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Spontaneous otoacoustic emission recordings during contralateral pure-tone activation of medial olivocochlear reflex

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We hypothesized that cochlear frequency discrimination occurs through medial olivocochlear efferent (MOCE)-induced alterations in outer hair cell (OHC) electromotility, which is independent from basilar membrane traveling waves. After obtaining informed consent, volunteers with normal hearing ($n = 10$; mean age: 20.6 ± 1.2 years) and patients with unilateral deafness ($n = 10$; mean age: 30.2 ± 17.9 years) or bilateral deafness ($n = 8$; mean age: 30.7 ± 13.8 years) underwent a complete physical and audiological examination, and audiological tests including transient evoked otoacoustic emission and spontaneous otoacoustic emission (TEOAE and SOAE, respectively). SOAE recordings were performed during contralateral pure-tone stimuli at 1 and 3 kHz. SOAE recordings in the presence of contralateral pure-tone stimuli showed frequency-specific activation out of the initial frequency range of SOAE responses. Basilar membrane motion during pure-tone stimulation results from OHC activation by means of MOCE neurons rather than from a traveling wave. Eventually, frequency-specific responses obtained from SOAEs suggested that OHC electromotility may be responsible for frequency discrimination of the cochlea independently from basilar membrane motion.

Keywords: otoacoustic emissions, spontaneous, hair cells, auditory, outer, cochlea, audiometry, pure-tone, medial olivocochlear efferents

Introduction

The separation of sound into component frequencies in the cochlea is thought to arise from the mechanical properties of the basilar membrane (2). Within the cochlea, the hydromechanical stimulus of sound leads to wave motions of the basilar membrane. These so-called "traveling waves" cause deflection of stereocilia on the apices of the hair cells. Deflection of a stereocilia bundle opens mechanically gated ion channels that allow potassium influx down through an electrochemical gradient from the potassium-rich endolymph fluid to cytoplasm of hair cell (14). Flow of potassium ions results in depolarization of the hair cell, which in turn stimulates afferent auditory nerve endings forming synapses with the basolateral aspect of the hair cell. A sound stimulus excites cochlear sensory epithelium by two mechanical forces: the pressure difference through the organ of Corti and the forces produced by contractility of outer hair cells (OHCs). Previous studies obtained important clues for the hypothesis that the mechanics of basilar membrane are determined by the intrinsic properties of OHCs (2). OHCs change their length in response to membrane potential alterations (21). OHC motility appears

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to actively amplify basilar membrane vibration, a process that is often referred to as cochlear amplification (2). OHCs are at the very center of cochlear amplification and frequency sensitivity (13, 17). A transmembrane motor protein called prestin was described in the lateral wall of OHCs. Prestin uses cytoplasmic anions as extrinsic voltage sensors and changes OHC length in response to membrane potential changes (11). In a recent study, prestin-based OHC motility was demonstrated to be necessary for mammalian cochlear amplification (12). Karavitaki and Mountain (22) elegantly demonstrated in gerbil cochlea that OHC contractions cause displacement of medial olivocochlear fibers and oscillatory fluid flow in the tunnel of Corti. They also suggested that such an OHC-driven fluid flow might be very important to cochlear function and hypothesized at the peak of the traveling wave, OHC contractions would push fluid into the tunnel of Corti, augmenting the original motion of the basilar membrane (22). Cochlear OHCs serve as both sensory receptors and biological motors (29). The contraction and relaxation properties of OHCs may play a significant role in discriminating the different frequency bands in the cochlea (22). The discovery of prestin supports this opinion (11, 12). The medial olivocochlear efferent (MOCE) branch synapses with OHCs, and the efferent pathway can be activated through electrical potential or a sound stimulus (18). Neurons of the MOCE system project to OHCs and convey signals that may control the sensitivity of the peripheral auditory system in a frequency-specific manner (9). Another type of hair cells, inner hair cells (IHCs), are considered to be stimulated by OHC-pushed fluid movement, which in turn leads to medial olivocochlear bundle induced inhibition of the first peak of the auditory nerve fiber response (19). IHCs are afferent transformers or primary receptors, whereas OHCs are efferent transformers or secondary receptors that obtain frequency selectivity.

Cochlear amplification of sound energy is evaluated by evoked otoacoustic emissions. Spontaneous otoacoustic emissions (SOAEs) are low-level acoustic signals measured in the human ear canal in the absence of any external stimulation. The presence of SOAEs suggests that cochlear hearing sensitivity is normal around the corresponding frequency band (5). A number of external conditions, such as pure-tones, ear canal pressure alterations, and contralateral acoustic stimuli affect SOAEs in various ways and are used for a better understanding of cochlear physiology. We studied the modification of SOAE recordings in the presence of contralateral pure-tone stimulation in humans. Interactions with pure-tones in the ipsilateral ear or contralateral stimulation with tonal or broadband signals were studied previously (10). In this study, we aimed to use pure-tones, i.e., 1 and 3 kHz, as contralateral acoustic stimuli. We hypothesized that efferent innervation of cochlea has a role in frequency discrimination function through OHC motility, rather than sound pressure-induced motility of basilar membrane.

Methods

Subjects

The study was designed and performed in accordance with the Declaration of Helsinki. After obtaining approval of the local ethical committee and informed consents, all volunteers underwent otoscopic examination, audiometry (subjective evaluation) and immitancemetry, and otoacoustic emissions (objective evaluation). Study group included individuals with normal hearing ($n = 10$; M/F, 4/6; mean age ± SD: 20.6 ± 1.2 years), unilateral deafness ($n = 10$; M/F, 6/4; mean age ± SD: 30.2 ± 17.9 years), and bilateral deafness ($n = 8$; M/F, 5/3; mean age ± SD: 30.7 ± 13.8 years). Exclusion criteria were tinnitus, middle-ear pathologies, or history of noise exposure and acoustic tumors.

Audiometric tests

Hearing threshold assessment and low-frequency audiometry (Interacoustic Clinical Audiometers AC-40, Denmark) were performed in a sound-isolated chamber. For high frequencies, Koss R/80 (Koss Co., USA) earphones were used, whereas for low frequencies, TDH-39 (Telephonics, USA) earphones were preferred. Airway-hearing thresholds were determined by routine audiological analyses for values between 0.5 and 8 kHz and by high frequencies of 8 and 10 kHz.

Immittancemetric test

Middle-ear pathologies and stapes reflexes were assessed by impedance audiometer (Interacoustic Audiometer AZ-7, Denmark) and a recording device (XYT Recorder AG-3, Denmark). The probe was set at 226 Hz and the pressure range of measurement was set at +200 to −400 daPa. Type "A" tympanograms (peak pressure: between +50 and −100 daPa) were accepted as normal.

Transient evoked otoacoustic emission (TEOAE) recordings

TEOAE tests were performed in a soundproof room using a Capella–Madsen adult OAE probe assembly (GN Otometrics A/S Taastrup, Denmark) fitted into the ear canal. The fast-screen menu option was used. Responses to clicks were windowed at 3–20 ms after stimulus onset and averaged following 2,080 repeated responses. The used stimulus was a non-linear, 40 μs click. Clicks were presented at 80 dB sound pressure level (SPL).

Spontaneus otoacoustic emission recordings

SOAEs were measured using Capella–Madsen adult OAE probe assembly (GN Otometrics A/S Taastrup, Denmark) fitted to the ear canal. Subjects were seated in a sound-isolated chamber. The equalized output of the system was flat (±5 dB) from 0.5 to 10 kHz with 12.7 Hz frequency resolution. The output from microphone was amplified. The response was subjected to spectral analysis. The SOAE sampling was based on averages of 500 accepted sweeps for the purpose of noise reduction. The grand average was calculated and the results were displayed. They were also characterized in terms of amplitude (dB SPL) and frequency (Hz). SOAEs were visually identified as narrow peaks in the frequency spectrum and through a cursor function.

Contralateral acoustic stimulus

Contralateral acoustic stimuli (Interacoustic Diagnostic Audiometer AD-17, Denmark) were delivered through a small transducer connected to the appropriate ear canal through E-A-R Tone 3A insert earphones (Aearo Co., Indianapolis, IN, USA). Contralateral pure-tone stimulus intensities of 50 or 60 dB SPL during testing time at 1 or 3 kHz were generated by the audiometer.

Results

Hearing threshold

In the control group, hearing threshold was within normal limits (i.e., below 20 dB HL) in all subjects. In the unilateral hearing loss group, hearing threshold was below 20 dB HL at the intact side, whereas it was above 120 dB HL at the affected side in all patients. In the total hearing loss group, hearing threshold was equal to or above 120 dB HL in all patients.

Stapes reflex threshold

In the control group, all subjects showed intact stapes reflex activation at both sides between 80 and 110 dB SPL for 1 and 3 kHz pure-tone stimuli. In the unilateral hearing loss group, stapes reflex was not generated at the affected side using ipsilateral 1 and 3 kHz pure-tone stimulation between 80 and 110 dB, whereas contralateral stimulation around 100 and 110 dB brought out stapes reflex. The stapes reflex threshold to ipsilateral 1 and 3 kHz stimuli was also elevated to 100–110 dB in the intact side of patients with unilateral hearing loss. In the total hearing loss group, ipsilateral or contralateral 1 and 3 kHz pure-tone acoustic stimuli between 80 and 110 dB SPL failed to activate stapes reflex in both ears. Stapes reflex threshold measurements are given in Supplementary Tables I–III.

TEOAEs

To assess OHC activation, TEOAE reproducibility data were given as the mean % value between 0.75 and 4 kHz. TEOAE responses in the control group showed that all participants had average response rate above 50%, which verified that OHC activation was within physiological limits. TEOAE responses in the unilateral hearing loss group showed that these patients had average response rates above 50% in the intact side, whereas they had average response rates below 50% in the affected side. TEOAE responses in the total hearing loss group showed that all patients had average response rates below 50%, which evidenced that OHCs of both ears were not functioning. TEOAE measurements are given in Supplementary Tables IV–VI.

SOAEs

We performed SOAE recordings under two different conditions. The first condition included routine SOAE recording as described elsewhere (7), whereas the second condition included presence of a contralateral pure-tone acoustic stimulus. In the control group, when pure-tone stimulus was applied contralaterally below the threshold value of the stapes reflex, the recorded ear showed frequency-specific responses. These responses were recorded at pure-tone frequency bands and out of the first SOAE (without contralateral stimulus) responses in Fig. 1. Figure 1 demonstrates a group of representative sample recordings of SOAE either in the presence or absence of contralateral pure-tone stimuli (1 and 3 kHz). Contralateral 1 kHz, 50 dB sound stimulus led to activation around the 1 kHz frequency band in SOAE. Similarly, 3 kHz, 50 dB sound stimulus led to activation around the 3 kHz frequency band. SOAE recordings either in the presence or absence of contralateral pure-tone (i.e., 1 and 3 kHz) stimuli were depicted in Fig. 2. In the absence of contralateral pure-tone stimulation, both graphics show activation around 9 kHz, which corresponds to the basal part of the cochlea. Interestingly, contralateral 1 kHz pure-tone stimulus resulted in activation mostly around 1 kHz frequency (Fig. 2A), whereas contralateral 3 kHz pure-tone stimulus leads to an activation around 3 kHz (Fig. 2B). In the total and unilateral hearing loss groups, we failed to observe any frequency-specific activation in the presence of contralateral pure-tone stimuli (Figs 3, 4, and 5). Interestingly, pure-tone acoustic stimuli applied to the intact ear did not lead to frequency-specific OHC activation in the affected side (Fig. 3). SOAE measurements are given in Supplementary Tables VII–IX.

Discussion

The main and novel finding of this study is that OHCs showed frequency-specific activity in the presence of pure-tone contralateral acoustic stimuli. OHCs may elongate and shorten in

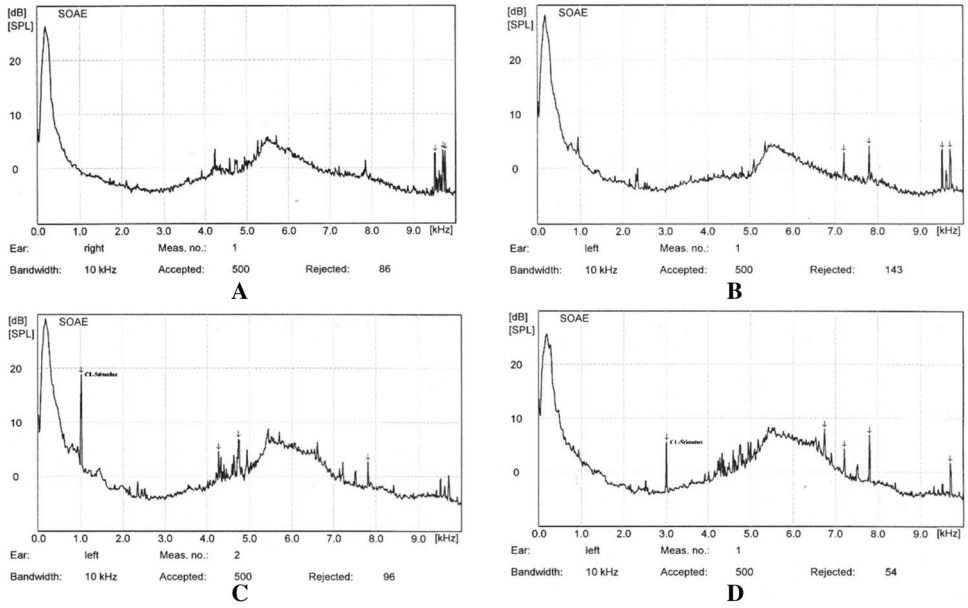

Fig. 1. Representative sample recordings of (A) SOAE right ear, (B) SOAE left ear, and (C and D) SOAE in the presence of contralateral pure-tone stimuli (1 and 3 kHz, respectively)

response to intracellular potential changes and these properties of OHCs are responsible for amplification of vibrations induced by a sound stimulus (2, 26). Active, non-linear mechanical processes present within the cochlea, interfered by the existence of OAE, stimulated further research into the function of the OHCs. The OHCs, with their efferent innervation, became the focus of attention for the source of mechanical energy. Isolated single OHCs have been demonstrated to contract as a result of electrical stimulation and altering the ionic environment of the bathing solution (4). Fast changes in OHC shape result from ATP-independent cellular electromotility (15) based on the activity of motor membrane protein prestin (33). Prestin is a direct electromechanical transducer providing the force required for cochlear amplification (12). The contraction and relaxation properties of OHCs may play a significant role in discriminating the different frequency bands in the cochlea (22). MOCE branch synapses with OHCs, and the efferent pathway can be activated through electricity or a sound stimulus (18). The activation of these medial efferents can change OHC motile responses (9) and convert signals that are capable of controlling the sensitivity of the peripheral hearing system in a frequency-specific manner (18). IHCs, on the other hand, convey auditory information to the brain (11). It had been well established that the IHCs were detectors of movement in the organ of Corti, directly stimulating the auditory nerve (5). The IHCs are therefore considered to be primary "sensory" cells of the cochlea, whereas OHCs are termed "effectors," applying a mechanical input to basilar membrane motion. Terminals of olivocochlear bundle innervate OHCs and form a feedback system, which can modulate the gain of the cochlear amplifier (29). This suggested us that a frequency-specific reflex arc with its anatomical connections may exist between IHCs and OHCs. OHCs are targets of efferent innervation originating from the brainstem and activation of OHCs results in elevation of hearing threshold, i.e., a decrease in the systems' sensitivity. The main neurotransmitter of this efferent system is acetylcholine (15, 18). Isolated OHC recording

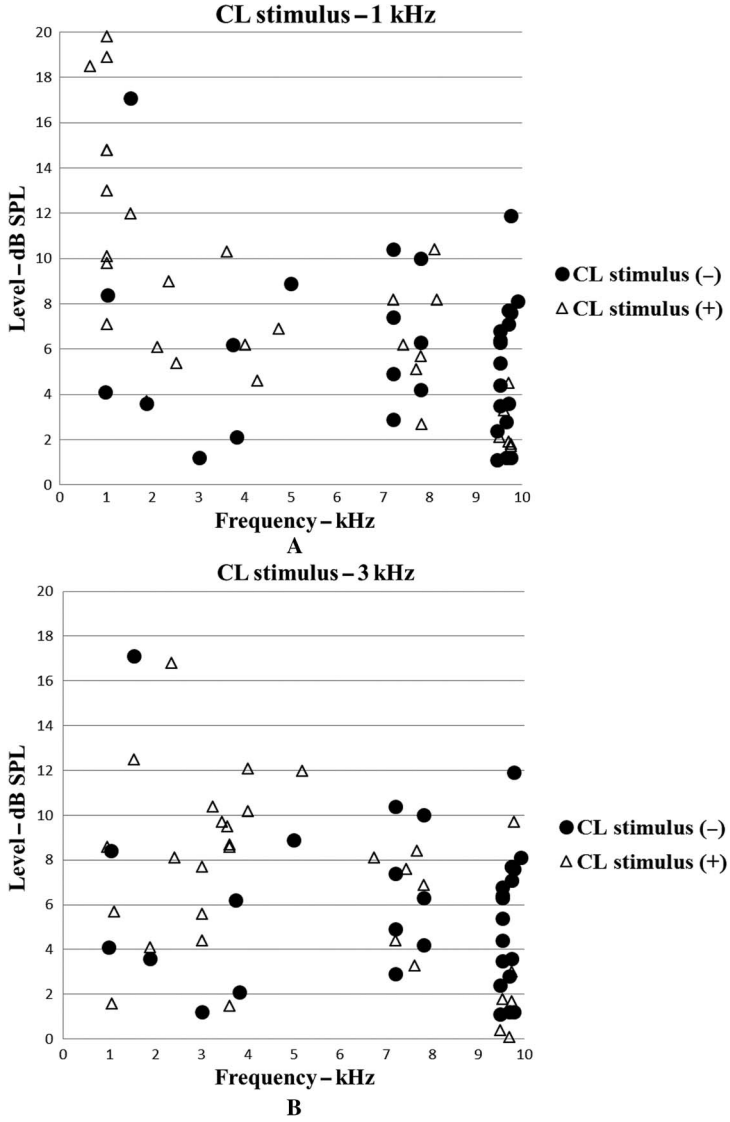

Fig. 2. SOAE recordings either in the presence or absence of a contralateral pure-tone [i.e., (A) 1 and (B) 3 kHz] stimulus (normal hearing). In the absence of contralateral pure-tone stimulation, both graphics show an activation around 9 kHz that corresponds to basal part of the cochlea. Interestingly, (A) contralateral 1 kHz pure-tone stimulus resulted in an activation mostly around 1 kHz frequency, whereas (B) contralateral 3 kHz pure-tone stimulus led to an activation around 3 kHz

studies have provided functional evidence for cholinergic receptors localized around the base of the cell where the efferent synapses are located (27, 31). The olivocochlear bundle or the auditory efferent system originates in the brainstem and projects to the inner ear. Although the anatomy and physiology of the efferents are relatively well known, their functional roles in auditory perception remain to be elucidated (31). Initially, OHCs and IHCs were thought to differ in shape and number but to have similar functions. Studies on the sensory and supporting cells and on the innervation revealed that these two cell types differ dramatically. IHCs show primarily afferent innervation, whereas OHCs show efferent innervation. Olivocochlear bundle medial efferent branch makes synapses with OHCs and can be activated through electrical and sound stimuli (5, 10). Efferent innervation of OHCs seems

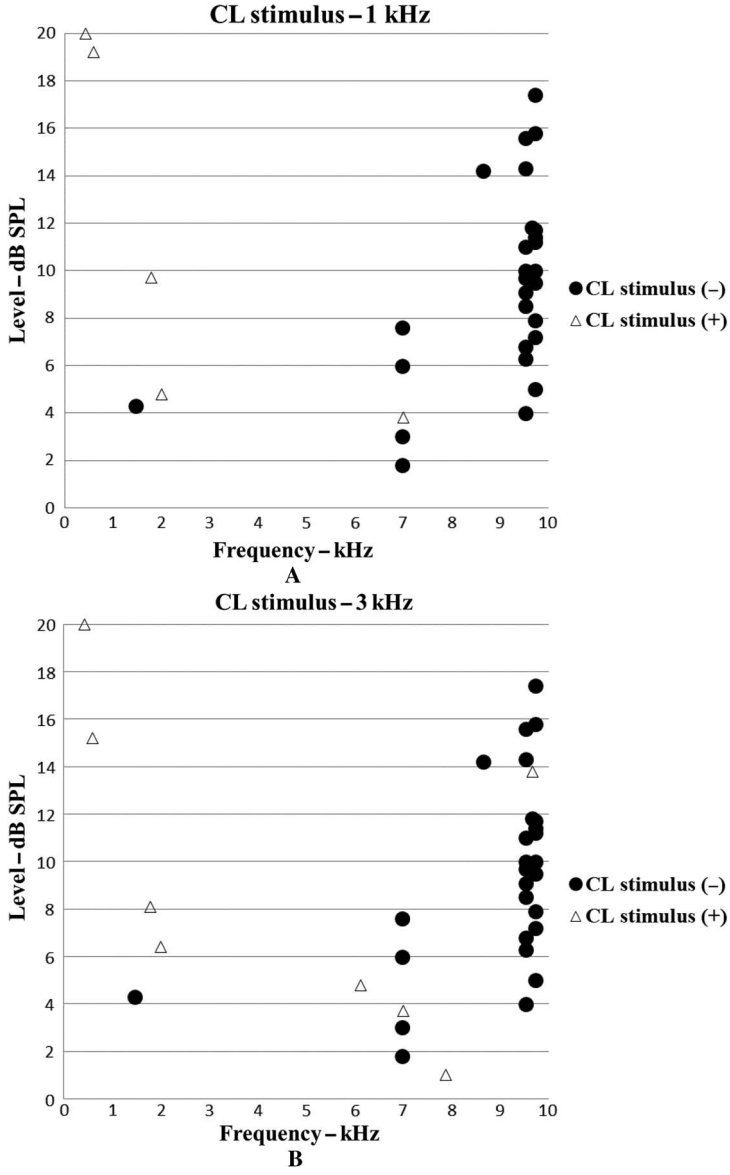

Fig. 3. SOAE recordings either in the presence or absence of a contralateral pure-tone [i.e., (A) 1 and (B) 3 kHz] stimulus (unilateral hearing loss). Contralateral pure-tone stimulation was applied to the intact ear, neither of the graphics lead to an activation around 1 and 3 kHz on the affected side

to modify the mechanical properties of the organ of Corti and basilar membrane (9, 27). This modification found in the organ of Corti is necessary for motion amplification at low SPLs (30). At different SPLs, basilar membrane vibrates in different frequency levels. At 30 dB SPLs, peak reticular lamina movements are twofold larger than those of the basilar membrane, a difference that becomes smaller as the stimulus level increases in the living cochlea. OHC motility is absent in postmortem period, which lacks cochlear amplification, and there is no phase or amplitude difference between the reticular lamina and basilar membrane in the postmortem period (32).

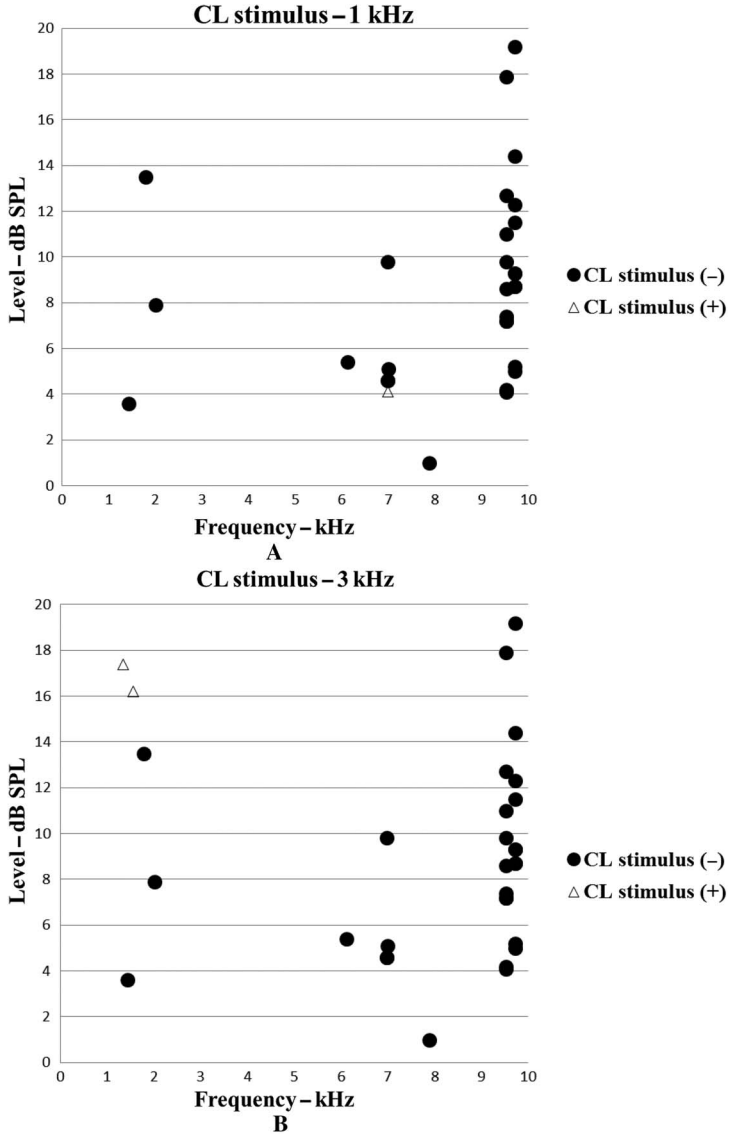

Fig. 4. SOAE recordings either in the presence or absence of a contralateral pure-tone [i.e., (A) 1 and (B) 3 kHz] stimulus (unilateral hearing loss). Contralateral pure-tone stimulation was applied to affected side, both graphics did not lead to an activation around 1 and 3 kHz in the intact ear

Pure-tone-induced frequency-specific activation in SOAE suggested a neural information transfer from one ear to the other. Furthermore, frequency discrimination may not be the result of basilar membrane vibrations, it may rather occur through a reflex pathway. In this study, we tried to obtain evidence for components of this hypothetic reflex arc: IHC as the receptive organ, connection from IHCs to superior olivary complex as the afferent way, synaptic connections in superior olivary complex as the center of reflex, connection from superior olivary complex to OHCs as the efferent way, and OHCs as the effector organs (6). This reflex activation occurs in all cochlear segments and uses IHCs, OHCs and the anatomic connections between them. Olivocochlear neural activation may play a key role in

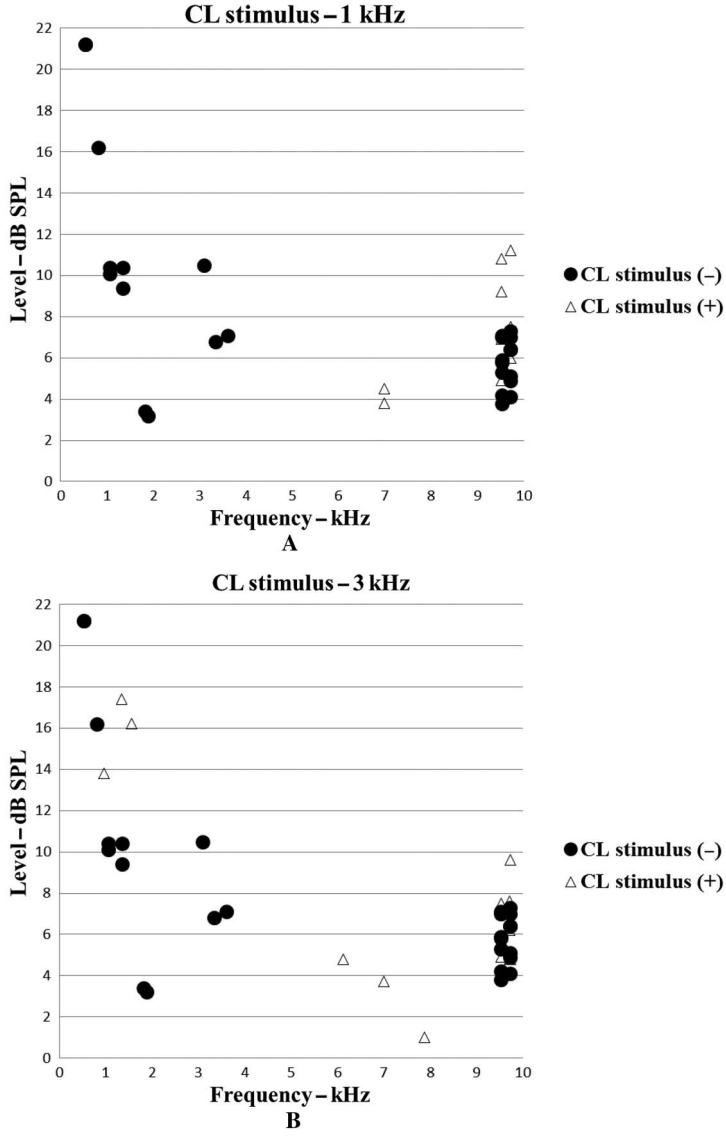

Fig. 5. SOAE recordings either in the presence or absence of a contralateral pure-tone [i.e., (A) 1,000 and (B) 3,000 Hz] stimulus (total hearing loss). In the presence of contralateral pure-tone stimulation, there was no activation around 1 and 3 kHz

this frequency discrimination with OHCs. Frequency-specific responses of OHCs suggest that the frequency information was received by the contralateral ear and then sent to the opposite ear. Therefore, OHCs in the ear that we recorded by SOAEs showed contractions in accordance with frequency information. Therefore, while initial SOAE recordings were around the frequency band of 9 kHz, they showed activity around the frequency band of corresponding stimuli in the presence of a contralateral pure-tone stimulus. We recorded OHC activity around 1 kHz, when the pure-tone stimulus was 1 kHz, and we recorded OHC activity around 3 kHz, when the pure-tone stimulus was 3 kHz. Previous studies demonstrated that contralateral sound suppressed both transiently evoked emissions (8) and distortion product emissions (23) in awake, human subjects. This suppression in response

implies that the medial olivocochlear neurons alter the activity of the OHCs in such a way as to reduce the production of otoacoustic emissions. Recent studies of Berezina-Greene and Guinan (3) demonstrated that electrical excitation of MOCE fibers most often decreases stimulus-frequency otoacoustic emissions (SFOAEs), while it sometimes enhances SFOAEs in the frequency regions that are away from response dips. We demonstrated a suppression in the amplitude of spontaneous activity around 9 kHz, besides that activity, we also recorded frequency-specific activation, which was dependent on the frequency of contralateral pure-tone stimuli. The most noticeable changes in SOAEs are frequency shifts upward by 2–20 Hz. It is widely believed that such changes occur as a result of stimulation of the crossed efferent pathways, which synapse directly on the OHCs (18). By using pure-tones and obtaining activations at the same frequency bands, we obtained strong evidence for such a crossed efferent pathway conveyance.

These frequency-specific responses were not due to the activation of an acoustic reflex arc, as the stimulus intensity was quite below the acoustic reflex threshold. Furthermore, in a previous study, Mott et al. (25) demonstrated that similar changes evoked by a contralateral tonal stimulus were not due to acoustic reflex activation. They measured contralateral acoustic reflex thresholds (CART) and observed longer latencies for supra-CART levels than for sub-CART levels; SOAE frequency and amplitude shifts observed during reflex activation conditions were larger than those observed during non-reflex conditions, and finally they measured reflex decay at 4,000 Hz and found that the reflex decayed 50% within 7 s and 100% within 20 s. However, under prolonged contralateral acoustic stimulus conditions SOAE frequency was elevated for the entire 4 min of the stimulation period. In another study, sub-CART stimuli lead to the suppression of distortion product autoacoustic emission responses without activating an acoustic reflex and signal crossover (28). In this study, unilateral and bilateral hearing loss groups failed to show frequency-specific activation in SOAE, which provided another evidence for neural transfer of frequency information from one ear to the other. Otherwise, frequency-specific activity would be present in these groups.

In conclusion, a fast reflex-type pathway, not involving the higher centers of the brain, has already been suggested to be implicated in the suppression of transient emissions, by the onset of contralateral suppression taking around 20 ms to occur (20). Althen et al. (1) demonstrated in gerbil cochlea that frequency-specific regulation of the cochlear amplifier was mediated by MOCEs that were activated by contralateral acoustics stimulus. Recently, Lamas et al. (24) demonstrated that acoustic input and efferent activity regulate the expression of prestin at both transcriptional and post transcriptional levels. Another study showed that the OHC-type II spiral ganglion neurons drive the MOCE reflex-mediated control of the cochlear amplifier (16).

We obtained further evidence for such a neural pathway that conveys frequency information to the contralateral ear and evoke frequency-specific activation in the OHCs in the presence of contralateral pure-tone stimuli. We also suggest that frequency discrimination in all cochlear segments is a function of OHC electromotility stemming from efferent innervation.

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