Predicting the role of OHC somatic motility and HB motility in cochlear amplification using a mathematical model

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Abstract

In most models of the mammalian cochlea, either mathematical or conceptual, the sensitivity of the BM to low level acoustic stimulus is explained by the presence of outer hair cell (OHC) somatic motility. However, recent experimental evidence indicates that OHC hair bundle (HB) motility can operate with submillisecond time constants. In this paper, we implement a simple phenomenological mathematical model of HB motility, based on the ansatz that HB forcing adds mechanical energy to the system. Our preliminary predictions using models that combine HB and somatic OHC motility indicate that HB motility is not necessary for cochlear amplification while OHC somatic motility is necessary. However we show how HB motility could work in synergy with OHC somatic motility to improve the sensitivity of the cochlea. Experiments to test and elaborate our claims are discussed.

1. Introduction

Outer hair cells (OHC) have been shown experimentally to exhibit somatic electromotility at frequencies covering the entire mammalian frequency range [4]. To predict the high sensitivity of the mammalian cochlea to low-level acoustic stimulus, previous mathematical models have included OHC somatic motility as in Mammano and Nobili ([8]), and Ramamoorthy *et al.* ([10]). These models can predict the high gain as well as the sharp tuning of the frequency response of the basilar membrane (BM) to low level acoustic input. When these models were developed there was no experimental evidence of active hair bundle (HB) motion in the mammalian cochlea. However, activity (as evidenced by distortion products and spontaneous otoacoustic emissions) and amplification without any OHC somatic motility in the hearing organ of non-mammalian vertebrates have been demonstrated. Experimental and theoretical studies have shown that the non-mammalian HB can produce a force due to the action of a calcium dependent process. This active force production is linked to the fast adaptation of the transduction current ([11]) and can amplify an external stimulus ([9]). Moreover, recent experiments show that the mammalian HB also exhibits fast adaptation of the transduction current ([7]) and can produce a force in a submillisecond time scale ([6]). This new evidence provides an alternative to the prevailing theory that somatic motility is the basis of the cochlear amplifier. In our mathematical model, we selectively include OHC somatic motility, HB motility and a combination of both, with the goal of understanding the role of these two active sources in the mammalian cochlea.

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2. Model

Our mathematical model is based on a box model of the guinea pig cochlea with a 3D representation of the fluid, as described in [10]. Viscous dissipation in the subtectorial space is included. The BM interacts with the fluid via linearized Euler relation and with the organ of Corti which is coupled to the tectorial membrane (TM). Each cross-section of the TM is modeled as a rigid body with two degrees of freedom corresponding to the motions in a transverse and radial direction (see Fig. 3 in [10]). Electrical conduction in the scalae of the cochlea is represented by longitudinal cables which allow current to pass down the length of the cochlea as well as into the transduction channels of the OHC (see Fig. 2 in [10]). The system is linearized about the stationary point to predict the response of the system to low level acoustic stimulation. We consider time harmonic vibrations ($e^{-i\omega t}$ time dependence). Somatic electromotility is modeled by linearized piezoelectric relations between the OHC deformation, u_{ohc}^{comp} , the fluctuating part of the transmembrane voltage, ϕ_{ohc} , the OHC force (per unit length of the BM), F_{ohc} , and the current (per unit length of the BM), I_{ohc} , which are given by:

$$F_{ohc} = K_{ohc} u_{ohc}^{comp} + \epsilon_3 \Delta \phi_{ohc} \quad (1)$$

$$Z_m - i\omega \epsilon_3 u_{ohc}^{comp} \quad (2)$$

where K_{ohc} is the stiffness (per unit length of the BM) of the OHC, ϵ_3 is the electromechanical coupling coefficient of the OHC and Z_m is the impedance of the basolateral portion of the OHC.

In a nonlinear physiological model of HB transduction and motility, the dynamics of the HB are fairly complicated. In the linearization of such a model the properties are expected to be frequency dependent (as discussed in [11]). Here, however, we use frequency independent properties and assume the transduction channel conductivity to be directly proportional to the stereocilia deflection, u_{hb} . Further the HB force is taken to be proportional to the HB deflection u_{hb} and velocity $-i\omega u_{hb}$. In this simple model, if the HB is to add energy to the system in a cycle by cycle manner, the real part of the HB impedance must be negative (*i.e.*, some form of negative damping). Hence the HB force in the shear or radial direction is:

$$F_{hb} = k_{hb} u_{hb} - i\omega c_{hb}^{act} u_{hb} \quad (3)$$

where k_{hb} is the HB stiffness and c_{hb}^{act} is the (negative) active damping coefficient. The constant c_{hb}^{act} is chosen to provide forces and energies that are in the physiologically relevant ranges, limited by experimental evidence given in [6] and [1], respectively. The energy is assumed to arise from a calcium binding event that is not included in other models ([8], [10]).

3. Results

The response of the BM to acoustic stimulation is plotted as a function of frequency in Fig. 1. The green dashed line represents the response of the BM in the passive system, *i.e.* neither somatic nor HB motility are included. It compares very well to the experimental measurements of de Boer and Nuttall ([3]) at 100dB SPL (shown in blue dashed line).

When we add somatic motility to the model (thick blue dashed line), we see an increase in the gain and in the sharpness of the tuning and a shift of about half an octave in the peak frequency as seen in the experimental data at 10dB SPL. In the results presented here, the

electromechanical coupling coefficient was chosen such that the model that includes both somatic and HB motility is stable. With this value of β_3 , the predicted magnitude of the BM gain of the model only including somatic motility is lower than the experimental value. However, if we use a slightly higher value for β_3 (about 16% higher), the prediction for the magnitude of the BM gain when only somatic motility is included can match the experimental value as shown in Ramamoorthy *et al.* [10]. Despite the basolateral RC filtering of the transmembrane voltage, somatic electromotility can amplify the BM motion thanks to an electromechanical resonance in the organ of Corti and the high sensitivity of the transduction channels.

If we add HB motility to somatic motility (thick black solid line), there is another 10 dB increase in the gain. For a 0.5nm displacement (which corresponds approximately to a 20dB acoustic input), the magnitude of the OHC somatic force is about 60pN (on the order of magnitude predicted by Iwasa *et al.* [5]) and the power added to the system by HB motility is about 60zJ, which is lower than the maximum value postulated by Choe *et al.* (about 2000zJ, [1]). For this case (somatic motility and HB motility) as well as the previous one (somatic motility only), the tuning of the response is not due to an intrinsic tuning of somatic or HB motility, but to an electromechanical resonance in the organ of Corti.

However, when only HB motility is included (red solid line) using the same active damping coefficient, c_{act}^{hb} , as in the previous calculations, the response is similar to the passive model response, with a low gain and broad tuning. When the active damping coefficient is increased, the model becomes unstable before the maximum gain of the BM reaches the experimental value for low level sounds.

4. Conclusions

In these preliminary results with a simple HB model, OHC somatic motility is necessary for cochlear amplification whereas HB motility is not. This is consistent with measurements on prestin-knockin mice ([2]) which also show that prestin-based somatic motility is necessary for normal cochlear function. With the parameters used here and the current experimental data, HB motility does not appear to be necessary to predict the BM gain to acoustic stimulus. However, as our results suggest, HB motility could still play a significant role and work in synergy with somatic motility to provide a higher BM gain and sharper tuning than with OHC motility alone. A more realistic HB model needs to be developed in order to make more conclusive remarks about the relative roles of OHC somatic and HB motility.

5. New experiments needed to change or elaborate our claims

- *In vitro* measurements of the mechanical response of mammalian HB to a stimulus more rapid than the time course of adaptation: The mechanical response of mammalian HB have only been measured with a stimulus having a time constant similar to or greater than the adaptation time constant. Measurements of HB with a faster time scale and/or with a small harmonic stimulation in the 5-20kHz frequency range would help to find realistic parameters for a linearized HB model in the mammalian auditory frequency range, which are needed for a more precise prediction of the role of HB motility.
- *In vivo* measurements of the BM response to acoustic input in a cochlea perfused with salicylate: Current evidence that prestin somatic motility is necessary for normal cochlear function is based on prestin-knockin mice. The transduction channel of these mutant mice appear to be normal. However the genetic mutation could affect other properties of the mouse cochlea during the development of the animal. Moreover data is only available for mice since genetic mutation have only

performed on mice. Measurements of the BM response in a cochlea perfused with salicylate could be another way to block somatic motility while not affecting HB motility. It could potentially validate or invalidate the claim that prestin is necessary for cochlear amplification.

- Measurements of the BM frequency response to acoustic stimulation with endolymph with reduced calcium concentration: Using a perfusing scheme similar to Zheng *et al.* [12], a controlled alteration of the endolymphatic calcium concentration can be reversibly applied. Reduction of the calcium concentration should slow down adaptation, increase the transduction current and reduce the magnitude of the active HB force. Because of the increase in the transduction current, it should also increase the magnitude of the OHC somatic force. Since OHC somatic motility is the main source of cochlear amplification according to our present model, we expect a net increase of the gain of the BM (provided the phase of the increased current is not deleteriously altered).
- *In vivo* measurements simultaneous measurements of the motion of the BM, the TM and the different structures of the organ of Corti in response to acoustic stimulation: Our mathematical model of the cochlea predicts the relative amplitude of the motion of the TM and the BM that are difficult to verify due to the lack of experimental data. In our results the gain of the BM and TM are similar. If HB motility had a greater effect than what we predict, we should expect the TM to have a much higher gain than the BM since the HBs are attached directly to the TM and can apply a force in the TM shear direction.

Acknowledgments

This research was supported by National Institutes of Health Grant NIH-NIDCD R01-04084.

References

- [1]. Choe Y, Magnasco MO, Hudspeth AJ. A model for amplification of hair-bundle motion by cyclical binding of Ca^{2+} to mechanoelectrical-transduction channels. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95(26):15321–15326. [PubMed: 9860967]
- [2]. Dallos P, Wu XD, Cheatham MA, Gao JG, Zheng J, Anderson CT, Jia SP, Wang X, Cheng WHY, Sengupta S, He DZZ, Zuo J. Prestin-based outer hair cell motility is necessary for mammalian cochlear amplification. *Neuron*. May; 2008 58(3):333–339. [PubMed: 18466744]
- [3]. de Boer E, Nuttall AL. The mechanical waveform of the basilar membrane. iii. intensity effects. *Journal of the Acoustical Society of America*. 2000; 107(3):1497–1507. [PubMed: 10738804]
- [4]. Frank G, Hemmert W, Gummer AW. Limiting dynamics of high-frequency electromechanical transduction of outer hair cells. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96(8):4420–4425. [PubMed: 10200277]
- [5]. Iwasa KH, Adachi M. Force generation in the outer hair cell of the cochlea. *Biophys. J.* Jul.1997 73:546–555. [PubMed: 9199816]
- [6]. Kennedy HJ, Crawford AC, Fettiplace R. Force generation by mammalian hair bundles supports a role in cochlear amplification. *Nature*. 2005; 433(7028):880–883. [PubMed: 15696193]
- [7]. Kennedy HJ, Evans MG, Crawford AC, Fettiplace R. Fast adaptation of mechanoelectrical transducer channels in mammalian cochlear hair cells. *Nature Neuroscience*. 2003; 6(8):832–836.
- [8]. Mammano F, Nobili R. Biophysics of the cochlea: Linear approximation. *Journal of the Acoustical Society of America*. 1993; 93:3320–3332. [PubMed: 8326060]
- [9]. Martin P, Hudspeth AJ. Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96(25):14306–14311. [PubMed: 10588701]

- [10]. Ramamoorthy S, Deo NV, Grosh K. A mechano-electro-acoustical model for the cochlea: Response to acoustic stimuli. *Journal Of The Acoustical Society Of America*. May; 2007 121(5): 2758–2773. [PubMed: 17550176]
- [11]. Ricci AJ, Crawford AC, Fettiplace R. Active hair bundle motion linked to fast transducer adaptation in auditory hair cells. *Journal Of Neuroscience*. Oct; 2000 20(19):7131–7142. [PubMed: 11007868]
- [12]. Zheng J, Deo N, Zou Y, Grosh K, Nuttall AL. Chlorpromazine Alters Cochlear Mechanics and Amplification: In Vivo Evidence for a Role of Stiffness Modulation in the Organ of Corti. *J Neurophysiol*. 2007; 97:994–1004. [PubMed: 17122316]

Figure 1.

Response of the BM to acoustic stimulation at the 17kHz best place. The responses are normalized to the maximum passive BM response. The model predictions are compared to measurements from de Boer and Nuttall ([3]) at 20dB and 100dB SPL (thin blue dashed lines). The parameters used in the simulations are, for OHC somatic motility, $\gamma_3 = -8.4 \times 10^{-6} \text{ N/m/mV}$ and for HB motility $c_{act}^{hb} = -3.15 \times 10^{-8} \text{ N/m/s}$. The passive model prediction (thick green dashed line) follows closely the measurements at 100dB SPL. When somatic motility is included (thick blue dashed line), the peak gain is about 20dB higher than in the passive case and the tuning of the response is sharper as in the experimental data at 20dB SPL. When somatic motility and HB motility are included (thick solid black line), the gain is about 10dB higher than in the previous case. For the case when only HB motility is included (red solid line), the response is almost the same as the passive model response.