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Responses to sound of the basilar membrane of the mammalian cochlea

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Abstract

Recent evidence shows that the frequency-specific non-linear properties of auditory nerve and inner hair cell responses to sound, including their sharp frequency tuning, are fully established in the vibration of the basilar membrane. In turn, the sensitivity, frequency selectivity and non-linear properties of basilar membrane responses probably result from an influence of the outer hair cells.

Introduction

Mechanical to electrical transduction in the cochlea, the hearing organ of mammals, is mediated by vibrations of the basilar membrane, on which rests the sensory epithelium—the organ of Corti—with its complement of inner and outer hair cells (for reviews, see [1•–3•]). In spite of the central role of the basilar membrane, its responses to sound have been measured in only a few laboratories. By far the most celebrated series of investigations were carried out by Georg von Békésy, for which he was awarded the 1961 Nobel Prize for Physiology or Medicine [4]. Working principally in the temporal bones of human cadavers, Békésy showed that the cochlea performs a spatial frequency analysis. According to Békésy's observations, each site of the basilar membrane responds to sound stimuli by vibrating linearly, i.e. in proportion to sound pressure. As the vibration at each site of the basilar membrane phase lags the vibrations of more basal sites, a displacement traveling wave propagates on the basilar membrane from the cochlear base toward its apex. As it propagates, the traveling wave grows in amplitude, reaches a maximum and then decays. The location of the peak is a function of stimulus frequency: vibrations in response to high-frequency sounds peak near the cochlear base, while very low-frequency sounds travel all the way to the cochlear apex.

A turning point in the understanding of cochlear mechanics came in 1971, when Rhode [5] demonstrated that, at least in the cochlea of the live squirrel monkey, vibrations of the basilar membrane could be non-linear, growing at a rate of less than 1 dB of vibration magnitude per 1 dB of stimulus increment. Further, he showed that this compressive non-linearity was frequency specific, being demonstrable only at stimulus frequencies close to that to which the basilar membrane site was most sensitive, i.e. its characteristic frequency (CF). Unfortunately, Rhode's discovery of a cochlear non-linearity in the squirrel monkey could not be confirmed in other species, in spite of repeated attempts, for nearly a decade (for a review, see [6]). Therefore, in order to harmonize the apparently linear and poorly frequency-tuned mechanical vibrations of the basilar membrane with the non-linear and sharply frequency-tuned responses of auditory nerve fibers, it was proposed that a 'second filter' exists in the organ of Corti [7]. The present review will outline recent evidence demonstrating that the second filter is unnecessary and that, in fact, probably all frequency specific non-linear properties of auditory nerve and inner hair cell responses have mechanical counterparts in the vibration of the basilar membrane. Evidence is also presented

which indicates that the sensitivity and frequency selectivity of basilar membrane responses result from an influence of the outer hair cells.

New methodology

Both Rhode's discovery of a CF-specific basilar membrane non-linearity, and subsequent confirmation and extensions of his findings were obtained largely using a method based on the Mössbauer effect [5,8–12]. Because this method is extremely non-linear, accurate measurements are possible only over a narrow range of response magnitudes, making it difficult to record vibration waveforms with large peaks (such as responses to clicks and other transients), and confounding the distinction between cochlear non-linearities and those introduced by the method itself. Recently, Doppler-shift laser velocimetry systems have been applied to the measurement of basilar membrane vibration. These instruments are highly linear and at least one order of magnitude more sensitive than the Mössbauer technique [13 15,16•]. Many of the recent findings presented in this review were obtained using laser velocimeters.

Responses to tones

The basilar membrane responds to single tones with a transverse AC sinusoidal vibration. Responses to tones with a frequency well removed from the CF grow linearly as a function of stimulus intensity. Responses to tones with frequencies near the CF, on the other hand, usually grow linearly for stimulus levels close to neural threshold, but at slower rates—slopes as low as 0.2 dB/dB at the CF and even lower immediately above the CF—at moderate stimulus intensities (Fig.1a) [8–10,12,16•]: It is not yet clear whether this compressive non-linearity persists at intense stimulus levels, as indicated by the earlier Mössbauer studies. Some recent reports show CF input—output curves whose slopes tend to become linear at 80–100 dB sound pressure level (SPL) [17••,18••]. If the responses to tones are plotted as families of iso-intensity contours, they strongly resemble the equivalent plots for auditory nerve fibers (Fig.1b). Responses plotted as iso-velocity or iso-displacement curves (i.e. sound intensities required to elicit a constant response magnitude) are very similar to the frequency-threshold tuning curves of auditory nerve fibers with a comparable CF (Fig.1d) [8,12,19]. It is not certain whether neural thresholds are more closely matched to displacement or velocity of basilar membrane motion, Measurements in the 17 kHz region of the guinea pig basilar membrane suggest that neural threshold at the CF corresponds to a basilar membrane velocity of 40 μm s^{-1} or a displacement of 0.35 nm [8]. For the chinchilla 9 kHz site, corresponding values are 100 μm s^{-1} or 2 nm [12]. Theoretical analyses of frequency tuning in the basilar membranes of healthy guinea pigs and chinchillas suggest that such tuning cannot be achieved by passive mechanisms, powered solely by the energy of the acoustic stimulus. Rather, it seems, basilar membrane responses to sound draw additional energy from an active process, the 'cochlear amplifier' [20–25].

There is some evidence that *in vivo* basilar membrane responses to tones may contain, in addition to sinusoidal vibrations, CF-specific DC and/or very low-frequency components [15,26,27]. The existence of such displacement responses remains in doubt, as they were obtained principally in severely damaged cochleae, using very intense stimuli [26,27]. DC responses may have also been recorded in healthier cochleae [15]. A preliminary report of another study, using a specially suitable displacement- (rather than velocity-) sensitive laser interferometer, emphatically states that DC components are absent in responses of the basilar membrane at the base of the cat cochlea (NP Cooper and WS Rhode: *Association for Research in Otolaryngology, Midwinter Meeting Abstracts* 1992, 19).

Responses to clicks

Basilar membrane responses to clicks have been recorded in live animals using the Mössbauer technique [11], a capacitive probe [28], and laser velocimetry [16•,29••]. While the earlier studies were hampered by non-linear methodology [11] and/or the severely deteriorated state of the experimental cochleae [28], they revealed responses that grew non-linearly with click intensity in a manner qualitatively consistent with responses to tonal stimuli. Responses to low-level clicks, recorded with laser velocimetry in the basal region (3.5 mm from the oval window) of sensitive chinchilla cochleae, consist of transient oscillations with periodicity appropriate to the CF (Fig.2a). These responses have nearly symmetrical spindle-shape envelopes with delays to the maxima (average group delays) of roughly 0.7 ms, measured relative to the onset of stapes motion (Fig.2a, top). As click level is raised, the envelopes become skewed, with earlier cycles of oscillation growing faster than later cycles, which grow at non-linear (compressive) rates. At high stimulus intensities, the initial cycle of oscillation emerges from the baseline noise, growing linearly. This linear cycle has an irreducible latency of 0.1 ms, presumably corresponding to travel time from the oval window to the recording site, 3.5 mm away. Fourier transformations of the time-domain responses match excellently the non-linear frequency and level dependencies evident in responses to tones (Fig.1) [29••]. Thus, the full frequency selectivity of basilar membrane responses at the base of the chinchilla cochlea appears to be developed within 0.6 ms of the arrival of the traveling wave. Conceivably, this delay could result from the operation of the ‘cochlear amplifier’.

Two-tone suppression

Two-tone rate suppression is a non-linear auditory nerve phenomenon consisting of a reduction in the response to one tone due to the presence of a second tone (for a review, see [30]). Rate suppression is frequency specific in that only responses to probe tones with a frequency near the CF can be suppressed. A mechanical counterpart of two-tone rate suppression was first shown by Rhode in the squirrel monkey cochlea [31] using intense probe and suppressor tones. More recently, studies involving much healthier cochleae of chinchilla and guinea pig have demonstrated that most characteristics of neural rate suppression are shared by mechanical suppression in the basilar membrane [18••,32,33•,34]. Thus, the mechanical suppression effect can be elicited by moderate-level suppressor tones with frequencies both higher and lower than the CF, which, when presented alone, evoke responses smaller than the response to the probe tone alone. The effect is CF-specific and physiologically vulnerable, is largest at low-probe tone levels, and grows with suppressor level at faster rates for lower-than-CF suppressors than for higher-than-CF suppressors [18••]. In the case of low-frequency suppressors, the suppression effect waxes and wanes with a periodicity corresponding to the suppressor frequency [18••,34].

Two-tone distortion

When listening to pairs of tones, humans can hear additional tones that are not present in the acoustic stimulus. These two-tone distortion products are also known as combination tones because their pitches match those of combinations of the primary frequencies (f_1 and f_2, $f_2 > f_1$), such as f_2-f_1 and $2f_1-f_2$. Abundant psychoacoustical and neurophysiological evidence (for a review, see [30]) long pointed to a cochlear origin of combination tones, but basilar membrane studies failed to demonstrate them convincingly [31,35]. Cubic ($2f_1$-f_2) and other higher-order distortion products have recently been detected in basilar membrane responses to tone pairs [33•,36–38], Although detailed studies have yet to be published, it is clear that the magnitude of these mechanical distortion products (effective levels as large as 17 dB below primary levels [37,38]) can account well for the presence of their counterparts in the

auditory nerve. A mechanical f_2-f_1 distortion product has also been recorded from the basilar membrane of the guinea pig cochlea [39•].

Lability of responses to sound

The CF-specific non-linearity that Rhode discovered in the basilar membrane of the squirrel monkey disappeared after death [40]. With hindsight, it now appears obvious that failure to demonstrate sensitive and non-linear basilar membrane responses in other studies in live animals (for a review, see [6]) was due to surgical damage inflicted during experimental manipulations of the cochlea. This became evident when an independent, sensitive and frequency-specific measure of cochlear function, namely the threshold of tone-pip-evoked compound action potentials, was shown to correlate well with mechanical sensitivity [8,12]. A causal relation between loss of mechanical sensitivity and non-linearity, on the one hand, and elevation of compound action potential thresholds, on the other, was suggested by a parallel deterioration of both measures in cochleae that produced initially sensitive responses to tones [8,12]. More recently, the strength of mechanical two-tone suppression and the sharpness of tuning displayed by basilar membrane responses to clicks have also been linked to the sensitivity of mechanical responses to CF tones [16•,29••,33•]. In addition, stimulation with intense sounds seems to have been responsible for eliminating the CF-specific non-linearity in two guinea pig cochleae [8,41].

While the foregoing studies clearly indicated that basilar membrane non-linearities and sensitivity were physiologically vulnerable, they could not identify the cells affected by surgical or acoustic trauma. A clue to their identity was the finding of outer hair cell damage in cochleae where basilar membrane recordings had been performed [42]. The clearest link to date between organ of Corti function and basilar membrane vibration has been established by measuring the effects of systemic furosemide injection on basilar membrane responses to sound [17••]. Furosemide, a diuretic, drastically but reversibly alters cochlear function primarily by abolishing the endocochlear potential and reducing the receptor potentials of inner and outer hair cells. Upon intravenous injection in chinchilla, furosemide causes a large CF-specific reduction and linearization of basilar membrane responses to tones and clicks (Fig.2b). These results almost inescapably imply that the receptor potential of outer hair cells controls the vibration of the basilar membrane (presumably via a motile response; reviewed in [1•,3•]). Although furosemide must also affect inner hair cells, it is the outer hair cells that are implicated here because of the demonstration of a differential effect on inner hair cells of DC currents applied extracellularly or intracellularly [43]. Injecting negative DC currents into Scala media (a procedure analogous to decreasing the endocochlear potential by means of furosemide) causes CF-specific reductions in auditory nerve and inner hair cell sensitivity [43,44]. In contrast, alterations in inner hair cell responses induced by intracellular current injection are not frequency specific [44]. Thus, it appears that the cochlear amplifier resides in the outer hair cells, which draw energy from the large positive endocochlear potential.

Responses to sound of *in vitro* cochleae and isolated hair cells

An important step toward a more complete analysis of cochlear mechanical processes was taken recently with the development of an *in vitro* method for studying apical regions of isolated guinea pig cochleae, which are sufficiently viable to retain endocochlear potentials of 30–50 mV and moderate-size microphonics [45,46,47•,48,49•,50•,51••] Application of this method, combining a confocal microscope with either a very sensitive laser velocimeter or video recordings, has yielded surprising and potentially very important results. According to the initial reports, outer hair cells within the apical organ of Corti respond to intense sound with AC vibrations that are “several hundred times greater than the response of the

basilar membrane," and are as sharply frequency-tuned as the responses of hair cells or auditory nerve fibers *in vivo* [46]. Fascinatingly, super imposed on the AC vibrations is a steady low-velocity response component whose frequency tuning and displacement magnitude far exceed those of the AC response (Fig.3) [51••], This position shift of the organ of Corti appears to reflect a form of outer hair cell motility. When stimulated acoustically with sinusoidal stimuli, isolated outer hair cells apparently undergo a steady (DC) length change, whose polarity depends on whether they are extracted from basal or apical cochlear sites [52]. The length change is vulnerable to metabolic inhibitors [53•] and is sharply frequency tuned, with the most effective frequency correlating well with outer hair cell length (which itself is highly correlated with longitudinal cochlear location) [54]. At face value, these findings suggest that (in contradiction with long-held beliefs [55]) sound pressure is an adequate stimulus for hair cells, that hair cells function intrinsically as extremely sharp mechanical frequency filters, and that "the sharply tuned …responses measured in the basilar membrane … are induced by the vibrations of the outer hair cells" [46]. The foregoing findings and implications, if confirmed, would be revolutionary. For the moment, these findings should be interpreted with caution, as they may not apply to *in vivo* cochleae, particularly at their basal region, when using low- or moderate-level stimuli.

Conclusions and prospects

It is now clear that sharp frequency tuning at the base of the cochlea is fully established at the level of vibrations of the basilar membrane [8–10,12,16•,19,29••]. Further, probably all the CF-specific non-linearities of auditory nerve responses also have correlates in the basilar membrane [5,8,11,12,16•,17••,18••,28,29••,31,32,33•,34,36–38,39•]. Thus, the concept of the 'second filter', at least as originally conceived (i.e. interposed between the basilar membrane and the auditory nerve in a unidirectional path of cochlear signal flow, peripheral to central), is unnecessary and probably invalid. However, mounting evidence links the non-linear, labile, and frequency-selective properties of basilar membrane motion to the physiological state of the organ of Corti [56], in particular to the receptor potentials of outer hair cells [17••]. Thus, the original 'first filter,' the basilar membrane, must now be viewed as being inextricably linked to the organ of Corti, forming a feedback loop. Important questions concerning cochlear mechanics remain unanswered. What mechanical signal transformations intervene between basilar membrane motion and deflection of inner hair cell stereocilia? Does the mechanical CF-specificity of the basilar membrane/organ of Corti complex arise dynamically out of an interaction among elements (outer hair cells, basilar membrane and tectorial membrane), which, individually, are not frequency tuned or only mildly so, or are some elements (the outer hair cells?) intrinsically and sharply frequency tuned? What is the mechanism whereby outer hair cells influence the vibrations of the basilar membrane? And is the response of the basilar membrane at the apical region of the cochlea qualitatively similar to that at the basal region?

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CF	characteristic frequency
SPL	sound pressure level

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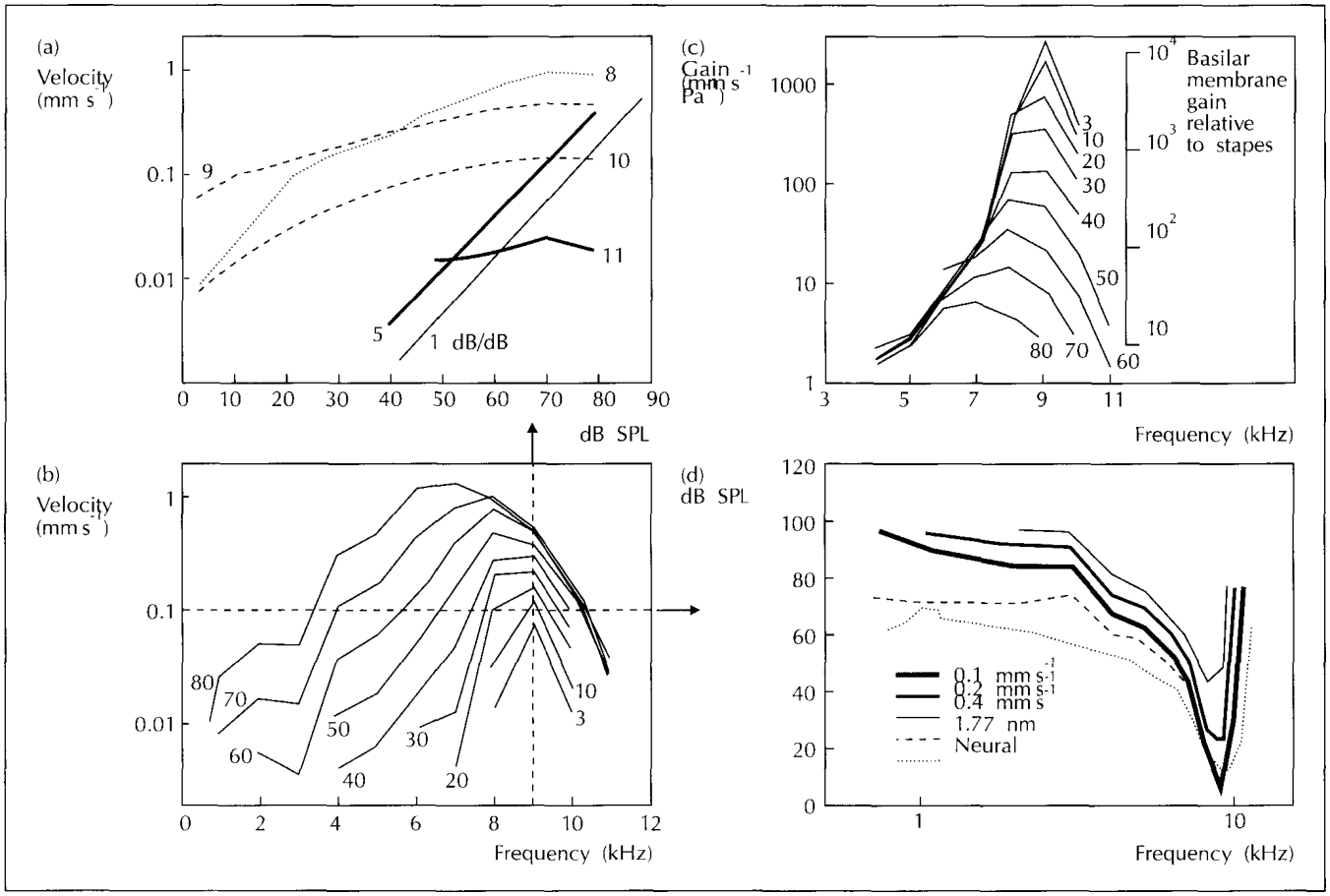

Fig. 1.

Non-linearity and frequency tuning in the basilar membrane. The panels depict four alternative representations of the same set of data: mechanical responses to tones in an exceptionally sensitive chinchilla cochlea. (a) Input-output functions: peak velocity of basilar membrane responses to tones as a function of tone intensity. The parameter is tone frequency in kHz. The thin solid line represents a hypothetical linear input-output function (i.e. velocity proportional to sound pressure). Responses at frequencies near the characteristic frequency (CF) (9 kHz) grow at increasingly non-linear, rates (i.e. slope becoming progressively smaller than 1 dB/dB) with increasing stimulus intensity. Responses at 5 kHz, a frequency well below the CF, grow linearly at all intensities. (b) Iso-intensity functions: peak velocity of basilar membrane responses to tones as a function of tone frequency. The individual curves connect responses obtained at the same sound pressure level (the parameter, expressed in decibels referenced to 20 μPa). Vertical slices through this plot produce input–output functions such as those in panel (a), while horizontal slices produce iso-velocity or frequency-tuning curves such as those in panel (d). (c) The velocity data of panel (b) are normalized to sound pressure level (left ordinate), yielding a family of iso-gain functions. In addition, gains are indicated relative to stapes motion (right ordinate) [57]. Due to the non-linear compressive growth of responses near the CF, the gains are largest and most sharply frequency tuned at the lowest sound pressure levels. Note that, at low stimulus levels, basilar membrane vibrations at the CF are more than 10,000 times larger than those of the stapes. (d) Frequency tuning in the basilar membrane and in the auditory nerve. Three iso-velocity and one iso-displacement functions (solid and dashed lines, respectively) for basilar membrane responses are compared with an average

frequency-threshold tuning curve (dotted line) from auditory nerve fibers. The basilar membrane iso-velocity curves (0.1, 0.2 and 0.4 mm s^{-1}) are separated from each other by 6 dB at low frequencies, indicating a linear response growth. In contrast, at the CF (9 kHz) the curves are separated by 17 dB and 25 dB, indicating compressive non-linear growth. Panels (b) and (d) are adapted from [16•]; panel (c) is adapted from [33•].

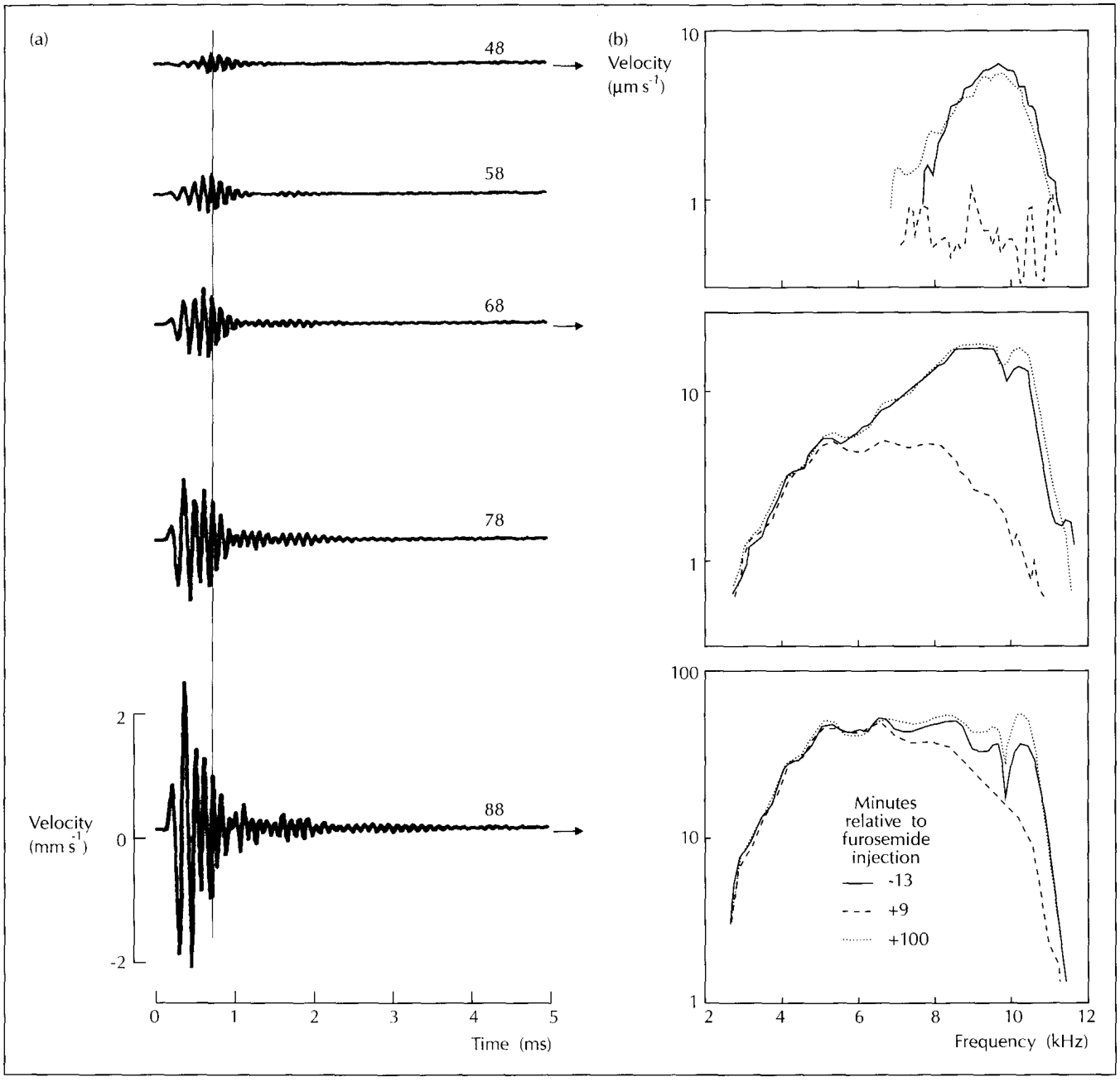

Fig. 2.

Basilar membrane responses to clicks in normal cochleae and in those transiently poisoned by furosemide. (a) The tracings depict normal time-domain responses to clicks presented at several peak intensities (dB SPL indicated next to each tracing). The abscissa indicates time (ms) elapsed since the arrival of the acoustic click at the tympanic membrane. (b) The solid lines depict the frequency spectra obtained by Fourier transformation of three of the waveforms (indicated by arrows) in (a). Dashed lines represent the frequency spectra for responses obtained immediately following an intravenous furosemide injection. Note that response sensitivity is drastically reduced at and near the characteristic frequency (CF), but not altered at low frequencies. Note also that the effect of furosemide is strong at a moderate stimulus level (48 dB), but small for intense clicks (88 dB). Furosemide reduced the

responses to 48 dB clicks (top panel) to such an extent that they became buried in the baseline noise. Responses were fully recovered 100 min after furosemide injection (dotted lines). Panels in (b) adapted from [17••].

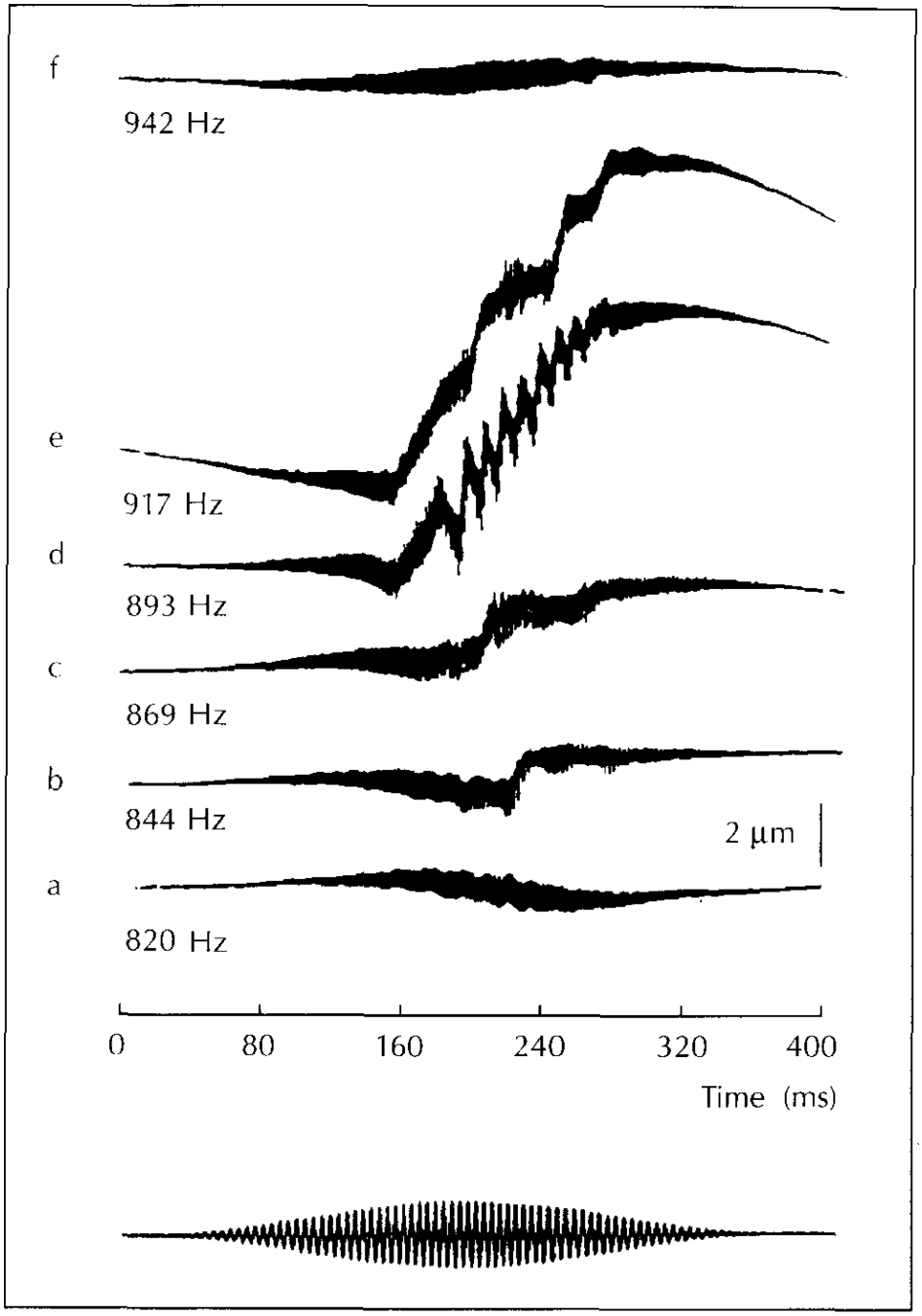

Fig. 3.

Organ of Corti response to intense amplitude-modulated Otones measured at the third turn of an isolated (*in vitro*) guinea pig cochlea. Cochlear vibrations were recorded with a laser velocimeter and subsequently integrated to extract displacement waveforms. The carrier frequency is indicated next to each tracing. The peak stimulus pressure at the tympanic membrane was 135 dB SPL (i.e. referenced to 20 µPa), but because of the attenuation due to fluid filling the middle ear, the effective pressure was 100 dB SPL. In response to earner frequencies between 844 Hz and 917 Hz the organ of Corti shifts its position (with a velocity of approximately 100 µm s^{-1}) toward the scala vestibuli, presumably due to a lengthening of the outer hair cells. Reproduced with permission from [51••].