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Rapid adaptation of the $2f_1-f_2$ DPOAE in humans: Binaural and contralateral stimulation effects¹

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Abstract

The present data were collected in humans to characterize the effects of monaural and binaural stimulation and contralateral noise on the $2f_1-f_2$ distortion-product otoacoustic emission (DPOAE) adaptation response. DPOAE levels ($f_2/f_1 = 1.21$, $L_1 = 70$ dB SPL, $L_2 = 65$ dB SPL) were measured in both ears for a range of f_2 frequencies (1.2 to 10.0 kHz). The f_2 frequency producing the largest amplitude DPOAE was used for further testing employing three different stimulus conditions: the primary tones were presented to only one ear for 4 s; the two tones were presented simultaneously in both ears; and, contralateral broadband noise (60 dB SPL) was presented for 5 s, beginning 4 s after the onset of the monaural primaries in the test ear. Acoustic reflex thresholds were measured to verify that the middle-ear muscles played no systematic role in the measured DPOAE reductions. Estimates of monaural rapid adaptation levels and time constants agreed well with previous human findings. The magnitude of the rapid adaptation time constants were comparable. With added contralateral noise, the average DPOAE suppression was 1.1 dB (0.3–2.7 dB). The magnitude of the monaural adaptation and the effects of binaural and contralateral stimulation, however, were smaller than those measured previously in experimental animals, though the time constants were in good agreement.

Key words: $2f_1-f_2$; Distortion-product otoacoustic emission; Rapid adaptation; Medial olivocochlear efferent system; Humans

1. Introduction

The olivocochlear efferent system was first described more than 50 years ago (Rasmussen, 1946). It was subsequently classified as being composed of two major pathways, lateral and medial, based on the relative sites of origin within the brainstem (Warr and Guinan, 1979; Guinan et al., 1984). The lateral olivocochlear pathway is composed mostly of unmyelinated fibers that originate in the lateral nuclei of the superior olivary complex and terminate post synaptically on primary afferent fibers below the inner hair cells. The medial olivocochlear (MOC) pathway, the cells bodies of which are located in the periolivary medial nuclei of the superior olivary complex, is comprised mostly of myelinated fibers that terminate on the base of outer hair cells (OHCs).

Little is known about the function of the lateral efferent tracts, primarily because of difficulties in recording from their thin, unmyelinated nerve fibers. On the other hand, it is generally acknowledged that the MOC system plays a central role in modulating the active mechanical behavior of the OHCs. Physiologically, the MOC system has an inhibitory effect on the ear, but depending on the stimulus conditions, the results can be

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Abbreviations: MOC, medial olivocochlear; OHC, outer hair cell; DPOAE, $2f_1-f_2$ distortion-product otoacoustic emission; MEM, middle-ear muscle

observed as either inhibitory or enhancing. In quiet backgrounds, MOC activation by contralateral noise or electrical stimulation at the midline results in the suppression of cochlear potentials (Fex, 1967; Konishi and Slepian, 1970), cochlear mechanical and distortion responses (Mountain, 1980; Siegel and Kim, 1982), distortion-product otoacoustic emissions (DPOAE) (Collet et al., 1990; Liberman et al., 1996; Kujawa and Liberman, 2001), inner hair cell receptor potentials (Brown et al., 1983), the ensemble background activity of the auditory nerve (Lima da Costa et al., 1997; Popelář et al., 1997) and responses of single auditory afferent nerve fibers (Wiederhold and Kiang, 1970; Buño, 1978; Gifford and Guinan, 1987; Guinan and Gifford, 1988; Warren and Liberman, 1989a,b; Kawase et al., 1993; Kawase and Liberman, 1993). In noise backgrounds, MOC activation *decreases* physiological thresholds and increases the response amplitudes to transient signals (Dirks and Malmquist, 1965; Nieder and Nieder, 1970; Winslow and Sachs, 1987, 1988; Dolan and Nuttall, 1988; Kawase et al., 1993; Kawase and Liberman, 1993).

Whether suppressive or enhancing, it is now generally presumed that the MOC acts by reducing the motility of the OHCs, the so-called 'cochlear amplifier', by altering the conductance of the OHC membrane (Flock and Russell, 1976; Art et al., 1984). In situations where the effects are enhancing, the result is a suppression of the OHC response to the concurrent, *sustained* masking noise, resulting in an unmasking of the response to the transient target stimulus (Winslow and Sachs, 1987, 1988; Kawase et al., 1993; Kawase and Liberman, 1993). Both suppressive and enhancing medial efferent effects are lost when the MOC tracts are sectioned.

While our understanding of MOC activity in experimental animals is well developed, a comparable understanding of the MOC physiology in humans is still emerging. Recent studies have offered a potentially powerful non-invasive technique for characterizing MOC physiological function that might be useful in studies with humans. Liberman et al. (1996) measured the adaptation of the $2f_1-f_2$ DPOAE in anesthetized cats. They showed that the magnitude of the DPOAE diminishes rapidly after primary tone onset and determined that two different adaptation processes were evident. The first, termed 'rapid' adaptation, decays with a time constant of 60 to 100 ms, and the second, or 'slow' component, acts with a time constant of approximately 1000 ms. When the MOC tracts were sectioned, the fast component was lost entirely, leaving only slow adaptation which persisted, being apparently unrelated efferent system activity (Liberman et al., 1996). The adaptation of the DPOAE with monaural primary tone presentation was equivalent to about 6 dB and reflected only the effect of the 'crossed'-MOC efferent tract. This ipsilaterally activated efferent subgroup represents approximately two-thirds of the total medial efferent population to the ear in the cat. With binaural presentation, where both ipsilaterally and contralaterally responsive MOC subgroups to the ear are activated, the magnitude of the rapid adaptation was increased by as much as 4 dB over that seen to monaural stimulation alone (Liberman et al., 1996), reflecting the addition of the 'uncrossed' medial efferents. More recent studies in non-human animals have shown that the DPOAE rapid adaptation phenomenon is comparable in guinea pigs (Kujawa and Liberman, 2001; Luebke et al., 2001), rats (Relkin et al., 2002), rabbits (Kim et al., 2002; Luebke et al., 2001), gerbils and mice (Sun and Kim, 1999; McGee et al., 2000).

Recently, Kim et al. (2001) measured DPOAE rapid adaptation to monaural primaries in humans. These investigators reported that the monaural adaptation time constants estimated by a two-component exponential function were 69 ms for the rapid component and 1.51 s for the slow component. They estimated, however, that the median magnitudes of the rapid and slow adaptation processes for their group of 21 subjects were approximately 0.65 and 0.40 dB, respectively, far lower than those estimated in cats (Liberman et al., 1996). Combining the magnitudes of the rapid and slow adaptation processes yielded a range of adaptation estimates of 0.4 to 3.0 dB. In general, Kim's human data are in good qualitative agreement with those recorded for non-human subjects and with an earlier, preliminary report for humans (Agrama et al., 1998).

DPOAE rapid adaptation offers a valuable, non-invasive tool for studying the function of the MOC system in humans. The present study sought to extend the existing DPOAE paradigm in humans to include the effects of binaural primary tone and contralateral noise presentation on the adaptation process.

2. Materials and methods

2.1. Subjects

Twenty-four human subjects participated in this study. A brief history was taken from each subject to document ear-related complaints and history of ear-infections, ear surgery, ototoxic medication use, noise exposure, and chronic medication use. Except for two subjects, who were older than 40 yr, all subjects were between 20 and 30 years of age. Most of the subjects (16) were females.

The sensitivity of both ears was determined by measuring DPOAE amplitude as f_1 , presented at 70 dB SPL, was stepped from 1.0 to 8.0 kHz (approximately seven steps/octave). The amplitude of evoked otoacous-



Fig. 1. Amplitude of $2f_1-f_2$ DPOAE for varying f_2 frequencies, for right and left ears, from one subject. The arrow points to the $2f_1-f_2$ emission in the right ear that was selected for study during that particular session. In this case, the relatively higher emission at ~6300 Hz was not chosen for study because of the high-frequency fall-off in the ER-1 transducers above this frequency.

tic emission is considered a good indication of the integrity of the auditory pathway from the ear canal up to, and including, the OHCs (cf., Whitehead et al., 1996).

All experiments were approved by the Internal Review Boards of Duke University Medical Center and The University of North Carolina at Chapel Hill School of Medicine.

2.2. Instrumentation, stimulus parameters and testing paradigms

The primary tones were generated digitally (Tucker-Davis Technologies, Gainesville, FL, USA; AP2, DA3-4, PA4) and fed individually to each ear through separate transducers (Etymotic Research, Elk Grove Villa, IL, USA; ER-1). The primaries and emissions were measured in the ear canal with a low noise microphone probe (Etymotic Research; ER10B+), sampled continuously at a rate of 40.9 kHz and amplified (40 dB), digitized (Tucker-Davis Technologies; DA2), and stored to the hard drive. At the end of the session, emission strength was analyzed using the heterodyne method as described by Kim et al. (2001).

The primary tone parameters used were $f_2/f_1 = 1.21$, f_1 level $(L_1) = 70$ dB SPL, and f_2 level $(L_2) = 65$ dB SPL. DPOAE levels were measured as the f_1 frequency was stepped between 1.5 and 8 kHz and the f_2 frequency producing the largest emission was selected for further study in a given session (Fig. 1). For an individual subject, this frequency varied from session-to-session. Primary tone duration for monaural and binaural adaptation measures depended on the condition tested and ranged from 4 s (for comparisons of monaural and binaural rapid adaptation) to 12 s (to characterize the effects of added contralateral noise on the DPOAE response). The rise/fall times of all stimuli (primaries and contralateral noise) were zero, with the primaries beginning at 0 amplitude to minimize frequency splatter. This splatter was further minimized as the DPOAE amplitude was measured as the $2f_1-f_2$ frequency peak in the fast Fourier transform.

Adaptation of the DPOAE was measured under three different stimulus conditions. In the first, the primary tones were presented to only one ear. In the second, the primary tones were presented simultaneously in both ears. In the third, the primary tones were presented to only one ear, while contralateral broadband noise (Tucker-Davis Technologies; WG2) was presented at 60 dB SPL for 5 s. The noise band was 100 Hz to 10.0 kHz and was flattened (± 2 dB) with an octaveband graphic equalizer (Radio Shack model 31-2030). The noise began 4 s after primary tone onset in the test ear, after which it was turned off, and the monaural tones were allowed to continue for another 3 s (see Fig. 6A,B). At least 128 runs of each condition were performed and averaged. The runs in each session were distributed into alternating blocks of 64 (64 monaural, then 64 binaural), starting with a different condition each time. This was done to minimize the influence of any systematic effects such as sequence of presentation or fatigue of the efferents, or change in the emission level.

The acoustic system output was calibrated in the subject's ear at the start of each session, and calibration tests were repeated at random intervals throughout the test session to detect the emergence of small changes in probe placement or orientation. Additionally, the measurement system monitored average primary tone levels on a run-by-run basis; any sudden change in the levels, usually indicating a displacement of the probe/microphone system in the ear canal, resulted in the session being interrupted. In these situations, the earphones were re-positioned and another calibration was performed.

2.3. Middle-ear reflex measurements

A potential confounding factor in the study of efferent activity was the possibility of contamination by middle-ear muscle (MEM) effects (Liberman and Guinan, 1998; Guinan, 2002). To exclude this possibility, MEM reflex thresholds were estimated in a subgroup (6) of subjects from this study and in additional (4) subjects from another otoacoustic emission experimental group. MEM reflexes were measured for presentations of ipsilateral pure tones at 2000 Hz and of contralateral broadband noise using a GSI 33 Middle Ear Analyzer (Grason-Stadler, Milford, NH, USA). The



Fig. 2. DPOAE adaptation curves under monaural and binaural conditions. (A) Curves for individual subjects KM and JB (upper and lower pair of curves, respectively). For KM, $f_2 = 2.155$ kHz, and for JB, $f_2 = 3.418$ kHz. (B) Group curves. The results of 22 testing sessions were averaged across all subjects. Rapid adaptation was 24% larger with the binaural primaries, as compared with monaural stimulation. The fitted two-component exponential function is super-imposed on each adaptation curve.

contralateral noise stimuli used for the MEM measurements were generated by the same Tucker-David Technologies (WG2) instrumentation employed in the DPOAE studies, whereas the pure tone stimuli were generated by the GSI 33. In all cases, the MEM reflex threshold for the contralateral broadband noise was at least 24 dB above the level of the contralateral broadband noise used in the DPOAE studies. Likewise, MEM reflex thresholds for monaural pure-tone stimuli exceeded 90 dB SPL for all subjects. These results were in accordance with thresholds reported in the literature, which ranged from 66 to 100 dB SPL for contralateral noise, with higher thresholds for younger subjects (Jerger et al., 1972; Habener and Snyder, 1974; Wilson and McBride, 1978; Collet et al., 1990; Margolis and Levine, 1991), comparable to those involved in this study.

2.4. Data analysis

A spectral analysis was performed on the response to each stimulus presentation, and the testing session was included in the analysis only if a clear frequency peak was evident at the $2f_1-f_2$ above the background noise in the majority of the responses. Data from eight subjects were thus excluded from the study group because of low DPOAE amplitudes. In all such cases, these subjects also had relatively low amplitude emissions across the frequency range tested.

Some subjects were tested more than once at the same frequency, but only the DPOAE adaptation curve

with the highest signal-to-noise ratio was included for analysis. Because MOC action is dependent on stimulus frequency, for the purposes of this study, three different frequency regions were defined: below 2 kHz, between 2 and 4 kHz, and above 4 kHz. Four subjects were tested in two different frequency regions, and one subject was tested at three different frequencies, all of which are included here. The results presented are from 22 testing sessions in 16 different subjects.

Estimation of the changes in DPOAE amplitude as a function of time was done by fitting a two-component exponential curve to the DPOAE adaptation curves. The use of a two-component exponential fit is based on previous studies in animals and humans (Liberman et al., 1996; Kim et al., 2001). The curves fitted were of the form:

$$Y(t) = A_{\mathbf{f}} \cdot e^{(-t/\tau_{\mathbf{f}})} + A_{\mathbf{s}} \cdot e^{(-t/\tau_{\mathbf{s}})} + C$$

where Y(t) is the DPOAE time course, A_f and A_s are the magnitudes of the fast and slow adaptation processes, respectively, τ_f and τ_s are the time constants for these adaptations, and C is the steady-state emission level. The exponential was fit using the MatLab[®] curve-fitting tool.

The two-component exponential fit was used to study the adaptation in response to monaural and binaural stimulation, as well as the onset and recovery of contralateral noise suppression. Results obtained for each subject under the three testing conditions were compared statistically using a paired *t*-test.

3. Results

3.1. Monaural stimulation

In general, the changes in the DPOAE level after the onset of the primary tones, are characterized by an initial rapid decrease in amplitude, followed by either a further gradual decrease, or a stabilization, in level (Fig. 2A, dashed lines for individual subjects KM and JB; Fig. 2B, upper, dashed line for averaged curve across all subjects). Under monaural stimulation, 19 of the 22 DPOAE adaptation curves were approximated by a two-component exponential time course (Fig. 2B, dark line superimposed on upper curve). The remaining three records could be approximated by a single exponential curve, as there was no apparent slow adaptation process. Across subjects, the total adaptation (combination of both rapid and slow components) ranged from 0.3 to 2.7 dB, with a mean of 0.8 dB. The magnitudes of the individual rapid and slow adaptation components overlapped considerably, and ranged from 0.0 to 1.0 dB, with a mean of 0.3, and from 0 to 1.7 dB, with a mean of 0.5 dB, respectively (Fig. 3A,B). Time constants estimated from the twocomponent exponential fit for both the rapid and slow processes are plotted in Fig. 3C. Time constant values ranged between 7 and 350 ms (median 72.9 ms) for the rapid adaptation and from 350 ms to 8 s (median 2.1 s) for the slow adaptation. These values are comparable to those reported in the literature for human subjects (Kim et al., 2001).

3.2. Effects of binaural primaries on DPOAE adaptation

Changes in the amplitude of the binaural DPOAE after binaural primary tone onset are shown in the lower curves (solid lines) of Fig. 2A for two individual subjects, and the averaged curve for all subjects is given in Fig. 2B. The magnitude of total adaptation in response to binaural stimulation ranged between 0.2 and 3.0 dB, with a mean of 0.9 dB. The rapid and slow adaptation components (Fig. 4A,B) ranged from 0.1 to 1.6 dB (mean = 0.4 dB) and from 0.0 to 1.4 dB (mean = 0.5 dB), respectively. As in the case of the monaural primaries, there was substantial overlap between the adaptation measured for the two processes (Fig. 4C).

Binaural stimulation resulted in relatively more adaptation in the DPOAE as compared with monaural stimulation (Fig. 5A; see also Fig. 2A,B). On average, the total DPOAE adaptation was 0.8 dB with monaural primaries and 0.9 dB for binaural primaries. A paired *t*-test showed that the magnitude of rapid adaptation was statistically greater for binaural, as compared with monaural, presentations (P < 0.05). There was no statistical difference, however, when comparing the magnitude of the slow adaptation process for monaural and binaural primary presentations.

With presentation of binaural primaries, the DPOAE adaptation followed a time course similar to that obtained for the monaural stimulation condition (Fig. 2B, solid line superimposed on lower curve). Median time constants, estimated from the fitted exponential, were



Fig. 3. Effects of monaural stimulation on the magnitudes of rapid (A) and slow (B) adaptation components and on time constants (C). There was considerable overlap in the distribution of the rapid and slow processes. Distribution of time constants was estimated from exponential fits and shows the relative distribution of the rapid and slow constants.



Fig. 4. Effects of binaural stimulation on the magnitudes of rapid (A) and slow (B) adaptation components and on time constants (C). As in the case of monaural stimulation, there was significant overlap in the distribution of magnitudes for the rapid and slow processes. Distribution of $2f_1-f_2$ time constants illustrate the two processes.

72 ms for the rapid component and 1.1 s for the slow component (Fig. 5B, right panel). Likewise, the measured time constants for both rapid and slow processes were not statistically different from those measured under monaural and binaural stimulation conditions.

3.3. Contralateral noise

The effect of the contralateral broadband noise on the DPOAE was studied in 17 of the 22 sessions. Activation of the MOC by contralateral noise resulted in a rapid decrease, or suppression, in the amplitude of the DPOAE (Fig. 6A,B). Fig. 6A shows the effect of the contralateral noise on the DPOAE adaptation curve for one subject, and Fig. 6B shows the DPOAE adaptation curve obtained by averaging across all 17 subjects and sessions. For the subject shown in Fig. 6A, the contralateral noise produced approximately 2.1 dB of suppression. Mean suppression, across all subjects and sessions (Fig. 6B), was approximately 1.1 dB (range = 0.3-2.7 dB).

After contralateral noise onset (labeled y in Fig. 6A), the changes seen in the DPOAE adaptation curves were also best approximated by a two-component exponen-



Fig. 5. Effects of monaural and binaural primary presentation conditions compared for both magnitude of adaptation (A) and time constants (B). Dashed line represents condition where monaural and binaural adaptation are equivalent. The best fit line for the rapid adaptation (thick line) had a slope of 1.2, indicating greater adaptation under binaural stimulation ($r^2 = 0.67$). The time course of the rapid adaptation was similar for both stimulation paradigms ($r^2 = 0.03$).



Fig. 6. Contralateral noise suppression. (A) Effects for one subject. Also shown are the two-exponential curves fitting monaural adaptation (x), contralateral noise suppression (y), and offset of the contralateral noise (z). (B) Average suppression for the 17 subjects.

tial time course. When compared directly (Fig. 7B), the contralateral suppression onset time course is similar to that measured with monaural and/or binaural rapid adaptation (in the absence of contralateral stimulation; see Fig. 2B). While differences were evident in the overall magnitudes of the adaptation and contralateral suppression, no statistical difference (paired *t*-test) were seen in the onset time course.

When the contralateral noise was discontinued (labeled z in Fig. 6A), the emission level returned to its precontralateral noise level, with a time course similar to that observed for both rapid adaptation and contralateral suppression onsets (Fig. 8A,B). For the averaged DPOAE adaptation curve (Fig. 8B) with the offset of the noise, the DPOAE level returned to approximate pre-suppression levels with a median time constant of 110 ms (range = 5–350 ms).

3.4. Effects of DPOAE frequency on rapid adaptation magnitude

The magnitude of rapid adaptation is plotted as a



Fig. 7. Comparison of the magnitudes of monaural rapid adaptation with contralateral noise (CLN suppression x and y in Fig. 6A) (A) and comparison of their onset time constants (B). There was no statistical difference between the rapid adaptation and the noise suppression measures. The two time constants were similar, as would be predicted due to their dependence on different components of the same neural system. Time constants are plotted only for those DPOAE adaptation curves that could be fit by a two-component exponential function.

Fig. 8. Changes in $2f_1-f_2$ level (y and z in Fig. 6A) (A) and between rapid and slow time constants (y and z) (B) at the onset and offset of contralateral noise (CLN). Values in A were obtained at noise offset and are plotted as absolute values.

function of the DPOAE frequency in Fig. 9. Data are shown for both monaural and binaural primary tone presentation for DPOAE frequencies of 1.925 to 6.032 kHz. There was little evidence of a relationship between frequency and the magnitude of adaptation. Across frequency, monaural adaptation ranged from 0.7 dB at 1.8 kHz, to < 0.1 dB at 6.05 kHz. As predicted, binaural adaptation was, in general, slightly higher in magnitude than that seen for monaural stimulus presentation, though, again, no effect of frequency was evident. Between the extreme frequencies tested, on average, the distribution of magnitudes showed no apparent systematic variations with frequency.



Fig. 9. Magnitude of rapid adaptation for both monaural and binaural primary conditions plotted as a function of f_2 frequency. Rapid adaptation is plotted for all subjects and f_2 frequencies reported in this study. There was no statistical relationship between f_2 frequency and adaptation magnitude.

4. Discussion

4.1. Monaural DPOAE adaptation

In the current study, continuous sampling of the otoacoustic emission level was used to monitor changes in the DPOAE under monaural primary presentation conditions. DPOAE responses generated by monaural primary tones decreased, or adapted, by following a time course that was approximated by a two-component exponential function. In our subjects, the measured (median) time constants were 72.9 ms and 2.1 s for the rapid and slow adaptation components, respectively. These results agree well, both qualitatively and quantitatively, with previous DPOAE adaptation data from humans (Kim et al., 2001) that showed median time constant measures of 69 ms and 1.51 s. The time course of human emission adaptation, as reported here and in the study of Kim and colleagues (2001), agrees well with acute studies in both cats (Liberman et al., 1996) and guinea pigs (Kujawa and Liberman, 2001).

As expected, the magnitudes of the different adaptation measures - total, rapid, and slow - are also in excellent agreement with the first study of monaural adaptation in humans (Kim et al., 2001). In our study, total monaural adaption ranged from 0.3 to 2.7 dB, with a mean adaption of 0.8 dB, values comparable to those reported by Kim et al. (range = 0.4–3.0 dB, mean = 1.1dB). While, as first noted by Kim et al., the time course of the adaptation is comparable across the species studied to date, the magnitude of the adaptation is significantly lower in humans as compared with experimental animals (Liberman et al., 1996; Kujawa and Liberman, 2001). In experimental animals, adaptation



can result in 20-dB reductions in the DPOAE levels, depending on stimulus conditions (Kujawa and Liberman, 2001).

The reasons for this discrepancy are uncertain, but could reflect species differences (Kim et al., 2001), differences in stimulus parameters and/or necessary differences in experimental techniques. Experimental animals, in general, have larger emission levels than do humans. For example, DPOAE levels in lightly anesthetized cats (0.3 mg medetomidine hydrochloride, given intramuscularly), using the same experimental facilities as those used in the present study show DPOAE amplitudes at levels 20 dB or more higher than those recorded under comparable stimulus conditions in humans (Smith, unpublished observations). In those survival animals, rapid adaptation magnitudes were as high as 5 to 6 dB, considerably above the 2.7-dB maximum reported here in humans.

To date, however, all non-human rapid adaptation studies have been carried out primarily in acute preparations, with animals under surgical-depth anesthesia. While anesthetic effects cannot be ruled out, they have most typically been shown to suppress efferent activity, leading to an underestimation rather than an overestimation of the magnitude of MOC influences on various cochlear measures (Lima da Costa et al., 1997; Boyev et al., 2002). A second issue more likely to lead to difficulties in direct comparisons of DPOAE levels in humans and non-human animals are differences in the placement of recording microphones relative to the tympanic membrane. Obviously, in human volunteers, insertion of the stimulation and recording devices is limited by both potential risk of damage to the tympanic membrane and discomfort for the subject. While the amplitude of the primary tones is repeatedly adjusted (based on frequent calibrations) to accommodate for changes in the volume of the ear canal with displacement of the ear tip, the amplitude of the returning DPOAE is not likewise adjusted and would be reduced with increases in distance (and volume) from the tympanic membrane. In acute studies, however, the measurement conditions can be optimized by surgically removing the external ear canal and visualizing the tympanic membrane, permitting placement of the probe tubes immediately adjacent to the membrane (cf., Liberman et al., 1996). Further support for this suggestion comes from comparisons of the magnitude of rapid adaptation reported in acute cats (Liberman et al., 1996), which can reach 10–20 dB, and the much lower levels we have found in chronic, survival cats where the eartips can not be inserted as deeply (5-6 dB; Smith, unpublished observations). Lastly, on a practical level, the inadvertent variations (increases) in the distance between the tympanic membrane and the recording microphone would likely be greater in awake human subjects as compared with anesthetized animals under comparable recording conditions.

4.2. Binaural primary presentation effects

Studies of the medial efferent system in different species have reported that most MOC efferents respond to sounds presented in the ear that they innervate (Guinan, 1996). The ratio of these crossed (or ipsilaterally responsive) to uncrossed (or contralaterally responsive) MOC fibers varies across species ranging from 3:1 in mice (Campbell and Henson, 1988) to roughly equal numbers in mustached bats (1.1:1) (Bishop and Henson, 1987). In the first report of the MOC-mediated rapid adaptation, Liberman and colleagues (1996) showed that the magnitude of the adaptation when primaries were presented simultaneously to both ears was as much as 4 dB larger than when the primaries were presented only to the ipsilateral, or test ear. In the monaural condition, only the ipsilaterally activated MOC, or two-thirds of the total MOC population at that cochlear location, are involved in the adaptation process. In cats, when the primary tones are presented binaurally, all the MOC fibers - both the ipsilaterally activated (two-thirds of the total) and the contralaterally activated (the remaining one-third of the MOC population) subgroup - will contribute to the measured response. In the binaural case, as the magnitude of the MOC action is roughly proportional to the number of fibers activated (Guinan and Gifford, 1988), it would be expected that the magnitude of the adaptation would be greater by one half than in the monaural primary condition.

While this admittedly represents a simplified view of the relationships between MOC innervation density and the magnitude of MOC effects, the present data suggest that the distribution of the medial efferents in humans is similar to that observed in non-human animals, with significantly more crossed than uncrossed MOC fibers. This extrapolation is strengthened by the fact that the stimuli to both ears were precisely the same, and would thus be expected to activate the same proportion of MOC fibers in each ear (ipsilaterally and contralaterally activated).

4.3. Contralateral suppression of the DPOAE

Changes in the monaural DPOAE measured in the presence of contralateral broadband noise showed an average suppression in DPOAE of approximately 1.1 dB. Contralateral acoustic stimulation activates only the uncrossed MOC fibers, which represent the smaller subgroup of the MOC tracts to the test ear. Based on our findings that the binaural stimulation increased in magnitude by only 24% (by extension, approximating a

4:1 crossed- to uncrossed-MOC relative innervation), we would therefore expect that contralateral noise would result in relatively less suppression than ipsilateral stimulation alone. Nevertheless, when the magnitude of the DPOAE adaptation with monaural primaries is compared with the magnitude of suppression produced by the contralateral noise(Fig. 7A), they are statistically indistinguishable. This is likely due to the fact that stimuli with larger bandwidths (e.g., noise) are more effective in stimulating the MOC system (Warren and Liberman, 1989b; Maison et al., 2000). This difference in both bandwidth and level, however, makes a straightforward comparison between these two test conditions difficult to interpret.

A further complication in comparisons is introduced by the relative timing of the two stimuli: the onset of the contralateral noise occurs 4 s after the onset of the primaries in the test ear. At this time, the crossed-MOC system had already been activated by the onset of the primaries, and the OHCs were likely set at a different operating point since they were in a partially 'adapted' state.

4.4. Time course of adaptation

When the onset time course of adaptation, measured in conditions of monaural and binaural primaries, was compared with contralateral suppression, all three time constants were similar. This is not an unexpected finding, as previous efferent experiments have found no difference between crossed and uncrossed medial efferents in this respect. In functional studies using contralateral acoustic stimuli, suppression usually reached a plateau within the same 1- to 3-s window as found with monaural stimulation in the current study (Liberman et al., 1996). Anatomical studies in animals also reveal no significant differences between the two groups of medial efferents (crossed and uncrossed), such as axonal size or type and/or extent of myelination, which might result in a difference in the time course (Warr, 1992). The only notable difference between the crossed and uncrossed medial efferents is that the crossed MOC forms a longer, double-crossed pathway in which both afferent and efferent limbs cross the midline (Warr and Guinan, 1979; Warr et al., 1986). This would likely result in slight differences in relative onset latencies between the two MOC subgroups.

MOC action on cochlear function is most typically described as suppressive in nature. When the MOC system is activated, the conductance of the OHC basal membrane is increased and the resting potential is shunted, thereby decreasing the gain of the cochlear amplifier (Guinan, 1996; Geisler, 1998). The resulting alterations in cochlear response measures follow a complex, two-component time course, having 'fast' and 'slow' effects, with estimated time constants of ~100 ms and 16 to 50 s, respectively (cf., Wiederhold and Kiang, 1970; Sridhar et al., 1995; Lima da Costa et al., 1997). Molecular studies have identified the α -9 receptor as being responsible for both effects, with the two time courses resulting from two relatively different receptor actions on the OHC (Dulon et al., 1990; Sridhar et al., 1995; Yoshida et al., 1999; Blanchet et al., 2000). Both effects are blocked, or are lost entirely when the MOC tracts are pharmacologically interrupted or are surgically cut.

In the case of DPOAE adaptation, which also follows a two-function time course, cutting the MOC system results only in loss of the rapid component, with the slow component unchanged (Liberman et al., 1996). The time constant for the rapid DPOAE adaptation is comparable to that for the fast MOC effects and likely reflects the same MOC-OHC mechanism (Liberman et al., 1996). In the case of the DPOAE, however, the time constant for the slow effect is much shorter than that estimated for the slow MOC effect, being approximately 1 s, as reported here and elsewhere, in humans and experimental animals (cf., Liberman et al., 1996; Kim et al., 2001). The origins of the DPOAE slow, non-MOC effect is unknown, as is its relations with the slow MOC response. Previous work from Kujawa et al. (1995), have suggested it might be related to adaptive changes in the mechanical response of the OHC, which, like the MOC-mediated adaptation, are observed as decreases in the DPOAE.

4.5. Stimulation levels and MEM reflex

The level of the primaries employed in these experiments were chosen to maximize the level of the DPOAE as well as to facilitate comparisons with previous studies. The objective was to achieve a sufficiently high signal-to-noise ratio to permit an accurate estimation of the time course of the adaptation processes. Furthermore, DPOAE input-output curves measured for many subjects (not shown), showed a plateau at an f_2 level of approximately 65 dB SPL. These stimulation levels, however, might have resulted in an under-estimation of the MOC effects. Previous studies have indeed suggested that there is usually more efferent-induced suppression of OAEs at lower primary levels, which decreases as primary levels are increased (Mountain, 1980; Moulin et al., 1993). There are, however, other studies showing that MOC activity increases with stimulus level (Guinan and Stankovic, 1996). Such low level stimuli are difficult to use in human subjects for several reasons. Otoacoustic emissions in humans are typically smaller than those observed in animals, and are usually at a level 40 to 50 dB lower than the primaries used to elicit them (Moulin et al.,

1993), giving a low signal-to-noise ratio. In addition, animal studies are usually performed under either anesthesia or restraint, conditions that would minimize the noise background introduced by myogenic artifacts, which cannot be as easily controlled in awake human subjects. Moulin et al. (1993) reported that, in a group of 36 human subjects in which primaries at 60 dB SPL were employed, only 10 had measurable DPOAE emissions at 0.5 kHz and 14 at 1.6 kHz. In light of these technical restrictions, primaries in the range of 65 to 70 dB SPL remain, in our experience, the best compromise for DPOAE studies in humans.

A major confounding factor in the study of efferent activity is the possibility of contamination by MEM effects. It is usually difficult to draw the line clearly between level changes produced by MEMs and those related to medial efferents. Some studies even suggest that, at least in some species, effects very similar to those obtained with the medial efferents are actually due to MEM activity (Liberman and Guinan, 1998; Relkin et al., 2002). Several lines of evidence, however, support a role for the MOC in the presently observed adaptation effects. In animal studies, the rapid component of adaptation disappears upon midline sectioning of the MOC (Liberman et al., 1996; Kujawa and Liberman, 2001). Also, severing the stapedius muscle tendon in cats does not result in any significant change in the presently observed adaptation effects (Liberman et al., 1996).

Involvement of the MEM reflex in the results of this study is unlikely, since MEM thresholds for contralateral noise for several subjects were greater than 20 dB above the contralateral stimulus levels used. Monaural primaries of 70 dB SPL and contralateral broadband noise with a 60 dB SPL overall level can, therefore safely be considered to be subthreshold for this group of subjects.

4.6. Dependence on frequency

The MOC innervation of OHCs is not uniformly distributed along the length of the organ of Corti (Warr et al., 1986). In cats, rodents, and non-human primates, the number of MOC terminals per OHC increases from apex to base (Liberman et al., 1990; Sato et al., 1999). This is thought to contribute to the variation in the strength of MOC-induced suppression observed for fibers of different best frequencies (cf., Wiederhold and Kiang, 1970; Guinan and Gifford, 1988). In this work, estimates of the magnitude of adaptation as a function of f_2 frequency revealed no such systematic variation (Fig. 9). The absence of a correlation, however, could indicate that in humans, the distribution of MOC fibers is relatively uniform in the range of frequencies tested (between 1.5 and 5.0 kHz). Indeed, there is a relatively uniform MOC innervation of OHCs in this frequency region in other species (Warr et al., 1986; Sato et al., 1999). Alternatively, the relatively small number of tests at each frequency, coupled with the large intersubject variability could have made it difficult to extract such an effect in our data set. Further study in humans and non-human animals is necessary to clarify this issue.

5. Conclusions

In this study, we measured the adaptation of the DPOAE under different stimulus conditions as a noninvasive measure of the MOC activity in human subjects. The time course and the magnitude of the adaptation processes under monaural primary presentation conditions are in good agreement with the available data from humans (Kim et al., 2001). Comparisons of the human results with those obtained under similar monaural stimulus conditions in non-human animals (Liberman et al., 1996; Kujawa and Liberman, 2001; Kim et al., 2002) show that both follow a similar time course, yet the magnitude of rapid adaptation is substantially greater in cats (Liberman et al., 1996; Smith, unpublished observations). Likewise, new findings from the present work, showing a relative increase in the magnitude of rapid adaptation with binaural primary presentation, are in good agreement with comparable data recorded in cats (Liberman et al., 1996). Lastly, contralateral suppression, resulting from the presentation of broad band noise in the opposite ear, also followed a time course similar to that seen in studies in experimental animals (Liberman et al., 1996). The magnitude of the suppression, however, was smaller in humans than in cats. There are, however, quantitative differences, with MOC-induced adaptation and suppression estimates being relatively greater in non-human animals. The reasons for the apparent differences are uncertain, but might reflect differences in species and/or necessary difference in experimental protocol used in the non-human animal studies. Yet, taken as a whole, these data argue that MOC function in humans is qualitatively similar to that observed in nonhuman species.

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