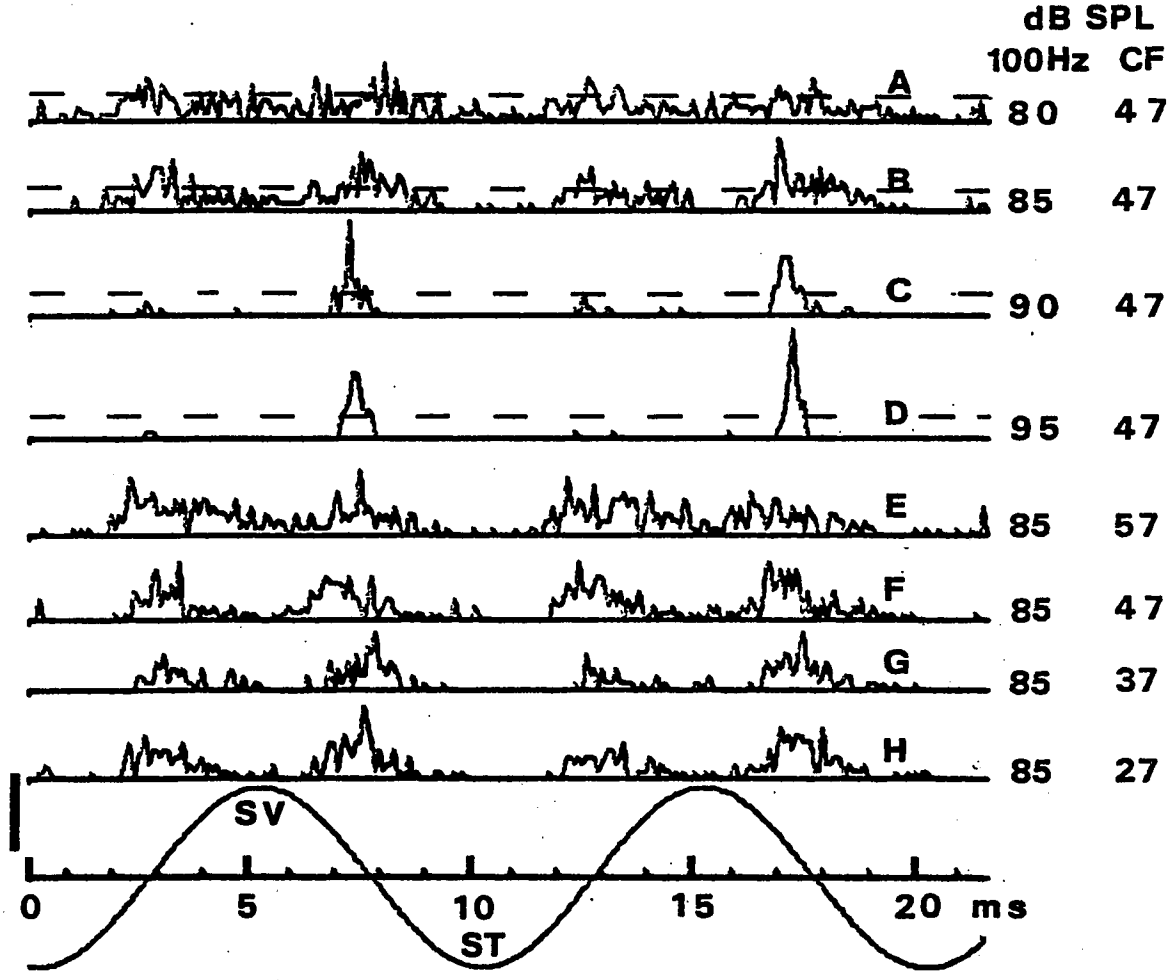

Figure 3.34 Responses of auditory fibers to a continuous tone at CF together with a 100 Hz tone. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW, shifted to the right by the latency of the fiber. Level of 100 Hz was varied in A to D; level of CF was varied in E-H. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A82-8; CF 3.5 kHz; SR .5 sp/s; Lat 2.0 ms. Bar=10 counts; N=400.

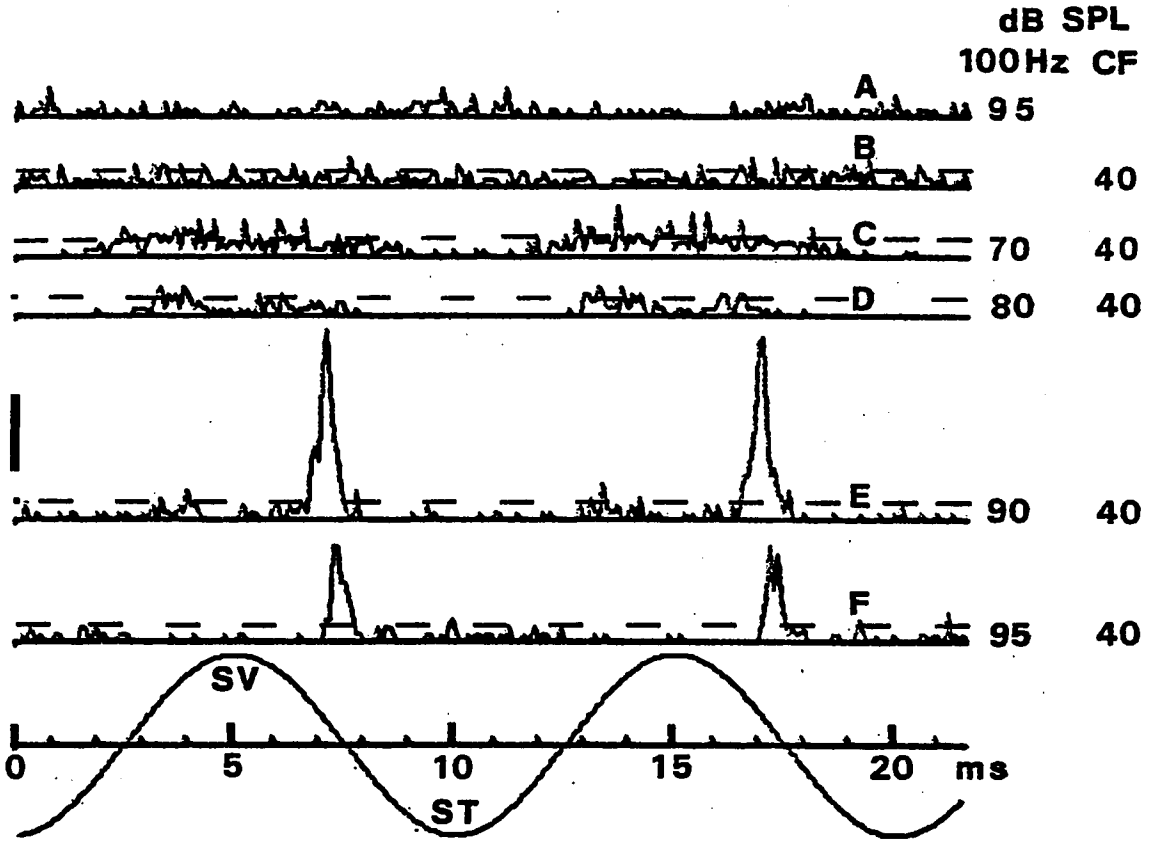

Figure 3.35 Responses of auditory fibers to a continuous tone at CF presented together with a tone at 100 Hz. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Note disappearence of activity in the ST-SV movement of the BM. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A84-1; CF 5.5 kHz; SR 26 sp/s; Lat 1.5 ms. Bar=10 counts; N=400.

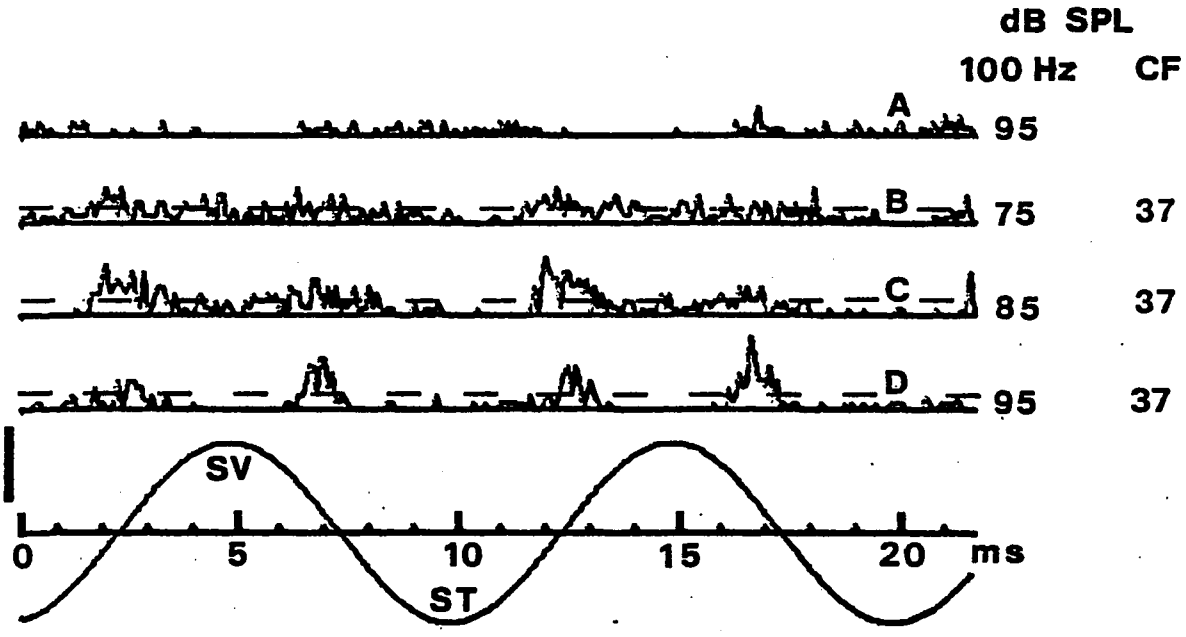

Figure 3.36 Responses of auditory fibers to a continuous tone at CF presented together with a tone at 100 Hz. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A82-1; CF 6.5 kHz; SR 80 sp/s; Lat 1.5 ms. Bar=10 counts; N=400.

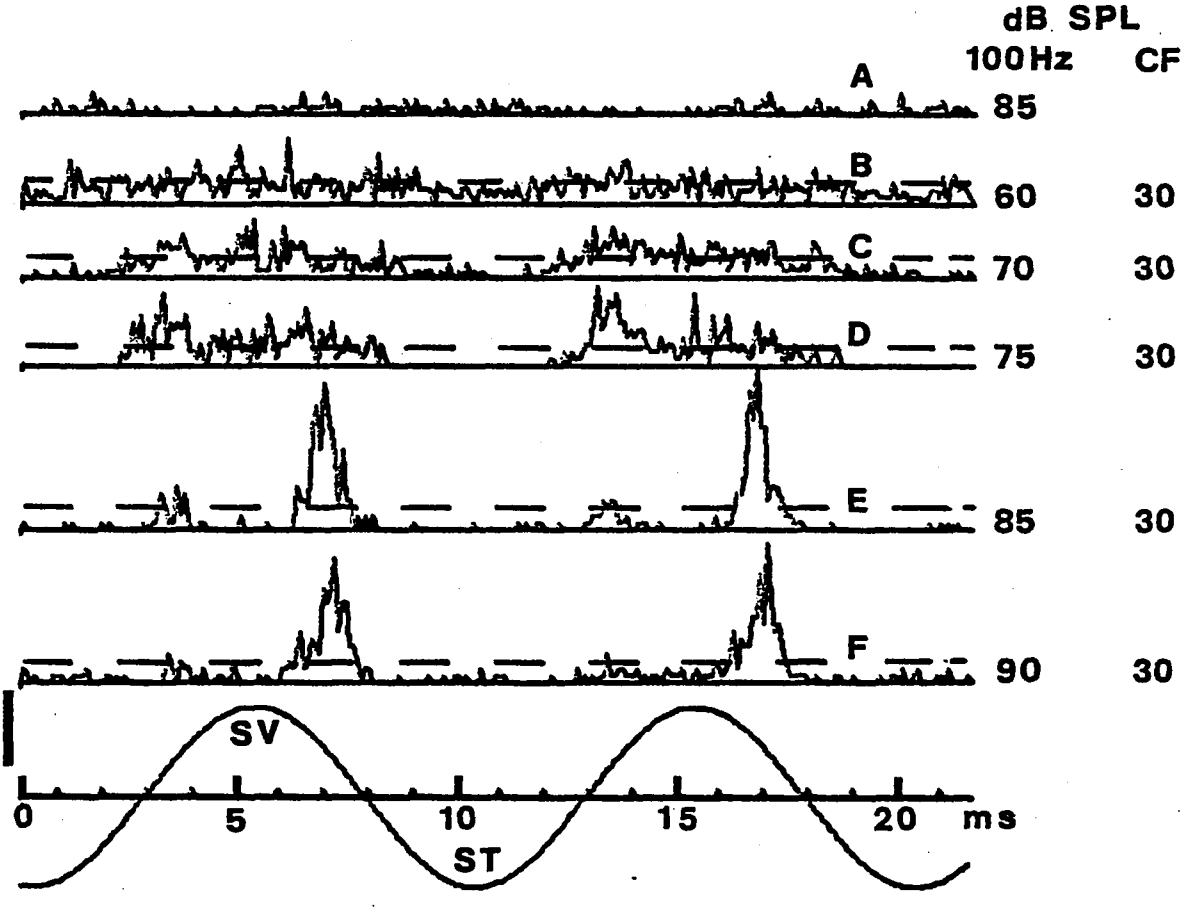

Figure 3.37 Responses of auditory fibers to a continuous tone at CF presented together with a tone at 100 Hz. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A84-8; CF 7 kHz; SR 23 sp/s; Lat 1.8 ms. Bar=10 counts; N=400.

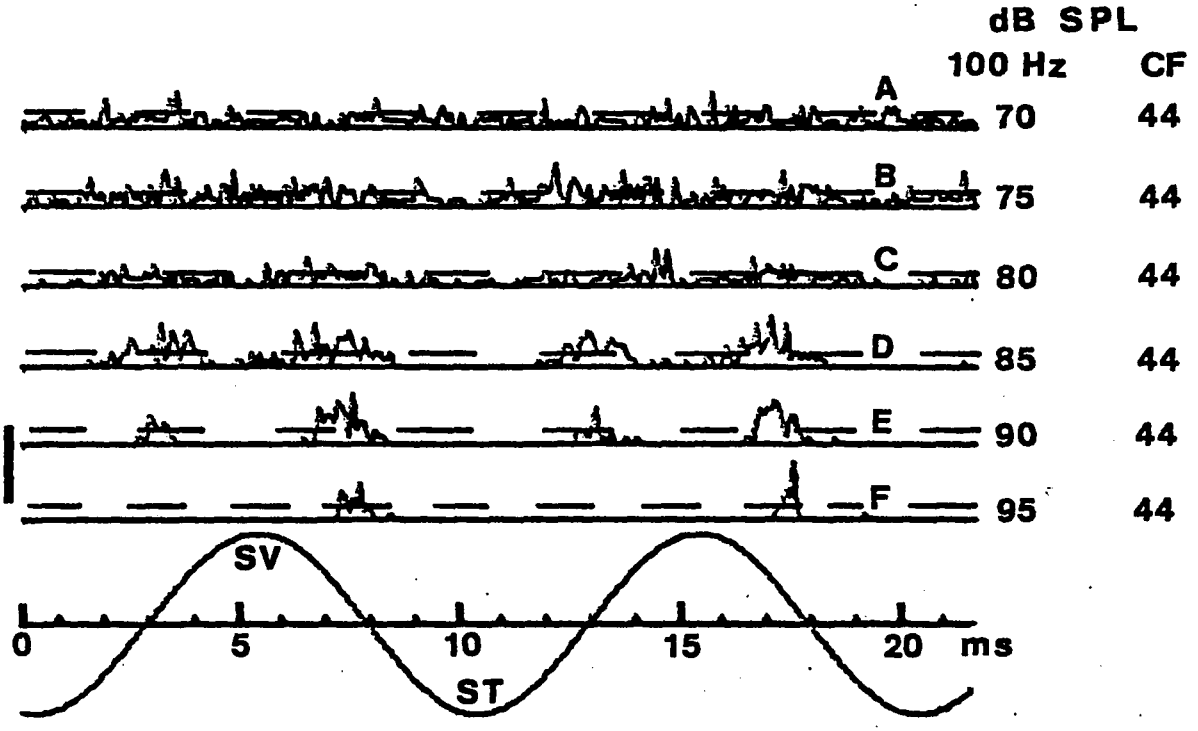

Figure 3.38 Responses of auditory fibers to a continuous tone at CF presented together with a tone at 100 Hz. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A84-9; CF 11 kHz; SR .3 sp/s; Lat 1.8 ms. Bar=10 counts; N=400.

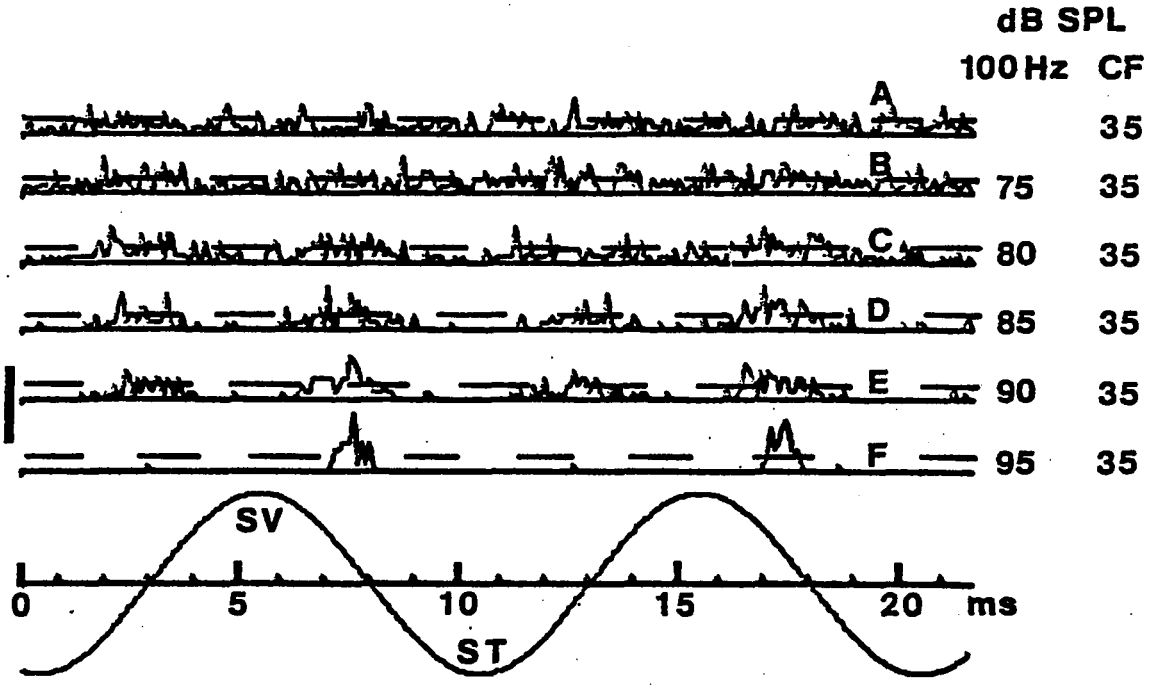

Figure 3.39 Responses of auditory fibers to a continuous tone at CF presented together with a tone at 100 Hz. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A84-10; CF 14 kHz; SR .2 sp/s; Lat 1.9 ms. Bar=10 counts; N=400.

present is evident from the shape of the histograms. Despite this, it is possible to find the momentary relative increase or decrease in rate from one region to another in a histogram.

Comparing these results to the results of the study of APs due to tone bursts superimposed on 100 Hz (figure 3.14), it is seen that the maxima of masking in the AP case coincide with the maxima of masking in the single fiber case. Assuming that these experiments - masking by LF tones of AP due to tone bursts and suppression by LF tones of unit activity due to continuous CF tones - are operating on the same mechanisms in the cochlea, it is demonstrated that both masking periods in the AP case are caused by suppression of activity at the single unit level, and not by a lack of synchrony due to excitation caused by the 100 Hz tone.

Gaussian-shaped impulses were presented instead of 100 Hz tones in experiments of the same kind as just described. The results are similar to the results with 100 Hz tones. The Gaussian impulses are not as effective maskers as are the 100 Hz tones. Figures 3.40 to 3.43 show some examples of activity of fibers responding to a tone at CF, modulated by Gaussian-shaped impulses. As a rule the maximum of masking takes place both in the inferred SV displacement and ST displacement. As in the 100 Hz study, increase in level of the impulse will produce more masking in the inferred SV direction of BM movement. This may be a reflection of the

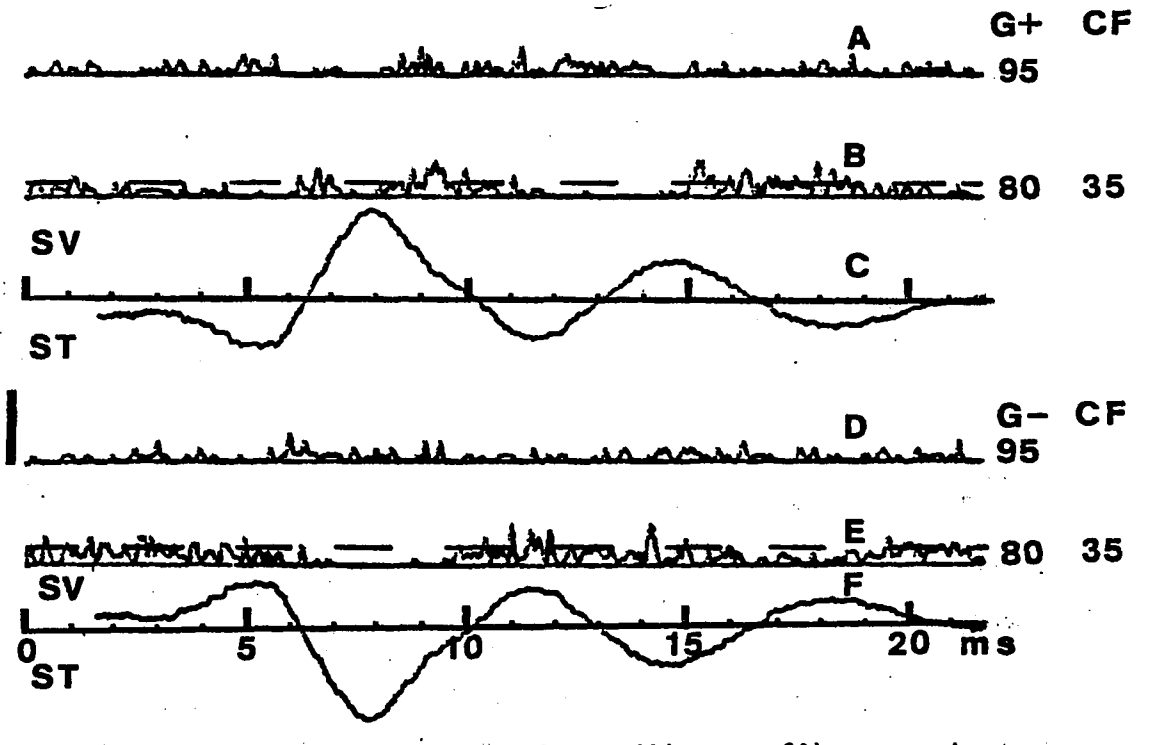

Figure 3.40 Responses of auditory fibers to a continuous tone at CF presented together with a Gaussian impulse. Continuous curves: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Note similarity with 100 Hz effect: In B two peaks, on each side of the time of maximum SV displacement: in E, total suppression in ST. Dashed line: Approximate level of activity of fiber driven by the CF tone presented alone. Unit A84-1: CF 5.5 kHz: SR 26 sp/s: Lat 1.5 ms. Bar=10 counts: N=400.

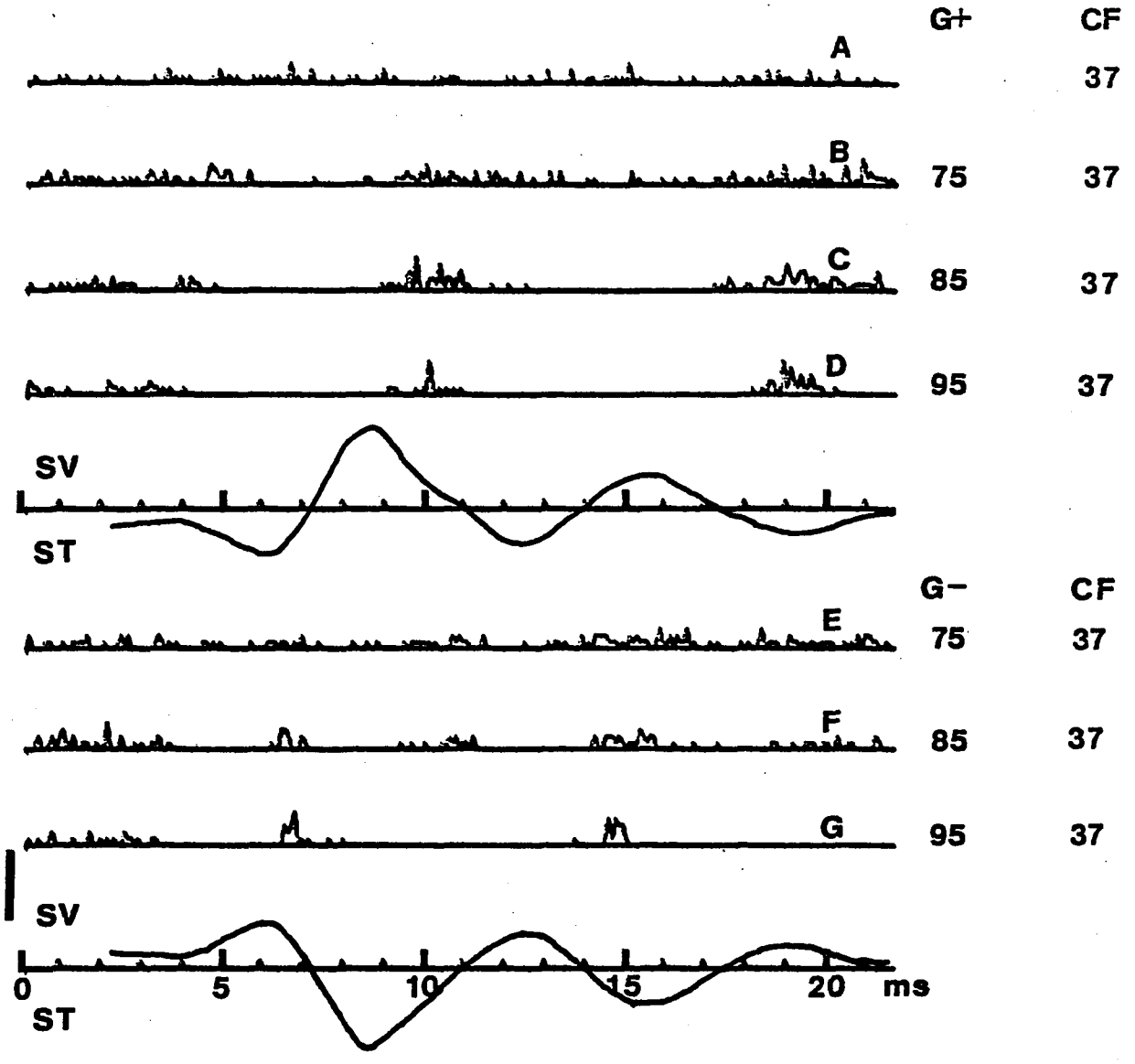

Figure 3.41 Responses of auditory fibers to a continuous tone at CF presented together with a Gaussian impulse. Continuous curves: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Traces B to D for condensation impulses, G+; traces E to G for rarefaction impulses G−. Unit 84-7; CF 2.2 kHz; SR 3 sp/s; Lat. 2.2 ms. Bar=10 counts; N=400.

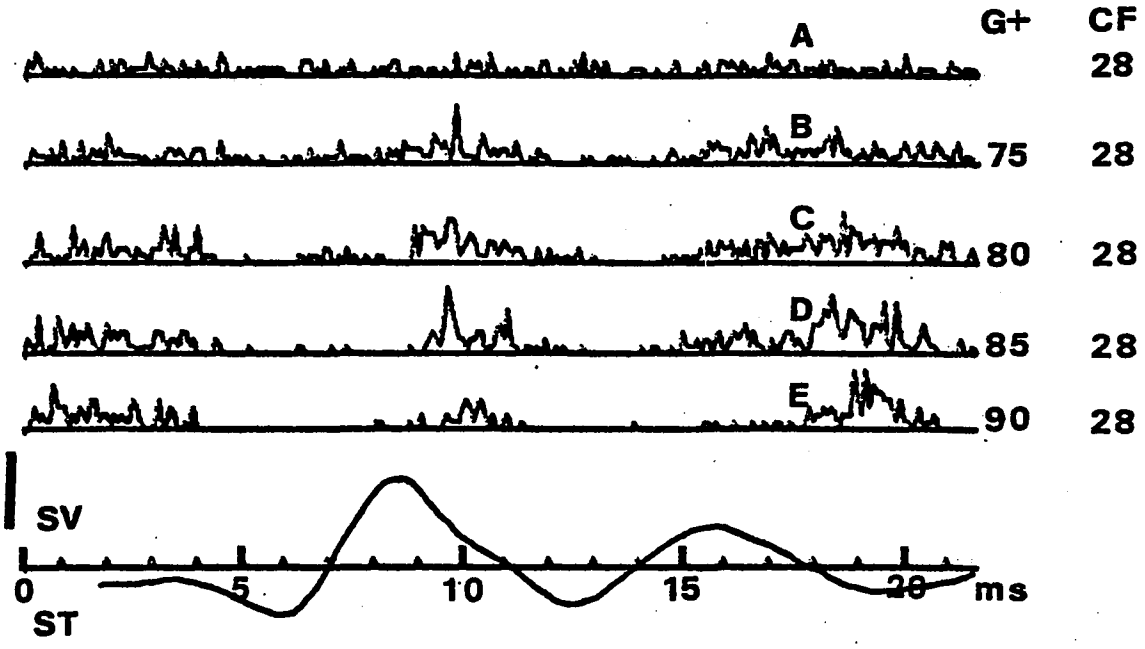

Figure 3.42 Responses of an auditory fiber to a continuous tone at CF presented together with a Gaussian condensation impulse. Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Unit 84-5; CF 5.5 kHz; SR 20 sp/s; Lat 1.9 ms. Bar=10 counts; N=400.

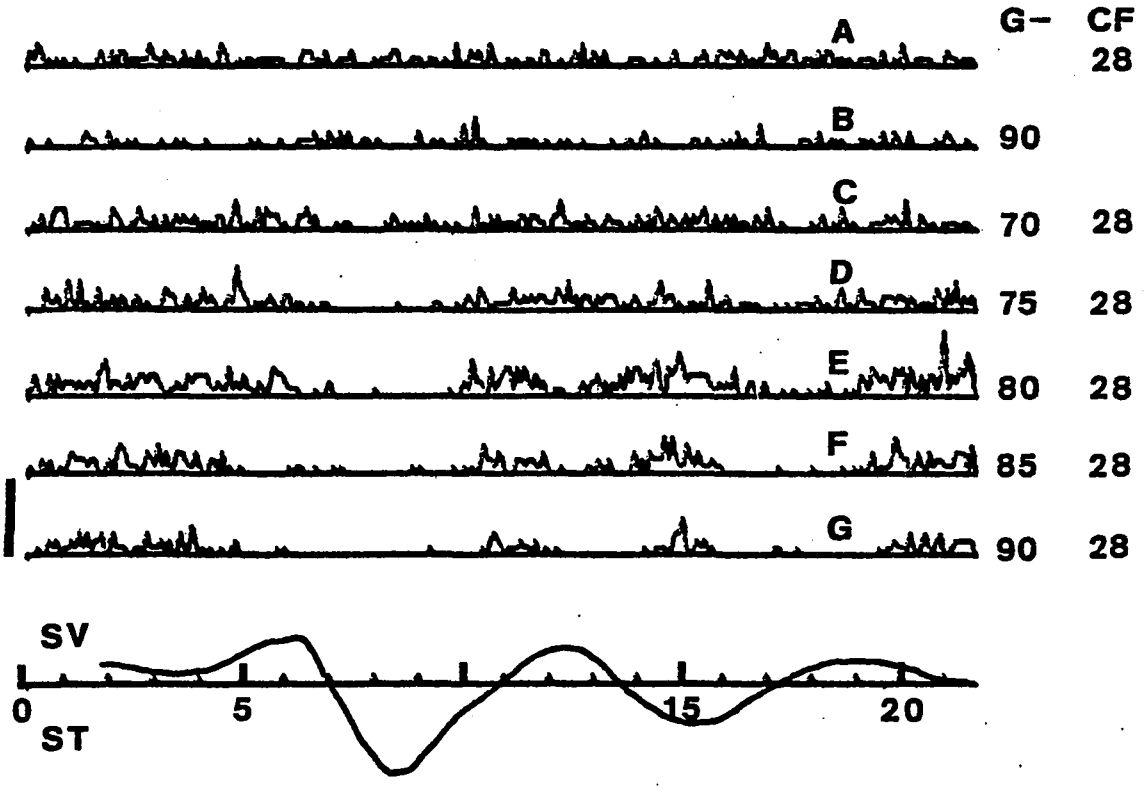

Figure 3.43 Responses of an auditory fiber (the same fiber as in figure 3.41) to a continuous tone at CF presented together with a Gaussian rarefaction impulse. Note the masking in SV, for higher levels of the impulse (traces E, F, G at 13 ms). Bottom trace: BM movement at the place of innervation of the fiber as excitation takes place, inferred from RW CM, shifted to right by the latency of the fiber. Unit 84-5; CF 5.5 kHz; SR 20 sp/s; Lat 1.5 ms. Bar=10 counts; N=400.

same mechanism that masks the activity due to the CF tone in SV in the 100 Hz tone experiment.

A difference in effect between a Gaussian masker and a continuous sinusoidal masker was shown to exist in the AP case. Figures 3.18 and 3.19 showed that most masking was attained in an ST displacement of the BM preceded by a SV displacement. The data presented here are not sufficient to decide whether this effect is to be seen at the single fiber level, but some hints are available: In figure 3.43 it is seen that the suppression is total at around 8 ms in trace D. This corresponds to a deflection of the BM towards ST preceded by a SV deflection. Similarly, in figure 3.43 trace B has a more pronounced suppression at 8.5 ms (the ST after SV displacement) than the counterpart for a Gaussian condensation impulse, figure 3.42 trace E at 6 and 10 ms.

In most examples of LF tones presented together with CF tones, there appears to be an enhancement of activity in the phase of inferred transition of the BM from SV to ST and ST to SV. Whether this is a true enhancement or merely a redistribution of the firing probability can only be decided by more quantitative data on spike count. Also in most examples, there seems to be a generalized suppression of unit activity in all phases but the SV to ST phase of BM motion for sufficiently high intensities of the LF tone. The SV to ST phase is not masked except for high levels of the LF tone. Note that this is the phase where in the AP

case, the responses due to tone bursts were least affected by the LF tone (figures 3.18, 3.19 and 3.20).

CHAPTER 4

DISCUSSION

The results of the experiments described in Chapter 3 show certain characteristics of the cochlear responses that have not been revealed before. Aside from these new findings, data from whole nerve action potentials and single unit responses are consistent with each other, and in agreement with the results of other investigations. In section 4.1 a comparison is made between our results and the results of similar experiments by others. Section 4.2 describes current views of hair cell excitation. In section 4.3 speculations are presented on the possible mechanisms underlying the results of our experiments.

4.1 Comparison of data.

The most prominent results of this research are summarized in figure 4.1. Here a summary of the main findings in Chapter 3 and comparison to other available data are presented.

A) Action potentials due to low frequency stimuli.

In section 3.3A it was demonstrated that the AP elicited by a low frequency stimulus can be correlated with the occurrence of the negative peak in the RW CM. The AP occurs 2.1 to 3.2 milliseconds after this negative deflection. The CFs of the fibers that mainly contribute to

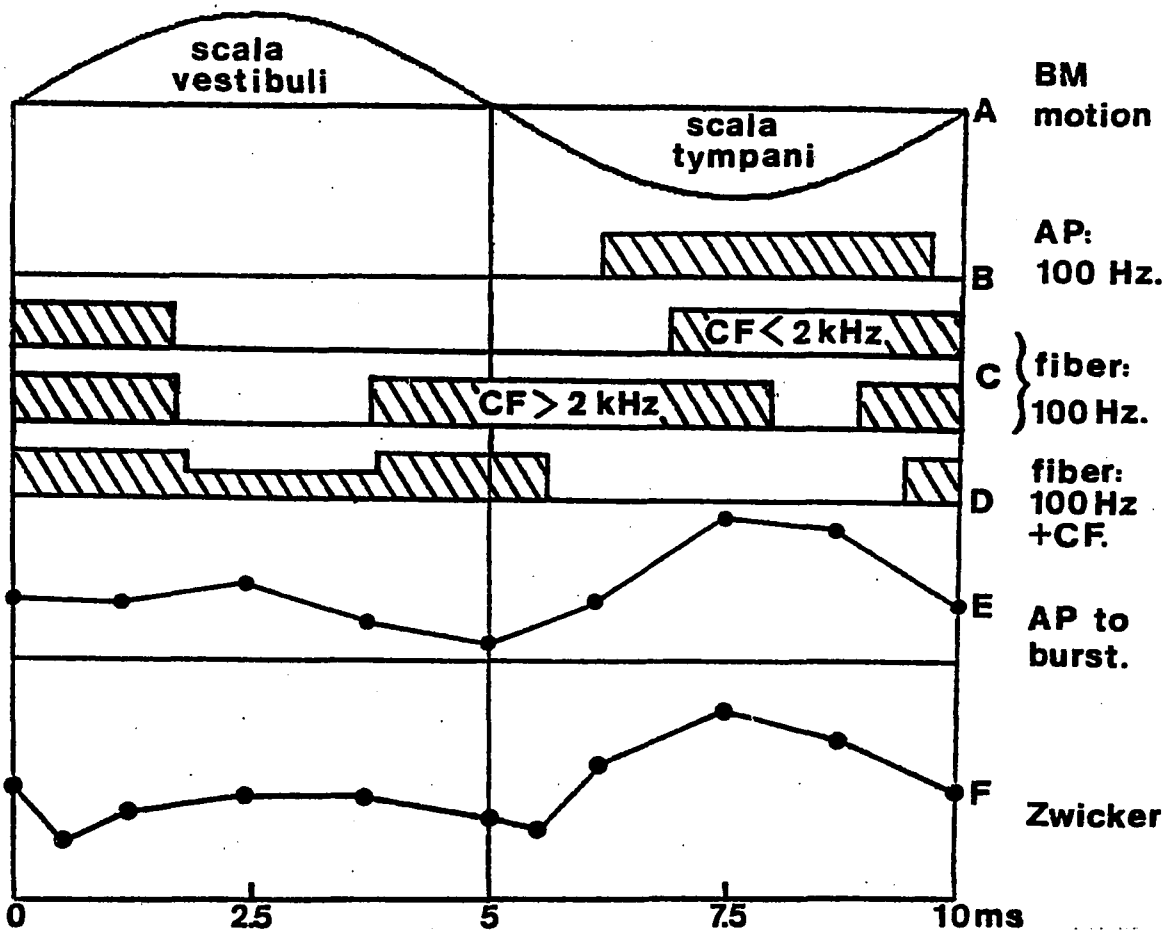

Figure 4.1 Comparison of data. A. Inferred BM movement at place of innervation. Here 100 Hz was used, but results apply for a wider range (50 to 200 Hz). B. Regions with hatching indicate where single unit discharges are assumed to occur, derived from AP data. C. Preferred phase of single unit responses due to 100 Hz presented alone. D. Preferred phase of single unit responses due to a tone at CF presented together with a tone at 100 Hz. The lower hatching area indicates the region where the secondary phase of suppression occurs as the LF tone level is increased. E. Level of tone burst to restore size of AP, as this AP is masked by the presence of a LF tone (section 3.3B), i.e. more masking is up in diagram. F. Zwicker's (1977) psychoacoustic data for 20 Hz, for comparison. It has been scaled in time and shifted to comply with Zwicker's assumption on the BM movement (see figure 1.4).

the AP are not known. Therefore, assuming that the latency of the fibers was in the interval 1.1 to 3.5 ms, we concluded that fibers were excited in the interval -1.4 to 2.1 ms around the displacement of the BM towards ST. This interval is shown in figure 4.1B. Similar conclusion was arrived at by Eldredge in 1976. He found that best correlation with CM was gotten by relating the time of occurrence of the AP to the positive peak of the DIF CM (equivalent to the negative peak of RW CM). The AP occurred in the interval 1.1 to 1.4 ms after the said positive peak deflection of the DIF CM. Eldredge used "low pass 400 Hz clicks", also known as thumps. These stimuli produce a pattern of CM similar to the Gaussian pulses used in the present work, the difference being mainly that the low pass clicks were shorter than the 10 ms Gaussian impulses (the maximum and minimum CM occurred at an interval of 1.4 ms, whereas for the 10 ms Gaussian this interval was 2.3 ms). The thumps most probably stimulated higher CF fibers than did the Gaussian pulses used here. Figure 4.2 is from the work of Eldredge, showing the time of occurrence of the AP for different types of low pass clicks.

B. Unit activity due to LF stimuli.

A dichotomy of firing time was shown to exist between low and high CF fibers. Low CF fibers fired around 9.7 ms; high CF fibers fire at 6.1 ms after the BM is inferred to be at the zero crossing movement from ST to SV, due to a 100 Hz

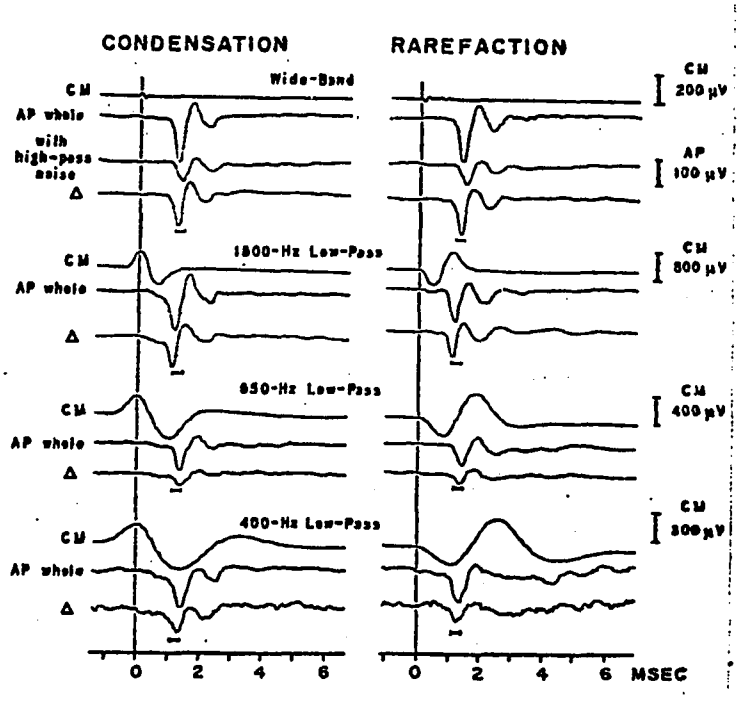

Figure 4.2 Action potentials elicited by thumps of different duration, gotten by low-pass filtering clicks. Note the small variability in the time of occurrence of the AP as related to the time of positive peak of CM (corresponding to negative peaks in RW CM traces). In rarefaction data the start of the negative going CM was used as reference time.Traces marked with delta represent the portion of the AP that is eliminated if a 6 kHz high pass noise is presented together with the click. (From Eldredge 1976).

tone, as seen in figure 3.27.

The data presented in figure 3.27, and showed schematically in figure 4.1C, agree with the data of Konishi and Nielsen (1973, 1978) only in an expanded interpretation: Whereas these researchers found most fibers to be excited by a deflection of the BM towards scala tympani, figure 3.27 indicates that fibers seem to fire anywhere except at the time of inferred SV displacement of the BM. Sokolich et al. (1976) presented results in general agreement with the ones presented in figure 3.27: Fibers of low CF increase the firing during motion of the BM from ST to SV. Fibers of medium CF showed reversed polarity, i.e. they fired in the inferred SV to ST motion of the BM. Fibers of high CF tended to fire in both velocity maxima of BM motion, from ST to SV and from SV to ST.

C. Comparison between A and B.

The APs due to LF tones should have correlates at the single unit level. The auditory nerve fibers show definite preference of phase of firing to low frequency stimuli, as is evident from the above data, but the particular phase of firing seems to depend not only on the BM movement, but on the type of low frequency stimulus, its intensity and the CF of the fiber. Other important factors may be the physiological condition of the cochlea, adaptation effects and past history of stimulation. Any and all of those

factors may have contributed to the spread of maximum activity observed in figure 3.27.

A rigorous demonstration that the APs have correlates at the single unit level is not possible on the basis of the available data. We can only state that the results are not in conflict: Single units do not fire as the BM is displaced towards SV (figure 3.27) but fire in other phases of the LF stimulus, whereas whole nerve action potentials are generated as the BM is displaced towards ST (-1.4 to 2.1 ms around maximum ST displacement).

D) APs due to tone bursts influenced by LF stimuli.

A low frequency stimulus will suppress the AP due to a tone burst, as the tone burst is superimposed on certain phases of the LF tone. This suppression is a stable and predictable function of the BM movement. This was shown in section 3.3B, and is shown schematically in figure 4.1E. The general finding is that the LF stimulus will mask the AP due to the tone burst when this stimulus displaces the BM towards either SV or ST, the ST deflection being more effective in masking the AP. The AP study in section 3.3B on tone bursts superimposed on LF stimuli is also in general agreement with the work of Eldredge (1976). He performed an experiment using thumps, similar to our Gaussian impulses, and clicks as the stimulus for eliciting APs, in the same fashion as short tone bursts were used in the present study.

The results are presented in figure 4.3. Both negative and positive deflections of the CM due to the thump correspond in time to the masking of the AP produced by the click, when higher levels of the thumps are used. The line-up of maximum CM and maximum masking in Eldredge's experiment (figure 4.3) is not as evident as in the experiments with Gaussian impulses (figures 3.18 and 3.19). This is because the thumps were considerably shorter than the Gaussian impulses, making small deviations in time more apparent.

A rather important discrepancy is to be seen, however, within Eldredge's data, and when one attempts to correlate it with ours: In the case of a condensation thump, the maximum of masking occurs as the DIF CM is negative, which we infer to be the phase where the BM is displaced towards SV. In our data and in Eldredge's experiment with rarefaction thumps, maximum masking occurs in the inferred ST direction of the BM movement. The larger masking produced by a condensation thump in SV can be due to the asymmetry of the thump: The second deflection of the CM is larger than the first, giving larger masking both in the condensation and rarefaction cases.

Sellick et al. (1981) demonstrated the same masking effect by LF tones on APs due to tone bursts in guinea pigs. They used tone bursts superimposed on 40 Hz sinusoids, and found the masking in the inferred ST displacement of the BM to be larger, as in our data.

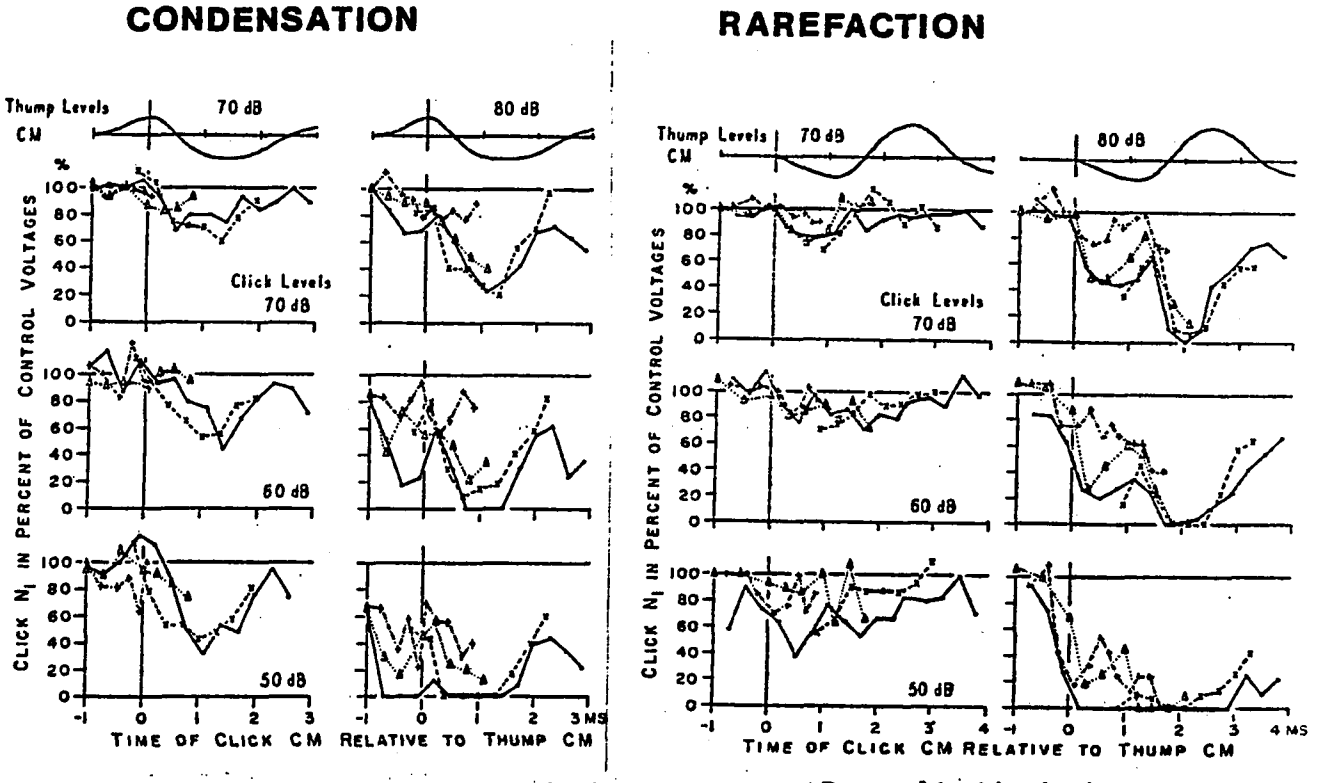

Figure 4.3 Influence of thumps on APs elicited by clicks. Two left columns are for condensation thumps, two right columns for rarefaction thumps. CM graph is from differential electrodes, therefore a positive deflection corresponds to inferred BM movement towards scala tympani. Individual data are from representative ears. The discrepancy between these data and the AP data of section 3.3B is seen in the condensation case, where an inferred displacement of the BM towards SV gives larger masking than displacement towards ST. (From Eldredge 1976).

E) Fiber responses to CF tones influenced by LF stimuli.

When a continuous tone at CF is presented together with a low frequency stimulus, the auditory fibers respond in a conspicuously homogeneous fashion, as evidenced in figure 3.33 and schematized in figure 4.1D. At a moderate intensity, the first effect of a low frequency stimulus on the activity of a fiber due to a CF tone is a supression of this activity in the inferred ST displacement of the BM. If the level of the LF tone is increased, or if the level of the CF tone is decreased, another suppression area is seen, in the inferred SV displacement phase of the BM (figure 3.34). High level LF tones have a general suppression effect on the activity due to CF, but this suppression is less prominent at the time of inferred zero crossings of the BM. Higher levels of the CF tone would probably suppress the activity completely, unless the LF tone by itself produced a response. All the fibers tested displayed very similar patterns, independent of their CF. The influence of the LF tone on the fiber's firing due to the CF tone seems therefore to be a well behaved function of basilar membrane motion.

Results similar to these were obtained by Sellick et al. (1981), for high CF units. They used a continuous tone at CF and a 40 Hz LF tone. Sachs and Hubbard (1981) reported the same effect in the cat.

As mentioned in Chapter 1, Romahn and Boerger (1978) studied single unit responses, using basically the same paradigm as the one used in the AP study of section 3.3B. They found no modulation to be present in a large majority of the fibers (93%), in sharp contrast to our material, and also to that of e.g. Sachs and Hubbard (1981), where modulation of the response to a continuous CF tone by a LF tone is seen in over 90% of the cases. A possible explanation is that these researchers used LF tones of lower level than ours, or CF tone bursts of higher level. It is also conceivable that the behavior of the cochlea is very different for continuous tones (used in the present work) than it is for pulsed tones (used by Romahn and Boerger). However, the data on APs to tone bursts masked by LF stimuli shows that the AP to a tone burst is strongly masked in certain phases of a LF tone presented simultaneously with the tone burst.

F) Comparison between D and E.

The agreement between the behavior of the masking areas found in the AP study of section 3.3B and the single unit study of section 3.4B is remarkably good: The maximum masking of the AP due to the tone burst occurred in the inferred displacement of the BM (by the LF stimulus) towards ST. As intensity of the LF tone was increased, a secondary masking region appeared in the SV displacement of the BM. Equivalent results were obtained in the single fiber study,

where suppression of fiber activity occurred in the same phases of the BM movement as the masking in the AP study.

The LF stimulus enhances the fiber activity due to a CF tone the phase of transition of the BM between maximum displacements towards either scala. It is not possible from the present data to determine whether this is a true enhancement, i.e. whether the average firing rate increases, or if it is a redistribution of the activity from suppression intervals to enhancement intervals, without increasing activity.

As stated in Chapter 3, the good correlation between the events at the AP level and at the single unit level is assumed to be a demonstration that the two masking peaks in the AP occur because of suppression at the single fiber level, not because of refractoriness, excitation, or lack of synchrony of the fibers.

A legitimate criticism of the parallels that have been drawn between the experiments above is the question of the dynamic versus static behavior of the auditory fiber responses. The single fiber experiments were performed with continuous tones at CF whereas the AP study employed short tone bursts. Many experiments indicate a different behavior of single fibers to the onset of a tone burst from that of a steady state tone. Kiang et al. (1965) described the onset response for tone bursts and noise bursts. The histograms start with a sharp peak at the onset of the response,

decaying to a steady state in 100 to 200 ms. This peak is less prominent for bursts of lower intensity. Similarly, Smith and Brachman (1980) showed that fibers have a larger dynamic range when this range is calculated from responses to modulated tones, than when calculated merely by changing the level of continuous tones. In other words, when the maximum discharge rate was subtracted from the minimum discharge rate within the period of modulation, this difference was larger than when the discharge rates were obtained directly from a steady state discharge rate due to a CF tone of intensity equivalent to the maxima and minima of the modulated CF tone.

These differences between the behavior of single auditory fibers to continuous versus pulsed stimuli indicate that caution should be used when comparing the AP data (pulsed stimuli) with the single fiber data (continuous stimuli). A common mechanism behind the good agreement between the phase of masking in the AP study and the suppression in the single fiber study is therefore suggested but not proven.

G) Psychoacoustic correlates.

The results of the AP study in section 3.3B are in good qualitative agreement with the psychoacoustic data of Zwicker (1977). A masking of the probe tone occurs in one phase of the low frequency stimulus that is presented

together with the probe tone. Another smaller masking region appears at the opposite phase of the LF tone, as the level of the LF tone is increased. From considerations of the size of the helicotrema and the correlation of masking pattern with the second derivative of the sound pressure of a 20 Hz sinusoidal, Zwicker concluded that the large masking peak corresponded with a displacement of the BM towards ST and the small one with displacement towards SV. Although a more direct proof of the phases of BM movement for humans is desirable, e.g. by CM measures, the phases of masking inferred by Zwicker are in full agreement with the phases inferred in the AP study of section 3.3B.

Figure 4.1 summarizes the relations found between the various results presented above. A 100 Hz sinusoid is used in the example, but Gaussian impulses or sinusoids of frequency between 50 and 200 Hz give comparable results. Some of the results of our experiments cannot be explained with commonly held views on the mechanisms of hair cell excitation that are presented in the next section. Perhaps the most intriguing finding is that fibers are inhibited to fire in the BM deflection towards SV due to a low frequency tone presented alone, whereas they are inhibited to fire in the ST deflection of the BM, when a CF tone is presented together with a LF tone.

4.2 Current views of underlying mechanisms.

Here a brief review is made of some contemporary notions on the mechanisms for inner hair cell depolarization that leads to spike initiation. The results of the experiments described in Chapter 3, on the phase of suppression and masking, are only partially supportive of the present ideas on the phase of hair cell depolarization.

Current views on the mechanisms of hair cell depolarization are shaped by the work of many investigators, such as Davis (1965), Strelioff et al. (1976), Honrubia et al. (1976), Manley (1978), and Russell and Sellick (1980), and the knowledge of the anatomy of the organ of Corti. Our opinion on the relation between BM movement and cell depolarization is thus as follows:

It is assumed that inner hair cells can be depolarized by two means: electrical and mechanical. Honrubia et al. (1976) summarize their views of acoustical and electrical interactions in figure 4.4. They based their hypothesis on the responses of nerve fibers innervating the lateral line of Xenopus laevis (see figure 1.8), where cells are depolarized by mechanical displacement rather than velocity.

Figure 4.5 shows the inferred phase of depolarization due to mechanical stimulation. The cilia of the IHCs, it is assumed, do not contact the tectorial membrane. Dallos et al. (1972) show that regions depleted of OHCs have

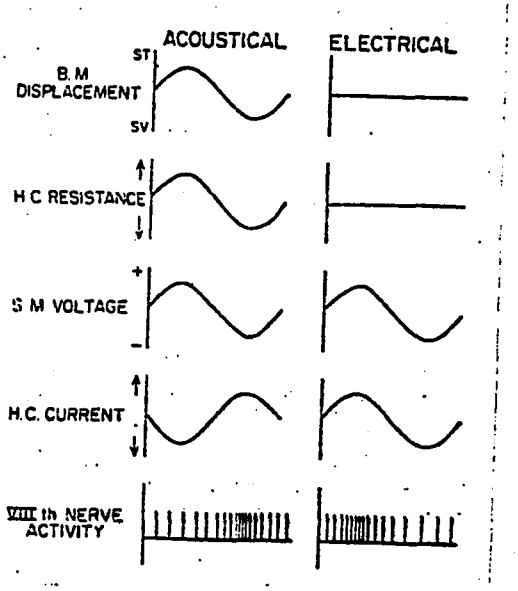

Figure 4.4. Theory of acoustical versus electrical stimulation of hair cells. Note the difference in the polarity of the SM voltage change (i.e. EP change) that produces auditory nerve activity. (From Honrubia et al. 1976).

responses proportional to the velocity of the BM. Sellick and Russell (1980) find a derivative relationship between CM and inner hair cell intracellular potential. These data suggest that indeed inner hair cells are velocity detectors, the explanation being that the cilia are maximally displaced when the fluid surrounding them has a maximum flux. Considering the direction of basilar membrane movement (e.g. Flock 1971), one concludes that depolarization due to mechanical forces takes place in the ST to SV maximal movement of the BM (figure 4.5D). This polarity is supported by the result of experiments by Dallos et al. (1972), and Sellick and Russell (1980).

As for the electrical stimulation of inner hair cells, it seems that the following reasoning is most compatible with known facts: Outer hair cells produce most of the extracellular cochlear microphonic and summating potentials (Dallos and Cheatham 1976). Several researchers believe that the changes in the endocochlear potential produced by OHC may influence the IHCs. In the case of the cochlea, OHCs produce a change in EP that may be sensed by the IHCs in a phase represented in figure 4.5B, producing a depolarization as in figure 4.5C.

Strelioff et al. (1976) propose the IHC-OHC interaction to be as follows: The stria vascularis produces the EP represented by VS (less the drop across Rs) in figure 4.6, that together with the intracellular hair cell

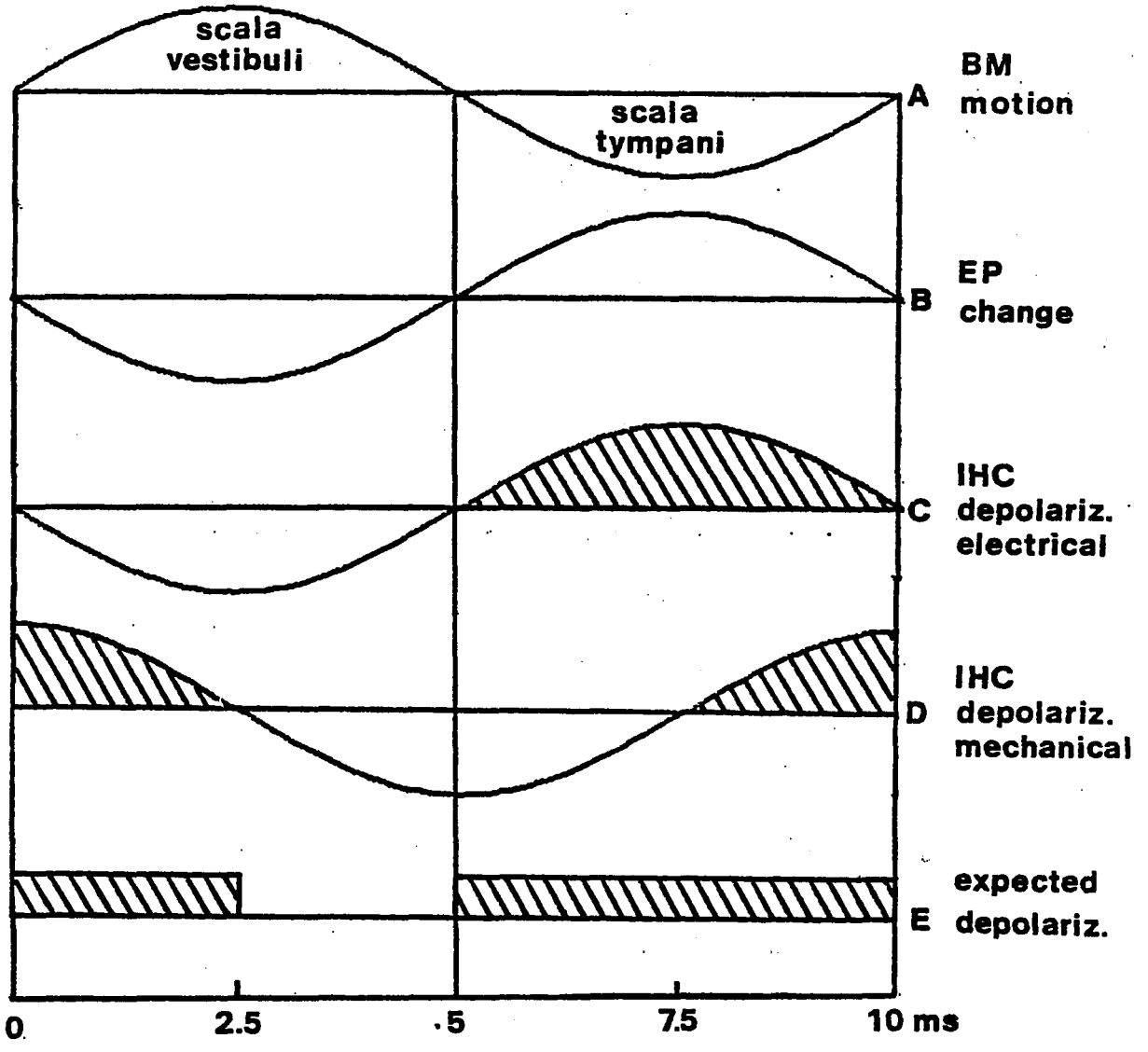

Figure 4.5 Current views of underlying mechanisms for IHC depolarization. A. Movement of the BM at the location of the IHC. B. EP change (i.e. the CM in the scala media) that fluctuates the potential above the cuticular plate of the IHC. C. IHC's intracellular potential fluctuation due to the EP. D. IHC's intracellular potential fluctuation due to mechanical stimulation of cilia by fluid flux. E. Expected phase for IHC depolarization due to C and D.

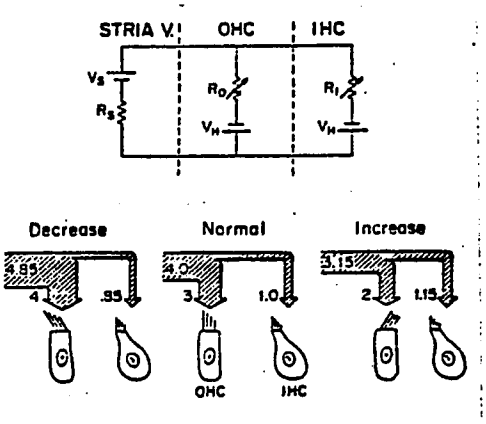

Figure 4.6 A possible interaction between inner and outer hair cells is via the endocochlear potential. The stria vascularis produces a current that flows through the hair cells. Rs being relatively large, maintains the total current approximately constant and the hair cells have to share it. This share is actually mediated by the change in the EP. (From Strelioff et al. 1976).

potential VH drives current through the hair cells. The numbers indicate predicted relative distribution of currents based on measurements of resistivity between various scalae and on the assumption that only OHCs change their resistivity with the stimulus. This assumption would be approximately true for frequencies well below the CF, given that IHC have their cilia free from the tectorial membrane. This is so because at low frequencies, the velocity of the fluid surrounding the IHC cilia is small, and the IHCs are influenced only by the changing electrical field due to the OHCs.

Maximum depolarization of the IHC due to the mechanical stimulation of the cilia will be in the ST to SV velocity phase of the BM movement; maximum depolarization of the IHC due to electrical influence from the OHC will be in the phase of maximum displacement of the BM towards ST, since the EP is maximum in that phase. Depending on the size of each of these two factors, the maximal depolarization of the may at various locations within the cycle. Figure 4.5E indicates the phase range where depolarization might be expected. The time 2.5 to 5 ms is then never expected to be depolarizing.

When a tone at CF is presented together with a LF tone, the depolarization of the inner hair cell should be a linear sum of the effect of each tone, if the above scheme is correct. The data in Chapter 3 show clarly that this is not

the case. A mechanism to explain this is suggested in the next section.

4.3 Physiological basis for the results.

The scheme portrayed in section 4.2 for depolarization is not sufficient to explain all the data from our experiments. The results of the experiments with low frequency stimuli presented alone are in general agreement with the scheme presented in section 4.2; however, there is a conflict between the scheme and results of experiments presenting CF tones and LF tones together.

A) Low frequency stimuli presented alone.

In the case where a low frequency tone is presented alone, fibers show a tendency to fire in the transitions of the BM movement from SV to ST and ST to SV. The spread of preferred phase of firing is obvious but so is the lack of fibers firing as the BM is displaced towards SV. The scheme above can readily explain the latter: The LF tone will cause a more negative EP to occur in the phase of the BM displacement towards SV, as this is the phase of OHC depolarization. This diminishes the available depolarizing current for the IHCs, and thus fiber activity decreases.

Figure 4.5E indicates that no depolarization is expected in the interval 2.5 to 5 ms. The experiments in Chapter 3 (figure 3.27) show that 17% of the fibers fired

during this time (25% would be the expected number, assuming random firing phase). In figure 3.27 it is also seen that no fibers fired in the interval between 1.7 and 3.7 ms. A shift of 1 ms would relocate the silent interval to overlap the theoretical area of no depolarization. There is therefore a time discrepancy of 10% between theory and data, that could be due to experimental errors. The error could also be in the assumption made, that the excitation time is found by subtracting the zero-cross of the RW CM and the latency of the fiber from the time of occurrence of the spikes within the cycle of the LF tone (see section 3.4A).

The dichotomy of firing of low versus high CF fibers is difficult to explain. Perhaps the low CF fibers fire in the ST to SV transition of the BM movement because the IHCs are stimulated by the velocity component of the BM movement. According to the scheme of hair cell interaction presented in section 4.2, fibers of high CF, not being stimulated by velocity of a tone of frequency much lower than the CF, should fire in the ST displacement of the BM (figure 4.5C). However, a majority of the high CF fibers fired in the SV to ST transition of the BM displacement.

These results are diametrically opposed to the data of Sellick and Russell (1980) who found that depolarization of high CF IHCs takes place in the ST to SV phase of the BM movement. The explanation of this apparent discrepancy appears elusive at this time.

As for the APs observed when a low frequency stimulus was presented alone, the scheme of section 4.2 is adequate to explain the results to the extent that APs are generated in the phase of the BM deflection towards ST. The reason for this is probably that in the ST displacement of the BM there is a positivity in scala media that increases the depolarizing current through the IHCs.

B) LF tones presented with CF tones.

When a CF tone was presented together with a LF tone a considerably different pattern of firing occurred, the most conspicuous aspect of it being that a clear suppression of fiber activity was seen as the BM was inferred to be displaced towards ST by the LF stimulus.

One way to explain suppression of fiber activity as the BM is displaced towards ST is to assume that IHC have their cilia attached to the tectorial membrane, and are being hyperpolarized as the BM is displaced towards ST, but this would be in conflict with our previous results and those of e.g. Konishi and Nielsen (1978), of the fibers firing as the BM was displaced towards ST when a LF tone is presented alone. On the other hand, the reduction of firing of fibers to a tone at CF as the BM is displaced towards SV by a loud LF tone can be explained by a reduction in EP caused by the LF tone increasing the current through OHCs.

We are therefore faced with the task of explaining how a displacement of the BM due to a low frequency stimulus towards ST is able to diminish the activity due to a tone at CF. The scheme of section 4.2 predicts that this direction of deflection increases the EP and thus the potential for driving current through the hair cells, therefore increasing neural activity. Thus this simple scheme does not predict the observed results.

A limitation of the OHC's output as the BM is deflected towards ST could explain the observed suppression. Such nonlinearity is described in the literature. The data of Nieder and Nieder (1971) and Durrant and Dallos (1974) showed that as the BM is displaced maximally by a LF tone, the CM and SP are reduced. This reduction is larger in the ST displacement than in the SV displacement of the BM, and this accounts for the observed larger suppression of fiber activity and masking of AP in the ST displacement of the BM. In our data (figure 3.14, for 270 degrees) a reduction of CM is seen in the phase of displacement of the BM towards ST due to a low frequency tone.

Hudspeth and Corey (1979) showed that an asymmetry is found in the change of intracellular potential as a function of movement of cilia. They showed in the bullfrog sacculus that displacement of cilia away from the kinocilium (equivalent to an ST deflection of the BM) produces 3 times less change in polarization than an equivalent displacement

towards the kinocilium, as seen in figure 4.7. If it is assumed that OHCs in the cochlea respond in a similar fashion as the hair cells in the bullfrog sacculus, and that the magnitude of stimuli is comparable, then a nonlinearity of this type could explain the diminished CM due to a high frequency tone as the BM is deflected maximally by a LF tone towards either scala. The asymmetry would explain the more pronouced effect seen in ST.

The sigmoid in figure 4.7 can be used to estimate the amount of CM produced by a CF tone when this tone is presented together with a LF tone. When a CF tone displaces the cilia by a small amount, the change in polarization of the cell will be proportional to the slope, or derivative, of the sigmoid in figure 4.7 (see lower panel of figure 4.7). A small displacement will produce a depolarization that has an approximately linear relationship to the displacement. If the BM is biased by a LF tone towards the saturation points, the CM produced by a CF tone that is presented together with the LF tone will be zero at displacements due to the LF tone where the slope of the sigmoid is zero.

In the experiments with CF tones presented together with LF tones (figures 3.32 to 3.43) the LF tone was presented typically at 40 to 50 dB higher level than the CF tone. At this level difference between the CF and the LF tones, the suppression in the SV phase of BM displacement

due to the LF tone, is already apparent but does not suppress entirely the activity due to the CF tone (see e.g. figure 3.36 C). It is therefore assumed that the displacement due to the LF tone is larger than the displacement due to the CF tone, although remembering that the BM is displaced more by a CF tone than by a LF tone at the CF location.

Assume that the LF tone displaces the BM to such an extent that the OHCs follow a depolarization path equivalent to a displacement of 1 micrometer in figure 4.7. The approximate depolarization of the OHC will then be as indicated in figure 4.8B. Figure 4.8C shows the depolarization of IHCs due to an electrical interaction with the OHCs, as described in section 4.2. Figure 4.8D represents the IHC depolarization due to mechanical displacement of their cilia, as described in section 4.2. The amplitude of CM produced by a CF tone presented with a LF tone will be determined by the derivative of the curve in figure 4.7, as discussed above. This is depicted in figure 4.8E, for three different levels of the sinusoidal LF stimulus.

Observe the similarity between this curve and the shape of histograms for single unit activity (figures 3.32 to 3.43). For lower levels of the LF (figure 4.8E1) the CM amplitude has one peak per cycle, since the LF tone does not drive the OHCs to saturation; For intermediary levels

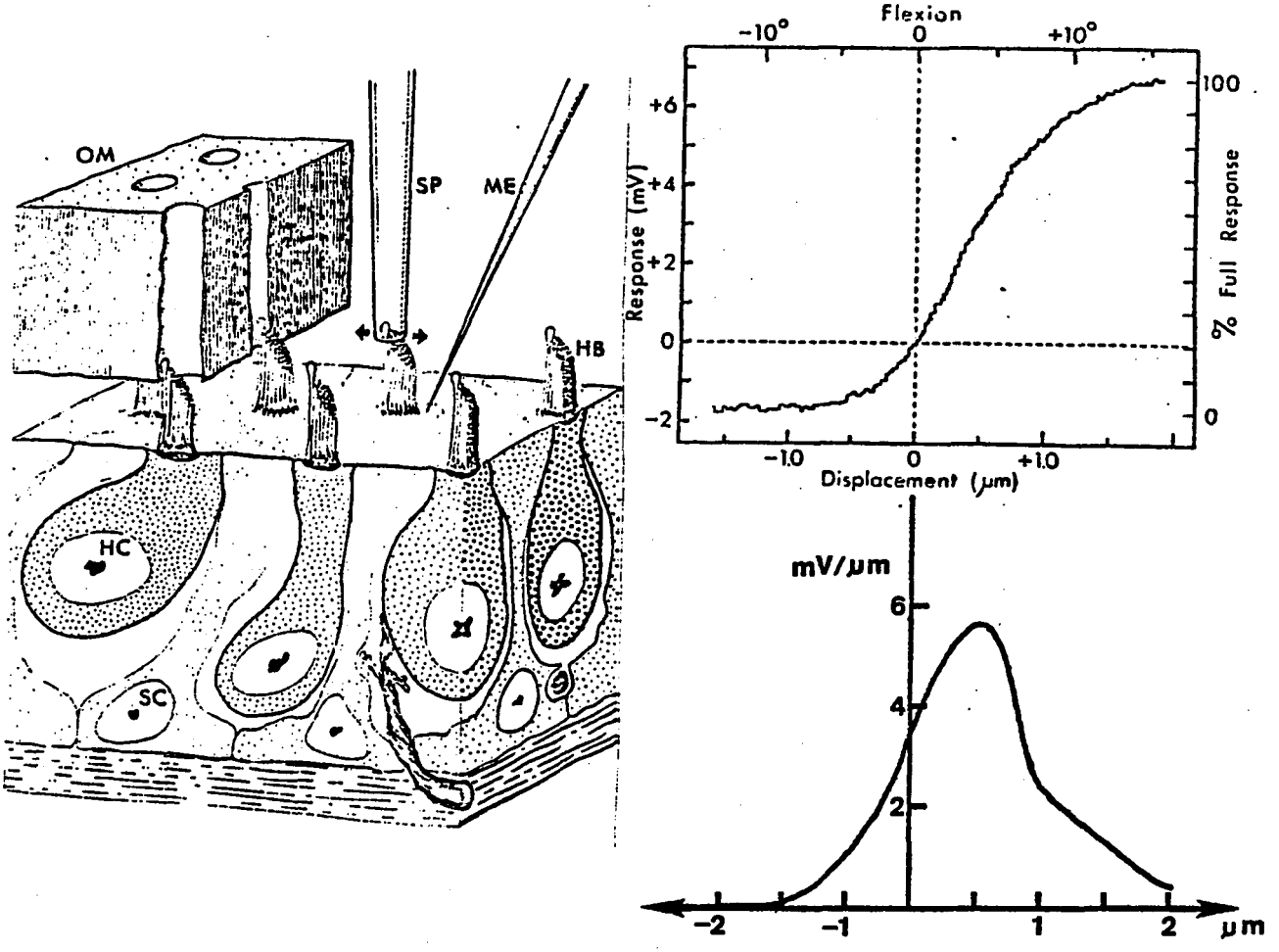

Figure 4.7 Left panel shows experimental setup in the bullfrog sacculus. Upper right panel: record from electrode ME to displacement of the cilia by the micropipette SP. Positive displacement is towards the kinocilium. From Hudspeth and Corey 1977. Lower right panel:Derivative of curve above. This derivative is the "amplification" of the cell, i.e. dV/dx, where V is the amount of depolarization and x is the displacement of the cilia. This curve is also the amount of depolarization produced by low intensity tones when the cilia are biased by a low frequency stimulus of high intensity.

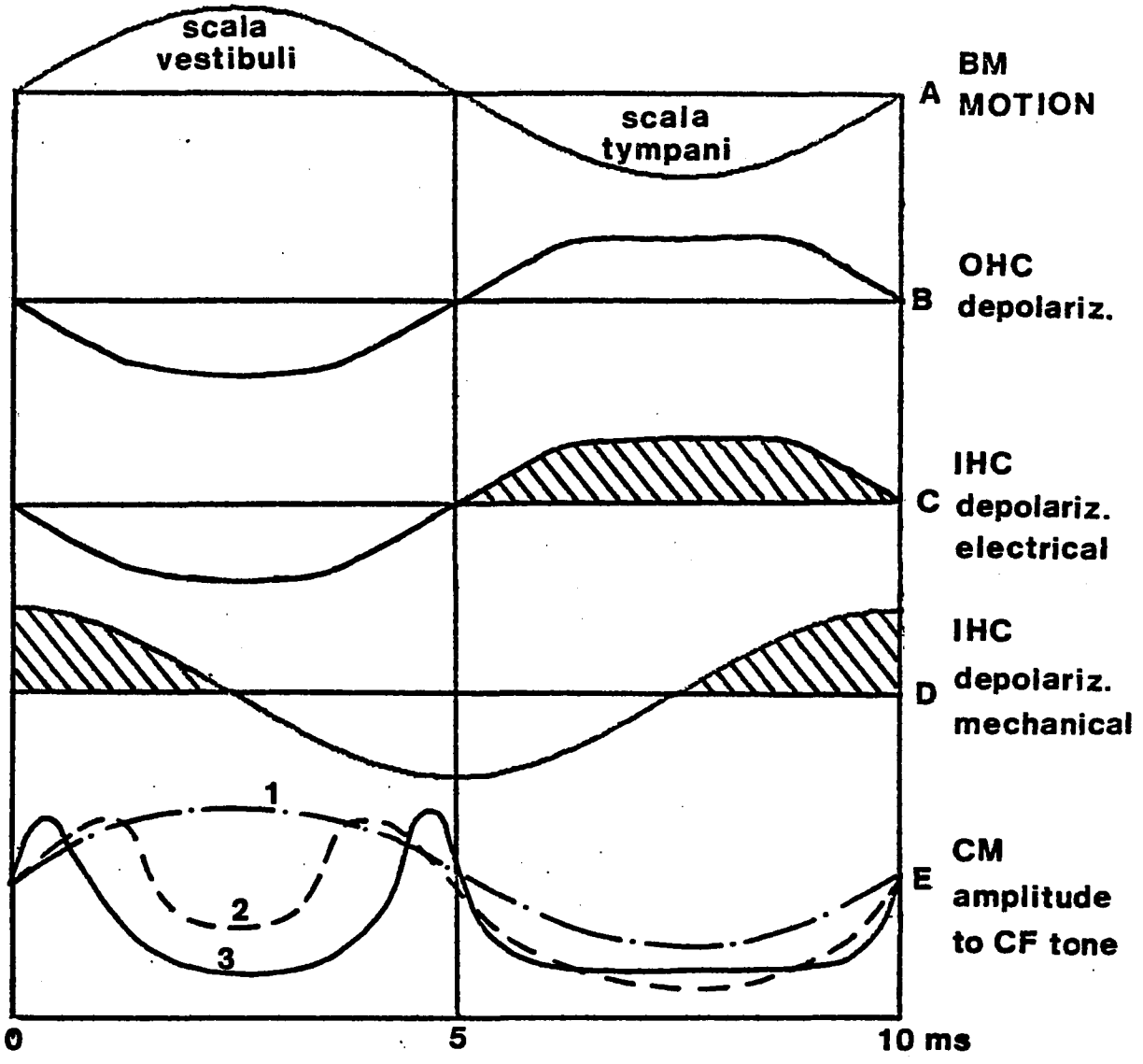

Figure 4.8 Possible mechanisms for the observed responses of auditory fibers to CF tones presented together with LF tones. A. BM movement due to the LF tone. The CF tone is assumed to displace the BM at least an order of magnitude less than the LF tone, because it is presented at a lower level. B. OHC depolarization, level such that saturation in ST is clearly seen, saturation in SV less clearly seen. C. IHC depolarization due to electrical interaction with OHCs, as discussed in section 4.2 (see figure 4.5). D. IHC depolarization due to mechanical stimulation. E. Amplitude of CM by OHCs due to the CF tone and presented with the LF tone; 1, 2 and 3 for successively higher levels of the LF tone (.5, 1 and 2 micrometers displacements were used from figure 4.7).

(figure 4.8E2), the ST saturation is reached, and for high levels, both deflections produce saturation. The peaks of the curve in figure 4.8E2 are not at the zero-crossings of the BM movement, but at one to two ms into the SV phase of the BM movement. This is perhaps the cause of the skewness seen in the peaks of the histograms in figures 3.39 to 3.43; they occur slightly into the SV displacement of the BM. The curve in figure 4.7 seems therefore to be able to reproduce the main features observed in the histograms of figures 3.32 to 3.43.

4.4 Summary

The purpose of this work was to gain better understanding of the basic relation between basilar membrane movement in the cochlea and the auditory fiber activity in the eighth cranial nerve. This was done by stimulating the ear with continuous tones or tone bursts, superimposed on low frequency stimuli (LF). Sinusoids and Gaussian-shaped low frequency impulses were used as LF stimuli.

The LF stimuli displaced the BM in a quasi-static fashion, and the effect of this biasing on the response to the continuous tones and tone bursts was studied.

The results of these experiments are in agreement with previous research by others, and with the recent results of Sellick et al. (1981) and Sachs and Hubbard (1981), that were published while this thesis was being written.

Chinchillas were used in these experiments. The cochlear microphonic at the round window was used to estimate the BM movement in the basal region of the cochlea. Two measures of the influence of the LF stimuli on the cochlear responses were used, the whole nerve action potential (AP) and the single auditory nerve fiber activity (spikes).

The LF stimulus alone elicited APs in each cycle of a continuous sinusoidal (frequencies between 50 and 200 Hz were used). In the case of Gaussian-shaped impulses, each

deflection of the CM (reflecting a deflection of the BM) of sufficient intensity also elicited an AP (see figures 3.3, 3.4, 3.9 and 3.10). The phase of the AP was such that the spike activity generating the AP was inferred to occur as the BM was displaced by the LF stimulus toward scala tympani (ST). The phase of maximum single unit spike activity due to a 100 Hz continuous LF tone from 75 fibers was found to be less well defined than the AP phase (see figure 3.27). Fibers with characteristic frequency (CF) lower than 2 kHz fired preferentially in the SV to ST (maximum velocity) transition of the BM. Fibers with CF higher than 8 kHz fired in the opposite velocity phase; fibers with CF between 2 and 8 kHz fired in both these phases and in the ST displacement of the BM.

The results of these experiments indicate thus that when a LF stimulus is presented alone, fiber activity does not occur as the LF stimulus displaces the BM towards SV.

The randomness of single unit responses due to LF tones has been reported by others; it is remembered that LF signals are not ideal stimuli for fibers of high CF (e.g. CF>2 kHz). The intensity of the LF signals used had therefore to be high, introducing the possibility that distortion in the sound system caused the observed spread. We contend instead that the spread is an indirect indication that inner hair cells (IHCs) do not have their cilia attached to the tectorial membrane: If the cilia were

attached, then one would expect activity of single fibers to be restricted to the SV displacement of the BM, because this is the phase of depolarization of the hair cells, as inferred from the morphology of the organ of Corti and also seen in the phase of the CM.

Another indication that the instrumentation and assumptions made when finding the phases above were proper is the outcome of experiments using tones presented together with LF stimuli. The phases of activity proved to be stable, well defined and repeatable functions of BM movement.

The APs due to tone bursts were maskable by LF stimuli, when the bursts were presented in certain phases of the LF stimulus (figures 3.14 to 3.19). The most effective masking was observed as the BM was inferred to be displaced towards ST. As the level of the LF stimulus was increased, another phase of masking was obtained, in the SV deflection of the BM by the LF tone. A slight enhancement (sensitization?) was seen in the transition phase of the BM movement, from SV to ST (figure 3.17A).

At the single unit level, the spike activity due to continuous CF tones was suppressed by LF stimuli in the same phases as above: ST deflection of the BM by the LF tone was the most effective suppressing phase, and when the LF stimulus level was increased, another phase of suppression was seen, in the SV deflection of the BM (figures 3.32 to

3.43).

From the similarity in phase of these experiments at the AP level and at the single unit level, we conclude that the masking of the AP is a result of suppression of fiber activity, and not a lack of sychrony or excitation of fibers. The latter would be true if the maximum deflections of the BM due to the LF tone gave increased activity due to the CF tone.

An attempt to explain these findings follows:

The results of experiments presenting LF stimuli alone are in broad agreement with the current view of hair cell function. The decreased spike activity in SV is explained recalling that the EP is decreased in this phase, and the IHCs have thus less potential to depolarize (see figure 4.5). It is pointed out that there is a 1 ms discrepancy between the phase of silence in the experimental result (see figure 3.27), and the theoretical phase of no depolarization in figure 4.5.

The APs, being generated in the BM deflection towards ST, are explained by the same mechanism, namely that in this deflection, the EP is more positive, increasing the depolarization current through the IHCs (figure 4.5).

The two suppression phases in the spike activity per period of LF tone (when the cochlea is stimulated with the LF tone and a CF tone) and the similar effect in the AP

study can be explained by invoking a nonlinear mechanism that has been reported to exist in hair cells of the bullfrog sacculus (see figure 4.7). Due to a saturation of the output of the OHCs caused by the LF stimulus, the CF tone cannot produce the same amount of CM in the maximum deflection of the BM. The saturation being greater in the ST than in the SV displacement of the BM explains the more prominent suppression and masking in that direction of deflection. In such a scheme, the amplitude of the CM produced by the CF tone when presented with a LF tone is pictured in figure 4.8E. The similarity between the behavior of this function and the histograms of single units (e.g. figure 3.32 C, D, and E) is apparent.

It is not possible to exclude the possibility of mechanical interaction between cell populations. The modulation of the CM caused by a LF tone on the response of fibers to CF tones is clearly related to the events seen at the single unit level, but a causal relationship is not proven. It is not known whether the sigmoid shape of the curve seen in figure 4.7 is due to ion channel saturation or simply due to a stiffness increase towards the maximum displacement of the cilia from their equilibrium position. If the former is true, namely that the sigmoid shape in figure 4.7 is due to ion channel saturation, then the theory of electrical interaction between hair cell populations is favored; if the sigmoid shape is due to mechanical stiffness, then the coupling between hair cell populations may have a mechanical component as well.

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VITA

Kristjan Ingvarsson

Born March 18, 1947 in Reykjavik, Iceland.

Education:

B.S. 1971, University of Iceland, Electrical Engineering.

M.S. 1975, Royal Institute of Technology, Stockholm, Sweden. Engineering Science.

Ph.D. 1981, Northwestern University, Evanston, Illinois. Biomedical Engineering.

Publication:

Ingvarsson, K., and Dallos, P. (1979). Modulation of cochlear nerve fiber activity by low frequencies. J. Acoust. Soc. Amer. 66, S48(A).