Coupled hair bundles could endow the cochlear amplifier with sharp frequency tuning and nonlinear compression

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The key signatures of the auditory amplifier are (i) a frequency tuned and sensitive response to weak stimuli, (ii) a compressive nonlinear response over a large amplitude range, and (iii) spontaneous otoacoustic emissions (Dallos, 1992; Hudspeth, 2008). These signatures are reflected in observed basilar membrane vibrations (Robles and Ruggero, 2001) and can be understood as the consequence of the presence of nonlinear dynamic oscillators operating in a critical regime (Camalet et al., 2000; Eguiluz et al., 2000; Duke and Jülicher, 2003). This suggests that the working of the cochlear amplifier is based on nonlinear oscillators. It is commonly thought that active amplification is mediated by mechano-sensory hair cells (Dallos, 1992; Hudspeth, 1997; Manley et al., 2001; Fettiplace and Hackney, 2006). Two important features of hair cells have been suggested to contribute: (i) outer hair cell electromotility can provide mechanical feedback to the basilar membrane vibrations (Brownell et al., 1985; Santos-Sacchi, 2003; Ashmore, 2008; Dallos et al., 2008) and (ii) mechano-sensitive hair bundles have been shown to be active elements which can generate spontaneous movements and noisy oscillations (Crawford and Fettiplace, 1985; Martin and Hudspeth, 1999; Martin et al., 2001; Kennedy et al., 2005). Individual hair bundles can act as nonlinear oscillators capable to amplify stimuli (Martin and Hudspeth, 1999, 2001) albeit with restricted performance which is limited by intrinsic noise at the cellular scale (Nadrowski et al., 2004). This limitation as well as the small forces associated with movements of individual hair bundles have put doubts on the role of active hair-bundle motility for the cochlear amplifier.

In many vertebrate inner ear organs hair bundles are linked to overlying elastic membraneous structures, such as otolithic and tectorial membranes (see Fig. 1a) and (Freeman et al., 2003). This introduces the possibility that the cooperation of hair bundles plays a role to enhance the properties of hair-bundle-mediated amplification (Manley and Köppl, 2008). Recently, we have shown that small groups of hair bundles which are coupled by elastic elements can respond much more sensitively to periodic stimuli than isolated hair bundles. Furthermore, such groups of hair bundles display spontaneous movements with sharply peaked power spectra and behave as sharply tuned amplifiers that exhibit compressive nonlinearities over a wide range of signal amplitudes (Dierkes et al., 2008).

In our study we employed a model of the single hair bundle that can account quantitatively for its active mechanical properties and the stochastic features of hair bundle motility (Nadrowski et al., 2004; Tinevez et al., 2007). The model incorporates stereociliar pivotal stiffness, channel gating elasticity, the properties of adaptation motors, as well as calcium feedback on these motors. Fluctuations reflecting thermal interactions of the hair bundle with the surrounding fluid, stochastic transitions of transducer channels and adaptation motors are also taken into account. Limitations of the single hair bundle's ability to respond faithfully to an external stimulus (see Fig. 1b, broken red lines) are consequences of these fluctuations (see Fig. 1b, black solid line). Fluctuations thereby limit the detector's sensitivity to weak stimuli and also the sharpness of frequency tuning, as well as the amplitude range over which nonlinear amplification occurs.

Our results were obtained by considering groups of $N \times M$ hair bundles that are arranged on a square lattice with their excitatory directions aligned along the same lattice axis. Coupling is described by linear springs of stiffness K that connect nearest neighbors including diagonal connections. Homogeneous systems of identical hair bundles as well as heterogeneous systems of hair bundles with varying characteristic frequency were considered. In the homogeneous case the quality of spontaneous oscillations exhibits a threshold-like dependence on coupling strength K. A sudden increase of quality occurs for $K \approx K_{SP}$, with K_{SP} denoting the stereociliar pivotal stiffness. When a group of hair bundles is driven by a weak periodic stimulus at the characteristic frequency (see Fig. 1b, broken red lines), the system shows an enhanced phase-locking to the external signal (see Fig. 1b, cf. blue and green solid lines to black solid line). This higher degree of phase-locking leads to an increase of the time-dependent average of the response amplitude (see Fig. 1b, dotted lines). Thus coupling of hair bundles increases the sensitivity (defined as the ratio of the mean response amplitude to the stimulus amplitude) in response to a weak stimulus (see Fig. 1c). For increasing stimulus amplitude, the sensitivity decreases, indicative of the compressive nonlinear response of the system. The range of stimulus amplitudes over which this nonlinear response is observed increases for increasing system size (see Fig. 1c). The response to strong stimuli is determined by the passive stiffness of the single hair bundles and does not depend on system size. As a consequence the amplification gain, which is the ratio of sensitivities to weak and strong stimuli, increases almost linearly with system size. For a system of 81 hair bundles a gain of up to 400 is obtained for optimal coupling strength.

In the mammalian cochlea, nonlinear compression of the basilar membrane vibration amplitude in response to stimuli at the local characteristic frequency have been reported, that range up to four orders of magnitude of sound pressure amplitude (Robles and Ruggero, 2001). The corresponding amplification gains are of the order of 1000 (Robles and Ruggero, 2001). These properties can be understood as resulting from the combination of a global excitation of the basilar membrane (the traveling wave) and the effects of nonlinear active elements which govern the basilar membrane vibration in the vicinity of the characteristic place (Nobili and Mammano, 1996; Duke and Jülicher, 2003). While the properties of the active elements in the cochlea exceed by far the abilities of an isolated hair bundle, our work suggests that groups of coupled hair bundles can approach their performance.

In the mammalian cochlea the basilar membrane exhibits a graded profile of characteristic frequencies and the sensory hair cells display a morphological gradient (Dallos et al., 1996). This raises the question whether enhanced signal detection due to coupling can also work in heterogeneous systems. We thus performed simulations of systems of 3×27 hair bundles (representing three rows of outer hair cells) with varying intrinsic frequencies, result-

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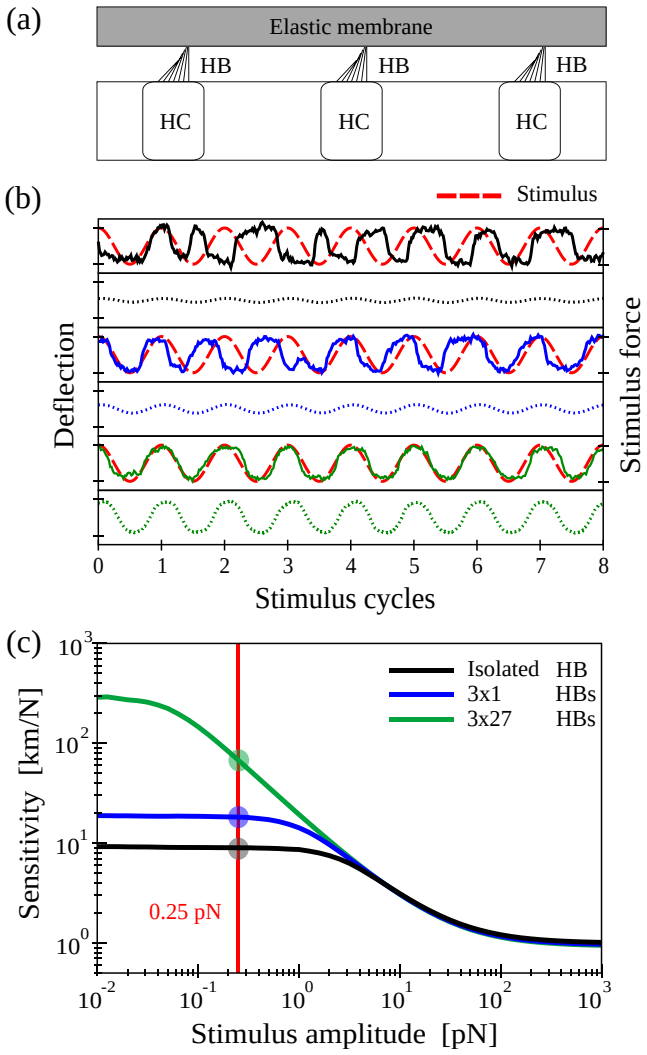

Fig. 1. (a) Schematic of three hair cells (HC) with their hair bundles (HB) coupled elastically via an overlying membrane. (b) Illustration of phase-locking for an isolated (black) and the central hair bundle of groups of coupled hair bundles (3×1 HBs, blue; 3×27 HBs, green). Sample trajectories of simulation results (solid lines) are shown together with the periodic stimulus force $F(t) = A\cos(2\pi f_0 t)$ with $A = 0.25$ pN (broken red line) for coupling stiffness matched to stereociliar pivotal stiffness, $K = K_{SP} = 0.6$ pN/nm. Each system is driven at its characteristic frequency f_0 ($f_0 = 8.91$ Hz (1×1), 9.90 Hz (3×1), 10.54 Hz (3×27)). The respective time-dependent average responses over many repetitions of the stimulus are shown as dotted lines below. Distance between ticks is 40 nm for deflection and 0.5 pN for stimulus force. (c) Nonlinear response of coupled hair bundles. For the three systems studied in (b) the sensitivity (average response amplitude divided by stimulus amplitude) is displayed as a function of stimulus amplitude. The red vertical line indicates the stimulus force used in (b). Note that the sensitivity to weak stimuli and the amplitude range of nonlinear compression increase with increasing system size.

ing from a gradient of pivotal stiffness. For intermediate coupling strength $K \approx \overline{K}_{SP}$, where $\overline{K}_{SP}$ is the average pivotal stiffness of the hair bundles, the amplification gain is still enhanced by coupling, while a frequency gradient is also maintained (Dierkes et al., 2008). This implies that in order to make use of mechanical coupling in the cochlea the elasticity of the overlying membrane has to be locally adjusted to the hair bundle pivotal stiffness. It has been shown that hair bundle stiffness as well as tectorial membrane stiffness vary gradually along the cochlea in such a way that coupling strength and the stereociliar stiffness could indeed be matched (Strelioff and Flock, 1984; Gueta et al., 2006; Richter et al., 2007).

What does the above imply about the cochlear amplifier? There is strong evidence that outer hair cell electromotility plays an important role in cochlear amplification (Dallos et al., 2008). Electromotility introduces an electro-mechanical feedback that couples hair bundle movements back to basilar membrane vibrations (Ashmore, 2008; Nowotny and Gummer, 2006). However, electromotility does not exhibit significant nonlinearities for physiological voltage variations and it does not show frequency tuning (Ashmore, 2008). In contrast, small groups of hair bundles do show all the necessary features: sharp frequency tuning, high sensitivity and compressive nonlinearity (Dierkes et al., 2008). However, there are two limitations. Firstly, the high amplification gain observed in the cochlea is not easily reached in our model if at the same time a frequency gradient is maintained. Secondly, hair bundle movements may be inefficient to significantly drive basilar membrane vibrations. These issues could be resolved by regarding the cochlear amplifier as a combination of outer hair cell electromotility and active motility of locally coupled hair bundles. In this scenario, the frequency selectivity and the compressive nonlinear properties of the cochlear amplifier are provided by coupled hair bundles. Outer hair cell electromotility is a largely linear element that may allow hair bundle movements to efficiently drive basilar membrane vibrations. By varying properties of the electromotile feedback the sensitivity and amplification gain of the amplifier could be adjusted. Careful regulation of nonlinear amplification is important to guarantee the stable operation of nonlinear oscillators in the inner ear (Camalet et al., 2000) and thereby to enhance the detection of complex sounds in varying environments. The electromotile feedback is well suited to mediate such a regulation. This may explain why outer hair cells receive signals from the brain via efferent fibers which could influence electromotility.

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The origin of the cochlear amplifier

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The mammalian cochlea is a unique cellular array the properties of which vary systematically along the organ. These range from the stiffness and size of gross features such as the basilar and tectorial membrane and the dimensions of the outer hair cells (OHCs) (Lim, 1986) to the amplitude of the mechanotransducer channels (Beurg et al., 2006). All features must ultimately conspire to establish the tonotopic map. Passive mechanical tuning is augmented by the cochlear amplifier which endows sharp frequency selectivity and accounts for the 20–60 dB of extra tip to the tuning curves measured for vibrations of the mammalian basilar membrane (Robles and Ruggero, 2001). The amplifier incorporates a compressive non-linearity such that the gain and sharpness of tuning are diminished at higher sound levels. The underlying process is thought to involve electromechanical feedback by the OHCs probably through a filter whose frequency characteristics change along the tonotopic axis (Fig. 1). Work over the past 20 years has demonstrated voltage-dependent contractility of the OHCs underpinned by aggregation of the motile protein, prestin, in the lateral membrane (Ashmore, 2008). However, somatic deformation of the OHC is only one step in a feedback pathway that also includes motion of the tectorial membrane and hair bundles, mechanoelectrical transduction and generation of a receptor potential to drive the prestin motor. It is assumed that OHC contractions supply force to boost the vibrations of the basilar membrane. A primary argument for the somatic motor is that molecular modifications or knock out of prestin largely abolish amplification (Liberman et al., 2002; Dallos et al., 2008). A criticism of this approach is that interfering with prestin merely alters a feedback loop, any part of which could be the site of amplification. For example, knock out of the mechanotransducer channel protein (although not currently feasible) would presumably also eliminate amplification. An alternative view is that amplification is linked to active hair bundle motion, powered by calcium influx promoting fast adaptation of the mechanotransducer channels (Ricci et al., 2000). To appreciate the contributions of the different processes, it is necessary to understand the micromechanics of the organ of Corti and how forces generated by the OHC somatic and hair bundle motors vibrate the basilar membrane and are transmitted to inner hair cells that also exhibit similar sharp tuning.

The prevailing view, that the somatic motor is at the heart of cochlear amplification, is strongly endorsed by recent work mutating prestin or proteins of the tectorial membrane (Dallos et al., 2008; Mellado Lagarde et al., 2008). However, there are several details not fully explained. How is the somatic motor controlled on a cycle-by-cycle basis at high frequencies where the periodic component of the receptor potential will be filtered by the OHC time constant? Several solutions have been proposed (summarized in Ashmore, 2008) but none has been fully confirmed experimentally. How does the somatic motor supply frequency selective feedback? In many attempts to simulate the sharp basilar membrane tuning, an additional filter or phase shift is introduced to match simulations with experimental results but somatic motility itself is not inherently frequency selective. The extra filter invoked in modeling is often assigned to a resonant tectorial membrane (Nobili and Mammano, 1996). Although the properties of the tectorial membrane, both stiffness and mass, change substantially along the cochlea (Richter et al., 2007), the evidence for membrane resonance is controversial. Finally how do OHC properties change to generate the necessary forces at high frequencies to counter the increase in viscous load and basilar membrane stiffness? Again in simulations, the force achieved by OHC contraction is assumed to increase (sometimes >100-fold; Lu et al., 2006) in progressing from the low- to high-frequency end of the cochlea. However, there is no evidence for such an increase in force generation (Iwasa and Adachi, 1997) and if the prestin concentration in the OHC lateral membrane shows little variation with cochlear location (Mahendrasingam et al., 2008), force production remains constant despite different cellular dimensions. Most of the direct evidence for performance of the somatic motor has accrued from measurements on isolated OHCs which invariably lack forward transduction. The operation of the motor may be clarified by studying OHC mechanics in an intact organ of Corti preparation.

The case for a role of the hair bundle motor is based on its properties in non-mammals. In those animals it can amplify the extrinsically induced hair bundle vibrations in a frequency selective manner (Martin et al., 2000; Ricci et al., 2000). The frequency selectivity stems at least partly from tonotopic variation in the fast adaptation time constant for mechanotransduction. Why should it be less important in

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