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How Do the Medial Olivocochlear Efferents Influence the Biomechanics of the Outer Hair Cells and thereby the Cochlear Amplifier? Simulation Results.

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Abstract. The bottom-up signal pathway, which starts from the outer ear and leads to the brain cortices, gives the classic image of the human sound perception. However, there have been growing evidences in the last six decades for existence of a functional descending network whereby the central auditory system can modulate the early auditory processing, in a top-down manner. The medial olivocochlear efferent fibers project from the superior olivary complex at the brainstem into the inner ear. They are linked to the basal poles of the hair cells by forming synaptic cisterns. This descending network can activate nicotinic cholinergic receptors (nAChR) that increase the membrane conductance of the outer hair cells and thereby modify the magnitude of the active force generated inside the cochlea. The aim of the presented work is to quantitatively investigate how the changes in the biomechanics of the outer hair cells, caused by the efferent activation, manipulate the cochlear responses. This is done by means of a frequency-domain biophysical model of the cochlea [12] where the parameters of the model convey physiological interpretations of the human cochlear structures. The simulations manifest that a doubling of the outer hair cell conductance, due to efferent activation, leads to a frequency-dependent gain reduction along the cochlear duct with its highest effect at frequencies between 1 kHz and 3.5 kHz and a maximum of approximately 10 dB gain reduction at 2 kHz. This amount of the gain inhibition and its frequency dependence reasonably agrees with the experimental data recorded from guinea pig, cat and human cochleae where the medial olivococlear efferents had been elicited by broad-band stimuli. The simulations also indicate that the efferent-induced increase of the outer hair cell conductance increases the best frequency of the cochlear responses, in the basal region. The presented simulations quantitatively confirm that activation of the medial olivocochlear efferents can biomechanically manipulate the cochlear responses, in a top-down manner, by inhibiting the gain of the cochlear amplifier as well as altering the frequency-position map (tuning pattern) of the cochlea.

INTRODUCTION

The processing of incoming sound is believed to initiate in the organ of corti [2]. It becomes more complex as the sound-induced signals ascend toward more central parts of the auditory system and brain cortices [2, 11]. Over six decades ago Rasmussen discovered the olivocochlear efferents, fiber projections that descend from the superior olivary complex in the brainstem toward the inner ear [9]. It is well known today that hearing involves various ascending (afferent) and descending (efferent) pathways interacting with each other on different levels [10, 11, 13].

Olivocochlear efferents are categorized into two major groups: 1) Lateral olivocochlear (LOC) neurons that terminate on the inner hair cell - auditory nerve (IHC-AN) synapse, and 2) Medial Olivocochlear (MOC) neurons that form a synaptic cistern on the outer hair cells (OHCs). Unlike the LOC system which is less known, the physiology of the MOC system has been extensively studied [1, 2 ,3, 7]. The activation of the MOC efferents triggers a morphological chain of actions which leads to the release of acetylcholine (ACh) on its synaptic cistern formed at the basal pole of the OHCs [3]. This activates the nicotinic receptors that allow calcium ions to flow into the OHC and increase the OHC basolateral conductance [5]. The MOC mechanism is highly time-variant consisting of fast and slow adpations [1]. The presented simulations apply to the fast MOC responses which can occur on the order of 10 ms [1, 3]. This is fast enough to manipulate the operation of the cochlear system almost in synchrony with incoming sound.

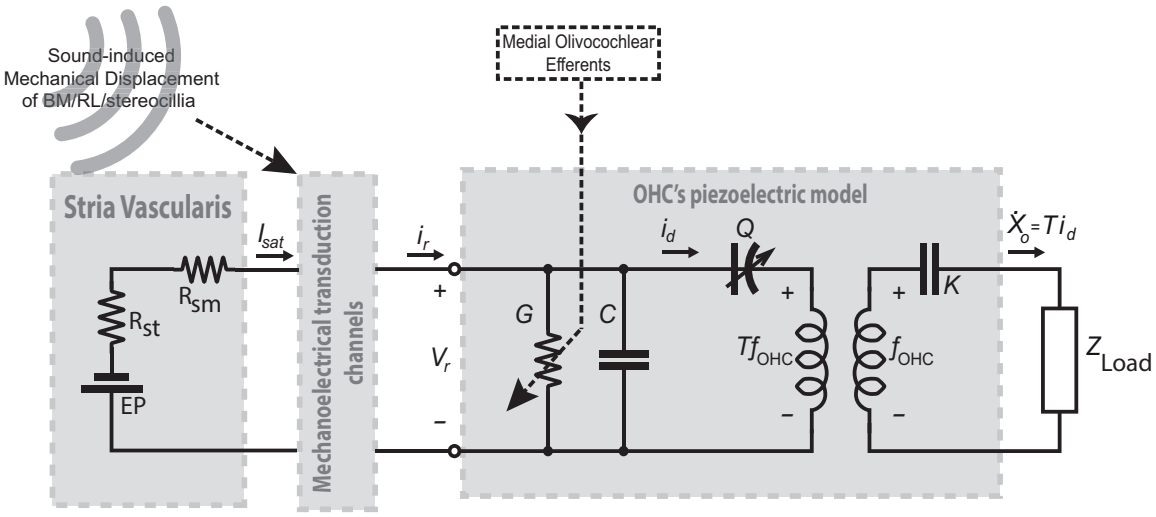

FIGURE 1. A model for the active force generation mechanism inside the mamalian cochlea. The sound-induced displacement of the stereocillia induces a receptor current which triggers the OHC somatic motor leading to production of mechanical force. To simulate the effect of the efferent-induced increase of the OHC conductance on the magnitude of the cochlear amplifier, G is regarded as the variable in presented simulations.

MODELING METHOD

Saremi and Stenfelt [12] presented a linearized frequency-domain model of the mammalian cochlea where each parameter represented a specific biophysical property of the human cochlear structures. The idea is to use physiologically-justified parameters, as far as possible, to be able to simulate how manipulation of certain structures, due to metabolic changes or external disturbances, would modify the characteristics of the cochlear responses. A thorough description of the auditory model can be found in [12]. In what follows, a short overview of the model is given.

The passive structures are modeled with the classic mass-spring-damper combination and are longitudinally coupled with each other forming the transmission line in [12, Fig. 1] which extends from base to apex. The active force generation mechanism is modeled using the schematic shown in Fig. 1 which comprises three parts: 1) Stria vascularis, 2) Mechanoelectrical transduction (MET) channels and 3) The OHC somatic motor. The strial vascularis is modelled by a battery (EP) together with R_{st} and R_{sm} which represent the resistance of the stria vascularis and scala media, respectively. Stria vascularis provides the MET channels with the necessary electrical charge (i_{sat}) to function optimally. The sound induced displacement of the stereocillia opens the MET gating channels which induces a receptor current (i_r). This current is believed to hyperpolarize the OHC's membranous body and trigger the OHC elctromotility (somatic motor). The OHC somatic motor is modelled here by a piezoelectric element [6] which converts the gating current (i_d) into mechanical force (f_{OHC}) with the piezoelectric transform ratio of T.

$$X_o(j\omega) = \frac{\frac{T(\alpha_d + \alpha_v . j\omega)}{c_g}}{j\omega . c_g + (G + j\omega . C)[1 + T^2 . c_g (K + j\omega . Z_{load})} \tag{1}$$

Equation (1) describes the active mechanical force generated by the circuit shown in Fig. 1 as a function of the stereocillia displacement. α_d and α_v are displacement-sensing and velocity-sensing coefficients, respectively, and are dependent to the micromechanics of the MET channels as described by Eq. (6) in [12]. Furthermore, G and C denote conductance and capacitance of the OHC membranous body and c_g represents the non-linear gating capacitance of the OHC. Also, the static OHC axial stiffness is denoted by K. The active force generated by this system acts on Z_{load} which consists of two parallel loads: the basilar membrane (BM) on one side, and reticular lamina (RL) on the other side, as depicted in [12, Fig. 2]. This eventually boosts the magnitude of the vibration that is propagating along the transmission line.

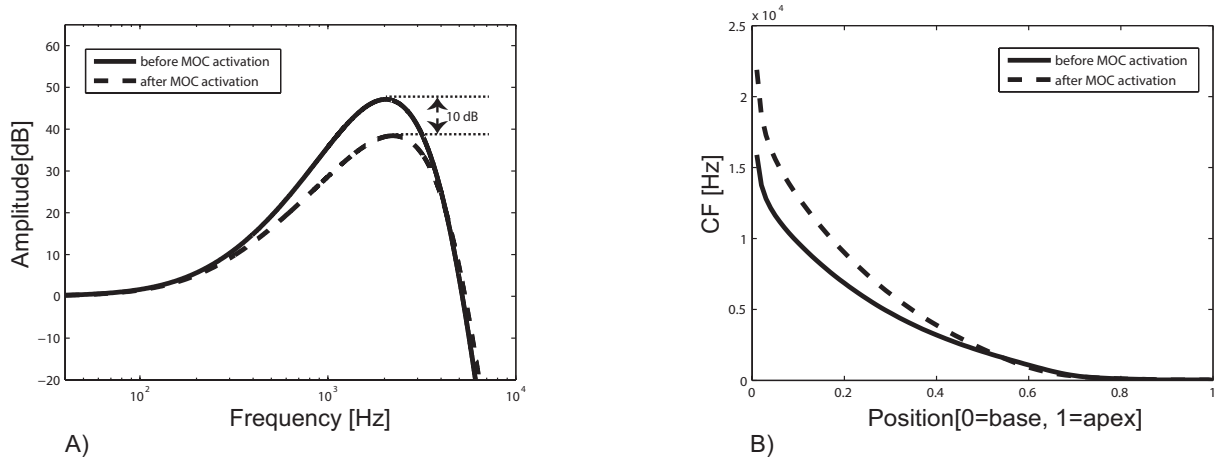

FIGURE 2. A) The gain of the cochlear amplifier in the middle of the cochlear duct for two cases: before the fast MOC activation and a few milliseconds after the fast MOC activation. B) The position-frequency map of the cochlea for the above two cases.

SIMULATIONS

As described in the introduction, the activation of the MOC efferents allows additional influx of electrically-charged Ca^{2+} into the OHC which induces inhibitory postsynaptic currents (IPSCs) that consequently increase the conductance of the OHC body (G in Fig. 1). Oliver et al. [8] acutely dissected OHCs from 2-3 week old rats and applied 10 uM Ca^{2+} and nAChR-midiated currents to the OHCs with duration of 5, 10 and 50 ms, and the corresponding induced currents were recorded at a holding voltage of -81 mV.

Their results [8, Fig. 4] demonstrated that the induced IPSC rose to approximately 500pA within few milliseconds (the fast MOC response). This amount of induced IPSC is comparable to the maximum receptor current induced by opening of the MET channels, which is also at the range of 500pA [6]. Therefore, it is plausible to assume a two-fold increase of the OHC conductance due to this amount of additional IPSC. As shown in Fig. 1, the conductance of the OHC (G) is taken as the variable to simulate its increase on the gain of the cochlear amplifier. Here, G is assumed to increase by 100% due to the fast activation of the MOC, in line with the experimental data [8].

Simulation Results

According to Eq. (1), the increase of G inhibits the magnitude of the active force [proportional to $X_o(j\omega)$] generated by the OHC electromotility. Figure 2 (a) shows the magnitude of the cochlear frequency response (the gain of the cochlear amplifier) in the middle of the duct (position=0.5) to low intensity stimuli before the MOC activation, and a few milliseconds after the MOC activation when the induced IPSC is maximum. Figure 2 (a) demonstrates that the peak magnitude of the frequency response decreases more than 19% from 47.1 dB to 37.5 dB, due to the MOC activation. This indicates an approximately 10-dB peak-to-peak inhibition in the gain of the cochlear amplifier.

Figure 2(b) depicts the position-frequency map (tuning pattern) of the cochlea for these two cases. It shows that the best frequency (BF) of the cochlear partition response has notably increased (moved toward apex) in the basal half of the cochlear duct (positions 0 to 0.5). In the apical half of the duct (positions 0.5 to 1), however, the tuning pattern is almost intact.

Figure 3(a) summarises these MOC-induced peak-to-peak reductions as a function of frequency. It demonstrates that the gain reduction begins at 4 dB for low-frequency stimuli, becomes most dominant at frequencies between 1 to 3.5 kHz with its maximum of over 10 dB at 2 kHz. This range where the gain reduction is maximal (1 to 3.5 kHz) matches with the frequency range at which the cochlear amplification is highest. Figure 3(a) also depicts that a broad-band MOC activation yiels a frequency-dependent inhibition of the cochlear gain.

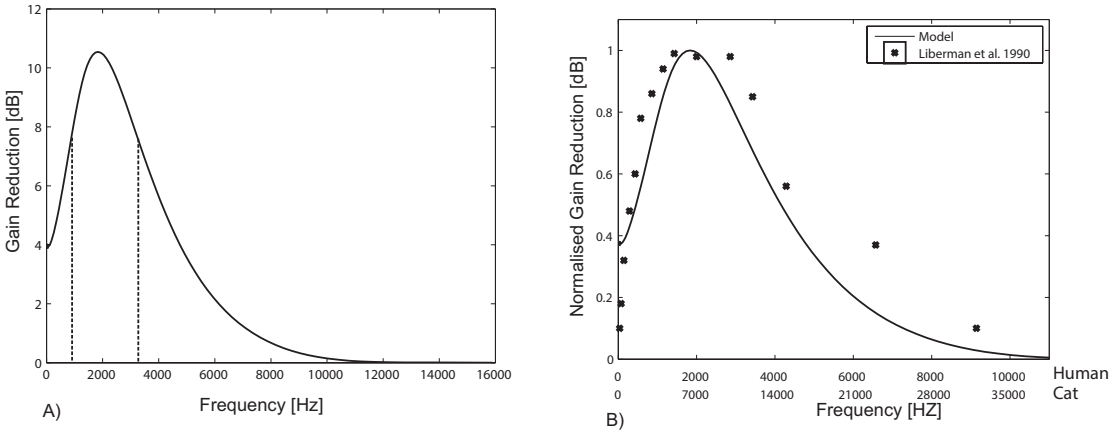

FIGURE 3. A) The MOC-related gain reduction of the Cochlear amplifier as a function of CF. The dashed lines indicate the frequency range (1 to 3.5 kHz) where the MOC effect is highest. B) Normalised gain reduction, predicted by the model, compared with Liberman et al. 1990 data recorded inside the cat cochleae [5].

Comparison with Experimental and Clinical Data

The regular experimental approach to activate the MOC efferents *in Vivo* is to place stimulating electrodes at the floor of the fourth ventricle [1,3]. Cooper and Guinan [1] stimulated the MOC efferents in 24 guinea-pigs by presenting 300*us*-wide pulses and simultaneously recorded the BM motion at the basal turn of the cochleae using laser interferometer. The results were compared to the BM motions before the MOC activation which indicated a 13-dB inhibition in the BM motion due to fast MOC activation.

Liberman et al. [5] measured the innervation of the OHCs along the cat's cochlear duct and showed that the strength of the efferent response elicited by broad band stimuli follows the same trend as a function of the characteristic frequency (CF). Figure 3 (b) illustrates these cat data versus the MOC-induced gain reduction predicted by the model, as a function of the CF. To be able to make this comparison, the gain reductions predicted by the model [Fig. 3(a)] have been normalised to a 0-1 scale and shown in Fig. 3(b).

Furthermore, Mishra and Lutman [7] stimulated the MOC efferents in 18 normal hearing young humans using 30-dB SL contralateral broad band noise (0.125-12 kHz) and recorded the Click-Evoked OtoAcoustic Emissions (CEOAEs) simultaneously. OAEs are produced in the inner-ear and their level is an important physiological indicator of the underlying OHC gain properties of the cochlea [4]. Their results [7] demonstrated an average 17.21% decrease in the CEOAE level due to the contralateral activation of the MOC efferents, which is comparable with the simulation results here [Fig. 2(a)] showing a 19% gain reduction in the middle of the cochlea.

DISCUSSION

As stated earlier, the most common experimental technique to activate the fast MOC efferents in animals is to electrically stimulate the medial axons at the floor of the fourth ventricle in the brainstem [1, 10]. This generally activates the entire olivocochlear bundle innervating the entire cochlear length. Similarly for humans, the common clinical approach is to present broad band contralateral stimuli to activate the efferent network [3]. However, these experimental and clinical methods are unable to stimulate limited number of efferents innervating specific cochlear regions, which might be the real-life case. To allow comparison with existing experimental data, we therefore decided to change the conductance of the OHCs (represented by G in Fig. 1) uniformly across the length of the cochlea. Even so, as Fig. 3 illustrated, the MOC reduction of the gain was prominently frequency-dependent. Furthermore, it is important to note that the simulations presented in this study are valid for a specific time shortly after the MOC activation (corresponding to the fast MOC response). Because the MOC mechanism is highly time-variant [1, 3], time-domain models are required to simulate the time-course of the MOC-induced effects, a feature that is not possible to analyze in the present frequency-domain model.

The current study focused on investigating the effect of fast efferent-induced increase of the OHC conductance on the

gain of the cochlear amplifier. However, it has been experimentally observed that the MOC activation also reduces the endocochlear potential (EP) by approximately 3 mV. Although this small reduction may have only a minimal effect on the OHC somatic motor and hence ignored here, Saremi and Stenfelt [12] quantitatively demonstrated how the EP reduction significantly inhibits the firing rate of the auditory nerve (AN) fibers which can have a significant impact on the intensity and temporal coding of the sound. Furthermore, very little is known about the physiology of the LOC efferents that synapse on the IHC-AN and how they might manipulate the intensity and temporal coding of the cochlear responses. Finally, there are descending circuits which terminate on central structures of the auditory system, such as inferior colliculus [10]. If the main task of the auditory efferents is to modulate the incoming signal by manipulating the cochlear responses only, then what is the role of such centrally-terminated efferents?

CONCLUSION

It is well known today that higher cognitive processes can modulate the auditory periphery via descending pathways and control what auditory information reaches the brain cortices [10, 11, 13]. In the presented work, the effect of biomechanical changes, induced by MOC efferents, on the gain of the cochlear amplifier was investigated by means of a physiologically-based model. The simulation results confirm that a twofold increase of the OHC conductance along the cochlea, due to fast MOC activation, leads to inhibition of the cochlear amplifier. The simulations demonstrated that the amount of this gain inhibition is frequency-dependent with a maximal effect (at the range of 8 to 11 dB) for frquencies between 1 and 3.5 kHz. This was shown to reasonablly agree with the experimental data recorded from guinea pig, cat and human cochleae [1, 5, 7] where the MOC efferents had been externally elicited by broad-band stimuli.

ACKNOWLEDGMENTS

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