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A Mechanism for Active Hearing

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Abstract

The remarkable sensitivity, frequency selectivity, and nonlinearity of the cochlea have been attributed to the putative "cochlear amplifier," which consumes metabolic energy to amplify the cochlear mechanical response to sounds. Recent studies have demonstrated that outer hair cells actively generate force using somatic electromotility and active hair-bundle motion. However, the expected power gain of the cochlear amplifier has not been demonstrated experimentally, and the measured location of cochlear nonlinearity is inconsistent with the predicted location of the cochlear amplifier. We instead propose a "cochlear transformer" mechanism to interpret cochlear performance.

Introduction

Because most physiologically significant sounds, such as speech, music, and laughter vary their amplitude, frequency, and phase on the scale of microseconds, the ear must analyze sounds with high intensity and time resolution. This enormous signal-processing task is accomplished in real-time by the cochlea, which decomposes incoming complex acoustic signals and encodes their temporal and amplitude information in auditory nerve activity. Humans can discriminate two acoustic tones differing in frequency by only 0.2–0.5% [1], a capability dependent on the sharp tuning of the basilar membrane (BM) [2]. Although a typical filter with sharp tuning has poor time resolution as it requires a long time constant, a remarkable capability of the cochlea is that it affords high-frequency resolution without compromising time resolution. As an acoustic sensor, the sensitivity of the cochlea is extremely high; a recent measurement shows that human ear is able to detect a tympanic-membrane vibration with less than 1 pm displacement [3•]. Moreover, mammals can hear sounds over an intensity range of more than million-fold, also achieved through the activity of the cochlea.

The term "active hearing" describes phenomena that result from a cochlear "active process", which produces the extraordinary sensitivity, frequency selectivity, and wide dynamic range of the auditory system. The term "active process" is used interchangeably with "cochlear amplifier", which refers more specifically to a hypothetical local feedback mechanism that consumes metabolic energy to amplify the mechanical responses of the cochlear partition to sounds [1,4].

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Originally suggested by Thomas Gold in 1948 [5], the cochlear amplifier concept was proposed to suggest how the cochlea achieves its remarkable sensitivity. Kemp's discovery that the cochlea not only receives but also generates and emits sounds, including spontaneous otoacoustic emissions [6,7], lent strong support to the amplifier concept. Discovery of somatic electrically induced motility (electromotility) of outer hair cells (OHC), mediated by the protein prestin [8], suggested a reasonable energy source for the proposed cochlear amplifier. Identification of active hair bundle motion in mammals [9–11] suggested an alternative model for OHC active force generation. How the cochlea uses OHC-generated forces remains unclear; we propose the concept of a "cochlear transformer" as an alternative interpretation of active hearing.

Active forces generated by outer hair cells

Many believe that OHCs supply power to the hypothetical cochlear amplifier using somatic electromotility. An isolated OHC rapidly changes its shape in response to electrical stimulation [12–14]; transmembrane potential stimuli lengthen or contract cells by 3–5% [15]. This electromotile response is sometimes called reverse transduction to distinguish it from forward, mechanical-to-electrical transduction. OHCs elongate when they are depolarized, and shorten when hyperpolarized [14] in a nonlinear manner [15,16]. In the isolated cochlea, the cochlear partition distorts in response to electrically driven OHC length changes and produces place-specific vibration of the BM [17]. Similarly, *in vivo* electrical stimulation of the cochlear partition evokes otoacoustic emissions [18,19]. The electromotile response is accompanied by a voltage-dependent change in axial stiffness of as much as ~10-fold [20], which could be exploited for amplification [8].

Using suppression subtractive hybridization PCR [21], prestin was identified as the likely motor protein. Prestin is abundantly expressed in OHCs and shows voltage-dependent charge movement and motility [22]. Demonstrating the importance of prestin for the cochlear amplifier, a targeted deletion of prestin in mice results in loss of OHC electromotility and a 40–60 dB hearing loss [23]. Cochlear microphonic potentials in homozygotes manifested harmonic and intermodulation distortion, showing a nonlinear forward transduction [24,25]. OHCs isolated from prestin knockout mice also show large asymmetric transducer currents similar to those in wild-type controls [26], indicating that OHC forward transduction is normal in null mice and that the observed hearing loss likely resulted from loss of reverse transduction.

There was no significant difference in OHC electromotility, cochlear sensitivity, or frequency selectivity between wild-type mice and those with only one copy of the prestin gene [27]. Interestingly, immunocytochemistry and western blot analysis indicated that prestin protein in heterozygotes is near wild-type levels [27] and that prestin mRNA is significantly less abundant in heterozygotes than in wildtype mice [23]. These results suggested that production of prestin protein is autoregulated and that one copy of the prestin gene is sufficient for normal cochlear function.

An alternative mechanism of force generation by OHCs is active hair bundle movement [9]. Hair bundles manifest spontaneous oscillations and non-linear responses to applied forces. Spontaneous hair bundle oscillation at frequencies of 5–80 Hz with amplitude up to 50 nm was originally found in turtle and frog hair cells [28–30]. The oscillation frequency increased with the external Ca^{2+} concentration, indicating Ca^{2+} current involvement in the feedback pathway [31]. Blockage of mechanical transduction channels with gentamicin or suppression of myosin motors with butanedione monoxime abolished oscillations. An excitatory force applied by a flexible glass fiber attached to the bundle resulted in an initial movement toward the kinocilium that opens the mechanotransducer channels, followed by a fast response in the opposite direction, pushing back against the applied deflection of the bundle. Following this

fast response, a slow movement developed in the same direction as the initial force [32,33]. The observed fast movement, a recoil with a time constant identical to "fast adaptation" of the transducer current, which was most prominent for small stimuli. The time constant of the fast response of the bundle in turtle auditory hair cells correlated with characteristic frequency of the cell [34]. The slow movement has been believed to be a consequence of the myosin-based motor responsible for slow adaptation of the transducer current [29,35]. External force-induced increase in tip-link tension initially opens the channel; channels then close due to slipping of the upper attachment point of the link, resulting in further displacement of the bundle due to decrease of tip-link tension [36].

As in non-mammals, transducer currents recorded from mammalian OHCs [37,38] and inner hair cells [39••] show fast adaptation [37,40–42]. This adaptation is more than an order of magnitude faster than in nonmammalian vertebrates [43] and may generate more force [44]. Since the stiffness of the bundle may affect the impedance of the cochlear partition [45], forces generated by the active bundle movement can in principle amplify the BM vibration. Direct evidence for such amplification was provided by the observation that non-linear mechanical responses in an *in vitro* cochlear preparation was abolished by blocking the mechanotransducer channels [46]. However, amplification from active bundle movements has not yet been directly demonstrated; blocking the transducer current can affect membrane potential, which affects the prestin motor and produces somatic motile responses [26,47••].

Fettiplace has proposed [9,10] that active bundle movement and somatic motility may work together to achieve cochlear amplification. Fast active bundle movement works as positive feedback mechanism to boost the cochlear partition vibration while somatic motility optimizes active amplification by adjusting the operating point of the transducer channels.

What is the cochlear amplifier gain?

The mammalian cochlear amplifier is defined as an OHC-based local feedback mechanism that amplifies the cochlear-partition vibration. According to this definition, the cochlear amplifier should produce a power gain at the level of the cochlear partition. The sensitivity, sharp tuning, and nonlinearity of the cochlear partition responses are vulnerable to the cochlea's metabolic state [2]; the vibration amplitude of the cochlear partition in the transverse direction at the characteristic frequency location can decrease >100 times when the cochlea becomes passive. These cochlear mechanical changes always result in >40 dB hearing loss, as has been observed in prestin knockout mice. It is commonly held that the cochlear amplifier can boost cochlear partition vibration by >100-fold [23,48,49]. Measurements of hearing threshold or BM vibration amplitude provide no information on the power gain of the cochlear amplifier, however.

An experimental measurement of the cochlear amplifier gain compared the distortion-product otoacoustic emission [6] to the auditory nerve fiber response while the emission generation site was moved through the amplification location [50]. The results showed that the cochlear amplifier gain was <10 dB, which was interpreted that there is no cochlear amplifier. This puzzling result was confirmed by recent experiments, albeit with different interpretations [51,52••]. The impedance of the cochlear partition was derived from the intracochlear pressure, and negative resistance, an indicator of cochlear amplification was detected only in some instances [53]. For calculating the cochlear amplifier gain, BM vibration data were interpreted using a nonlinear three-dimensional model of the cochlea. The spatial-domain response was obtained based on the frequency-domain data measured from a single location using a cochlear model-based analysis. In a sensitive cochlea stimulated by low-intensity stimuli, the impedance function shows a longitudinal region where the BM is able to amplify vibration [54]. Thus, the

expected 100- or even 1000-fold cochlear amplification remains to be demonstrated experimentally.

Where is the cochlear amplifier?

Understanding how the cochlea employs OHC-generated forces to amplify the cochlear partition vibration requires knowledge of the longitudinal location of the cochlear amplifier. Several modelling studies predicted that OHC-generated energy is introduced basal to the best frequency (BF) place and that the active region extends over several millimeters [50,55]. This proposal is attractive because the travelling wave would pass through the active region and be amplified before reaching the BF site. Because nonlinearity is an inherent property of the cochlear amplifier, the location and extent of the BM region responsible for amplifying the travelling wave has been studied by measuring the location of the nonlinearity in the cochlea. BM responses to ~15 kHz tones was measured at multiple locations over 12.5- to 27 kHz longitudinal locations in guinea pig using a laser diode-based self-mixing interferometer [56]. For low-level tones, the maximum vibration was centered at the tone's frequency place. The gain of BM vibration declined progressively with sound intensity at the BF place, from 1000-fold at 15 dB SPL to 10-fold at 100 dB SPL. The gain also decreased rapidly with distance from the BF place [56]. In another study, BM vibration measured from up to eight longitudinal locations in chinchilla showed both non-linear growth at the BF location and a peak shift toward the base with increasing intensity [57]; growth became linear at locations outside the BF region.

BM vibration measured as a function of longitudinal location in gerbil [58] showed that the maximal response location for 16 kHz at 10 dB SPL was ~2500 μm from the base, with a longitudinal extent of ~0.6 mm. The velocity magnitude at 2500 μm increased from ~10 to ~1,500 $\mu\text{m/s}$ (<45 dB) for a stimulus intensity increase from 10 to 90 dB SPL (80 dB), indicating a nonlinear compression. The location of the nonlinearity was centered at the BF location and distributed over <1-mm range, with greater compressive nonlinear growth on the apical side of the BF location than the basal side. The response peak broadened more toward the base than toward the apex with increases in intensity [58].

In spite of differences in the observed longitudinal extent of BM vibration in these studies, a common finding was that the cochlear nonlinear compressive growth was restricted over a narrow longitudinal range, centered at the BF place. These experimental data are inconsistent with theoretical predictions that cochlear amplification occurs over a range basal to the BF place [Figure 1(b)]. These discrepancies between data and models indicates either that nonlinearity may not indicate the cochlear-amplifier location, or that the cochlea achieves high sensitivity through mechanisms other than from a cochlear amplifier.

A mechanism for active hearing: The cochlear transformer

External sounds excite the cochlea by inducing fluid displacement by the stapes. The BM vibration starts at the cochlear base and propagates toward the apex; as the wave propagates, its speed decreases and its vibration magnitude increases. The vibration reaches its maximum at the BF location and quickly decreases beyond this site [Figure 1(a)] [59]. In a living cochlea, the amplitude of the BM vibration at the BF site in the transverse direction can be up to a 1000-fold that of in-out vibration of the stapes, a gain increase which some assign to the cochlear amplifier [2,56,60–62]. Although the BM vibration in the transverse direction is the physiologically relevant stimulus to sensory hair cells, measurement of transverse vibration alone provides no information on longitudinal and radial extents of the vibration.

Like the BM vibration gain measured based on single location data, a BM volume displacement gain can be measured as the ratio of the BM volume displacement to that by the stapes. Due to the rigid stapes footplate, the volume displacement amplitude of stapes vibration can be

quantified by multiplying the area of the stapes footplate – about 0.8-mm² in gerbil [63] – with the displacement amplitude from a single location [59]. The volume-displacement amplitude of the BM vibration can be measured as the maximum volume-displacement over a BM segment one half-wavelength in length, centered at the BF. Based on a BM width of ~0.2-mm [64] and a half wavelength of ~0.15-mm at the 16 kHz location [58], the estimated in-phase vibrating area of the BM centred at the BF site is ~0.03-mm². The ratio of the in-phase vibration area of the stapes to that of the BM is thus ~27. Under iso-volume conditions, this area ratio alone increases BM vibration by ~27-fold. Considering that the area of the BM vibrating in phase is not a rigid plate, the average displacement over this area could be smaller than that at the BF location. Consequently, the volume displacement gain of the BM should be >27 times smaller than that based on the data from a single location. Figure 1(c) graphically presents the mechanism of the cochlear transformation. In a pilot experiment (unpublished), we measured the volume-displacement of BM vibration using a scanning laser interferometer and found the volume-displacement gain of the BM to be ~10-fold, much smaller than the expected cochlear amplifier gain.

We propose the concept of a "cochlear transformer" as an alternative interpretation of cochlear mechanisms previously attributed to the cochlear amplifier. Like the cochlear amplifier, the cochlear transformer relies on the activity of OHCs; in contrast to the cochlear amplifier, activity of OHCs in the cochlear transformer does not result in substantial power amplification at the level of the cochlear partition. Instead, active force generated by OHC somatic motility [12,14,38] and/or active bundle motion [10,36,46,65] is used for concentrating incoming power to a highly restricted space at the BF region.

Conclusions

In the mammalian cochlea, active hearing is thought to result from an outer hair cell-based "active process" or "amplifier". Cellular and molecular studies have demonstrated OHC-generated forces through mechanisms of somatic motility and/or active bundle movement. Prestin has been identified to be the motor protein of somatic motility and prestin knockout mice show severe hearing loss. Active bundle movement originally discovered in nonmammalian vertebrates has been shown in the mammalian cochlea. However, how the cochlea employs OHC-generated forces to amplify cochlear-partition vibration remains unanswered. In spite of three decades of intensive studies, the expected power gain of the cochlear amplifier has not been demonstrated experimentally. The extremely restricted longitudinal pattern and location of the cochlear nonlinearity at the peak-response place are both inconsistent with predictions based on available theories. Although the concept has yet to be fully developed experimentally and theoretically, the proposed cochlear-transformer model provides an alternative interpretation of active hearing previously attributed to the cochlear amplifier.

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Figure 1.

The relationship between stapes and basilar membrane (BM) vibrations, the location of the cochlear amplifier, and the mechanism of the cochlear transformer. (a) The amplitude of BM vibration at the best frequency (BF) location in the transverse direction can be thousand times greater than that of in-out vibration at the stapes. (b) Although power amplification is predicted to occur over a range of a few millimeters basal to the BF place, the location of the cochlear nonlinearity has been observed to be at a spatially restricted range centered at the best frequency site (CA, cochlear amplifier; NL, nonlinearity). (c) Because the volume displacement is determined by the in-phase vibrating area and the amplitude of the vibration, under iso-volume conditions, the vibration amplitude is inversely related to the vibrating area. The area difference between the stapes footplate and the in-phase vibrating BM segment centered at the BF place is responsible for most of the large gain of the BM vibration in transverse direction.