Nanomechanical mechanisms of cochlear amplification

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At the heart of the extraordinary sensitivity and frequency selectivity of peripheral auditory neurones is a nanomechanical amplifier posited within the cochlea. The basis of this amplifier is nonlinear feedback, with the forward pathway deriving from mechanoelectrical transduction in the stereocilia of the outer hair cells (OHCs), the reverse pathway from electromechanical transduction in the OHC basolateral wall and the battery from the endocochlear potential together with the OHC resting membrane potential (*e.g.* Patuzzi, 1996).

The electromechanical response derives from motor molecules in the OHC basolateral wall, which in response to a change of transmembrane potential undergo a conformational (area) change (Dallos *et al*., 1991), and which when coupled to the OHC cytoskeleton generates a mechanical somatic force, on a cycle-by-cycle basis up to frequencies well above the functionally relevant frequency limit (Frank *et al*., 1999). The electromechanical force is injected into the cochlear partition, both at the basal pole of the OHC, where the basilar membrane (BM) is located, and also at the apical pole, where the reticular lamina (RL) and tectorial membrane (TM) are located.

Provided the phase difference between the forward and reverse pathways is appropriate, the injected force results in reduction of the effective mechanical damping of the BM. This yields a BM vibration response of high gain. The amount of gain depends on the best BM place for the given stimulus frequency, with the gain being largest (*ca*. 80 dB) in the high-frequency and smallest (*ca*. 20 dB) in the low-frequency BM regions (*e.g.* Robles & Ruggero, 2001). However, unlike classical high-gain amplifiers, the relative bandwidth is wider than might be expected for the (large) amount of gain. Instrumental in producing high gain but relatively large bandwidth is cooperative electromechanical action of neighbouring OHCs. Central to both cooperative action and phase synchronicity is the TM. Indeed, in the tuned region of the BM frequency response, relative phase between the forward and reverse pathways appears to be controlled by radial inertial motion of the TM (Gummer *et al.*, 1996) and cooperativity by longitudinal travelling-wave motion on the TM (Ghafferi *et al.*, 2007).

The electromechanical force injected at the apical pole produces not only shearing (*radial*) motion between the TM and the RL - the classical mode of stereocilia deflection - but also a *counter-phasic* transversal motion between the TM and the RL at the inner hair cell (IHC) (Nowotny & Gummer, 2006, 2011). This counter-phasic motion has been observed in all turns of the cochlea and is limited to stimulus frequencies below about 3 kHz. Counter-phasic motion at the IHC is due to two important experimental observations for intracochlear electrical stimulation: 1) the TM moves radially in-phase along its lower surface, rotating like a stiff element about a point in the limbal zone, and 2) the RL rotates like a stiff element about the apex of the pillar cells, causing the apical surfaces of the OHC and IHC to move in opposite phase (Nowotny & Gummer, 2006, 2011). Since the TM and RL are firmly attached at the OHCs through the tallest stereocilia, these two rotational properties cause the TM and RL at the IHC to move apart for OHC elongation (hyperpolarization) and in apposition for OHC contraction (depolarization). Both theoretical (Nowotny & Gummer, 2006) and experimental (Chiaradia *et al.*, 2009) data have shown that the ensuing radially directed fluid motion in the subtectorial space deflects the IHC stereocilia. Importantly, this mechanism enables *direct* coupling of OHC electromechanical force to the IHC stereocilia, without involving the BM. This mechanism could be called a *second* cochlear amplifier; it operates in all cochlear turns for stimulus frequencies up to about 3 kHz, and unlike the classical (*first*) cochlear amplifier described above, is not tuned to stimulus frequency.

In summary, there appears to be at least two different types of cochlear amplifier, each dependent on the electromechanical force produced by the OHC acting in synergy with the vibration of the TM, the first amplifier relying on radial TM motion and the second on rotational TM motion.

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