What Drives Mechanical Amplification in the Mammalian Cochlea?

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The recent report by Peter Dallos and colleagues of the gene and protein responsible for outer hair cell somatic motility (Zheng, Shen, He, Long, Madison, & Dallos, 2000), and the work of James Hudspeth and colleagues demonstrating that vestibular stereocilia are capable of providing power that may boost the vibration of structures within the inner ear (Martin & Hudspeth, 1999), presents the tantalizing possibility that we may not be far away from answering the question what drives mechanical amplification in the mammalian cochlea? This article reviews the evidence for and against each of somatic motility as the motor, and a motor in the hair cell bundle, producing cochlear mechanical amplification. We consider three models based on somatic motility as the motor and two based on a motor in the hair cell bundle. Available evidence supports a hair cell bundle motor in nonmammals but the upper frequency limit of mammalian hearing in general exceeds that of nonmammals, in many cases by an order of magnitude or more. Only time will tell whether an evolutionary dichotomy exists (Manley, Kirk, Köppl, & Yates, 2001).

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Without doubt the most vexing problem facing auditory biophysicists interested in mammalian cochlear function is what drives mechanical amplification in the mammalian cochlea? The idea of a motor in the cochlea was first suggested by Thomas Gold in 1948, the existence of such a motor being necessary to overcome the viscous forces associated with the fluids in the cochlea and so provide the observed frequency selectivity seen in mammalian audition. Over time, evidence has accumulated to implicate outer hair cells (OHCs) as the origin of this cellular mechanical amplification (Dallos, 1992; Yates, Johnstone, Patuzzi, & Robertson, 1992); however, the mechanism by which these cells mechanically amplify basilar membrane vibration is not known.

The cochlear amplifier (Davis, 1983) is a level-dependent, physiologically vulnerable process within the cochlea that amplifies basilar membrane vibration. Inherent in the operation of the cochlear amplifier is a motor or active process* that imparts mechanical energy into the basilar membrane. Mechanical amplification improves hearing sensitivity, frequency selectivity, and increases dynamic range† (Patuzzi, 1996). Enhancement of basilar membrane vibration associated with the operation of the cochlear amplifier is depicted schematically in Figure 1. A hypothetical basilar membrane traveling wave in response to a pure tone is shown for the passive and the active cases. The operation of the cochlear amplifier increases basilar membrane vibration (the active case), but only near to the place where the cochlea is tuned to that particular frequency. Remote from this characteristic frequency (CF) place, basilar membrane vibration is the same for both the active and passive cases. It is likely that the cochlear amplifier operates all along that part of the cochlear partition stimulated by the pure tone but that it is only effective near the CF place (Johnstone, Patuzzi, & Yates, 1986).

Figure 2 (from Sellick, Patuzzi, & Johnstone, 1982) demonstrates the increased auditory sensitivity and frequency selectivity produced by cochlear mechanical amplification. Measurement of basilar membrane vibration was made at the 18 kHz CF place in a cochlea in good condition, subsequently when the condition of the cochlea had deteriorated, and finally postmortem. With the cochlea in good condition, the stimulus level to evoke a "threshold response" was about 15 dB SPL at the best or most sensitive response frequency (18 kHz). With deterioration in cochlear condition, the cochlear amplifier had been affected‡, and it then took a >60 dB SPL stimulus to evoke a "threshold response" at 18 kHz. The tuning curve was also less sharp with cochlear damage, i.e., frequency selectivity was poorer. The

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*In this article, motor and active process are used synonymously. Strictly speaking, the motor is part of the active process, where the active process represents the electrical to mechanical transduction stage of the cochlear amplifier feedback loop.

†The increase in dynamic range is a result of the intensity-dependence of this mechanical amplification, the amount of amplification being greatest at low stimulus levels.

‡Basilar membrane measurements reflect only the cochlear mechanical response. Damage to IHCs presumably does not affect basilar membrane measurements. However, damage to OHCs, the generator of cochlear mechanical amplification, will affect the basilar membrane response.

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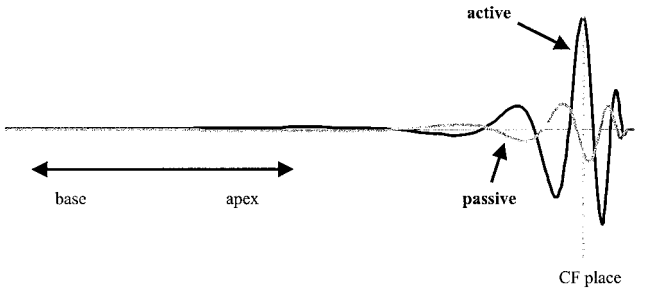

Figure 1. Schematic of hypothetical basilar membrane travelling wave in response to a pure tone in the active and the passive case, illustrating the increased amplification of the basilar membrane response near the CF place associated with the action of the cochlear amplifier. The horizontal line represents the basilar membrane "at rest."

cochlear amplifier provides up to ~60 dB of gain (Patuzzi & Rajan, 1992; Rajan & Patuzzi, 1992) and provides for much finer resolution of frequency. It is also apparent from Figure 2 that the cochlear amplifier is effective only within a limited region near the CF place—basilar membrane responses to stimuli with frequencies below 12 kHz were unaffected by the loss of cochlear mechanical amplification.

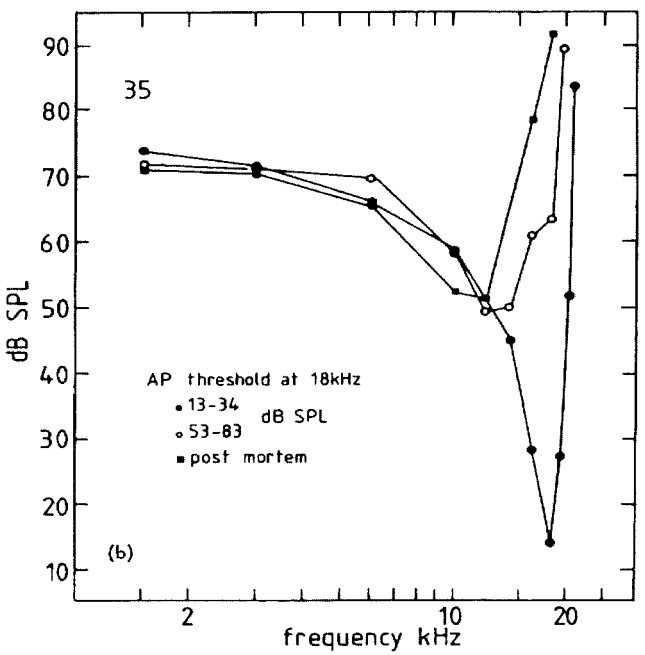

Figure 2. Basilar membrane iso-response functions from measurements made in the first turn of a guinea pig cochlea. Filled circles represent the cochlea in good condition, unfilled circles when cochlear condition had deteriorated (from Sellick et al., 1982). Comparison of the stimulus level to generate a "threshold response" at 18 kHz when the cochlea was in good condition versus when it had deteriorated reveals a 50 dB change due to loss of cochlear mechanical amplification. (Reproduced from Figure 15(b) of Sellick et al. (1982), Journal of the Acoustical Society of America, 72, 131–141, with permission).

Associated with the action of the cochlear amplifier may be an alteration in the effective stiffness of the basilar membrane (Kolston, 2000), producing a change in basilar membrane tuning. This can readily be inferred from Figure 2: initially with the cochlea in good condition the basilar membrane was sharply tuned with the most sensitive response at 18 kHz; with a deterioration in cochlear condition the basilar membrane was not as sharply tuned and the most sensitive response shifted to near 12 kHz. The site of measurement on the basilar membrane, however, had not changed, i.e., the basilar membrane at the site of measurement was initially tuned to 18 kHz with the cochlea in good condition and then to 12 kHz with a deterioration in cochlear condition. This shift in tuning for the same place on the basilar membrane may demonstrate the effect of mechanical cochlear amplification on basilar membrane tuning—the shift in tuning might be due to a change in effective stiffness of the basilar membrane produced by the operation of the cochlear amplifier, i.e., there is an alteration in the resonant place (resonance meaning that place where the reactive elements cancel, not the position of maximum basilar membrane vibration). It may also be that the operation of the cochlear amplifier does not alter the effective stiffness of the basilar membrane. Rather, the resonant place is unaltered and the change in frequency at which maximal vibration occurs is not due to a change in tuning but to a reduction in effectiveness of cochlear mechanical amplification (Shera, 2001). Both cases are illustrated in Figure 3.

The difference between an amplifier that alters basilar membrane tuning and one that does not is not a trivial one—it has significant implications for how mechanical amplification might be achieved.

So, given that we do not know what drives mechanical amplification in the mammalian cochlea, do we have any good ideas? At present, the two best theories are 1) somatic motility or changes in cell-body length (this is perhaps the most well known), and 2) a motor in the hair cell bundle.

Before considering both of these theories in detail it is provident to review first what we know about the cochlear amplifier and what is required for mechanical amplification in the cochlea to occur.

The Cochlear Amplifier

Positive Feedback Process • Cochlear mechanical amplification is thought to be achieved by a positive feedback process (see Fig. 4). Positive feedback processes are prone to instability (hence spontaneous otoacoustic emissions) but have the virtue

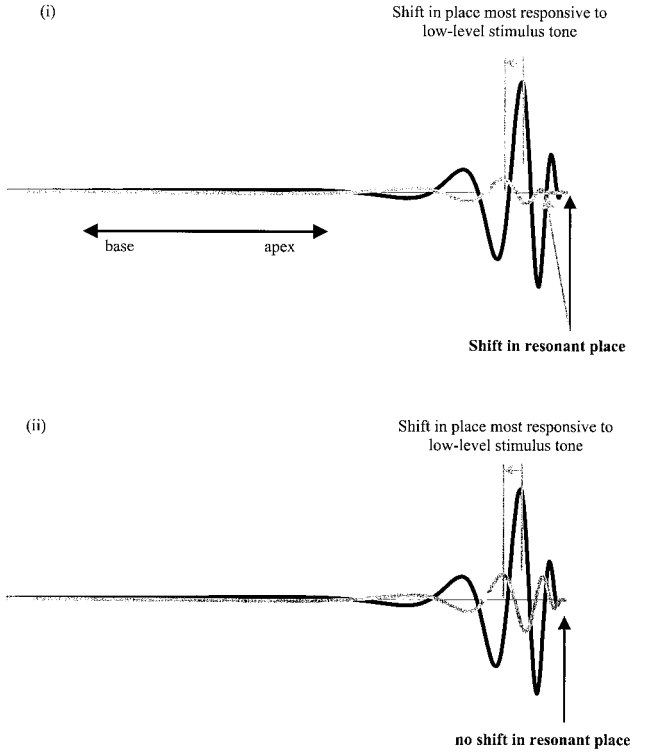

Figure 3. Schematic of basilar membrane travelling wave illustrating (i) a shift in basilar membrane stiffness producing a shift in the resonant place, and (ii) no change in basilar membrane stiffness with the resonant place unaltered, but the place of maximum vibration is shifted due to a reduction in effectiveness of cochlear mechanical amplification (Shera, 2001). In each case, the travelling wave is in response to the same low-level stimulus (no change in frequency), the darker line representing a cochlea in good condition, the lighter line when the same cochlea has deteriorated and the cochlear amplifier is less effective. The horizontal line represents the basilar membrane "at rest to." Note: The resonant place is that place where the reactive elements cancel; this is not the place of maximal basilar membrane displacement but rather the place after peak displacement at which basilar membrane displacement is effectively zero (damping is thought to have dissipated all the energy in the travelling wave just before the resonant place is reached [Lighthill, 1991]).

that existing conditions are amplified or boosted. The first step in the amplification process is the displacement of the basilar membrane produced by stapes vibration-induced volume displacement of fluids in the cochlea. This volume displacement produces a pressure gradient across the basilar membrane. Deformation of the basilar membrane produces a shearing action between the tectorial membrane and the reticular lamina, producing a deflection of the stereocilia of the receptor cells. Both inner and outer hair cells have fine (tip) links that mechanically join adjacent stereocilia. Deflection of the stereocilia is thought to produce a force on the transduction channels via these links, opening the

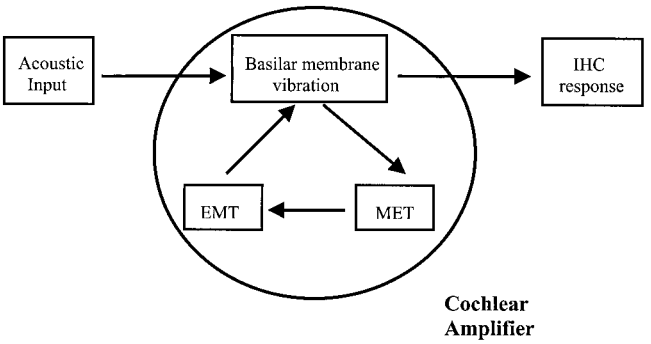

Figure 4. The Cochlear Amplifier. A positive feedback process that enhances basilar membrane vibration on a cycle-by-cycle basis. MET or mechanical to electrical transduction involves a modulation of the flow of ions through ion channels at the top of the stereocilia as a result of stereocilial deflection. EMT or electrical to mechanical transduction involves the conversion of an electrical event into a mechanical event. See text for further details.

channels[§] (Pickles, Comis, & Osborne, 1984). Potassium ions flow through open transduction channels[‖] raising the intracellular potential and altering the potential difference across the basolateral wall, which in the inner hair cells (IHCs) results in a release of neurotransmitter at afferent synapses (see Fig. 5).

The flow of ions through these transduction channels located at the top of the stereocilia as a result of stereocilial deflection is termed mechano-electrical transduction, or MET. Positive ion flow through transduction channels is occurring constantly. This ion flow is a product of the electromotive force or positive charge that is maintained in Scala Media by the active pumping of potassium ions through the Stria Vascularis, and the negative intracellular charge or cell resting membrane potential. This constant ion flow is termed a "standing current to." Deflection of the stereocilia modulates this standing current so that current flow is increased when stereocilia are deflected away from the modiolus (excitatory direction), and current flow is decreased when stereocilia are deflected towards the modiolus (inhibitory direction).

Mechanical amplification by OHCs is achieved when an electrical event (the current flow or a voltage difference) is converted into a mechanical event. This is called electromechanical transduction

[§]The opening of hair cell transduction channels is more complex than presented here, being probabilistic in nature. The probability of a channel being open or closed is described by Maxwell-Boltzmann statistics; deflection of stereocilia changes the likelihood of a channel being open or closed.

[‖]These transduction channels are cation selective (Kros, 1996). Potassium, by virtue of it being the predominant cation in endolymph, provides most of the ion current through these channels.

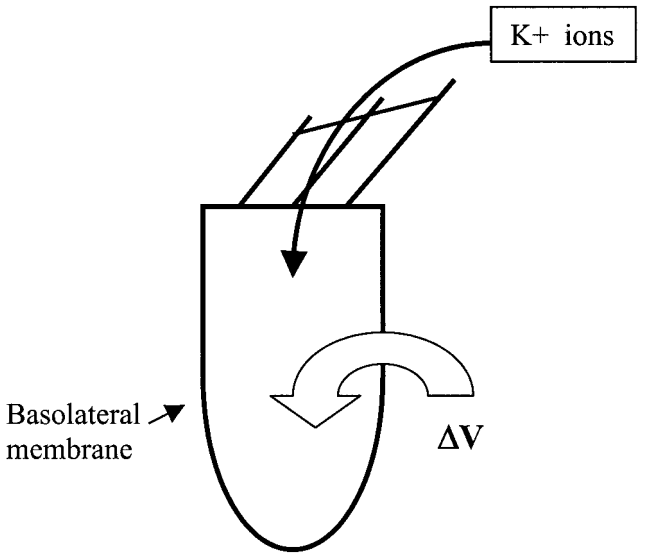

Figure 5. Schematic of a hair cell. The flow of potassium ions through open transduction channels depolarizes the hair cell, altering the trans-membrane voltage (ΔV). In inner hair cells, the alteration in this membrane potential opens voltage-gated calcium channels in the basolateral membrane, allowing calcium to flow in to the cell. Calcium mediates the release of neurotransmitter at the afferent synapse of the inner hair cell.

(EMT) or the active process. The mechanical event (whatever it is) generates a force in phase with basilar membrane velocity that increases basilar membrane vibration. The increase in basilar membrane vibration further deflects the stereocilia at the top of the hair cells, increasing the modulated current that flows through the transduction channels, which in turn increases the power added by the active process. Accordingly, there is an inherent rise time for cochlear mechanical amplification to reach a stable level where the modulated current flowing through the transduction channels at the top of the stereocilia of OHCs is in balance with the resultant mechanical force on the basilar membrane.

Requirements for the Active Process in the Cochlea to Work

The active process, whatever it is, must possess the following properties (Yates, 1995):

1. It has to be fast. The upper limit to mammalian hearing is in excess of 100 kHz, with some whales, for instance, having hearing that extends to 100 to 140 kHz (Hemilä, Nummela, & Reuter, 2001). So the active process must operate on a time scale of microseconds (or faster) to influence basilar membrane vibration on a cycle-by-cycle basis.
2. The force generated by the active process must oppose friction. The force generated by the active process must be in phase with basilar membrane velocity. Viscous forces associated with cochlear fluids oppose basilar membrane vibration and a force in phase with this vibration or basilar membrane velocity will act to counter these viscous forces, i.e., will produce a negative damping.

What is the Active Process?

Somatic Motility • In the mid 1980s, William Brownell and coworkers reported that mammalian OHCs in a dish (termed in vitro) demonstrated somatic motility, i.e., the cell bodies were observed to contract and elongate (Brownell, 1983; Brownell, Bader, Bertrand, de Ribaupierre, 1985). This somatic motility is voltage-dependent (Iwasa & Kachar, 1989; Santos-Sacchi & Dilger, 1988), being produced by changes in trans-membrane potential (Dallos, Evans, & Hallworth, 1991). The basis of this somatic motility was not known until recently, but was thought to be due to voltage-dependent conformational (shape) changes in proteins embedded in the cell membrane (Dallos et al., 1991).

In 2000, Peter Dallos and coworkers identified "the motor protein of the cochlear outer hair cell" (Zheng et al., 2000, p. 149). This protein, called Prestin, is expressed in OHCs but not in IHCs, and is a trans-membrane protein; when Prestin is present in a cell, the cell can undergo voltage-induced changes in shape (Zheng et al., 2000).

Somatic motility, if present in vivo, provides a possible cellular mechanism for cochlear mechanical amplification. But what is the source of the voltage drive in situ?

Receptor Potential: One possibility is the voltage that develops across the basolateral membrane with the change in intracellular potential that follows modulation of the standing current with stereocilial deflection, i.e., the receptor potential. However, the cell membrane of an OHC (an IHC, and all other cells, in principle) possesses the property of not being able to develop a significant voltage at high frequencies due to its low-pass filtering characteristic[¶#] (Santos-Sacchi, 1992) (see Fig. 6). This means that as frequency increases, there will be a point above which there is insufficient receptor potential to provide a motile response that could amplify

[¶]The cell membrane possesses resistance and capacitance; the resistance is quantified by the ion channels in the membrane, the capacitance by the ability of the membrane to separate charge.
[#]Santos-Sacchi's (1992) measurements of the OHC cut-off frequency were qualified by the fact that the cut-off frequency he obtained was concordant with the voltage clamp amplifier he used.

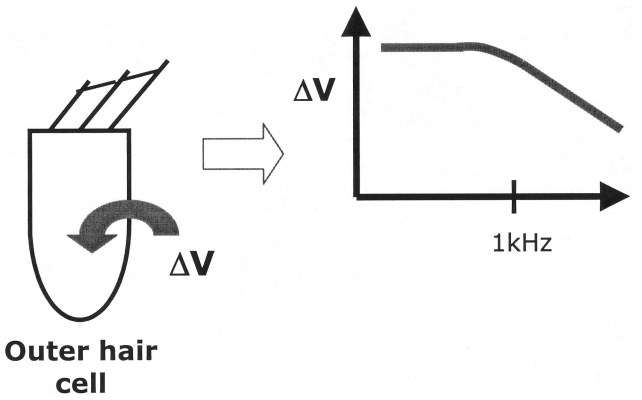

Figure 6. The Receptor Potential. As frequency increases, a frequency may be reached above which the receptor potential cannot drive somatic motility due to low-pass filtering by the membrane capacitance.

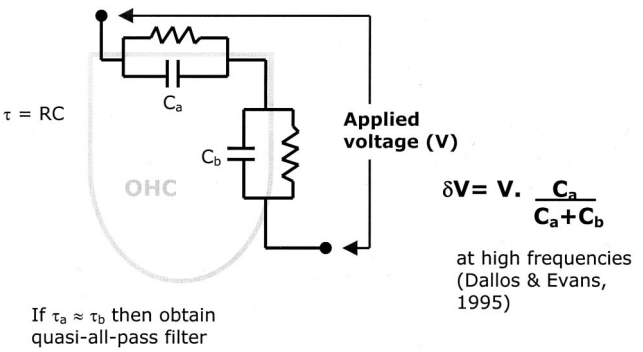

Figure 7. The outer hair cell electrical impedance modeled as two R-C (resistor-capacitor) components in series (Dallos & Evans, 1995), where the apical cell membrane facing endolymph and the basolateral membrane facing perilymph are each comprised of a resistance and capacitance in parallel. At high frequencies, the coupling between the apical and basolateral membranes is capacitive, i.e., a capacitive voltage divider.

basilar membrane vibration. Dallos (1996) estimated this frequency to be approximately 6 kHz.

It has been observed though that without knowledge of the in vivo mechanical impedance of the OHC and its load, one cannot be certain that the electrically low-pass filtered receptor potential is insufficient to drive somatic motility** (Mountain & Hubbard, 1994).

Extracellular Voltage-Drive: Dallos and Evans (1995) have suggested that an extracellular voltage source could overcome the frequency limitation set by membrane filtering. This extra-cellular voltage source is the voltage drop that is a stimulus-related consequence of current flow into the OHC. The electrical impedance of an OHC is treated as having two R-C (resistor-capacitor) components in series, where the apical cell membrane facing endolymph and the basolateral membrane facing perilymph are each comprised of a resistance and capacitance in parallel (see Fig. 7). At high frequencies the resistive elements can be ignored and the coupling between the two components is capacitive (a capacitive voltage divider). The extracellular voltage source is the weighted vector sum of contributions from OHCs basal to the CF place (Dallos, 1996). Such a mechanism can be independent of frequency if the time constants of the impedance elements of the OHC (the two R-C elements in series) are the same (Dallos & Evans, 1995).

It has been observed that OHCs in vitro are capable of somatic motility up to at least 79 kHz, with a force that is constant up to 50 kHz (Frank, Hemmert, & Gummer, 1999). If such properties translate to in vivo, OHCs would be capable of a speed that goes some way towards that necessary to provide for cochlear mechanical amplification up to 100 to 140 kHz (the upper limit for mammalian hearing). However, a constant force production may be insufficient—the force generated by the active process must increase at ≥6 dB/octave to overcome viscous forces (Yates, 1995).

A capacitively coupled extra-cellular voltage-driven motor is perhaps at odds with some recent work by Yates and Kirk (1998). In this article, electrically evoked otoacoustic emissions (EEOAEs) were recorded that resulted from current injection into Scala Media. To examine whether the voltage that results from such a current source is capacitively coupled to the extracellular spaces within the organ of Corti, an acoustic low-frequency biasing tone was introduced that would bias the state of the OHC transduction channels. Yates and Kirk found that the EEOAE was modulated by the presence of the biasing tone (see Fig. 8), arguing for much of the electrical current to have passed through the transduction channels, as distinct from a capacitive coupling where the state of the transduction channels should be unimportant, i.e., the EEOAE would not be modulated by the biasing tone if the current did not flow through the transduction channels.

To elucidate further the feasibility of the model of Dallos and Evans, appropriate measurements within the organ of Corti are needed.

Electrical Energy as Drive Source: Santos-Sacchi, Kakehata, Kikuchi, Katori, and Takasaka (1998) have suggested that there is no frequency limitation due to membrane filtering, arguing that the impor-

**Mountain and Hubbard (1994) observed that at resonance the impedance could be quite low such that the receptor potential may be sufficient to drive somatic motility. However, extrapolating the in vitro findings of Frank et al. (1999) of constant force production suggests that the outer hair cell plus load impedance at resonance would have to reduce concurrently with receptor potential.

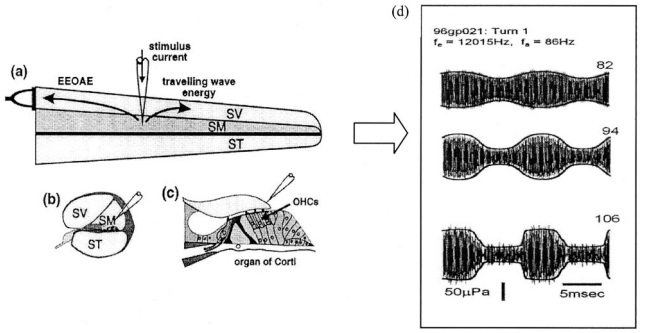

Figure 8. Amplitude-modulation of electrically evoked otoacoustic emissions (Yates & Kirk, 1998). Electrical current was injected into Scala Media, as illustrated in (a) and (b). The position of the electrode tip relative to the organ of Corti is illustrated in (c). Panel (d) shows the amplitude-modulated electrically evoked otoacoustic emissions obtained for an electrical current frequency of 12,015 Hz and a low-frequency acoustic biasing tone of 86 Hz at three different sound pressure levels (82, 94, 106 dB). (Reproduced in adapted form from Figures 1 and 4, Yates and Kirk (1998), Journal of Neuroscience, 18(6), 1996–2003, with permission. Copyright 1998 by the Society for Neuroscience).

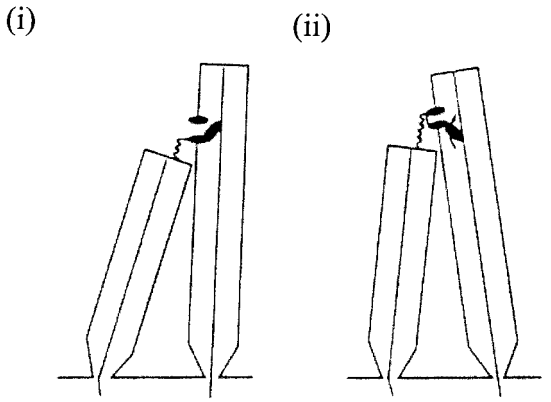

Figure 9. Myosin Motor Model. (i) Displacement of the hair cell bundle in the positive direction (away from the modiolus) triggers the contraction of myosin molecules associated with the tip-links. (ii) Contraction of myosin molecules alters tip-link tension, producing hair bundle movement in the negative direction. (Reproduced in adapted form from Figure 1, Current Opinion in Neurobiology, 7, Hudspeth, Mechanical amplification of stimuli by hair cells, 480–486, Copyright 1997, with permission from Elsevier Science).

tant quantity is the electrical energy ($Q \times V$) supplied to the OHC basolateral membrane. The lateral membrane[††] motor protein density of an OHC is predicted to increase with decreasing cell length (cell length decreases as one goes from apex to base in the cochlea). So while V (receptor potential) is decreasing with increasing frequency, Q (the charge density, which is equivalent to the motor protein density) is increasing with frequency by the same amount, giving a constant electrical energy source.

The end-product of such a model presumably would be an active process with constant force production along the cochlear partition, and as has been stated previously, a constant force production may not be adequate for cochlear mechanical amplification (Yates, 1995). However, if Q increased sufficiently rapidly with frequency, the force production could increase with frequency sufficient to overcome viscous forces. Increased motor-protein density with decreasing cell length is inconsistent with the findings of Frank et al. (1999).

A Motor in the Hair Cell Bundle • An active process powered by the hair cell bundle located at the top of the OHC was suggested as early as 1982 (Weiss, 1982). Indeed, in nonmammalian vertebrates such as birds and lizards, available evidence argues strongly for a mechanical motor driven by the stereocilia or hair cell bundle, nonmammals not having any cell in the cochlea that resembles the mammalian OHC (Manley et al., 2001; Manley & Köppl, 1998). But how could such a motor work?

Hudspeth (1997) posited two possibilities:

1. A Myosin motor. Displacement of the hair-cell bundle away from the modiolus "triggers the contraction of myosin molecules associated with the tip links" (Hudspeth, 1997, p. 481), this contraction associated with an interaction between the myosin molecules and actin filaments within the stereocilium (Hudspeth & Gillespie, 1994). Actin-myosin interactions are more commonly associated with the sliding filament model of skeletal muscle contraction, a process that is ATP dependent. It is suggested that the interaction of myosin and actin in this model would alter tip-link tension, moving the hair-cell bundle in the opposite direction (see Fig. 9).

A myosin-based motor, however, may be subject to a speed or frequency constraint: the rate at which ATP hydrolysis (breakdown of ATP) can occur (Martin, Mehta, & Hudspeth, 2000). It has been suggested that this speed constraint could be overcome if not every myosin molecule must contribute on every cycle of oscillation (Hudspeth & Gillespie, 1994; Manley & Gallo, 1997); however, it has been suggested that it is difficult to conceive how such a motor could operate at speeds of 100 kHz and greater (Choe, Magnasco, & Hudspeth, 1998).

2. A MET channel motor. Displacement of the hair cell bundle away from the modiolus opens the MET channel, resulting in an increase in

[††]The lateral membrane is the outer layer of the lateral cortex or cell membrane. It is this layer that contains the proteins thought to undergo voltage-induced length changes (Holley, 1996).

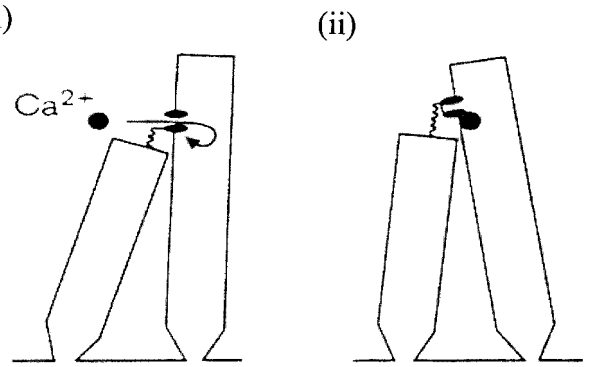

Figure 10. MET Channel Motor Model. (i) Displacement of the hair cell bundle in the positive direction (away from the modiolus) opens MET channels, allowing potassium and calcium to enter the cell. Calcium is hypothesized to bind to a site on the interior aspect of the channel, promoting channel reclosure. (ii) Channel reclosure alters tip-link tension, moving the hair cell bundle in the opposite direction. (Reproduced in adapted form from Figure 1, Current Opinion in Neurobiology, 7, Hudspeth, Mechanical amplification of stimuli by hair cells, 480–486, Copyright 1997, with permission from Elsevier Science).

potassium and calcium entering the cell. Calcium, it has been hypothesized, binds to a site on or related to the channel, promoting channel re-closure. This channel re-closure produces a "rise in tip-link tension [that] jerks the hair bundle back in the negative direction" (Hudspeth, 1997, p. 481) (see Fig. 10).

As with myosin, there may be a speed limitation, in this case the rate of binding and disassociation of calcium to and from the binding site (Choe et al., 1998). And as with myosin, this constraint could be overcome at higher frequencies if only some fraction of the total number of MET channels contributes on each cycle of oscillation.

Both 1 and 2 suggest a force associated with channel re-closure. To be effective, this force must be in-phase with the inhibitory direction of stereocilia deflection. This requires a frequency-selective mechanism for force delivery (see Choe et al., 1998; Hudspeth, 1997), such tuning perhaps being inherent in the physical properties of the stereocilia, e.g., elastic properties of the hair bundle (Camalet, Duki, Jülicher, & Prost, 2000).

Active hair-bundle movement, i.e., bundle movement larger than the stimulus, which represents a source of power that could drive cochlear mechanical amplification, has been observed in isolated hair cells from the sacculus of the bullfrog (Martin & Hudspeth, 1999) and the auditory papilla of the turtle (Ricci, Crawford, & Fettiplace, 2000). To date, such active hair-bundle movement has been observed on the order tens of hertz and perhaps thousands of hertz (Fettiplace, Ricci, & Hackney, 2001; Martin & Hudspeth, 1999; Ricci et al., 2000). Further, in vivo evidence of a motor in the hair cell bundle in a nonmammalian vertebrate operating at least on the order of a kilohertz has been reported recently by Manley et al. (2001)[‡‡].

Isolating the Active Process

The active process or EMT is contained in a feedback loop that makes isolating it difficult, if not impossible. The operation of any element in a feedback loop is dependent on the operation of all other elements within the loop. Interfering with one or more elements affects all of the elements with the result that one cannot ascertain which element is the active process.

Experiments have been performed with pharmacologic agents that in vitro have been found to damage the basolateral membrane of the OHC, perhaps the most widely investigated involving the perfusion of salicylate into Scala Tympani. Salicylate alters the properties of the OHC basolateral membrane (Shehata, Brownell, & Dieler, 1991; Stypulkowski, 1990) and interferes with somatic motility (Kakehata & Santos-Sacchi, 1996) while seemingly (in the short term) not affecting MET channels at the top of the stereocilia nor entering the cell through these MET channels (Fitzgerald, Robertson, & Johnstone, 1993). After salicylate perfusion in to Scala Tympani, it has been observed that: 1) cubic-distortion tone otoacoustic emissions ($2f_1$-f_2) are reduced; 2) compound action potential thresholds are elevated; and 3) the cochlear microphonic measured at the round window in response to a 1 kHz tone is increased in magnitude (endocochlear potential did not change) (Fitzgerald et al., 1993). Such findings are consistent with an alteration in the properties of the basolateral membrane and interference with an active process involving somatic motility; however, a shift in operating point[§§] associated with depolarization of the OHC would presumably also account for such findings. Indeed, Frank and Kossl (1996) observed changes in the cubic and quadratic distortion tone otoacoustic emis-

[‡‡]Manley et al. (2001) measured electrically evoked otoacoustic emissions that were amplitude modulated by a low-frequency acoustical stimulus, the unique modulation pattern being traceable to a hair cell bundle motor (made possible by a unique hair cell bundle arrangement in the lizard in the high-frequency region where bundles are oppositely oriented).

[§§]The operating point reflects the probability of a transduction channel being open versus closed in the absence of sound. In OHCs, the open channel probability is dependent on stereocilial displacement—shortening of the cell body associated with depolarization of the OHC increases the open channel probability, i.e., shifts the operating point.

sions initially after salicylate perfusion in to Scala Tympani that are consistent with an operating point shift.

DISCUSSION

Nonmammalian vertebrates would seem to have a motor in the hair cell bundle that provides cochlear mechanical amplification (Manley et al., 2001). OHCs appear to be unique to mammals, demonstrating a somatic motility not seen in nonmammalian vertebrate hair cells. So if mammals have a hair cell bundle motor as it appears do nonmammalian vertebrates, what is the purpose of somatic motility—an automatic gain control via shifts in operating point, or does indeed an evolutionary dichotomy exist?

The determination of what mechanism is responsible for "the active process" in the mammalian cochlea presupposes that there is only one mechanism. Indeed, this article has considered cochlear mechanical amplification in mammals due to a motor in the hair cell bundle versus a motor based on somatic motility. It may be that the active process in the mammalian cochlea consists of more than one mechanism, i.e., cochlear mechanical amplification in mammals may be achieved by a motor in the hair cell bundle and a motor based on somatic motility (Manley, 2001), or indeed, the motor may be spatially dependent, e.g., a different mechanism may operate in the base versus the apex of the cochlea. Of course, such a dual motor system introduces the additional complication of timing differences in the operation of each of the motors.

With the discovery by Dallos and coworkers of Prestin, the protein in OHCs that provides for somatic motility, the next step presumably in the quest for isolating the active process is the development of a "knock-out" mouse, a mouse lacking the gene for Prestin. Of course, concomitant with a hair cell deficient in this protein may be changes in cochlear function that preclude a simple answer to the question of the location of the motor in the mammalian OHC.

The determination of what is the active process involves understanding how electrical energy is converted into mechanical energy with the generation of a force that amplifies basilar membrane vibration. This can only be achieved by being able to answer the following questions:

1. what is the molecular motor?
2. how does this motor utilize electrical energy to produce mechanical energy?
3. how is the force produced by this motor coupled in to the organ of Corti with a phase that opposes viscous forces so as to enhance basilar membrane vibration?

Only by being able to answer all of the above questions can we be certain that the active process has truly been found (and in the process of course satisfying the constraint of speed, i.e., operating on a time scale of microseconds or faster).

For nonmammalian vertebrates a general consensus has been reached that the motor is in the hair cell bundle. It remains to be seen whether mammals have evolved a different solution for mechanical amplification in the cochlea.

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