Published in final edited form as:

J Neurophysiol. 1997 May ; 77(5): 2385–2399.

Two-Tone Distortion on the Basilar Membrane of the Chinchilla Cochlea

LUIS ROBLES¹, MARIO A. RUGGERO², and NOLA C. RICH³

¹Departamento de Fisiología y Biofísica, Facultad de Medicina, Universidad de Chile, Santiago, Chile

²Institute for Neuroscience and Hugh Knowles Center Department of Communication Sciences and Disorders, Northwestern University, Evanston, Illinois 60208-3550

³Department of Otolaryngology, University of Michigan, Minneapolis, Minnesota 55455

Abstract

Basilar membrane responses to pairs of tones were measured, with the use of a laser velocimeter, in the basal turn of the cochlea in anesthetized chinchillas. Frequency spectra of basilar membrane responses to primary tones with frequencies (f_1 , f_2) close to the characteristic frequency (CF) contain prominent odd-order two-tone distortion products (DPs) at frequencies both higher and lower than CF (such as $2f_1 - f_2$, $3f_1 - 2f_2$, $2f_2 - f_1$ and $3f_2 - 2f_1$). For equal-level primaries with frequencies such that $2f_1 - f_2$ equals CF, the magnitude of the $2f_1 - f_2$ DP grows with primary level at linear or faster rates at low stimulus levels, but it saturates or decreases slightly at higher levels. For a fixed level of one of the primary tones, the magnitude of the $2f_1 - f_2$ DP is a nonmonotonic function of the level of the other primary tone. For low intensities of the variable tone, the $2f_1 - f_2$ DP grows at a rate of ~ 2 dB/dB with f_1 level and 1 dB/dB with f_2 level. DP magnitudes decrease rapidly with increasing primary frequency ratio (f_2/f_1) at low stimulus levels. For more intense stimuli, DP magnitudes remain constant or decrease slowly over a wide range of frequency ratios until a critical value is reached, at which DP magnitudes fall with slopes as steep as -300 dB/octave. As stimulus level grows, DP phases increasingly lag large f_2/f_1 ratios, but exhibit leads for small f_2/f_1 ratios. Cochlear exposure to an intense tone that produces large sensitivity losses for the primary frequencies (but only small losses for tones with frequency equal to $2f_1 - f_2$) causes a substantial decrease in magnitude of the $2f_1 - f_2$ DP. This result demonstrates that the $2f_1 - f_2$ DP originates at the basilar membrane region with CFs corresponding to the primary frequencies and propagates to the location with CF equal to the DP frequency. $2f_1 - f_2$ DPs on the basilar membrane resemble those measured in human psychophysics in most respects. However, the magnitude of basilar membrane DPs does not show the nonmonotonic dependence on f_2/f_1 ratio evident in DP otoacoustic emissions.

INTRODUCTION

When listening to pairs of tones, one often hears pitches corresponding to frequencies not present in the stimulus. These two-tone distortion products (DPs, also known as combination tones) were discovered by the Italian violinist and music composer Giuseppe Tartini (circa

Copyright © 1997 The American Physiological Society

reprint requests: M. A. Ruggero, Northwestern University, 2299 N. Campus Dr., Evanston, IL 60608-3550.

Present address of Nola C. Rich: 1193 Liberty Church Rd., Mocksville, NC 27028.

We thank M. A. Cheatham, N. Cooper, L. Dreisbach, B. Evans, J. Goldstein, and S. Narayan for comments on previous versions of this paper.

1714) (Jones 1935) and were later extensively studied by psychophysicists. They are perceived at frequencies corresponding to combinations of the primary frequencies (f_1 and f_2 , $f_2 > f_1$), such as $f_2 - f_1$, $(n+1)f_1 - nf_2$ and $(n+1)f_2 - nf_1$ ($n = 1, 2, 3, \dots$). Among two-tone DPs, the best studied in psychophysical experiments are the difference tone, with frequency $f_2 - f_1$, and the cubic difference tone, with frequency equal to $2f_1 - f_2$. Both of these DPs are lower in frequency than the primary tones (Goldstein 1967; Hall 1972; Smoorenburg 1972a,b). DPs at frequencies higher than the primaries (e.g., $2f_2 - f_1$ and $f_1 + f_2$) are more difficult to perceive but have also been measured with the use of psychophysical procedures (Zurek and Sachs 1979).

The existence of DPs in the auditory percept implies that acoustic signals are subjected to nonlinear processing in the auditory system. von Helmholtz (1862) thought that DPs corresponded to objective tones within the cochlea and postulated that they were generated in the middle ear as a consequence of overload at high stimulus intensity. A competing theory stated that there are no cochlear DPs and that their pitches arise from temporal periodicities produced by linear combination of the primary tones (for short historical reviews, see Goldstein and Kiang 1968; Smoorenburg 1972a). More recent psychophysical experiments have shown that the $2f_1 - f_2$ distortion component has a relative size nearly independent of stimulus level, but highly dependent on stimulus-frequency separation (Goldstein 1967). Because of this frequency dependence, the psychophysical evidence suggested that the $2f_1 - f_2$ DP should originate in the mechanics of the cochlea (Goldstein 1967; Smoorenburg 1972b). Such an origin is consistent with the presence of DPs in recordings of cochlear microphonics (Gibian and Kim 1982) and responses of auditory nerve fibers (Buunen and Rhode 1978; Goldstein and Kiang 1968; Kim et al. 1980; Siegel et al. 1982), cochlear nucleus neurons (Smoorenburg et al. 1976), and inner hair cells (Nuttall and Dolan 1990). Furthermore, experiments showing that neural responses to DPs can be reduced or abolished by hair cell damage at cochlear sites corresponding to the primary frequencies led to the conclusion that DPs are generated at these sites and propagate along the cochlea to the locations tuned to the DP frequencies (Siegel et al. 1982). Additional support for the propagation of DPs in the cochlea came from the discovery of DP otoacoustic emissions (Kemp 1979; Kim et al. 1980). Although early attempts failed to find DP components in basilar membrane (BM) responses to two-tone stimuli (Rhode 1977; Wilson and Johnstone 1973), the presence of DPs in these responses has recently been demonstrated directly (Nuttall et al. 1990; Rhode and Cooper 1993; Robles et al. 1990, 1991). We report here on the dependence of these mechanical DPs on stimulus frequency and intensity and on their vulnerability to acoustic trauma. Our results strongly support the idea that $2f_1 - f_2$ DPs arise at the cochlear site tuned to the primary stimuli and propagate on the BM to the site tuned to $2f_1 - f_2$. A preliminary report on the present findings was presented at the XXIII Annual Meeting of the Society for Neuroscience (Robles et al. 1993).

METHODS

Responses to pairs of tones were measured in anesthetized chinchillas (pentobarbital sodium; initial dose: 65 mg/kg) at a BM site ~ 3.5 mm from the base of the cochlea (Robles et al. 1986). The surgical procedures and the methods used to measure velocity by means of a laser velocimeter (Dantec, Skovlunde, Denmark) coupled to a compound microscope were as previously described (Ruggero and Rich 1991a). BM velocity was determined from the Doppler-frequency shift of laser light reflected from glass microbeads (10- to 30- μ m diam) placed on the BM through a small hole made in the otic capsule of the cochlea at the scala tympani. The two primary tones, shaped at onset and offset by a half-period of a raised cosine waveform (rise/fall time 1.16 ms) and 25 ms in duration, were generated by means of a dedicated waveform generator and delivered independently through acoustically coupled earphones (Beyer DT-48). At the beginning of each experiment, calibration tables were

generated relating, at each stimulus frequency, the amplitude and phase of the acoustic stimulus to the magnitude and phase of the electrical signal. A Knowles (1842 or 1785) miniature microphone equipped with a probe tube was used to measure the sound pressure level within 2 mm of the tympanic membrane. The voltage output of the laser velocimeter was frequency filtered with a pass band of 1–15,000 Hz and sampled at 40 kHz under computer control. Velocity responses were averaged over 512 stimulus repetitions and their frequency spectra were obtained by Fourier transformation with the use of a Hanning window (approximately centered on the time span of the response). A silver wire electrode placed on the round window allowed the recording of the whole nerve action potential to monitor the physiological condition of the cochlea during surgery and data collection. Distortion levels in the acoustical stimulus, measured in an artificial cavity, were 70 dB below the level of the primary tones. Those generated in the velocimetry system were usually 50 dB below the magnitudes of the primary tone responses, but higher distortion levels could be observed when the magnitudes of the velocity or acceleration exceeded the manufacturer's specifications for the velocimeter's frequency tracker at the selected sensitivity range (see RESULTS).

RESULTS

DPs for stimulation with primary tones near the characteristic frequency

When a site of the chinchilla BM is stimulated by two tones with frequencies near its characteristic frequency (CF, frequency of maximum sensitivity), its responses include multiple DPs. Figure 1 displays the spectra of BM responses to equal-intensity primary tones with frequencies, 7.6 and 8.4 kHz, closely flanking CF (8 kHz). In addition to the peaks at the primary frequencies, f_1 and f_2 , the spectra contain prominent distortion components at frequencies around CF, such as $2f_1 - f_2$, $3f_1 - 2f_2$, $2f_2 - f_1$, and $3f_2 - 2f_1$. The magnitudes of these DPs decrease systematically as their frequencies increasingly differ from CF at rates that, in this case, vary from ~30 to 130 dB/octave. Two-tone DPs are robust phenomena in the chinchilla, because they were observed even in cochleas that had sustained appreciable losses in sensitivity and frequency tuning. The failure to find two-tone DPs in previous measurements of BM responses to two-tone stimuli (Rhode 1977; Wilson and Johnstone 1973) was probably due to severe cochlear damage and/or inadequate measuring methodology.

In some of the experiments, simple difference ($f_2 - f_1$ sum ($f_2 + f_1$)) and second-harmonic ($2f_1$ and $2f_2$) tones were also present in the BM responses (e.g., Fig. 1). Difference tones were usually weak and were most often detectable, in conjunction with DC shifts and other even-order DPs, in situations of misalignment of the laser beam associated with poor signal-to-noise ratio or when the limits of velocity or acceleration of the velocimeter's frequency tracker were exceeded at the selected sensitivity range. The magnitude of even-order DPs often could be reduced drastically by reducing the sensitivity setting of the Doppler-frequency tracker, suggesting that such DPs originated in the velocity measuring system, rather than in the cochlea. The 70-dB response spectrum in Fig. 1, for example, has higher levels of noise, DC, and $f_2 - f_1$ components than the spectra for responses to 60- and 80-dB primaries, which were measured with a lower sensitivity setting than the 70-dB response. Although we by no means rule out a BM origin of even-order DPs (Kim et al. 1980), we regard our data as insufficient to support such origin (see also Nuttall and Dolan 1993, 1994). The remainder of this report deals only with odd-order DPs with magnitudes well above those of artifactual DPs introduced either in the stimulus or velocimetry systems.

For a fixed cochlear position, the number of DPs detectable in BM responses decreases as the frequencies of the primary tones are increasingly separated. Figure 2A shows frequency spectra computed from responses to primary tones with closely spaced frequencies such that

$2f_1 - f_2 = CF$ and $f_2/f_1 = 1.05$. The spectra display multiple distortion components at frequencies both higher and lower than CF. For DP frequencies lower than CF, the magnitudes of the components decrease at a mean rate of 73 dB/octave; for DP frequencies higher than CF, they decrease at a mean rate of 135 dB/octave. Figure 2B shows spectra of responses to primary tones with widely spaced frequencies ($f_2/f_1 = 1.25$), chosen so that $2f_1 - f_2 = CF$. At the highest stimulus levels, the spectra display peaks at the primary frequencies and, in stark contrast to Fig. 2A, only one DP, larger than the primary components, at the $2f_1 - f_2$ frequency. At moderate stimulus levels (60 and 70 dB SPL), the primary spectral components (whose magnitudes decrease almost linearly with stimulus level) disappear in the noise, leaving the $2f_1 - f_2$ DP (which behaves highly nonlinearly) as the only detectable peak in the responses. Both the linear growth of the responses to the primary tones and the larger magnitude of the DP component vis-à-vis the responses to the primary tones are consistent with the notion that DPs are not generated locally. Rather, DPs most likely originate at a more basal site in the cochlea (where the responses to the primary tones behave nonlinearly and are larger than at the recording site) and propagate to the BM recording location (see also discussion of Fig. 11).

Magnitude of the $2f_1 - f_2$ DP as a function of stimulus level

Most of the experiments were conducted with the use of a stimulus paradigm that maintained a specific DP ($2f_1 - f_2$, most commonly, or $2f_2 - f_1$) at a fixed frequency (usually CF). Figure 3A shows the growth of the $2f_1 - f_2$ DP, measured with the use of this paradigm at a BM site with CF = 9 kHz, as a function of the intensity of equal-level primary tones. The curves without symbols indicate DP magnitudes for tone pairs with frequency ratios of 1.05–1.4 (parameter). In response to low-level stimuli (30–40 dB SPL), the magnitude of the $2f_1 - f_2$ DP grows with primary level at a mean rate of ~1.3 dB/dB. At higher stimulus levels, DP magnitude saturates or even decreases slightly (e.g., at levels 60 dB SPL). The data of Fig. 3 are representative of those from several other cochleas in exhibiting linear or faster-than-linear DP growth rates at low stimulus levels and saturation at high stimulus levels.

For comparison with the DP curves, Fig. 3A depicts the velocity-level function for a single tone at the DP frequency (curve with circles). For each value of DP magnitude, a DP “equivalent level” was computed as the level of a single tone at the DP frequency required to elicit a response of the same magnitude as the DP produced by the two-tone stimulus. The DP equivalent levels may be expressed in relation to the stimulus SPL by measuring the horizontal distances from the DP curves to the single-tone curve in Fig. 3A. These “relative equivalent” levels, plotted in Fig. 3B as a function of stimulus level, are counterparts of the psychophysical relative distortion data (e.g., Goldstein 1967). Relative equivalent DP magnitudes decreased moderately with increasing stimulus level. For frequency ratios of 1.05–1.2, relative equivalent DP magnitude decreased by only 16–26 dB as primary level increased by 50 dB. In this cochlea, relative equivalent distortion levels were as large as –20 dB (10%) at low stimulus intensities and –34 dB (2%) at the highest stimulus intensities. In other cochleas (not shown), relative equivalent DP levels were as high as –16 dB (15%) at low stimulus levels.

For a fixed f_2 tone level, the amplitude of the $2f_1 - f_2$ DP varies nonmonotonically with the f_1 tone level. Figure 4 displays curves of DP magnitude as a function of f_1 tone level measured in three cochleas, for f_2 tones at fixed levels (40–80 dB SPL) and primary frequencies at ratios of 1.1 and 1.2. For low f_1 tone levels, DP-magnitude grows at a rate of ~2 dB/dB (— —). The DP magnitude in response to equal-level primaries is marked in each curve (●, ■, ▲). With a single exception (f_2 at 80 dB SPL, A), the DP curves have their maxima at f_1 levels 5–10 dB higher than the f_2 levels, with the largest differences in level occurring consistently at the lowest f_2 levels. Equivalent distortion levels computed from the

DP values in Fig. 4 (not shown) are also nonmonotonic functions of the f_1 level, and reach maxima of -25 , -28 , and -21 dB relative to the level of the f_1 tone (f_2 at 60, 50, and 50 dB SPL, respectively, in *A–C*). These peak values decrease systematically with f_2 level for f_2 levels >50 dB SPL.

Figure 5 presents curves of DP magnitude as a function of f_2 tone level measured in the same cochlea represented in Fig. 4*A*. The stimuli were tone pairs with fixed f_1 levels of 70 and 80 dB SPL and frequency ratios of 1.1 (—) and 1.2 (---). At low stimulus levels, DP amplitude grows as a function of f_2 level at rates that approximate 1 dB/dB (—), in contrast with the 2-dB/dB DP rate of growth with f_1 level (Fig. 4). The maximum relative distortion amounts to -24 dB for the f_1 tone fixed at 70 dB SPL and $f_2/f_1 = 1.1$.

Magnitude of the $2f_1 - f_2$ and $2f_2 - f_1$ DPs as a function of the frequency separation between the primary tones

In general, for fixed $2f_1 - f_2$ (=CF), DP magnitude decreases with increasing frequency ratio (f_2/f_1) of equal-level primary tones (Fig. 6). For low primary levels, DP magnitudes decrease rapidly with increasing primary frequency ratio; for more intense stimuli, DP magnitudes decrease slowly or not at all at small frequency ratios and rapidly at higher ratios. For large frequency separations, the curves have slopes as steep as -300 dB/octave (---). Figure 7 shows DP magnitude as a function of f_2/f_1 , for several stimulus levels, in another cochlea. These data closely resemble those of Fig. 6. Orderly and monotonic behavior of DP magnitude with primary tone frequency separation and level was demonstrated in two other cochleas (not shown) with the use of frequency ratios as low as 1.025. Decreases in DP magnitude for frequency ratios approaching 1, such as reported in the case of DP otoacoustic emissions (Harris et al. 1989; Probst et al. 1991), were never observed on the BM.

Data on the dependence of the $2f_2 - f_1$ DP on primary frequency ratio (f_2/f_1) were obtained in two cochleas (Fig. 8). The behavior of the $2f_2 - f_1$ DP resembles that of the $2f_1 - f_2$ DP in that, for low primary levels, DP magnitudes decrease rapidly with increasing frequency ratio, whereas, for more intense stimuli, DP magnitudes decrease slowly at small ratios and more rapidly at higher ratios (compare Fig. 8 with Figs. 6 and 7). However, the magnitude of the $2f_2 - f_1$ DP appears to decrease at a lower rate with increasing f_2/f_1 than that of the $2f_1 - f_2$ DP.

Frequency tuning of $2f_1 - f_2$ DPs

The frequency tuning for $2f_1 - f_2$ DPs was measured in two cochleas by systematically varying the frequencies of pairs of tones while maintaining fixed stimulus intensities and frequency ratios (f_2/f_1 of 1.1 and 1.15, Fig. 9). Tuning curves for the $2f_1 - f_2$ DP resemble those for responses to single tones (Robles et al. 1986; Ruggero et al. 1997), implying that BM DPs are frequency filtered much as single tones. The peak-response frequencies appropriately match the CFs (9 kHz in *A*, 8 kHz in *B*) and the high-frequency slopes are steeper than the low-frequency slopes. Also in agreement with responses to single tones, responses at DP frequencies lower than CF grow at a faster rate than responses at CF and higher frequencies. As a result, the tuning curves in both cochleas are more broadly tuned at higher primary levels than at lower levels and their centers of gravity shift toward lower frequencies with increasing SPL.

The magnitudes of the numerous DPs present in responses for primaries with closely spaced frequencies (see Fig. 2*A*) must be partially determined by the frequency tuning at the 3.5-mm BM site. However, DP magnitudes in those responses decrease with increasing frequency distance from CF at rates somewhat higher than expected solely on the basis of the filter characteristics measured for single tones. This suggests that, at the site of DP

origin, DP magnitudes decrease with increasing DP order (e.g., the $3f_1 - 2f_2$ level is lower than the $2f_1 - f_2$ level).

Phases of the $2f_1 - f_2$ DPs

Phases of the $2f_1 - f_2$ DP varied systematically with stimulus level and primary frequency ratio. The phases of the responses represented in Figs. 3A and 7 are plotted in Fig. 10 as a function of the level of equal-level primaries at various frequency ratios. The curves have been normalized to the phase measured at the lowest level for each frequency ratio. As stimulus level grows, DP phases increasingly lag for large primary frequency ratios, but lead for small f_2/f_1 . The trends for DP phases depicted in Fig. 10 are representative of measurements in three other cochleas.

Frequency-selective effects of acoustic overstimulation on the $2f_1 - f_2$ and $2f_2 - f_1$ DPs

Exposure of the mammalian ear to intense tones produces elevations of hearing thresholds that are largest at frequencies about half an octave above the exposure frequency (Davis et al. 1950; Hood 1950). Corresponding reductions in sensitivity have been measured in responses of auditory nerve fibers (e.g., Cody and Johnstone 1980,1981; Lonsbury-Martin and Meikle 1978), hair cells (Cody and Russell 1988), and the BM (Cooper and Rhode 1992; Patuzzi et al. 1984; Ruggero et al. 1993,1996; Sellick et al. 1982). We used acoustic overstimulation in three cochleas to try to ascertain the place at which DPs are generated. In each 2 and cochlea we first measured the amplitudes of the $2f_1 - f_1$ and $2f_2 - f_1$ DPs as a function of stimulus intensity, with the use of primary frequencies f_{1a} , f_{2a} , f_{1b} , and f_{2b} such that $2f_{1a} - f_{2a} = 2f_{2b} - f_{1b} = CF$ (9 kHz), and $f_{2a}/f_{1a} = f_{2b}/f_{1b} = 1.25$. As we also a control of response sensitivity at the CF, we also obtained the input-output function for 9-kHz single tones. The chinchilla ear was then exposed to an intense tone presented for 4–4.5 min and the measurements of the input-output functions for the DPs and the 9-kHz single tone were repeated. Figure 11 displays results obtained in one of these experiments. The frequency of the intense tone (10.6 kHz, 100 dB SPL, 4.5 min in duration) was chosen to lie above CF, so that a sensitivity loss should occur selectively at BM sites with CFs corresponding to the frequencies of the ($2f_{1a} - f_{2a}$) DP primary tones ($f_{1a} = 12$ kHz, $f_{2a} = 15$ kHz).

After the exposure, there was a strong decrease of $2f_{1a} - f_{2a}$ DP magnitudes (■), contrasting with small decreases of $2f_{2b} - f_{1b}$ DP magnitudes (▲) and of responses to single CF tones (●). The small effect of overstimulation on responses to the $2f_{2b} - f_{1b}$ DP probably reflects the slightly diminished sensitivity for 9-kHz (CF) single tones, rather than an effect of overstimulation on responses to f_{1b} and f_{2b} , i.e., the primary tones for the $2f_{2b} - f_{1b}$ DP. In the absence of substantial effects of overstimulation on responses to CF tones, the sensitivity loss for the $2f_{1a} - f_{2a}$ DP must reflect correspondingly large losses at the BM sites of its primary frequencies (i.e., f_{1a} and f_{2a}). These results support the notion that $2f_1 - f_2$ DPs originate at the sites of their primary frequencies and propagate to the sites with CFs equal to $2f_1 - f_2$. Similar contrasting effects of acoustic overstimulation on $2f_1 - f_2$ DPs, on the one hand, and on equal-frequency $2f_2 - f_1$ DPs, on the other, were demonstrated in two other cochleas.

DISCUSSION

DP magnitude as a function of stimulus level

The present results demonstrate that odd-order DPs are major components of the response of the chinchilla BM to two-tone stimuli and that they are present even in responses to fairly low-level stimuli (e.g., 30 dB SPL; Figs. 2A, 3, 6, and 7). For the $2f_1 - f_2$ DP, equivalent levels were as high as -16 dB relative to the level of the primaries. These DP magnitudes at the chinchilla BM are comparable with (or somewhat larger than) DP magnitudes measured

at the BMs of guinea pigs (-30 dB re primary levels) (Nuttall et al. (1990) and cat (-20 dB) (Rhode and Cooper 1993), and in guinea pig inner hair cells (-27 dB) (Nuttall and Dolan 1990). DP relative levels at the chinchilla BM are also comparable with values measured in psychophysical experiments. With the use of cancellation methods, DPs perceived by humans have been estimated to reach relative distortion levels as high as -15 dB (Goldstein 1967). Estimates obtained with the use of other psychophysical methods, in which the probe tone is presented nonsimultaneously with the stimulus tones (f_1 , f_2) have been ~ 6 – 7 dB lower than the cancellation levels (Smoorenburg 1972b).

The highest levels of BM distortion were obtained at the lowest stimulus levels. For increasing primary levels, there was a decrease in relative equivalent DP magnitude at a rate of ~ 0.2 – 0.45 dB/dB. A decrease in relative equivalent DP level with primary level can also be deduced from BM and inner hair cell data for guinea pig (Fig. 2 of Nuttall et al. 1990 and Fig. 4 of Nuttall and Dolan 1990, respectively). The $2f_1 - f_2$ DPs at the chinchilla BM resemble psychophysically measured DPs in humans (Goldstein 1967; Hall 1972) in that their relative magnitudes (Fig. 3B) decrease little over wide ranges of stimulus intensity. Psychophysical DPs in humans decrease at a rate of ~ 0.2 dB/dB over stimulus-level ranges of 40 – 50 dB (Goldstein 1967). The decrease of cochlear DPs with increasing stimulus intensity contrasts with the sharp increase in magnitude with primary intensity displayed by DPs generated in most other nonlinear systems.

For a fixed level of one of the primary tones, the magnitude of the $2f_1 - f_2$ BM DP is a nonmonotonic function of the level of the other primary tone (Figs. 4 and 5). Nonmonotonic curves of DP magnitude were first measured psychophysically (Goldstein 1967; Zwicker 1981) and have also been described for the cat BM (Rhode and Cooper 1993), guinea pig inner hair cells (Nuttall and Dolan 1990), and otoacoustic emissions (Probst et al. 1991). The data from the chinchilla BM are remarkably similar to psychophysical measurements in humans in that, for low intensities, the $2f_1 - f_2$ DP grows at a rate of ~ 2 dB/dB with varying f_1 intensity (and fixed f_2 level) and 1 dB/dB with varying f_2 intensity (and fixed f_1 level). Such rates of growth are appropriate for a DP generated by a cubic term in a power law nonlinearity. The rates of growth at the cat BM (Rhode and Cooper 1993) are similar to those in chinchilla. However, the corresponding growth rates for guinea pig inner hair cell receptor potentials (Nuttall and Dolan 1990) are somewhat lower than those found at the BM. This difference may be due to artifacts involved in high-frequency recordings in which microelectrodes were used (Nuttall and Dolan 1990).

DP magnitude as a function of primary frequency ratio

The frequency dependence of DP magnitude observed in psychophysical studies was the first evidence suggesting that DPs originate in a nonlinearity located at the BM or a structure closely coupled to it (Goldstein 1967; Smoorenburg 1972b). In the chinchilla BM, as in psychophysical measurements, DP magnitude decreases monotonically with increasing frequency ratio of the primaries (Figs. 6 and 7). The f_2/f_1 ratio at which DP magnitude starts to decline rapidly depends on the level of the primaries. For low-level primary tones, DP magnitudes decline at low frequency ratios; for primaries at higher levels, DP magnitudes change little at low frequency ratios but very rapidly at higher ratios. The behavior of DP magnitude as a function of stimulus level and frequency ratio is consistent with the variation of BM frequency tuning as a function of stimulus level (Rhode 1971; Robles et al. 1986; Ruggero and Rich 1991a; Ruggero et al. 1992, 1997; Sellick et al. 1982). It is instructive to compare Figs. 6 and 7 with families of BM isointensity curves for single tones (e.g., Fig. 3 in Ruggero and Rich 1991a). At low stimulus levels, responses to single tones are sharply tuned and, therefore, the interaction between responses to the primary tones is confined to a narrow frequency range. As a result, the DP magnitude decays rapidly with increasing primary frequency ratio. At high stimulus levels, responses to single tones are broadly tuned:

they have shallow slopes at frequencies lower than CF but they retain a steep high-frequency slope. Thus the magnitude of interaction between two intense tones should remain invariant or decrease only slightly over a wide frequency range. Accordingly, DP magnitudes remain relatively constant or gradually decrease over a wide range of primary frequency ratios until a critical (level-dependent) frequency ratio is reached, whereon DP magnitude falls at steep rates.

The behavior of DP magnitudes as a function of frequency separation between the primary tones at the BM very much resembles that observed in psychophysical experiments but differs from the nonmonotonic behavior of DP otoacoustic emissions (Probst et al. 1991). The highest rates of decrease of DP magnitude with increasing f_2/f_1 ratio at the chinchilla BM (e.g., -300 dB/octave) are comparable with those found in psychophysical measurements (Goldstein 1967). Further, families of curves illustrating the variation of DP magnitude with frequency ratio and primary tone level are strikingly similar at the BM and in psychophysical studies (compare our Figs. 6 and 7 with Figs. 5, 8, and 15 in Zwicker 1981).

DP phases as a function of primary level and frequency ratio

The dependence of the phases of $2f_1 - f_2$ DPs on primary levels is a controversial issue. A change of DP phase with stimulus level has been demonstrated in psychoacoustical studies (Goldstein 1967; Hall 1972; Smoorenburg 1972b), in some neurons of the anteroventral cochlear nucleus of the cat (Greenwood et al. 1976), and in inner hair cells of the guinea pig (Nuttall and Dolan 1990). In contrast, other recordings from neurons of the anteroventral cochlear nucleus of the cat (Smoorenburg et al. 1976) and from auditory nerve fibers of the cat (Buunen and Rhode 1978; Goldstein and Kiang 1968) have not found systematic level-dependent phase changes. In the chinchilla BM, DP responses exhibit phase lags with increasing stimulus level for large frequency ratios but display small phase leads for small frequency ratios (Fig. 10). BM phase shifts for stimulus frequency ratios of 1.2–1.3 and primary level increments of 30 dB amount to ~ 2 – 4° dB and compare well with phase shifts obtained for similar frequency ratios and level increases in psychophysical studies (Fig. 12 in Goldstein 1967) and in recordings from inner hair cells (Fig. 8 in Nuttall and Dolan 1990) and from cochlear nucleus neurons (Fig. 9 in Greenwood et al. 1976). However, whereas the variation of DP phase with stimulus level is greater at high levels than at low levels at the BM and in inner hair cells, the reverse is true in psychophysical and cochlear nucleus studies.

The dependence of DP phase shift on primary frequency ratio (Fig. 10) is a novel finding that may explain, at least in part, the apparent discrepancy between psychophysical and some physiological studies that found a dependence of DP phase on stimulus level, and certain physiological investigations that have sought but failed to find such dependence. In particular, the conclusion by Buunen and Rhode (1978) that there is no effect of stimulus intensity on DP phase was based on an analysis of auditory nerve fiber responses that disregarded the possible effect of primary frequency ratio, which in that study ranged from 1.05 to 1.4 (see Fig. 9 in Buunen and Rhode 1978). Interestingly, those authors entertained the possibility that frequency ratio might have an effect in DP phase and acknowledged that in some cases phase shifts of opposite polarity were observed at small and large frequency ratios.

Place of origin of BM DPs

When the stimulus tones had widely spaced frequencies (and $2f_1 - f_2 = CF$), responses to the primaries were small and grew nearly linearly, whereas the $2f_1 - f_2$ responses were relatively larger and grew compressively (Fig. 2B). This contrasting behavior suggests that

DPs are not generated at the recording site but rather arise at more basal locations and propagate toward the $2f_1 - f_2$ site. Further, the frequency tuning characteristics of $2f_1 - f_2$ DPs (Fig. 9) are similar to those of single tones, as predicted for DPs that are filtered at the site of measurement subsequent to their origin elsewhere in the cochlea.

Acoustic overstimulation with the use of a tone with frequency higher than CF (Fig. 11) produced a marked decrease of the $2f_1 - f_2$ DP (whose primary frequencies equal the CFs of cochlear sites that must have sustained large sensitivity losses) (Ruggero et al. 1993,1996) but had only small effects on responses to single tones with frequency equal to $2f_1 - f_2$ and on the $2f_2 - f_1$ DP (whose primary frequencies correspond to the CFs of more apical sites, which should have been unaffected by overstimulation). These differential effects constitute strong evidence that $2f_1 - f_2$ DPs originate at the BM region with CFs corresponding to their primary frequencies and propagate to the locations with CFs equal to $2f_1 - f_2$. This inference, however, should be tempered by the possibility that $2f_1 - f_2$ DPs are inherently more vulnerable to acoustic overstimulation than $2f_2 - f_1$ DPs or responses to single tones.

The frequency-selective effects of acoustic overstimulation on the BM response to pairs of tones are consistent with the seminal discovery that perceived $2f_1 - f_2$ DPs are abolished or reduced in human subjects with threshold elevations restricted either to the DP frequency or its primary frequencies (Sachs and Wightman 1974; Smoorenburg 1972b). The BM effects are also consistent with, and account for, the finding that $2f_1 - f_2$ DPs in auditory nerve fiber responses are abolished (or temporarily reduced) after cochlear exposures that produce permanent damage (or temporary sensitivity loss) at the sites of the primary frequencies (Siegel et al. 1982). The vulnerability of DP generation to acoustic overstimulation suggests that DPs first arise in the organ of Corti. The structures most likely to generate DPs are the outer hair cells, which are probably responsible, through a mechanical feedback, for the nonlinear behavior, as well as the sharp frequency tuning and high sensitivity, of BM responses (Dallos 1992; Davis 1983; Murugasu and Russell 1996; Ruggero and Rich 1991b).

Mechanoelectrical transduction at stereocilia (Hudspeth and Corey 1977; Russell et al. 1986) and electromechanical transduction at the basolateral membrane (Brownell et al. 1985; Santos-Sacchi 1992) of outer hair cells are substantially nonlinear processes that, under two-tone stimulation, could both give rise to DPs. Under whole cell voltage-clamp conditions, isolated outer hair cells produce motile responses to electrical sinusoids that contain harmonic distortion (Santos-Sacchi 1993). Such distortion is consistent with the nonlinearity of the electromechanical transduction characteristic (Boltzmann function). Similarly, the motile responses of isolated outer hair cells to pairs of electrical sinusoids include robust DPs (Hu et al. 1994). However, because of the low magnitude of hair cell receptor potentials, the mechanoelectrical transduction process is likely to be the dominant source of distortion components in the mechanical response of outer hair cells in vivo (Santos-Sacchi 1993; see also Patuzzi et al. 1989).

In vitro measurements of hair cells from the bullfrog's sacculus (Howard and Hudspeth 1988) and mouse cochlea (Russell et al. 1992) reveal nonlinear stiffness in hair bundles at small displacements from their resting position. When displaced by a pair of sinusoids, hair bundles of individual hair cells from the bullfrog's sacculus produce DP force components that may result from the nonlinear stiffness (Jaramillo et al. 1993). DPs generated by this nonlinearity could account in part for those measured in vivo at the BM only if the hair bundle stiffness amounts to an important fraction of the total stiffness of the cochlear partition.

Relation between perceived, BM, and otoacoustic emission DPs

Most of the characteristics of the $2f_1 - f_2$ DPs in the motion of the chinchilla BM resemble those observed in human psychophysics. BM and psychophysical data differ principally in one respect: BM $2f_1 - f_2$ DPs do not show the sharp notches measured under certain stimulus conditions in psychophysical input-output curves (Hall 1975; Smoorenburg 1972b; Weber and Mellert 1975) and commonly found in input-output functions for DP otoacoustic emissions (Brown 1987; Zwicker and Harris 1990). Apart from this difference, the similarity across species may imply that DPs are generated in the cochlear partition of most mammals by similar nonlinear mechanisms and that the psychophysical qualities of perceived DPs are mainly determined by the BM responses at the cochlear sites corresponding to their CFs.

Indeed, the similarity between the characteristics of perceived DPs, regardless of methodology (i.e., simultaneous cancellation and nonsimultaneous pulsation threshold), and those measured at the BM may be taken as additional evidence for the propagation of DPs on the BM. Presumably, propagation from the BM site of the primaries ($CF \cong f_1$ or f_2) and subsequent filtering at the site with $CF = 2f_1 - f_2$ attenuates interactions between the cancellation tone and the primary tones (which would otherwise yield large differences between simultaneous and nonsimultaneous estimates). In fact, psychophysical studies have shown that the difference between $2f_1 - f_2$ level estimates obtained with the use of simultaneous and nonsimultaneous methods decreases with increasing frequency ratio of the primaries (Fig. 12 in Smoorenburg 1972b). Similarly, modeling of BM data (Fig. 17) (corresponding text in Goldstein 1995) predicts DP levels that differ systematically for simultaneous and nonsimultaneous measurements, but that converge at low stimulus levels and also at higher levels, provided that the model includes sufficient frequency selectivity.

The relationship between DP otoacoustic emissions and BM DPs is more complex than that between perceived and BM DPs. Psychophysical and BM measurements of $2f_1 - f_2$ DPs differ from DP otoacoustic emissions in at least two respects: 1) the former give no indication of the “broadly tuned band-pass filter” that apparently shapes DP otoacoustic emissions (Brown et al. 1992; Harris et al. 1989) and 2) the former decrease in amplitude at a faster rate with increasing frequency ratio, f_2/f_1 , than DP otoacoustic emissions (Harris et al. 1989). Further, psychoacoustical and ear canal measurements of $2f_1 - f_2$ DPs in the same subjects have shown that cancellation of a perceived DP does not eliminate the corresponding DP otoacoustic emission (Furst et al. 1988; Zwicker and Harris 1990). Thus although perceived $2f_1 - f_2$ DPs may reflect, more or less directly, local BM vibrations at the cochlear site with CF equal to $2f_1 - f_2$, DP otoacoustic emissions probably comprise a more complex mixture of spatially distributed components, perhaps including contributions of cochlear structures other than the BM. The latter would be consistent with the existence of DP otoacoustic emissions in nonmammalian vertebrates that lack a BM (Manley et al. 1993; Rosowski et al. 1984).

Acknowledgments

This work was principally supported by National Institute of Deafness and Other Communications Disorders Grants 5-P01-DC-00110-21 and 5-R01-DC-00419-09. L. Robles was partially supported by FONDECYT (Chile) Grant 92-0976 and DTI, Universidad de Chile Grant B-2895.

REFERENCES

- Brown AM. Acoustic distortion from rodent ears: a comparison of responses from rats, guinea pigs and gerbils. *Hear. Res.* 1987; 31:25–38. [PubMed: 3429348]
- Brown AM, Gaskill SA, Williams DM. Mechanical filtering of sound in the inner ear. *Proc. R. Soc. Lond. B Biol. Sci.* 1992; 250:29–34.

- Brownell WE, Bader CR, Bertrand D, de Ribaupierre Y. Evoked mechanical responses of isolated cochlear outer hair cells. *Science Wash. DC.* 1985; 227:194–196.
- Buunen TJF, Rhode WS. Responses of fibers in the cat's auditory nerve to the cubic difference tone. *J. Acoust. Soc. Am.* 1978; 64:772–781. [PubMed: 701616]
- Cody AR, Johnstone BM. Single auditory neuron response during acute acoustic trauma. *Hear. Res.* 1980; 3:3–16. [PubMed: 7400047]
- Cody AR, Johnstone BM. Acoustic trauma: single neuron basis for the “half-octave” shift. *J. Acoust. Soc. Am.* 1981; 70:707–711. [PubMed: 7288033]
- Cody AR, Russell IJ. Acoustically induced hearing loss: intracellular studies in the guinea pig cochlea. *Hear. Res.* 1988; 35:59–70. [PubMed: 3182410]
- Cooper NP, Rhode WS. Basilar membrane mechanics in the hook region of cat and guinea-pig cochleae: sharp tuning and nonlinearity in the absence of baseline position shifts. *Hear. Res.* 1992; 63:163–190. [PubMed: 1464568]
- Dallos P. The active cochlea. *J. Neurosci.* 1992; 12:4575–4585. [PubMed: 1464757]
- Davis H. An active process in cochlear mechanics. *Hear. Res.* 1983; 9:79–90. [PubMed: 6826470]
- Davis H, Morgan CT, Hawkins JE Jr, Galambos R, Smith FW. Temporary deafness following exposure to loud tones and noise. *Acta Otolaryngol. Suppl.* 1950; 88:1–56. [PubMed: 14818771]
- Furst M, Rabinowitz WM, Zurek PM. Ear canal acoustic distortion at $2f_1 - f_2$ from human ears: relation to other emissions and perceived combination tones. *J. Acoust. Soc. Am.* 1988; 84:215–221. [PubMed: 3411050]
- Gibian GL, Kim DO. Cochlear microphonic evidence for mechanical propagation of distortion products ($f_2 - f_1$) and ($2f_1 - f_2$). *Hear. Res.* 1982; 6:35–59. [PubMed: 7054135]
- Goldstein JL. Auditory nonlinearity. *J. Acoust. Soc. Am.* 1967; 41:676–689. [PubMed: 6045077]
- Goldstein JL. Relations among compression, suppression, and combination tones in mechanical responses of the basilar membrane: data and MBPNL model. *Hear. Res.* 1995; 89:52–68. [PubMed: 8600132]
- Goldstein JL, Kiang NYS. Neural correlates of the aural combination tone $2f_1 - f_2$. *Proc. IEEE.* 1968; 56:981–992.
- Greenwood DD, Merzenich MM, Roth GL. Some preliminary observations on the interrelations between two-tone suppression and combination-tone driving in the anteroventral cochlear nucleus of the cat. *J. Acoust. Soc. Am.* 1976; 59:607–633. [PubMed: 1254789]
- Hall JL. Auditory distortion products ($f_2 - f_1$) and ($2f_1 - f_2$). *J. Acoust. Soc. Am.* 1972; 51:1863–1871.
- Hall JL. Nonmonotonic behavior of distortion product $2f_1 - f_2$: psychophysical observations. *J. Acoust. Soc. Am.* 1975; 58:1046–1050. [PubMed: 1194555]
- Harris FP, Lonsbury-Martin BL, Stagner BB, Coats AC, Martin GK. Acoustic distortion products in humans: systematic changes in amplitude as a function of f_2/f_1 ratio. *J. Acoust. Soc. Am.* 1989; 85:220–229. [PubMed: 2921404]
- von Helmholtz, HLF. *Sensations of Tone*. 2nd English ed. Dover; New York: 1862. p. 158 originally published 1954
- Hood JD. Studies in auditory fatigue and adaptation. *Acta Otolaryngol. Suppl.* 1950; 92:1–57. [PubMed: 14856693]
- Howard J, Hudspeth AJ. Compliance of the hair bundle associated with gating of mechanoelectrical transduction channels in the bullfrog's saccular hair cell. *Neuron.* 1988; 1:189–199. [PubMed: 2483095]
- Hu XT, Evans BN, He ZZ, Dallos P. Distortion products in electromotile responses of isolated outer hair cells. *Assoc. Res. Otolaryngol. Mid-Winter Meet. Abstr.* 1994; 17:125.
- Hudspeth AJ, Corey DP. Sensitivity, polarity and conductance change in the response of vertebrate hair cells to controlled mechanical stimuli. *Proc. Natl. Acad. Sci. USA.* 1977; 74:2407–2411. [PubMed: 329282]
- Jaramillo F, Markin VS, Hudspeth AJ. Auditory illusions and the single hair cell. *Nature Lond.* 1993; 364:527–529. [PubMed: 8336792]
- Jones AT. The discovery of difference tones. *Am. Phys. Teacher.* 1935; 3:49–51.

- Kemp DT. Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. *Arch. Otorhinolaryngol.* 1979; 224:37–45. [PubMed: 485948]
- Kim DO, Molnar CC, Matthews JW. Cochlear mechanics: nonlinear behavior in two-tone responses as reflected in cochlear-nerve-fiber responses and in ear-canal sound pressure. *J. Acoust. Soc. Am.* 1980; 67:1704–1721. [PubMed: 7372925]
- Lonsbury-Martin BL, Meikle MB. Neural correlates of auditory fatigue. Frequency dependent changes in activity of single cochlear nerve fibres. *J. Neurophysiol.* 1978; 41:987–1006. [PubMed: 681996]
- Manley GA, Köppl C, Johnstone BM. Distortion-product oto-acoustic emissions in the bobtail lizard. I. General characteristics. *J. Acoust. Soc. Am.* 1993; 93:2820–2833.
- Murugasu E, Russell IJ. The effect of efferent stimulation on basilar membrane displacement in the basal turn of the guinea pig cochlea. *J. Neurosci.* 1996; 16:325–332. [PubMed: 8613799]
- Nuttall AL, Dolan DF. Inner hair cell responses to the $2f_1 - f_2$ intermodulation product. *J. Acoust. Soc. Am.* 1990; 87:782–790. [PubMed: 2307775]
- Nuttall AL, Dolan DF. Intermodulation distortion ($F_2 - F_1$) in inner hair cell and basilar membrane responses. *J. Acoust. Soc. Am.* 1993; 93:2061–2068. [PubMed: 8473618]
- Nuttall AL, Dolan DF. Comment on “Modulation of the hair cell motor: a possible source of odd-order distortion”. *J. Acoust. Soc. Am.* 1994; 96:2583–2584. [PubMed: 7963039]
- Nuttall, AL.; Dolan, DF.; Avinash, G. Measurements of basilar membrane tuning and distortion with laser Doppler velocimetry. In: Dallos, P.; Geisler, CD.; Matthews, JW.; Ruggero, MA.; Steele, CR., editors. *The Mechanics and Biophysics of Hearing*. Springer-Verlag; Berlin: 1990. p. 288-295.
- Patuzzi R, Johnstone BM, Sellick PM. The alteration of the vibration of the basilar membrane produced by loud sound. *Hear. Res.* 1984; 13:99–100. [PubMed: 6706867]
- Patuzzi R, Yates GK, Johnstone BM. Outer hair cell receptor current and sensorineural hearing loss. *Hear. Res.* 1989; 42:47–72. [PubMed: 2684949]
- Probst R, Lonsbury-Martin BL, Martin GK. A review of otoacoustic emissions. *J. Acoust. Soc. Am.* 1991; 89:2027–2067. [PubMed: 1860995]
- Rhode WS. Observations of the vibration of the basilar membrane in squirrel monkeys using the Mössbauer technique. *J. Acoust. Soc. Am.* 1971; 49:1218–1231. [PubMed: 4994693]
- Rhode, WS. Some observations on two-tone interaction measured with the Mössbauer effect. In: Evans, EF.; Wilson, JP., editors. *Psychophysics and Physiology of Hearing*. Academic; London: 1977. p. 27-38.
- Rhode WS, Cooper NP. Two-tone suppression and distortion production on the basilar membrane in the hook region of cat and guinea pig cochlea. *Hear. Res.* 1993; 66:31–45. [PubMed: 8473244]
- Robles L, Ruggero MA, Rich NC. Basilar-membrane mechanics at the base of the chinchilla cochlea. I. Input-output functions, tuning curves and response phases. *J. Acoust. Soc. Am.* 1986; 80:1364–1374. [PubMed: 3782615]
- Robles, L.; Ruggero, MA.; Rich, NC. Two-tone distortion products in the basilar membrane of the chinchilla cochlea. In: Dallos, P.; Geisler, CD.; Matthews, JW.; Ruggero, MA.; Steele, CR., editors. *The Mechanics and Biophysics of Hearing*. Springer-Verlag; Berlin: 1990. p. 304-311.
- Robles L, Ruggero MA, Rich NC. Two-tone distortion in the basilar membrane of the cochlea. *Nature Lond.* 1991; 349:413–414. [PubMed: 1992342]
- Robles L, Ruggero MA, Rich NC. Distortion products at the basilar membrane of the cochlea: dependence on stimulus frequency and intensity and effect of acoustic trauma. *Soc. Neurosci. Abstr.* 1993; 23:1421.
- Rosowski JJ, Peake WT, White JR. Cochlear nonlinearities inferred from two-tone distortion products in the ear canal of the alligator lizard. *Hear. Res.* 1984; 13:141–158. [PubMed: 6715262]
- Ruggero MA, Rich NC. Application of a commercially-manufactured Doppler-shift laser velocimeter to the measurement of basilar-membrane vibration. *Hear. Res.* 1991a; 51:215–230. [PubMed: 1827787]
- Ruggero MA, Rich NC. Furosemide alters organ of Corti mechanics: evidence for feedback of outer hair cells upon the basilar membrane. *J. Neurosci.* 1991b; 11:1057–1067. [PubMed: 2010805]

- Ruggero, MA.; Rich, NC.; Recio, A. Basilar membrane responses to clicks. In: Cazals, Y.; Demany, L.; Horner, K., editors. *Auditory Physiology and Perception*. Pergamon; Oxford: 1992. p. 85-91.
- Ruggero, MA.; Rich, NC.; Recio, A. Alteration of basilar membrane responses to sound by acoustic overstimulation. In: Duifhuis, H.; Horst, JW.; van Dijk, P.; van Netten, SM., editors. *Biophysics of Hair Cell Sensory Systems*. World Scientific; Singapore: 1993. p. 258-264.
- Ruggero MA, Rich NC, Recio A. The effect of intense acoustic stimulation on basilar-membrane vibrations. *Auditory Neurosci*. 1996; 2:329–345.
- Ruggero MA, Rich NC, Recio A, Narayan SS, Robles L. Basilar-membrane responses to tones at the base of the chinchilla cochlea. *J. Acoust. Soc. Am*. In press.
- Russell IJ, Cody A, Richardson GP. The responses of inner and outer hair cells in the basal turn of the guinea pig cochlea and in the mouse cochlea grown in vitro. *Hear. Res*. 1986; 22:199–216. [PubMed: 3733540]
- Russell IJ, Kössl M, Richardson GP. Nonlinear mechanical response of mouse cochlear hair bundles. *Proc. R. Soc. Lond. B Biol. Sci*. 1992; 250:217–227.
- Sachs RM, Wightman FL. Threshold dips and cubic difference tone perception (Abstract). *J. Acoust. Soc. Am*. 1974; 55(Suppl.):7.
- Santos-Sacchi J. On the frequency limit and phase of outer hair cell motility: effects of the membrane filter. *J. Neurosci*. 1992; 12:1906–1916. [PubMed: 1578277]
- Santos-Sacchi J. Harmonics of outer hair cell motility. *Biophys. J*. 1993; 65:2217–2227. [PubMed: 8298045]
- Sellick PM, Patuzzi R, Johnstone BM. Measurement of basilar membrane motion in the guinea pig using the Mössbauer technique. *J. Acoust. Soc. Am*. 1982; 72:131–141. [PubMed: 7108035]
- Siegel JH, Kim DO, Molnar CE. Effects of altering organ of Corti on cochlear distortion products $f_2 - f_1$ and $2f_1 - f_2$. *J. Neurophysiol*. 1982; 47:303–328. [PubMed: 7062102]
- Smoorenburg GF. Audibility region of combination tones. *J. Acoust. Soc. Am*. 1972a; 52:603–614.
- Smoorenburg GF. Combination tones and their origin. *J. Acoust. Soc. Am*. 1972b; 52:615–632.
- Smoorenburg GF, Gibson MM, Kitzes LM, Rose JE, Hind JE. Correlates of combination tones observed in the response of neurons in the anteroventral cochlear nucleus of the cat. *J. Acoust. Soc. Am*. 1976; 59:945–962. [PubMed: 1262594]
- Weber R, Mellert V. On the nonmonotonic behavior of cubic distortion products in the human ear. *J. Acoust. Soc. Am*. 1975; 57:207–214. [PubMed: 1110283]
- Wilson JP, Johnstone JR. Basilar membrane correlates of the combination tone $2f_1 - f_2$. *Nature Lond*. 1973; 241:206–207. [PubMed: 4700889]
- Zurek PM, Sachs RM. Combination tones at frequencies greater than the primary tones. *Science Wash. DC*. 1979; 205:600–602.
- Zwicker E. Dependence of level and phase of the $(2f_1 - f_2)$ -cancellation tone on frequency range, frequency difference, level of primaries and subject. *J. Acoust. Soc. Am*. 1981; 70:1277–1288.
- Zwicker E, Harris FP. Psychoacoustical and ear canal cancellation of $(2f_1 - f_2)$ -distortion products. *J. Acoust. Soc. Am*. 1990; 87:2583–2591. [PubMed: 2373793]

Fig. 1.

Spectra of basilar membrane (BM) responses to pairs of tones with frequencies near characteristic frequency (CF). The equal-level primary tones, presented at 60–80 dB SPL (re 20 μ Pa), had $f_1 = 7.6$ and $f_2 = 8.4$ kHz, closely flanking CF (8 kHz). Spectral peaks corresponding to distortion products (DPs) at $2f_1 - f_2$ and $2f_2 - f_1$ are indicated. In this and the following figures the levels for equal-level primary tones indicate those of each of the primaries.

Fig. 2.

Effect of frequency spacing on the spectrum of BM responses to tone pairs (f_1 , f_2 , chosen so that $2f_1 - f_2 = \text{CF}$). *A*: spectra of BM responses to pairs of tones with closely spaced frequencies near CF ($f_2/f_1 = 1.05$). The equal-level primary tones had $f_1 = 7.89$ and $f_2 = 8.28$ kHz, such that $2f_1 - f_2 = \text{CF}$ (7.5 kHz), and were presented at 30–80 dB SPL. *B*: spectra of BM responses to pairs of tones with widely spaced frequencies, such that $f_2/f_1 = 1.25$ and $2f_1 - f_2 = \text{CF}$ (10 kHz), presented at 60–100 dB SPL.

Fig. 3.

A: growth of the $2f_1 - f_2$ DP as a function of the level of equal-level primary tones. Curves without circles: DP magnitudes for several values of primary frequency ratio f_2/f_1 . Curve with circles: input-output function for a single tone at the DP frequency ($2f_1 - f_2 = \text{CF}$). In this and the following figures, arrows indicate velocity values that were in the noise. The baseline noise was computed as the mean of the spectral magnitudes at frequencies around (but not coinciding with) the DP frequency. **B:** DP equivalent levels in dB relative to primary tone SPL, as a function of stimulus level. DP relative distortion levels correspond to the horizontal separation (in dB) between the DP curves and the single-tone curve in **A**. Thick dashed line: upper bound of cubic-order acoustic distortion in the stimulus, as measured in an artificial cavity.

Fig. 4. Variation of the $2f_1 - f_2$ DP magnitude with f_1 tone level for fixed f_2 tone levels. *A–C*: measurements in different cochleas. ---, 2-dB/dB slopes.

Fig. 5. Variation of the $2f_1 - f_2$ DP magnitude with f_2 tone level for fixed f_1 tone levels. Data were obtained in the same cochlea represented in Fig. 4A. f_1 Tone levels: 70 dB ($\circ$, $\bullet$) and 80 dB SPL ($\square$, $\blacksquare$). Frequency ratios: 1.1 (—) and 1.2 (---). —, slope of 1 dB/dB.

Fig. 6. Magnitude of the $2f_1 - f_2$ DP as a function of primary frequency ratio f_2/f_1 for various primary levels and $2f_1 - f_2 = \text{CF}$. ---, slope of -300 dB/octave.

Fig. 7.
As in Fig. 6, but measured in another cochlea.

Fig. 8. Magnitude of the $2f_2 - f_1$ DP as a function of increasing primary frequency ratio measured in 2 cochleas ($2f_2 - f_1 = CF$). Curves with solid symbols: data obtained in the same cochlea represented in Fig. 7.

Fig. 9.

Frequency-tuning curves for the $2f_1 - f_2$ DP measured in 2 cochleas at 2 primary levels and at fixed frequency ratios of 1.1 (A) and 1.15 (B).

Fig. 10.

Variation of the $2f_1 - f_2$ DP phase as a function of the level of equal-level primary tones. Phase curves, obtained at various frequency ratios in 1 cochlea, have been normalized to the phase measured at the lowest level for each frequency ratio.

Fig. 11.

Frequency-selective reduction of $2f_1 - f_2$ DP magnitude after exposure of the ear to an intense tone. Solid symbols and continuous lines: preexposure data. $\square$, Δ , $\square$, ---: postexposure data. $\blacksquare$, amplitudes of the $2f_{1a} - f_{2a}$ DP [$2f_{1a} - f_{2a} = 9$ kHz (CF), $f_{1a} = 12$ kHz, kHz, $f_{2a} = 15$ KHz]. $\bullet$, magnitudes of the $2f_{2b} - f_{1b} = 9$ kHz, $f_{1b} = 6$ KHz, $f_{2b} = 7.5$ KHz.) $\bullet$, input-output functions for a single tone at the DP frequency (9 kHz). - - -, linear growth.