# New and Notable

## New Insights into Cochlear Amplification

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The high sensitivity and narrow tuning of mammalian hearing depend on mechanical amplification of the cochlea's response to sound, a process called cochlear amplification. Many aspects of this process are understood, but how they all work together to produce amplification is not understood. In particular, it has been a mystery how the push from outer hair cells (OHCs, the motors for this amplification) is timed so that cochlear vibration is enhanced instead of diminished. This is where Dong and Olson (1) provide important new (to my knowledge) insights.

Cochlear amplification, in brief, works like this: Sound causes a traveling wave along the basilar membrane (BM), a flexible membrane that separates the cochlea into two fluid compartments (refer to Dong and Olson, their Fig. 1). BM vibration peaks at a best-frequency region along the length of the cochlea that depends on the frequency of the sound. High frequencies peak in the cochlear base and low frequencies peak in the cochlear apex. BM motion causes vibrations in the sensory tissue sitting on the BM, the organ of Corti; the differing internal dynamics of these tissues causes deflections of sensory structures on OHCs called stereocilia. Deflecting OHC stereocilia opens ion channels that allow $K^+$ to flow into and depolarize the OHCs. OHCs are endowed with a high piezoelectric effect by a type of molecule unique to OHCs, called prestin, which lines the OHC lateral walls and changes shape with changes in OHC transmembrane voltage. The net effect of this piezoelectric OHC somatic motility is that OHC depolarization causes the OHCs to contract. The OHC somatic motility pushes and pulls on the BM and if this is timed correctly relative to the motion of the BM, it can amplify the motion.

To understand what controls the timing of OHC forces, we must dig deeper into the micromechanics of the organ of Corti. The tops of the OHCs are embedded in the reticular lamina (RL) at the top of the organ of Corti, and when the BM moves up, the OHCs move up. In contrast, the tectorial membrane (TM), a gelatinous structure similar to cartilage, is attached to the organ of Corti only through the OHC stereocilia and can vibrate radially as well as transversely (see Dong and Olson, their Fig. 1: radial, right-left; transverse, up-down). The difference in radial motion between the TM and the top of the OHCs (the RL) is what deflects OHC stereocilia, opens channels, and produces forces through OHC somatic motility. The deflection of the OHC stereocilia cannot be measured directly, but Dong and Olson obtained an indirect measure of this deflection from the voltage change just outside of the BM. Their electrical model shows that the location of their electrode was close enough to sense current that flows through the OHC stereocilia from the opening of local OHC stereocilia channels. By their innovative, simultaneous measurement of voltage and BM motion, they were able to directly relate the phase of the OHC current to the phase of BM motion.

Theory dating from a century ago postulated that the different pivot points of the organ of Corti and the TM cause shearing between these two structures, deflecting the OHC stereocilia in the excitatory direction for upward BM motion. With this theory, the peak deflection of OHC stereocilia, and therefore peak current, would be at the peak BM displacement, which was what Dong and Olson found for sound frequencies that were a half-octave or more below the local best frequency. The resulting OHC somatic motility is controlled by the OHC transmembrane voltage, and because of filtering by the OHC membrane capacitance, the OHC voltage lags behind the current. Dong and Olson, from the data of Johnson et al. (2), calculate that this lag is ~60°. The net effect of these factors is that for frequencies a half-octave or more below the local-best frequency, the OHCs exert their maximum upward force on the BM while the BM is moving down. This is not the phase needed to produce cochlear amplification. The most important new (to my knowledge) finding by Dong and Olson is that for frequencies within approximately a half-octave of the local best frequency, the phase of the OHC current is advanced by ~130° from the classically expected phase, which then puts the OHC force at a phase of BM velocity that enhances the motion. Significantly, as frequency is increased, the ~130° phase shift occurs abruptly at a frequency very close to the frequency at which cochlear amplification becomes evident. The implication is that the abrupt phase shift changes the phase of the OHC force so that it is nearly the same phase as BM velocity and therefore adds energy to the BM traveling wave.

Another way to determine whether energy is added to the traveling wave is to look at the impedance of the organ of Corti as seen by the cochlear fluids. Dong and Olson's measurements of BM motion and fluid pressure provide a direct measurement of organ of Corti impedance. They show that the real part of the organ of Corti impedance

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is negative in the frequency region where the phase of OHC current has shifted from the classical expectation. This negative impedance indicates that the organ of Corti is adding energy into the fluid, i.e., amplifying the traveling wave.

How does the abrupt phase shift of the OHC current come about? The simplest explanation is that it comes from an abrupt change in motion of the TM. One theory, presented in 1980 (3,4), hypothesized that the TM vibrates radially and has a resonance that is approximately a half-octave lower in frequency than the local BM best frequency. Because of this resonance, as the drive to TM motion (which is through the OHC stereocilia) is changed in frequency from below to above the TM resonance, the TM changes from being stiffness-dominated to being mass-dominated and its radial-vibration phase (relative to BM phase) would shift 180°. At first glance, the Dong and Olson finding of an abrupt phase shift in the OHC current seems to uphold this theory. However, recent measurements of TM properties indicate that the situation is more complex. These measurements show that the TM can carry a transverse wave of radial motion (5), and that changes in TM properties that shorten the space constant of the TM transverse wave also sharpen cochlear and BM tuning (6,7). These findings show that more is in play than a local change from TM radial motion that is dominated by stiffness, to one dominated by mass. Yet another possible influence is nonlinearity in the bending stiffness of OHC stereocilia caused by channel openings. (At the high-frequency region where Dong and Olson made their measurements, $Ca^{2+}$-induced modulation of the OHC stereocilia mechanical nonlinearity—i.e., stereocilia motility—seems unlikely because the high-affinity $Ca^{2+}$ receptor would produce buffered diffusion and would have to have extremely short binding and unbinding time constants.) A final factor that determines the deflection of OHC stereocilia is motion of the RL. Reticular lamina motion is different from BM motion (8) because of the changes in OHC length that power cochlear amplification. The interplay of these many factors makes understanding this part of cochlear amplification a challenging task.

Dong and Olson's measurements were in the high-frequency cochlear base where BM motion is a good proxy for cochlear mechanical output. However, the final mechanical output of the cochlea is the drive to inner hair cells and this drive may be quite different from BM motion. At frequencies <~3 kHz, cochlear mechanical processes and cochlear amplification may be substantially different than is found in the high-frequency base (9). It is not clear to what extent Dong and Olson's observations hold for the apical half of the cochlea.

Despite the fact that we cannot pinpoint the exact causes for the abrupt phase shift in OHC current found by Dong and Olson, their measurements are a big step forward in our understanding of the details of cochlear amplification. The measurement of a negative impedance for the organ of Corti and the coincidence of the frequency of the abrupt phase shift with the frequency at which cochlear amplification starts show that OHC somatic motility provides the motor push for cochlear amplification as well as how the phase of this push is arranged to produce cochlear amplification. These measurements point to the relative motion of the TM and RL as important areas requiring further elucidation before we fully understand cochlear amplification.

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