THE AGE-RELATED STRIAL DEGENERATION INHIBITS THE INNER HAIR CELL-AUDITORY NERVE COMPLEX: A COMPUTATIONAL INVESTIGATION.

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1 Introduction

The stria vascularis is a vascularized tissue at the lateral wall of the mammalian cochlea which injects electrically-charged potassium ions (k+) into the scala media [1]. This is directly linked to the 89-mV endocochlear potential (EP) measured inside the healthy human cochlear duct [1]. Because of the age-related degeneration of the stria vascularis, the k+ recycling is impaired and is not capable of maintaining the optimal EP, leading to a common type of hearing loss known as the metabolic presbyacusis [2].

The effects of the age-related deficits of the EP on the outer hair cell (OHC) motile forces and the associated decline of the 'cochlear amplifier' have been investigated both experimentally [3] and theoretically [4]. Nevertheless, much less is known about the additional effects of the age-related EP reduction on the sensory inner hair cells (IHCs) function. Here we quantitatively analyze the effects of the EP reduction on the IHC membrane potential and, thereby, the auditory nerve (AN) neurotransmitter release by means of two physiologically-based computational models of the IHC [5] and the AN synapse [6].

2 Methods

2.1 Modeling Method

Figure 1 shows the two publicly-available models which have been integrated and used for this computational analysis. The IHC model used here [5] is a lumped-element biophysical model that consists of cell-level parameters such as the capacitance and conductance of the cell body, the mechanical sensitivity of the potassium channels, and the EP. The input to this model is the IHC stereocilia displacement and its output is the IHC membrane potential.

The auditory synapse model used here [6] to simulate the neuronal activity of the AN is developed according to the parameters based on the time-varying three-store diffusion synapse model. The model is excited by the IHC membrane potential and gives the neuronal spikes on the high spontaneous rate (HSR) AN fibers in its output. Based on the spikes, the post-stimulus time histograms (PSTH) can be estimated for a bin width of 0.4 ms.

2.2 Definition of the Hearing Threshold

It is believed that the hearing threshold occurs in the human auditory system at a 2-nm displacement of the IHC stereocilia [1]. This amount of displacement is regarded as the reference intensity (0 dB) in this analysis. Accordingly, the IHC model is excited by a sinusoid at 0 dB and the output of the AN model is assessed. Due to the probabilistic nature of the neuronal activity, the simulation is repeated five times for any given level. The level of the input is increased with steps of 1 dB until a spike is formed at the output of the AN model, in all five repetitions (PSTH=1). The corresponding level that caused this is regarded as the hearing threshold. In other words, the threshold is defined as the minimum stimulus intensity that yields a firing probability of 100% on the HSR AN fibers.

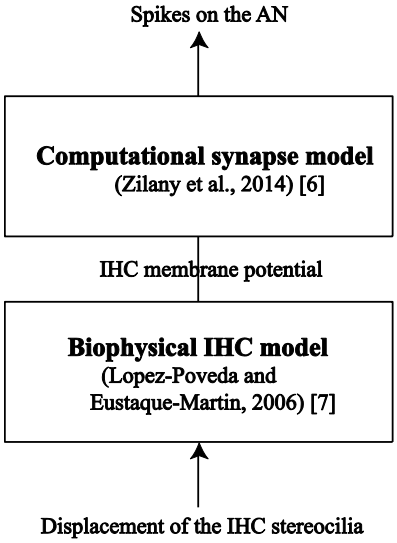

Figure 1: Our modeling approach consists of a biophysical model of the IHC [5] and a computational model of the AN synapse [6]. These two models were integrated to simulate the AN neuronal activity in response to the displacement of the IHC stereocilia.

2.3 Simulation Method

The EP parameter in the IHC model is set to -89 mV and the model is excited by a sinusoid at 0 dB. The amplitude of the sinusoid is increased until the hearing threshold is reached. This is repeated for characteristic frequencies (CFs) from 0.1 to 6 kHz to estimate the hearing thresholds for the condition in which the EP is optimal (healthy condition).

The EP parameter in the IHC model is then decreased to 50% of its optimal value and the hearing thresholds are assessed for CFs between 0.1 and 6 kHz, according to the procedure explained above. These hearing thresholds are compared with the thresholds estimated in the healthy condition, to yield the corresponding threshold elevations (hearing loss) caused by the EP reduction.

3 Results

Figure 2(A) shows that the hearing thresholds vary between 0 and 4 dB for the healthy cochlea (Mean=0.44 dB, SD= 0.84 dB). This average hearing threshold (0.44 dB) corresponds to 2.1 nm displacement of the IHC stereocilia. Figure 2(A) also illustrates the hearing thresholds for the presbyacusis condition (EP=-44.5 mv) which show a frequency-dependent elevation. Figure 2(B) shows the hearing loss associated with the hearing threshold elevations seen in Fig. 2(A). The hearing loss was calculated by subtracting the hearing thresholds of the presbyacusis cochlea from those of the healthy cochlea.

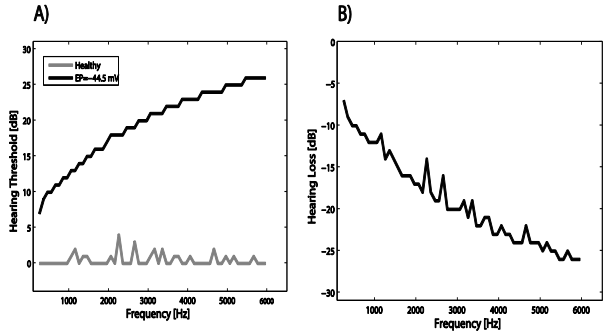

Figure 2. A). The hearing thresholds for two conditions : (i) the healthy condition (EP=-89 mV), and (ii) the EP reduced to half of its optimal value (EP=-44.5 mV). **B)** The hearing loss corresponding to the threshold elevations seen in panel A.

4 Discussion

Our simulations show that the IHC-related hearing threshold elevations caused by a 50% decrease of the EP are frequency dependent as the threshold elevations increase from 6.5 dB at 100 Hz to 27 dB at 6 kHz. This is in general agreement with the observed high-frequency profile of presbyacusis [2] [3] [4].

Due to the lack of explicit experimental data on the AN activity in response to the IHC stereocilia displacement, our simulations have not been compared to any experimental references, and therefore, remain solely theoretical in nature. However, the models used here have been validated by successfully reproducing various experimental data in other studies [5] [6]. This makes the model predictions presented here noteworthy.

The presented predictions suggest, at least theoretically, that the EP decline caused by the age-related degeneration of the cochlear lateral wall affects the hearing thresholds by inhibiting the IHC-AN functions while the OHCs and IHCs were totally intact and healthy. This is opposed to the minimalist view that reduces the origins of all cochlear hearing losses to merely structural lesions of the OHCs and IHCs, undermining the potential roles of the pathologies in the stria vascularis.

5 Conclusion and Future Works

Several investigations have quantified the effects of the age-related EP reduction on the decline of the motile active forces generated by the OHCs, leading to the deficit of the cochlear amplification, and thereby hearing threshold elevations [3], [4]. They showed that a 50% decrease of the EP leads to a sloping high-frequency hearing loss that reaches approximately 40 dB at 4 kHz.

Here, we studied an additional contribution of the EP reduction to the hearing loss, using a computational model of the IHC-AN complex (Fig. 1). The hearing thresholds, defined as the minimum displacement of the IHC that results in a 100% probability of the neurotransmitter release on the AN, were assessed for the healthy condition (EP=-89 mV) and the presbyacusis condition (EP=-44.5 mV). These two hearing thresholds were subtracted from each other to give an estimate of the hearing loss associated with the EP decrease.

The presented results demonstrate that a 50% decrease of the EP suppresses the IHC-AN functions and yields threshold elevations that increase from 6 dB at 100 Hz to 27 dB at 6 kHz. This additional IHC-related hearing loss is independent of the OHC-related hearing loss, caused by the decline of the cochlear amplification due to the EP reduction. In other words, our results suggest that age-related EP reduction not only restrains the OHC motile forces [4], but also causes additional hearing loss by directly inhibiting the membrane potential of the IHC. The analysis presented in this paper can be developed to pave the way toward differentially understanding the underlying mechanisms involved in the age-related hearing loss.

Acknowledgments

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