

The Membrane-based Mechanism of Cell Motility in Cochlear Outer Hair Cells[□]

Gregory I. Frolenkov,* Marco Atzori,* Federico Kalinec,[†] Fabio Mammano,[‡] and Bechara Kachar*

*Section on Structural Cell Biology, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, Maryland 20852-3320; [†]Department of Cell and Molecular Biology, House Ear Institute, Los Angeles, California 90057; and [‡]Biophysics Laboratory, International School for Advanced Studies, Trieste, Italy

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INTRODUCTION

The sensitivity of the mammalian inner ear is extraordinary. At the threshold of hearing, the incoming sound produces vibrations inside the organ of Corti that are of the same order of magnitude or less than the thermal noise motion (Hudspeth, 1989, 1997; Dallos, 1996). Such sensitivity is achieved through an energy-dependent process commonly referred to as "cochlear amplifier," i.e., the cycle-by-cycle amplification of the intracochlear vibrations that neutralizes viscous losses by positive mechanical feedback (Patuzzi and Robertson, 1988; Ashmore and Kolston, 1994; Kolston, 1995). The mechanical feedback force that makes the amplification possible is thought to be provided by cochlear outer hair cells (OHCs), a class of specialized sensorimotor cells hosted within the organ of Corti (Lim and Kalinec, 1998; Nobili *et al.*, 1998). Direct support to the feedback hypothesis comes from the fact that OHCs possess a unique ability to change significantly their shape in response to electrical stimulation (Brownell *et al.*, 1985; Kachar *et al.*, 1986), a phenomenon called electromotility.

VIDEO MOVIES

Movie 1: OHC Electromotility in an External Electric Field

This movie shows contraction and elongation of a guinea pig's OHC placed in an external alternating electric field (Figure 1). Isolated OHCs were obtained by mechanical dissociation from strips of the organ of Corti after mild enzymatic treatment (Collagenase type IV; Life Technologies, Grand Island, NY; 1 mg/ml, 10–15 min). Two Ag-AgCl electrodes were placed ~2 mm apart along the cell body. Alternating voltage steps applied to the electrodes (2 V, 2 Hz) produced an

electric field approximately parallel to the cell body. Under these experimental conditions the electrically evoked length changes could be as large as ~1 μm for 70- to 90-μm-long cells.

A variety of stimuli, chemical (Zenner *et al.*, 1985; Zenner, 1986), thermal (Gitter, 1992), electrical (Brownell *et al.*, 1985), mechanical (Canlon *et al.*, 1988; Brundin *et al.*, 1989; Brundin and Russel, 1994) and UV light (Dulon *et al.*, 1989), have been reported to affect OHC length. Among them, electromotility attracted particular attention, because electrically evoked changes in OHC length are sufficiently fast to follow stimulation on a cycle-by-cycle basis at acoustic frequencies (Kachar *et al.*, 1986; Ashmore, 1987; Reuter *et al.*, 1992, Gale and Ashmore, 1997). Thorough investigation of this phenomenon became possible with the application of the whole-cell patch-clamp recording technique to OHC studies (Ashmore, 1987).

Movie 2: OHC Electromotility in Whole-Cell Patch-Clamp Conditions

This movie shows OHC motility evoked by changes of intracellular potential under conditions whereby intracellular voltage was imposed on the cell by the patch-clamp amplifier (Figure 2). The potential of the cell was held at -70 mV, and square depolarizing pulses of 60 mV amplitude were delivered at the rate of one per second (stimulation mark is on the bottom left of the frame). Depolarization produced contraction, whereas hyperpolarization resulted in elongation of the cell. Reduction or reversal of transmembrane current in these conditions by various manipulations did not interfere with OHC mechanical response, which led to the suggestion that OHC motility is driven by transmembrane voltage rather than current (Santos-Sacchi and Dilger, 1988). This conclusion has been confirmed by the observation that OHC mechanical response in an external electric field disappeared after membrane permeabilization (Iwasa and Kachar,

[□] Online version of this essay contains video material for Figures 1–9. Online version available at www.molbiolcell.org.

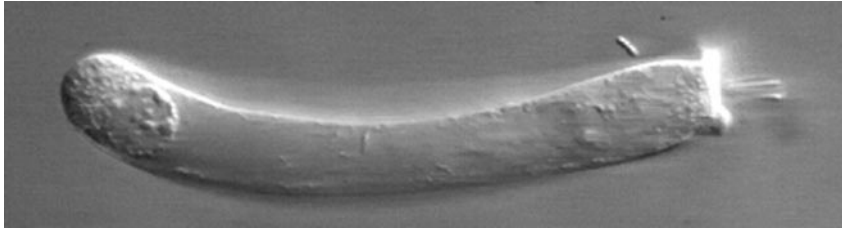


Figure 1. OHC electromotility in an external electric field.

1989). Later it was shown that the driving stimulus is indeed a local transmembrane voltage drop and that the cellular motor consists of independent elements, distributed along the lateral cell membrane and its associated cortical structures (Holley and Ashmore, 1988b; Dallos *et al.*, 1991; Kalinec *et al.*, 1992). OHCs respond to this local stimulus with local changes of membrane area (Kalinec *et al.*, 1992).

The transitions between contracted and elongated states shown in Movie 2 are too fast to be resolved at a standard TV frame rate. Indeed, it was shown that the speed of the OHC motile response in these conditions is limited only by the time constant of the whole-cell recording, which is set essentially by the time required to charge the plasma membrane capacitance through the access resistance of the patch pipette (typically <1 ms; Santos-Sacchi, 1992). The real speed limit

of the OHC motor is even higher than can be obtained in whole-cell patch-clamp experiments and does approach the frequency limit of mammalian hearing (tens of kilohertz; Gale and Ashmore, 1997).

In vivo, the intracellular potential is assumed to change after the influx of ionic current through the mechanoelectric transduction channels located at the OHC stereocilia. The channels are opened by displacement of the stereocilia bundles toward the tallest one when the organ of Corti oscillates in response to incoming sound vibrations (Ashmore and Kolston, 1994). Nevertheless, this way of changing the intracellular potential has essentially the same frequency limitations as the experimental whole-cell patch-clamp technique. To overcome this problem, Dallos and Evans (1995) suggested that extracellular potential variations resulting from transduction current

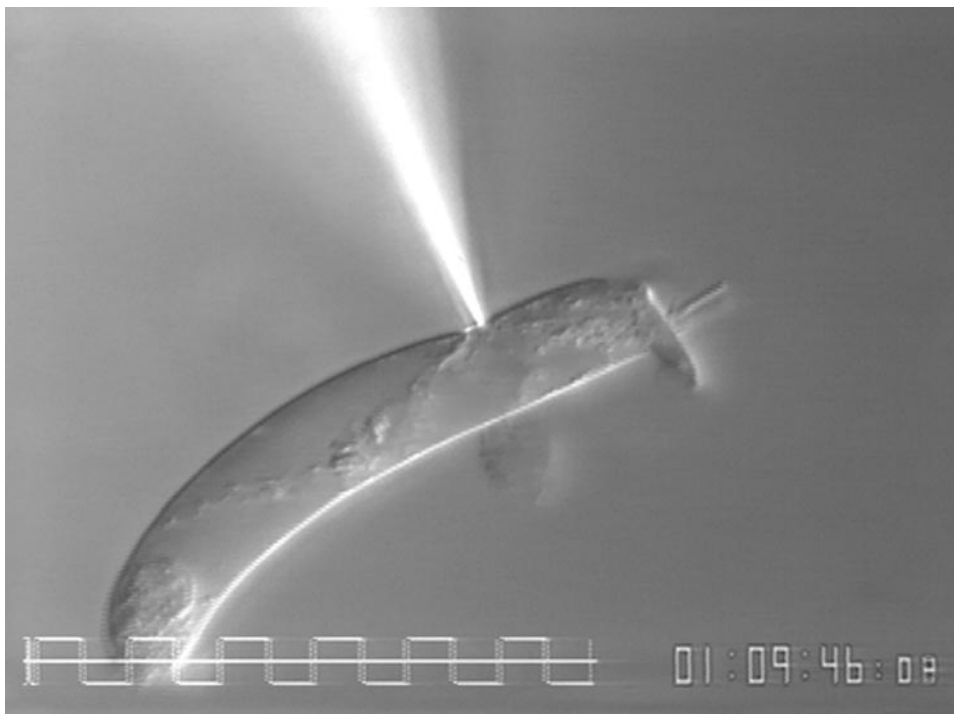


Figure 2. OHC electromotility in whole-cell patch-clamp conditions.

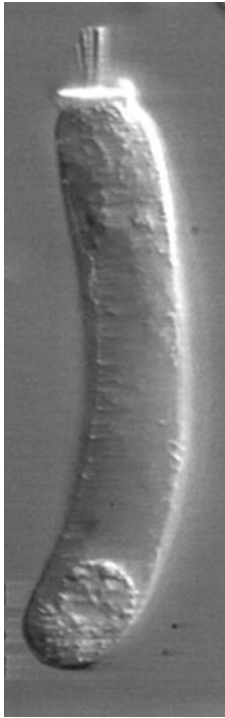


Figure 3. Bending of the OHC in an external electric field

changes could be a driving force for high-frequency OHC motility *in vivo*.

Movie 3: Bending of the OHC in an External Electric Field

An extracellular electric field is able to drive OHC motility at high frequencies (Reuter *et al.*, 1992; Dallos and Evans, 1995). It may also modify significantly the OHC motile response if there is a component of the voltage gradient across the cell diameter. This movie shows OHC shape changes in an external electric field oriented perpendicularly to the cell axes (Figure 3). Stimulation is the same as in Movie 1. Because of the relative axial symmetry, the OHC may be considered as a conductive liquid compartment enclosed by a membrane with relatively high resistance (Frolenkov *et al.*, 1997). In an external electric field this compartment undergoes charge separation, producing depolarization on one side of the cell and hyperpolarization on the other side. The result is the bending of the cell toward the negative electrode.

Movie 4: OHC Electromotile Force Is Sufficient to Produce Movement inside the Organ of Corti

This animation was built from a set of four images of the cochlear partition viewed from scala media at an angle bringing the full length of OHCs into focus (Figure 4) (data acquired in Prof. Jonathan F. Ash-

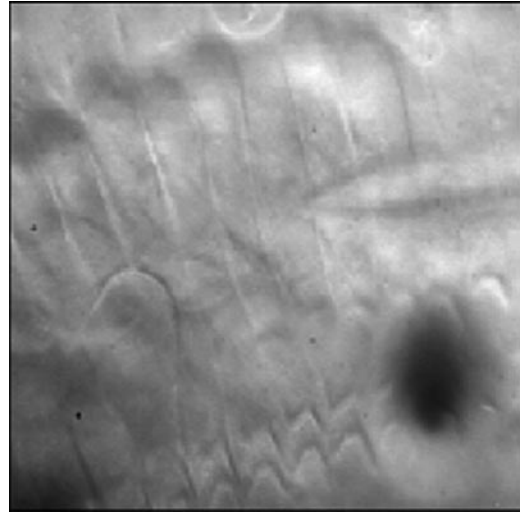


Figure 4. OHC electromotile force is sufficient to produce movement inside the organ of Corti.

more's laboratory at the Department of Physiology, University of Bristol, Bristol, United Kingdom; see Mammano *et al.*, 1995). The cell's stereocilia are visible, through the intact tectorial membrane, near the frame bottom. A patch pipette (entering from the right) was attached to a third-row OHC, incrementing cell potential by 25 mV between successive frames. The cell responded by shortening visibly when depolarized within the intact organ of Corti. Both the synaptic end and the stereociliary end of the OHC moved toward the patch pipette, in accord with the distributed nature of the molecular motors along the cell wall (Holley and Ashmore, 1988b; Dallos *et al.*, 1991). The movement of the synaptic end, cupped by a supporting Deiters' cell, could be as large as 1.5 μm when the cell membrane potential was stepped positive by 100 mV from rest. However, the movement of the stereociliary end was comparatively reduced as the cell cuticular plate was firmly held within the reticular lamina. The mean potential sensitivity of the motile responses *in situ* was $\sim 12 \text{ nm/mV}$. Cell movement caused appreciable displacement of neighboring cells in the organ of Corti, indicating that OHC forces are large enough to alter cochlear mechanics by distorting the cochlear partition.

Movie 5: OHC Electromotility and Intracellular Pressure

Normal intracellular pressure is essential for maintaining good mechanical responses in OHCs (Brownell, 1990; Chertoff and Brownell, 1994). This video clip demonstrates some significant features of the relationship between electromotility and intracellular pressure in an OHC from a ground squirrel

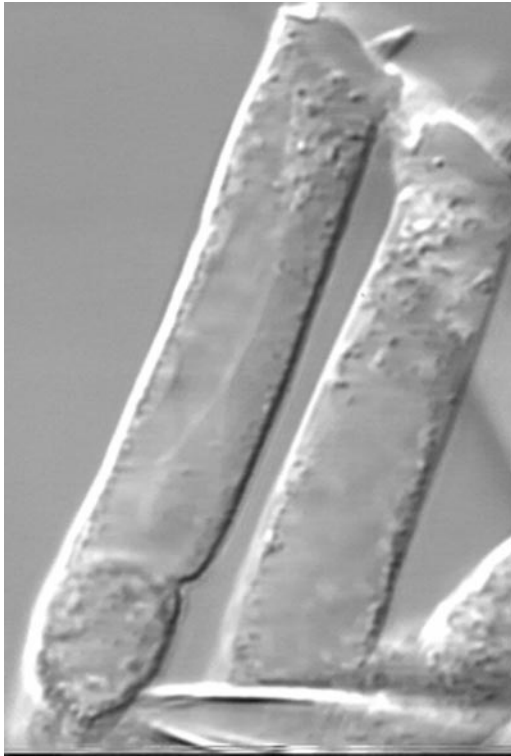


Figure 5. OHC electromotility and intracellular pressure.

(Figure 5). This particular cell lost some internal pressure after the rupture of the membrane patch under the pipette. Changes of transmembrane potential were still able to produce length changes, but of reduced amplitude. The surface of the cell behaved like a rubber balloon, inflating during depolarization and deflating during hyperpolarization. Two important conclusions may be drawn from such observations. First, deflating the cell did not disrupt the electromotile mechanism per se. Second, the OHC responded to intracellular potential variations with the shrinkage and expansion of its surface area, which in turn produced changes in intracellular pressure. Electromotility models predict pressure changes as large as 0.5 kPa for $\sim 0.5\text{-}\mu\text{m}$ -length changes (Dallos *et al.*, 1993).

Movie 6: Effect of Salicylate on the OHC Electromotility

This movie shows the mechanical response of a guinea pig's OHC in patch-clamp conditions before and during puff application of 20 mM salicylic acid (Figure 6). The animation in the top left corner of the frame shows command voltage. The motile response almost disappeared within 5–10 sec after salicylate application.

Salicylic acid is one of a few reagents that are known to block OHC electromotility, the other known block-

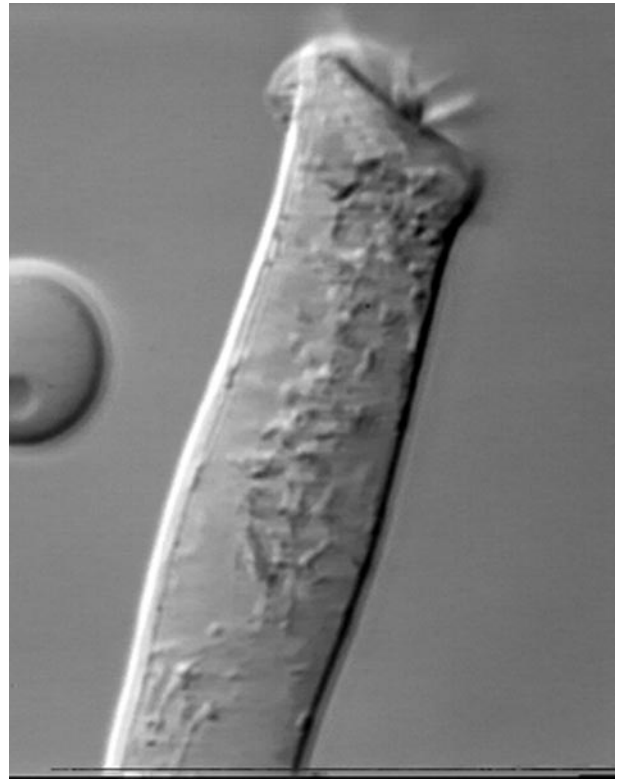


Figure 6. Effect of salicylate on the OHC electromotility.

ers being some sulfhydryl reagents (Kalinec and Kachar, 1993) and lanthanides (Santos-Sacchi, 1991; Kakehata and Santos-Sacchi, 1996). All these inhibitors are not specific because they affect a variety of other functions in the cell. No specific inhibitor of OHC electromotility has been reported so far.

The mechanism of OHC electromotility is clearly different from most other forms of cell motility. It does not depend on the presence of ATP (Kachar *et al.*, 1986; Holley and Ashmore, 1988b) and is resistant to the drugs affecting cycles of polymerization and depolymerization of actin and tubulin (Holley and Ashmore, 1988a). Inhibition by sulfhydryl reagents indicates the involvement of proteins (Kalinec and Kachar, 1993), whereas the dependence on the local transmembrane voltage locates the electromotility mechanism somewhere in plasma membrane and underlying structures (Dallos *et al.*, 1991).

Movie 7: Disruption of the OHC Cytoskeleton with Diamide Does Not Affect Electromotility

The self-supporting shape of OHC is maintained by its cortical structures and in particular by the cortical lattice, a two-dimensional cytoskeleton that lines the inner aspect of the lateral plasma membrane (Holley and Ashmore, 1988a, 1990). Circumferential actin fil-

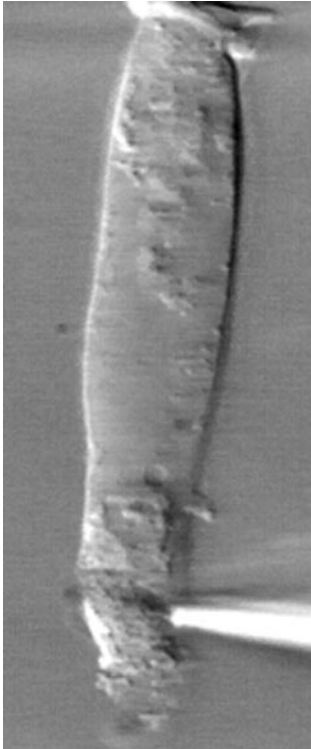


Figure 7. Disruption of the OHC cytoskeleton with diamide does not affect electromotility

aments with longitudinal spectrin cross-links determine the greater mechanical compliance of the cortical lattice in the longitudinal direction (Holley *et al.*, 1992; Tolomeo *et al.*, 1996), providing a mechanical frame for the OHC motile response that is oriented mainly longitudinally (Kalinec and Kachar, 1995). This cortical lattice frame seems to be mechanically passive, al-

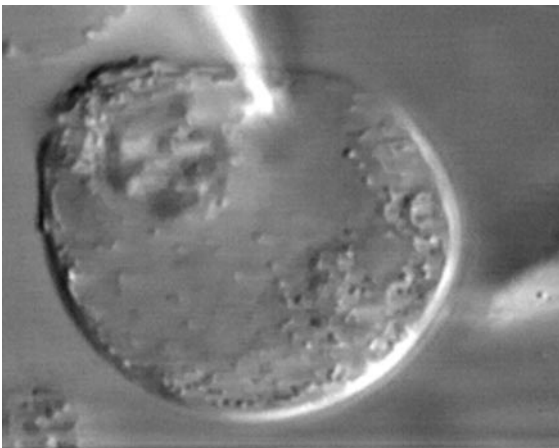


Figure 8. Electromotile mechanism requires only plasma membrane integrity.

Table 1. Ion channel blockers tested on OHC electromotility

Blocker	Concentration
K⁺ voltage-gated channel	
Agiotoxin	10 nM
α-Dendrotoxin	500 nM
β-Dendrotoxin	100 nM
γ-Dendrotoxin	100 nM
δ-Dendrotoxin	100 nM
Dendrotoxin-I	100 nM
Margatoxin	10 nM
MCD peptide	1 μM
Stichodactyla toxin	500 nM
Tityustoxin Kα	50 nM
L-type Ca²⁺ channel	
Calcicludine	10 nM
Calciseptine	14 nM
FS-2	10 nM
TaiCai toxin	500 nM
Waglerine-I	6 μM
Ca²⁺-activated K⁺ channel	
Apamin	1 μM
Charibdotoxin	100 nM
Iberiotoxin	50 nM
Kaliotoxin	100 nM
Noxiustoxin	100 nM
Paxilline	1 μM
Penitrem	1 μM
Non-L-type Ca²⁺ channel	
ω-Agatoxin TK	1 μM
ω-Conotoxin GVIA	33 nM
ω-Conotoxin MVIIA	18 nM
ω-Conotoxin MVIIC	10 nM
ω-Conotoxin SVIB	18 nM
FTX-3.3	1 μM
sFTX-3.3	10 μM
PLTX-II	50 nM

though the possibility exists in principle that spectrin may generate forces relevant for OHC length changes.

This movie shows electromotile response of an OHC incubated with 1 mM diamide and attached to the glass coverslip at its apical pole (Figure 7). Diamide is a bifunctional thiol reagent that oxidizes the sulfhydryl group of cysteine to the disulfide and affects spectrin but not actin (Becker *et al.*, 1986). After diamide application, the cell became less rigid and was easily stretched by displacing the patch pipette. The persistence of electromotile responses even after the cell body has been stretched extensively indicates clearly that the cell electromotility does not require an intact cytoskeleton.

Movie 8: Electromotile Mechanism Requires Only Plasma Membrane Integrity

The most reasonable suggestion is that the electromotility mechanism is located in the plasma membrane itself. To test this hypothesis the patch pipette was filled with solution containing trypsin (150 μg/ml) to produce enzymatic digestion of the cell content. This

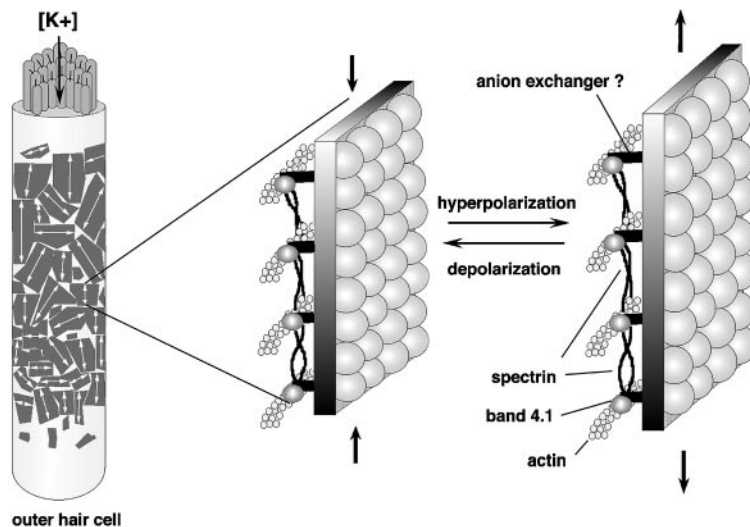


Figure 9. Schematics of OHC force generation unit.

movie shows that the electromechanical responses were still prominent several minutes after the start of intracellular dialysis with trypsin (Figure 8). These results indicate that electromotility depends on a mechanism secluded from the action of trypsin and therefore residing within the plasma membrane (Kalinec *et al.*, 1992). The dramatic disruption of subplasmalemmal structures by trypsin was confirmed by electron microscopy controls (Huang and Santos-Sacchi, 1994).

Freeze-fracture images of the lateral plasma membrane of OHCs revealed an unusually high concentration of intramembrane particles that were never observed in inner hair cells (Gulley and Reese, 1977). Freeze-etching of the membranes after partial extraction with detergent revealed that these intramembrane particles are organized in regular arrays (Kalinec *et al.*, 1992; Kalinec and Kachar, 1995). The center-to-center distance between particles in these arrays is ~ 13 nm (Kachar and Frolenkov, unpublished results), corresponding to a density of ~ 6000 per square micrometer. Such dense arrays of intramembrane particles could form the basis for a force-generating mechanism in OHCs.

Each of these large intramembrane particles may represent a sensorimotor protein complex that detects voltage changes across the membrane and undergoes either conformational changes by itself or changes in the packing within the arrays. Conformational changes in voltage-gated ion channels are associated with gating currents, which represent a total effective electrical charge moving across the membrane (Bezannilla and White, 1982). Similar voltage-dependent charge movement closely associated with the electromotile responses can be recorded in OHCs (Santos-Sacchi, 1991; Iwasa, 1993; Gale and Ashmore, 1997). If

the maximal gating charge and the later surface of OHCs are known, it is possible to estimate the effective number of elementary charges that move across the membrane. Recent estimates gave values of $7558 e^- / \mu\text{m}^2$ (Huang and Santos-Sacchi, 1993), $4200\text{--}8400 e^- / \mu\text{m}^2$ (Gale and Ashmore, 1997), and $12,900 \pm 400 e^- / \mu\text{m}^2$ (Frolenkov and Kachar, unpublished results) which are of the same order of magnitude as the density of intramembrane particles.

Molecular Identity of the OHC Motor

The challenge for the future remains the identification of sensorimotor protein structures at the molecular level. Although the motor is unlikely to be an ion channel, because no ionic current is associated with OHC electromotility, there exists the possibility that it is a modified channel with an integral voltage sensor but no conducting pore. Such molecular structures have been described previously (Olcese *et al.*, 1997), but attempts to use a variety of ion channel blockers to inhibit electromotility gave negative results (see Table 1). The other possibility is that the motor is a transporter protein linked with underlying cytoskeleton. There are reasons to suspect that the OHC motor could be a modified version of an anion exchanger protein (Kalinec *et al.*, 1993, 1997; Knipper *et al.*, 1995; Lim and Kalinec, 1998), but a complete molecular and functional characterization of this protein in OHCs is still lacking.

Movie 9: Schematics of OHC Force Generation Unit

The lateral plasma membrane of the OHCs of the organ of Corti contain "force generation units" composed of small domains of a semicrystalline array of motor proteins (Figure 9). Pillars, connecting these

motor proteins to an actin-spectrin meshwork inside the membrane, convey the forces generated in the plane of the membrane to the cell's interior. We propose that the pillars are composed of the anion exchanger protein and 4.1-band proteins, but it is unclear whether these proteins are just force conveyors or are themselves the motor proteins.

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