ELSEVIER

Hearing Research 89 (1995) 93–100

HEARING RESEARCH

# Effects of middle ear pressure on frequency representation in the central auditory system

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Received 29 November 1994; revised 20 May 1995; accepted 27 May 1995

**Abstract**

Changes in middle ear pressure (MEP) are known to produce an attenuation of sound transmission through the outer and middle ear, but the effects on frequency representation in the auditory system have not previously been studied. This issue is of particular interest because of changes in MEP occurring during episodes of otitis media. We have investigated the effect of changes in MEP on the tuning of neurons in the inferior colliculus (IC) of the gerbil to calibrated tone stimulation of the contralateral, pressurized ear. Both negative and positive non-atmospheric MEP produced an elevation of neural thresholds that was inversely related to IC neuron best frequency (BF). A robust, linear relationship was found between BF at atmospheric MEP (control) and BF at −20 daPa MEP. Higher resolution analysis was performed on a sub-sample of neurons that had particularly stable BFs with repeated, control MEP. For the majority of these neurons, alternation of MEP between control and −20 daPa had no effect on BF. However, a few neurons showed small (up to 5%), significant shifts in BF with −20 daPa MEP. These results are consistent with previous reports of the effects of MEP on spontaneous otoacoustic emissions. We conclude that non-atmospheric MEP acts as a high-pass filter on the input to the cochlea, but does not change the frequency organization of the auditory system to any marked extent.

*Keywords:* Hearing; Otitis media; Gerbil; Inferior colliculus

## 1. Introduction

Middle ear pressure (MEP) fluctuations can be produced by conditions that lead to closure of the eustachian tube (e.g., otitis media (OM), Takahashi et al., 1991; uvulopalatal surgery, Finkelstein et al., 1992), or by rapid variations in atmospheric pressure. Changes in MEP have long been known to alter sound transmission through the middle ear (see Wever and Lawrence, 1954). Both positive and negative pressure reduce, to about equal degrees, pure tone sensitivity in humans, particularly for low-frequency tones. Direct application of pressure to the middle ear of anesthetized cats (Wever et al., 1942) reduced the amplitude of the cochlear microphonic for frequencies from 0.1 to 10 kHz, logarithmically over the range 0–50 daPa (0–500 mm $H_2O$). This loss was equivalent to a sound attenuation, at 25 daPa, of between 18 dB (0.2 kHz) and 3 dB (10 kHz).

MEP is believed to influence sound transmission primarily by increasing the stiffness and damping of the tympanic membrane. However, there is also evidence that MEP influences the inner ear directly, via the round and oval windows and, indirectly, through changes in the mechanics of the ossicular chain (Wever and Lawrence, 1954; Møller, 1983). The question then arises as to whether the site of transduction along the cochlea is affected by MEP and, therefore, how frequency coding is influenced by non-atmospheric MEP.

Relatively small changes of MEP have been found to produce shifts in the frequency of spontaneous otoacoustic emissions (SOAEs) in humans (Kemp, 1981; Wilson and Sutton, 1981; Schloth and Zwicker, 1983; Whitehead, 1988). Shifts in SOAE frequency vary between 0 and 5%, without any apparent systematic relationship between absolute frequency and the degree of shift. For some ears, the

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*SSDI* 0378-5955(95)00125-5

shifts in SOAEs can be as much as 50 Hz. Unfortunately, these measurements, while useful for elaborating mechanisms underlying SOAEs, have provided data over only a limited frequency range (between 1 and 4 kHz; Whitehead, 1988). In addition, SOAEs represent the activity of only the most peripheral elements (the outer hair cells) in the auditory nervous system, and the relation between the frequency of SOAEs and their longitudinal site of generation within the cochlea remains unclear (Probst et al., 1991).

To investigate the effects of changes in MEP on sound frequency representation, we have used an approach based on the tonotopic organization of the central auditory system (Aitkin, 1986). The rationale for this approach is that, if MEP does change frequency representation in the cochlea, that change should be apparent throughout the higher auditory system, since the cochlea is mapped onto each level of the system. Thus, by recording the frequency tuning of single auditory neurons before, during, and after the application of MEP, a change in the transduction site in the cochlea will, within the resolution of a neuron's tuning, be reflected in a change in the neuron's best frequency (BF). A convenient place to record tonotopic organization is in the central nucleus of the inferior colliculus (ICC). Neurons in the ICC are as sharply tuned to frequency as those in other nuclei of the auditory system (Calford et al., 1983). Microelectrode penetrations that traverse the ICC in a dorsal to ventral direction enable recordings to be obtained from neurons with BFs covering an animal's audible range (Merzenich and Reid, 1974; Semple and Kitzes, 1985). In this study we have examined the frequency tuning of single neurons in the gerbil ICC during the application of MEP.

## 2. Materials and methods

### 2.1. Subjects

Fifteen young (4–7 months) adult Mongolian gerbils (*Meriones unguiculatus*) were used in this study. All animals had pathology-free outer and middle ears. Gerbils were anesthetized with an initial dose of sodium pentobarbital (Nembutal, 60 mg/kg, i.p.). Further anesthetic (0.2 ml of a mixture of ketamine (Vetalar, 37.5 mg/ml) and xylazine (Rompun, 2.5 mg/ml) s.c.) was administered, approximately hourly, as indicated by reflex withdrawal to a paw pinch. Atropine sulfate (0.04 mg, s.c.) was given at the time of initial anaesthesia and, in some cases, every 3–6 h thereafter. In each experiment the animal was placed in a double-walled, sound-attenuated chamber (IAC). The animal's core body temperature was maintained at 37.5°C with a DC heating pad commanded by a rectal thermistor. The care and use of the animals were approved by the University of Washington Animal Care Committee.

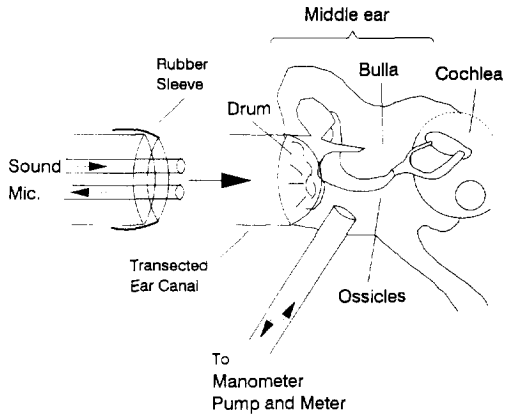


Fig. 1. Schematic representation of the acoustic stimulation, middle ear pressurization, and calibration systems.

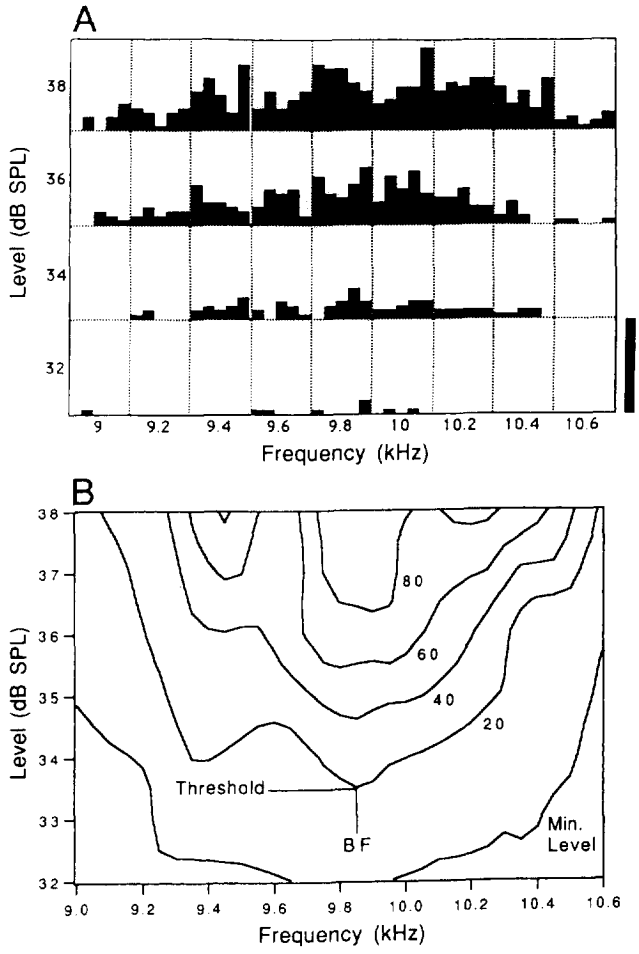


Fig. 2. Methods of data representation and analysis. A: frequency/level matrix of the responses of unit 92371505 (control MEP). Each histogram cluster shows the number of discharges produced by the unit on each of 5 presentations of an identical stimulus. The calibration bar to the right shows 60 spikes/s. Presentations were pseudo-randomly interleaved until the matrix was complete. B: isoresponse contours for the same unit shown in (A). Contours were interpolated between data collection points, and BF and threshold derivation are indicated. Details are presented in the text.

### 2.2. Middle ear pressurization

A schematic representation of the pressurization and pressure measurement system is shown in Fig. 1. The left bulla was exposed by clearing tissue through an incision slightly ventral and posterior to the pinna. The bone was thoroughly dried with alcohol. A 1–1.5 mm diameter hole was made in the dorsal, posterior chamber of the bulla, and a 10–15 mm piece of hard-walled polythene tubing (OD: 1.3 mm; ID: 0.9 mm) was sealed into the hole to a depth of about 3 mm with polyurethane adhesive. The distal end of this short tube was coupled via a stainless steel insert to a further 1 m length of the same tubing. The longer tube was attached to a remote valve and pressure transducer of a Grason Stadler 1720B tympanometer. The tympanometer was located outside the wall of the sound-attenuated chamber, thus allowing on-line monitoring of pressure stability during single-unit recording (see below). The patency of the system was initially assessed by applying variable holding pressures (range: −25 to +20 daPa) to the gerbil's middle ear and checking for stability over several minutes. The tympanometer was calibrated several times during the study using a U-tube manometer.

### 2.3. Acoustic stimulation

Pure tone bursts (100 or, routinely, 300 ms duration, 1 ms rise/fall, delivered at 1–2/s) were digitally synthesized and delivered to the transected ear canal by an Etymotic (ER-2) transducer mounted in an ER-10B coupler/microphone (Fig. 1). The seal between the speculum and the ear canal was complemented with Vaseline. Full details of this stimulus system are provided by Mills et al. (1993). The spectral purity of the tone bursts was measured by performing Fast Fourier Transforms (FFT) on both 100 and 300 ms bursts having a wide range of frequencies (100 Hz to 16 kHz). Analyses were performed with a Hewlett Packard 3561A Dynamic Signal Analyzer using a uniform window and 400 lines of resolution (frequency resolution: 1–10 Hz). The spectral splatter decreased symmetrically around the stimulus frequency. The splatter was greatest for the 100 Hz, 100 ms duration signal, where the 1/3 octave frequencies on the upper and lower sidebands were 20–25 dB down. For the more routinely used stimuli (> 500 Hz, 300 ms duration), the 1/3 octave sidebands were at least 40 dB down. The acoustic output of the system was calibrated in situ at the beginning of each experiment and, in some cases, during the application of MEP. MEP within the range used did not lead to any change in the system calibration.

### 2.4. Single-unit recording

The recording procedure followed closely that described by Semple and Kitzes (1985). Single neurons were isolated in the central nucleus of the right ICC, contralateral to the pressure-controlled and stimulated ear, using tungsten-in-glass microelectrodes. A midline incision was made along the length of the gerbil's scalp. The skull was cleaned and two small, stainless-steel screws were inserted and cemented over the frontal cortex. These screws were cemented to a steel rod held in a ball joint, allowing variable and rigid positioning of the gerbil's head. A small aperture was made in the bone overlying the right cerebellum. Microelectrode penetrations made through this hole, and angled at 30–45° to the vertical, passed through the ICC, as determined by physiological criteria (strong, sharply tuned responses to tones; Semple and Kitzes, 1985), in a dorso-caudal to ventro-rostral direction. Up to 5 penetrations were made in each animal.

Following isolation of a single unit, the approximate stimulus frequency range evoking a response was determined manually and a spike discriminator was adjusted. A variant of the spectral response plot method (Palmer and Evans, 1982; Kaltenbach and Saunders, 1987) was used to assess the threshold and BF of each unit. The controlling computer was set in an automated mode to present, in a random order, 5 stimuli at each of 12–50 points in a frequency/level matrix, to collect spike times and counts, and to arrange the counts in 2-D frequency/level/count histograms for on-line inspection (see Fig. 2A). The stimulus parameters were then adjusted, usually by narrowing the frequency and level range, and the above procedure was repeated until the BF of the neuron had been determined at high resolution.

Initial data were always obtained at atmospheric (control) MEP. MEPs were then usually applied in a stereotyped order: −20, −10, −15, −5, +5, +10, +20, +15, −20 daPa. For each MEP, the same data collection procedure described above was followed. Between each pressure application control data were obtained. Additional

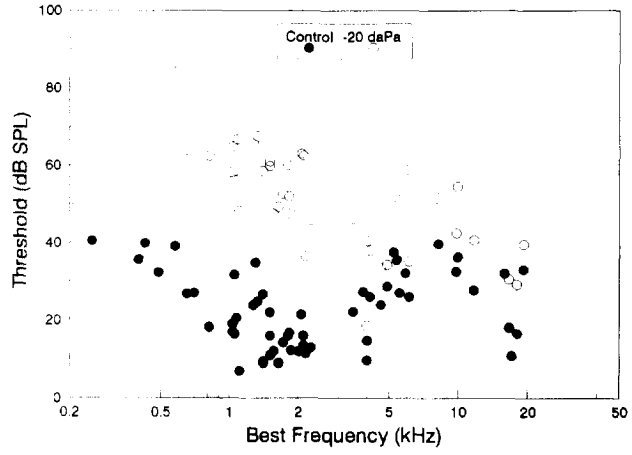


Fig. 3. The relation between BF and threshold for each unit recorded under control and -20 daPa MEP. Where multiple records were obtained in each pressure condition the mean values are shown.

data were collected at −20 daPa and −25 daPa in some cases. Full data collection for 1 unit took 1-−1.5 h.

### 2.5. Off-line analysis

Five isoresponse contours were computed for each frequency/level matrix (Fig. 2A). The minimum level (first contour) represented an average of 1 spike/2 stimuli, interpolated between data collection points. The remaining contours (see Fig. 2B) were the 20, 40, 60 and 80th percentiles of the maximum response (spike count/stimulus) in any cell of a given matrix, minus the minimum level. Thresholds and BFs were defined, respectively, as the most sensitive point on either the minimum level or 20th percentile contour (depending on the presence of spontaneous activity, and the regularity of the minimum level), and the frequency of that point. Sharpness of tuning was defined by the $Q_{10}$ index applied to the same contour used to define BF (see Fig. 2B). Once the appropriate contour had been chosen, each of these measures (threshold, BF, $Q_{10}$) was, therefore, determined objectively.

## 3. Results

An important analytical step in this study was to establish the scope, sensitivity and replicability of the data. Quantitative data (control threshold and BF) were obtained from 56 units, −20 daPa data were obtained from 44 units, and data from at least 4 non-zero pressures were obtained from 22 units. Mean control BFs were in the range 0.25–20 kHz and mean control thresholds varied from 7–40 dB SPL (Fig. 3). Repeated application of MEP in the range used had little effect on control thresholds or BFs. Fig. 4 shows the isoresponse contours of Unit 92371007 for 6 repetitions of the control pressure obtained over a 1 h period, with interleaved negative pressures. Control thresholds for this unit varied between 17 and 20 dB SPL and BF varied between 826 and 852 Hz. Most

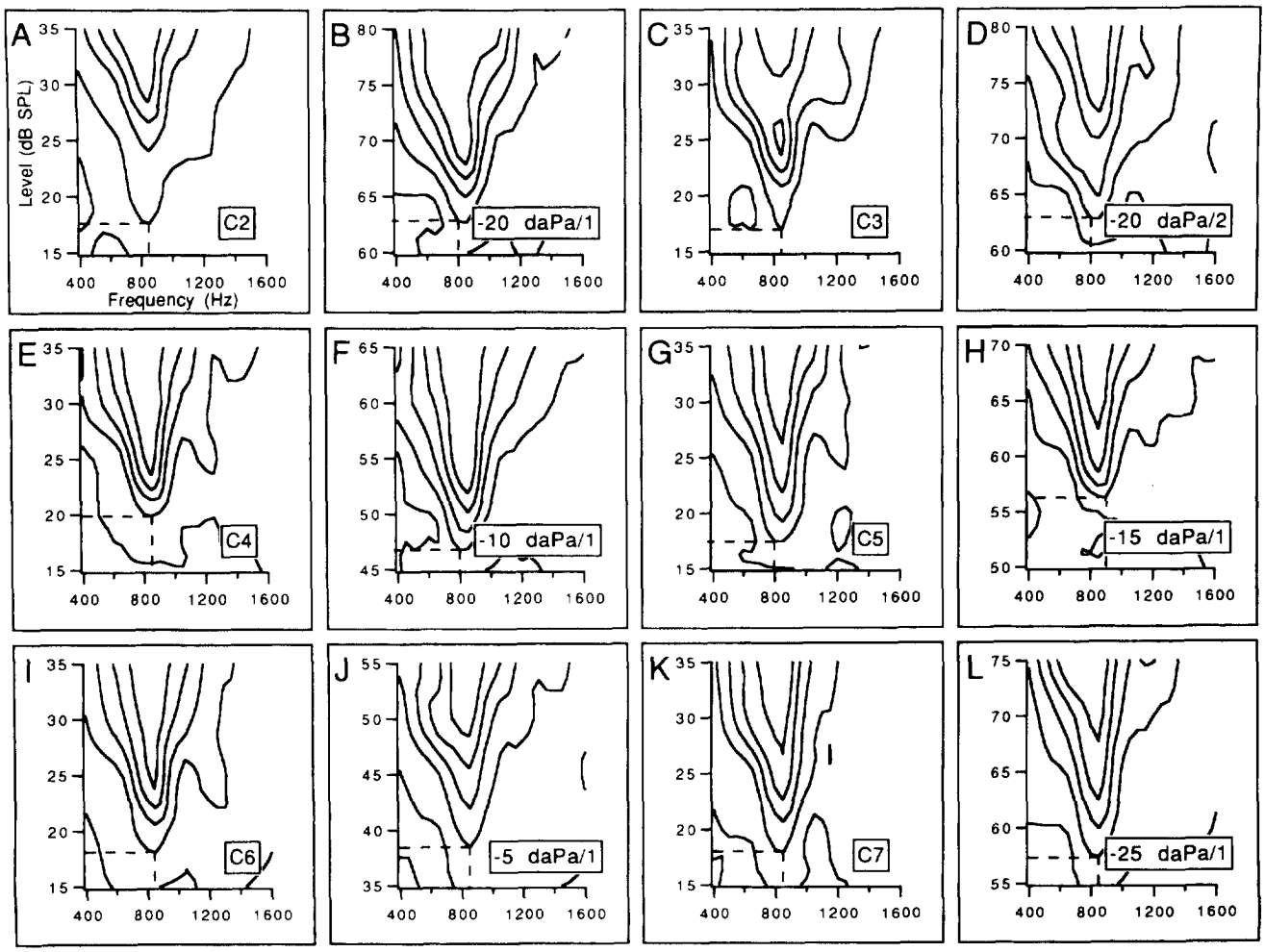


Fig. 4. Effect of repeated MEP application on isoresponse contours for unit 92371007. Each part of the figure shows interpolated data (see Fig. 2B and text) for a separate MEP. Control pressures (C2–C7) were interleaved with negative MEPs (-20 daPa/1 to -25 daPa/1). The presentation order of the figure (A–L) follows that of the various MEPs.

other units (34/37; Fig. 5) with 3 or more repetitions of the control pressure, had a threshold SD of less than 4 dB. In the frequency domain, control BF SD for the same sample was between 0.01 and 0.7 kHz (Fig. 6A). Expressed as a percentage of BF, the SD was generally lower for high-frequency sensitive units and higher for low-frequency sensitive units (Fig. 6B). Overall, 16/37 repeatedly tested units had a control BF SD that was less than 5% of the BF.

When negative MEP was applied, the sensitivity of unit 92371007 declined sharply (Fig. 4). However, the isoresponse contours maintained their control configuration, the BF remained stable, and the response was replicable under repeated applications of −20 daPa MEP. The generality of these MEP findings is shown in Figs. 3 and 7 and 8. Threshold at BF always increased with the application of −20 daPa (Fig. 3) and other (Fig. 7) MEPs. The negative MEP data in Fig. 7A were generally well-fit (Table 1), on the log–log axes, by the linear regression lines shown. For each MEP, the level of the threshold increase was inversely related to frequency. At low pressures, the threshold increase was directly related to MEP (Fig. 7A), but the effect of increasing pressure on thresholds appeared to plateau at 15–20 daPa, as indicated by the regression slope data in Table 1. Positive MEPs were tested less frequently, but the general relationships described for negative MEPs also held for positive pressures (Fig. 7B; Table 1). For example, the effect of both types of pressure on thresholds appeared to plateau at 15–20 daPa (Table 1). However, high positive pressures produced a smaller threshold shift than the equivalent negative pressure.

Changes in MEP had no obvious effect on frequency tuning. Fig. 8A shows, for each unit, the mean control BF plotted against the mean BF at −20 daPa. The linearity of the relationship was extremely robust ($r^2 = 0.996$) and the slope of the regression (0.984) was close to unity. Fig. 8B shows, at higher resolution, the relationship between control BF and the number of octaves change in BF produced by −20 daPa MEP. No evidence was found for a systematic change in BF with the application of this or any other MEP. Of the 44 units for which BF was measured under control and −20 daPa MEP, 26 (59%) had a BF difference of less than 5% and 14 (32%) had a BF difference of less than 2%.

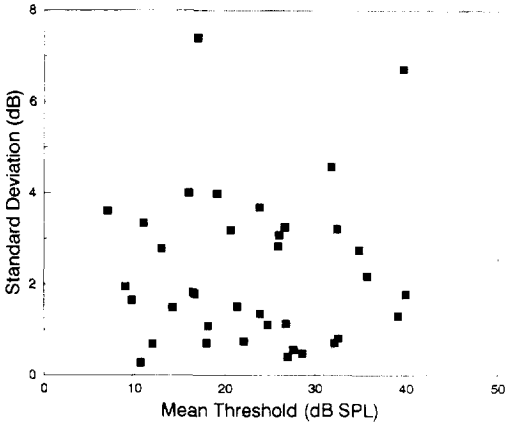


Fig. 5. Control threshold variability. Mean and standard deviation of the threshold of units repeatedly tested under control MEP.

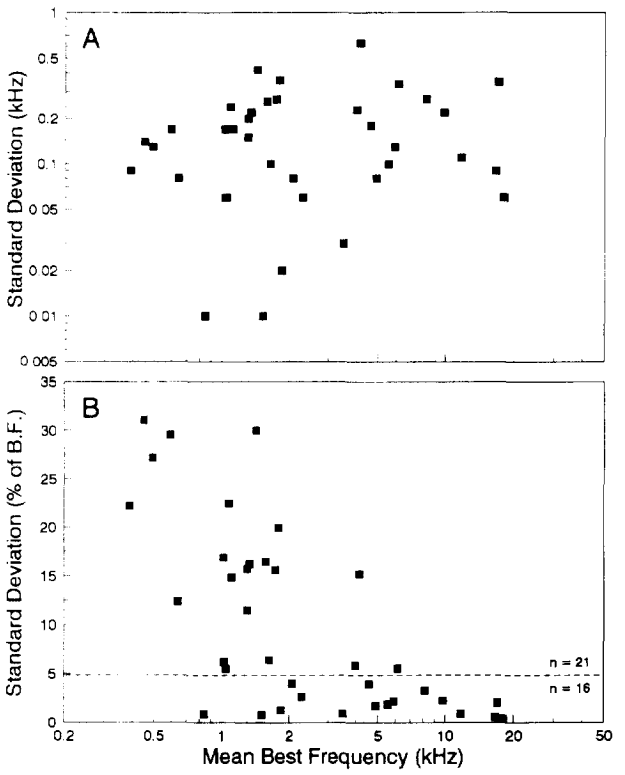


Fig. 6. Control BF variability. A: mean and standard deviation of the BF of units repeatedly tested under control MEP. B: data from (A) are replotted with the standard deviation (SD) expressed as a percentage of BF. The number of units having SDs less than 5% of the mean BF is indicated.

Although the data cited above show no obvious effect of MEP on unit BF, the question remains whether MEP produces a more subtle, but statistically significant, change in the frequency organization of the auditory system. We examined this possibility in two ways. In the first, we calculated the mean and the SD of the BF for units tested at least 3 times with the control MEP. For 9/37 of these units, the SD of the control BF was less than 2% of the mean. These units were chosen for further analysis because of their low BF variability. The mean BF of these 9 units at −20 daPa MEP ($n = 1$–4 measures) was expressed as a $z$ score, based on the control statistics. Six of the 9 units had a $z$ score with an absolute value less than 2, and the remaining 3 units had $z$ scores of −7.89, −5.34 and +3.86 for control BFs of 3.49, 11.72 and 1.84 kHz, respectively. Seven of the 9 units had negative $z$ scores, corresponding to an increase in BF with MEP. In the

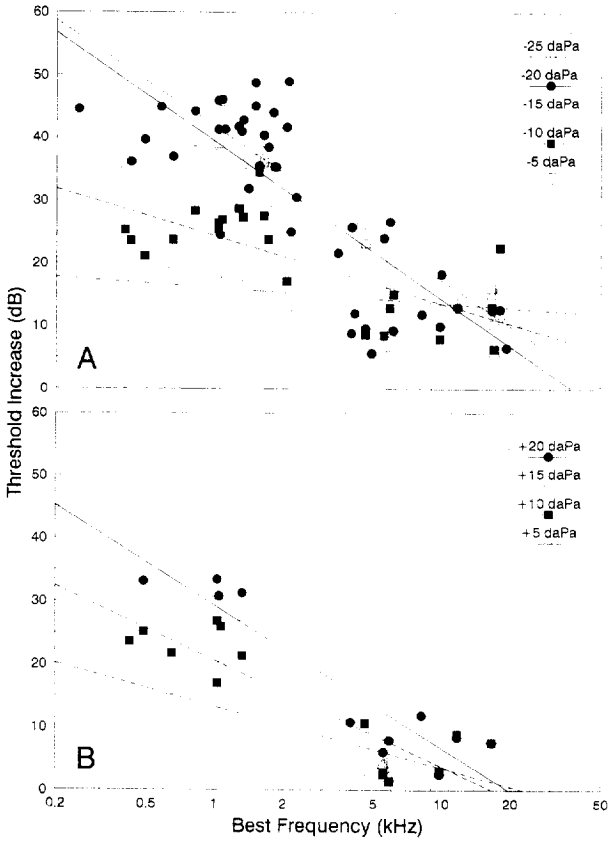


Fig. 7. Threshold increase produced by MEP. For each unit, the control MEP threshold (at BF) was subtracted from the negative (A) or positive (B) MEP threshold. Linear regression lines were fitted to the data for each MEP.

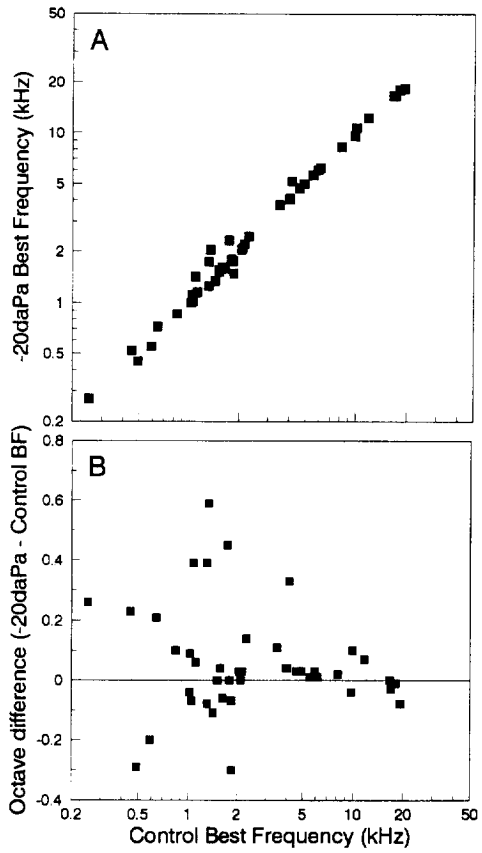


Fig. 8. Effect of negative MEP on BF. A: relation between BF under control and -20 daPa MEP. Each point shows the (mean) BF for a single unit tested under both conditions. B: difference (in octaves) between control and -20 daPa MEP for each unit.

second method, we examined the 8 units that were tested with 3 or more replications of −20 daPa MEP, in addition to 5–12 replications of the control pressure. For 7 of these units, there was no significant difference ($t$ tests) between the mean BF for each of the 2 MEPs. For the remaining unit, the mean control BF (1.84 kHz) was significantly ($t$ test: $t_6 = 3.29$; $P < 0.02$) higher than the mean BF under −20 daPa MEP (1.75 kHz). These high-resolution frequency analyses show that, for most units with low variability BFs, the BF was not significantly affected by −20 daPa MEP. However, for a small proportion of units, small, significant shifts of BF with MEP were observed. As suggested by their BFs, these units were intermixed, in the same electrode penetrations, with others for which no shift in BF occurred with MEP. The BF of the 1 unit that shifted significantly using both analytical methods decreased by 89Hz (4.8% of control BF) when MEP was applied.

Table 1
Numbers of units ($n$), fit of linear regression ($r^2$), and slope of the regression lines for the MEP group data shown in Fig. 7

| MEP (daPa) | $n$ | $r^2$ | Slope |
|---|---|---|---|
| -25 | 6 | 0.95 | -10.58 |
| -20 | 44 | 0.66 | -10.85 |
| -15 | 20 | 0.75 | -7.49 |
| -10 | 22 | 0.50 | -4.67 |
| -5 | 20 | 0.09 | -1.06 |
| +20 | 11 | 0.86 | -9.86 |
| +15 | 7 | 0.85 | -9.34 |
| +10 | 12 | 0.79 | -7.33 |
| +5 | 12 | 0.65 | -4.26 |

In Fig. 9A, $Q_{10}$ is plotted as a function of BF. As reported in numerous studies (e.g., Calford et al., 1983; Semple and Kitzes, 1985), $Q_{10}$ increases with frequency. Linear, least-squares regression lines were found, from a selection of algorithms, to make the best fit with the data in Fig. 9A and, for the control MEP, this regression gave an $r^2$ of 0.74. To examine the effect of MEP on the sharpness of frequency tuning we also measured $Q_{10}$ for a sample of neurons under −20 daPa MEP (Fig. 9A). A linear regression on these data ($r^2 = 0.69$) closely matched the control regression. The control $Q_{10}$ values were also subtracted from those obtained under −20 daPa MEP for

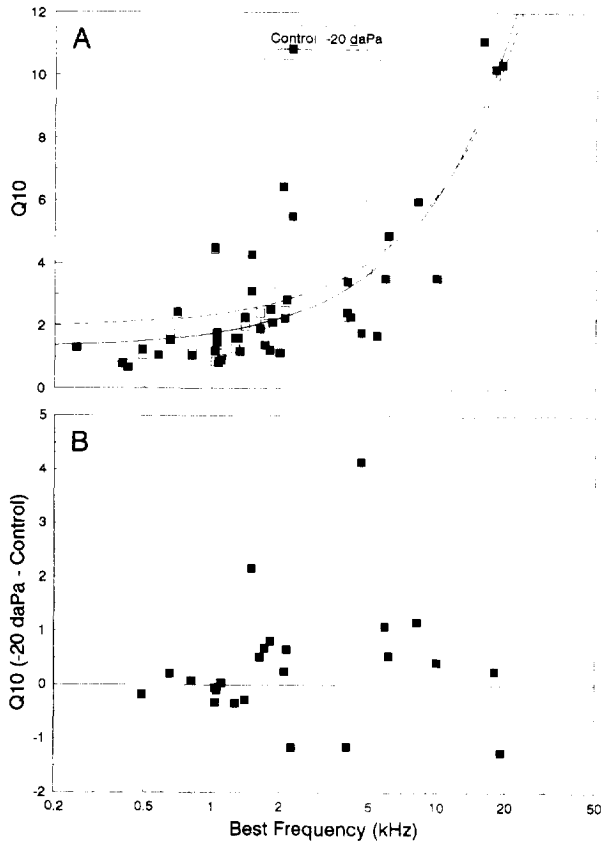


Fig. 9. Effect of negative MEP on width of tuning. A: $Q_{10}$ values under control and -20 daPa MEP for each unit. Linear regression lines for each data set are also shown. B: difference between $Q_{10}$ for control and -20 daPa MEP.

the same units (Fig. 9B) and, again, MEP was found to have no systematic or obvious influence on tuning.

## 4. Discussion

In this study we have shown that the frequency organization of the gerbil auditory system is not affected to any marked degree by changes in MEP covering the range measured in the middle ear of human children during OM episodes (Takahashi et al., 1991). Single neuron responses in the IC were affected by MEP in a frequency- and pressure-dependent manner, in line with expectations based on previous reports of the effect of MEP on sound transmission through the middle ear (Wever and Lawrence, 1954; Møller, 1983).

An important methodological issue in this study is whether the general failure to show a frequency change was due to an insensitivity of the measurement technique (IC neuron tuning curves). In studies of SOAEs referred to in Section 1, frequency shifts of up to 5% were found in the range 1–4 kHz. One index of frequency resolution available in the present study was the replicability of BFs obtained in the control pressure condition. For the majority of neurons, the variability of BFs was larger than would be required to detect a 5% change in BF. However, for 16/37 neurons examined repeatedly under the control condition, the SD of the BFs was less than 5%, and for 9/37 neurons the SD was less than 2%. These data suggest that a sub-sample of neurons had the potential to show very small changes in BF produced by MEP. Analysis of the −20 daPa data showed that, among this sub-sample, the majority failed to change BF with changes in MEP. For those that did change significantly, the changes were small and, apparently, non-systematic.

Studies of SOAEs have also reported small and variable changes in SOAE frequency with changing MEP. Wilson and Sutton (1981) described the results of 7 ears. Five of those ears showed increases in SOAE frequency with decreasing or increasing MEP, and the remaining ears showed asymmetric or decreasing frequency changes. Results presented from a 'typical' ear showed a variety of responses to MEP, the largest being a 55 Hz increase in a 1.14 kHz SOAE frequency component at ±40 daPa MEP. Whitehead (1988) examined the frequency shift produced by ±40 daPa MEP in a sample of 22 SOAEs. For half those SOAEs, the frequency shift produced by −40 daPa MEP was less than 0.5%. Although there is no clear relation between the generators of particular frequency SOAEs and IC neuron BFs, both measures reflect activity central to the middle ear and it is, therefore, gratifying that the results seem compatible.

### 4.1. Relation to otitis media

One motive for this study was the observation (Lambert et al., 1986) that OM was associated with a shift in the pattern of hair cell loss in an animal exposed to acoustic trauma (1.5 kHz tone). This finding suggested the possibility that changes in MEP accompanying OM might change the locus of maximal displacement on the basilar membrane produced by a tone of a given frequency and, therefore, frequency representation in the central auditory system. A frequency misrepresentation within the auditory system might explain, at a sensory level, some of the widely reported learning and cognitive problems experienced by children with OM (e.g., Freeman and Parkins, 1979; Brandes and Ehinger, 1981). The results of this study strongly suggest that transient MEP variation does not produce frequency misrepresentation in the central auditory system. Instead, non-atmospheric MEP acts in the same way as a simple high-pass filter applied to the auditory system input. The possibility remains that longer term middle ear pressurization, as may occur in chronic OM, could lead to mechanical alterations and frequency misrepresentation in the cochlea. This possibility requires further investigation.

## Acknowledgements

D.R.M. was supported by a Virginia Merrill Bloedel Visiting Scholar Award and by a grant from the Medical Research Council (UK). Research was supported by the MRC, and by NIH Grants DC00395 (E.W.R.) and DC00774 (W.R.L.). We wish to thank Dr. Rudolf Rübsamen for help, advice, and for the use of his facilities. Brandon Warren wrote the software used for stimulus generation, recording and analysis. Drs. Ed Burns, Doug Keefe and John Rosowski kindly provided comments on a preliminary draft of the manuscript. D.R.M. wishes to thank all members of the Virginia Merrill Bloedel Hearing Research Center who helped make his stay in Seattle useful and enjoyable.

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