Review

CHARACTERISTICS OF ELECTROMOTILITY OF OUTER HAIR CELL LATERAL WALL

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Summary

The aim of this work was to describe unique ultrastructural organization of the outer hair cell lateral wall. The molecular mechanism of electromotility is unknown but it is clear that the composition of plasma membrane, orientation of actin and spectrin molecules of the cytoskeleton and interaction between them could be important for the electromotile response of outer hair cells. Active cochlear mechanisms amplify movement along the basilar membrane and transmit mechanical information to the inner hair cell, thus improving audio perception capabilities in mammals. Outer hair cells have a complex trilaminar lateral wall composed of plasma membrane, highly organized cytoskeleton and subsurface cisternae, which form axial cylinders inserted into each other around the cell core. Recent discoveries have shown that a key component in the electromotility of outer hair cells is a motor protein prestin that is found in the cytoplasmic membrane of outer hair cells. Cytoskeleton nanostructure shows that it is not complete and uninterrupted, and is composed of separate domains, oriented to each other at different angles. Protein pillars are situated between the invaginations of the plasma membrane and actin filaments of the cytoskeleton. The innermost layer of the lateral cell is made up by subsurface cisternae associated with mitochondria.

Key words: outer hair cells, cytoskeleton, electromotility

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Hearing in mammals, unlike that of in other vertebrates, is a complex sensory system with a remarkable sensitivity and a wide range of sound frequency perception. Characteristic features of mammalian auditory system include sensitivity to high frequency sounds, faint sounds, and discrimination of tones of approximate frequencies. These unique properties, particularly those of the human ear, allow perceiving and distinguishing variations in speech. This perfection of auditory reception in mammals is attributed to the presence of passive and active cochlear mechanisms.

Passive cochlear mechanisms are related to systemic differences in the physical characteristics of the vibrating structures along the span of the cochlear spiral. These mechanisms determine the

destination of the maximum vibrations of the traveling wave, thus realizing the cochleotopic distribution of the sound frequencies. In the cochlear basal coil, the basilar membrane supports structures with less mass and more stiffness triggering maximum vibrations in response to high frequency sounds. In contrast, the apical coil has more mass and less stiffness and for that reason it vibrates at low frequency sounds.

Active cochlear mechanisms are associated with outer hair cell motility in the living cochlea. These mechanisms amplify movement along the basilar membrane and transmit mechanical information to the inner hair cells, thus improving audio perception capabilities in mammals. Embedded in the upper surface of the basilar membrane, these cells form the organ of Corti together with the inner hair cells and support cells of different origin [1, 2, 3, 4].

At the cochlear base, outer hair cells have elongated cylindrical bodies ranging between 15 and 20 μm in size, and 80-90 μm at the apex, near the helicotrema. The longest cells are situated at the outermost external row. The apical and basal ends of these cells are firmly attached to the reticular plate and Deiter's cells projections. The tips of the stereocilial bundle are embedded into the overlying tectorial membrane. In this fashion, they form a common functional complex between the basilar, reticular and tectorial membranes [5, 6, 7, 8].

Uncoordinated upward and downward movements along the tectorial and basilar membrane respond to sound pressure by deflection-flexion of stereocilia, which open and close the mechanosensitive canals on their apexes. Because of the positive endocochlear potential (approximately +80mV) and the high Na^+ and Ca^{2+} concentration in the endolymph, the opening of the transduction canals cause sharp changes in the transduction potential of the outer hair cells. In a unique way, these cells transduce membrane potential changes into movement, called electromotility [8, 9, 10, 11].

Outer hair cell electromotility is a change of form resulting from direct conversion of electric potential into mechanical force. Hyperpolarization potentials elongate all bodies, whereas the depolarization potentials reverse this process. In this way, every sound cycle of the outer hair cells generates mechanical energy, which is transferred to the tectorial and basilar membrane, and at the precise phase amplifies sound-induced vibrations in the cochlea. Force, produced by the outer hair cells does not equally amplify all frequencies. It affects only characteristic frequencies (maximum vibrations) so that the cochlea increases sensitivity to faint sounds, thus enhancing frequency discrimination.

Initially, outer hair cells electromotility was observed in isolated cells. Experiments later demonstrated that mechanical and electrical stimuli can provoke outer hair cell motility, and produce basilar membrane vibrations. Observations show that some drugs reduce outer hair cells electromotility in the living cochlea resulting in amplification failure, decline in frequency selectivity and cochlear nonlinearities. Molecular foundations and the locations of the motors involved in the outer hair cells electromotility has been the subject of extensive research [12, 13, 14].

A resourceful experiment with trypsinated outer hair cells with destroyed central cytoskeleton and cytoplasm shows that these cells preserve motility. This finding suggests that motility does not depend on these structures, hydrolysis of energetic phosphates such as ATP, or Ca^{2+} presence or the presence of signal and chemical cascades. According to this experiment however, it is the cell wall that houses motors involved in electromotility.

Outer hair cells have a complex trilaminar lateral wall, composed of plasma membrane, highly organized cytoskeleton and subsurface cisternae, which cisternae form axial cylinders inserted into each other around the cell core. The cell wall possesses self-reproduction and self-regeneration properties. The plasma membrane along the lateral surface of the outer hair cells is a wave-like enfolding. The lipid bilayer is characterized by low levels of cholesterol, which regulates the presence of integral proteins and facilitates conformational changes. Specific structural distinction is the presence of densely lined particulates along the internal bilayer side, comprising of integral proteins about 10 nm in diameter; their density ranging from 2500/ μm^2 [Saito, 1983] to 7000 μm^2 [Forge, 1991]. Particulates along the plasma membrane are not equally distributed. They are scattered in the regions of the cell ends. In the ontogenic development of the outer hair cells, the particulate density in white rats increases between days 2 to 16 after birth, until it reaches

adult density values. This process coincides with the initiation and development of motility in the outer hair cells in this species [15, 16, 17].

Recent discoveries show that a motor protein, prestin, is available in the cytoplasmic membrane of the outer hair cells, but it is not present in the membranes of the inner hair cells. This protein is homologous to the phosphate transporters, which facilitate the transfer of anions across membranes [14, 18, 19].

Prestin is a tetramer which has monomers consisting of three parts: N-end (~100 AC), hydrophobic middle part (~ 400 AC) and C-end (~240 AC). The hydrophobic part possesses 12 α -spirals (domains) which penetrate the lipid bilayer membrane. Prestin is a conserved protein over 90% identical with the amino acids in humans, mice and rats. Prestin is fully expressed in the outer hair cells, with well-manifested movement activity.

Prestin synthesis coincides with the onset of movement activity. It manifests longitudinal and radial gradient from the base to the apex and from the first to the third row of the outer hair cells. When prestin has heterologous expression in other types of cells, they start to adopt features seen in outer hair cells: voltage dependant NLC, change their form, electromechanical reversibility, and generation of mechanical force. All these results support the idea that prestin is a motor protein of the outer hair cells [14, 18, 19, 20, 21, 22, 23, 24, 25].

Although prestin is considered a key component in the electromotility of the outer hair cells, evidence suggests a number of other proteins, which take part in this process. For example, cGMP, an aquaporin-like protein, and sugar transporter Glut 5 are capable of influencing the motor functions of these cells. It is interesting to note that the conservative STAS-domain from the prestin molecule is associated with the pedrin protein, PAT-1, with в β1 subparticle of the NA/K ATP-ase, VCY2-IP1 homologues of MAP-1A and MAP-1B. These observations show that the motors of the outer hair cells do not function independently but in a very complex synchronization with many other molecules. After prestin was identified, many researchers focused their attention on its functional mechanism, which is similar to that in the chlorine anion canals in the cell membrane. These canals transport anions across the electrochemical gradient in the absence of macroergic molecules. Anions that are weakly bonded to the prestin molecule facilitate transportation across the cell membrane, as well as the maintenance of high electric potential needed for electromotility. Conformational changes occur when anions get attached to and then released from the prestin molecule. For this reason, prestin has been determined as a motor molecule responsible for electromotility: it converts one form of energy into another. Prestin can only operate within membranes of variable electric potential [26, 27, 28, 29].

The second component of the cell wall, the cytoskeleton, is located in the extracisternal space, between the plasma membrane and subsurface cisternae. This two-dimensional network consists of actin and spectrin filaments, which counteract cell deformations. Actin filaments are 6-7 nm in diameter, circumferentially coiled around the cell at a distance of 30-80 nm. Spectrin filaments are 2-3 nm thinner and branching. With their orientation parallel to the cell axis, they form transversal connections between the actin filaments. Acto-spectrin bonds are stabilized by an additional protein [1, 4]. Cytoskeleton nanostructure is not complete and uninterrupted - it is composed of separate domains, oriented to each other at different angles. Each domain contains 5 to 7 actin filaments lined in parallel to and connected with irregularly arranged spectrin molecules. Domains are connected by intermediary material, which plays the role of elastic springs and allows adaptation of their positions. Between the plasma membrane and the cytoskeleton, protein pillars 7-10 nm in diameter and 25 nm in length are situated. They are attached between the invaginations of the plasma membrane and the circumferential actin filaments at an interval of 30 nm. Interconnections between the plasma membrane and the cytoskeleton depend on the structural and functional features of the radial stems. They form a strong, dynamic system, which can disintegrate and reassemble, thus regulating the transmission of forces from the plasma membrane to the deep layers of the wall. Because the lateral wall of the outer hair cells is a firmly connected multilayer system, there is no gliding within the different layers; therefore deformation of the plasma membrane results in cytoskeleton deformation [30, 31, 32, 33].

Even though the cortical actospectrin cytoskeleton is a structure common to all cell

species known, its molecular organization, distribution and functions are cell-type specific. For example, red blood cells and the outer hair cells represent two extreme cases of functional adaptation of this structure. Red blood cells, similar to the outer hair cells, possess well-developed cortical actospektrin cytoskeleton but its elements are structured in a different way because of particular mechanical requirements. Their cytoskeleton resembles a spider-like network of long spectrin molecules, attached to short actin filaments. This arrangement allows the spectrin filaments to easily deform, which is a requirement for all cells passing through thin capillaries. In contrast, it is the cytoskeleton arrangement that ensures mechanical stability in outer hair cells. The long, non-elastic actin fibers provide support by surrounding cell bodies; the short, elastic spectrin molecules move along the length of the cells, allowing them to change in length and still remain cylindrical in shape. Therefore, the forces generated in the plasma membrane are limited in the circumferential direction, and are directed longitudinally. In this way, the cell is structurally capable to easily change its length, rather than its diameter [11, 28].

The cortical cytoskeleton also imposes a limiting effect on the lateral diffusion of the cell membrane integral proteins by facilitating aggregation of membrane components in well-defined micro-domains (e.g. membrane particles). In this way, the cytoskeleton plays the role of a sorting mechanism, which sets the location of the membrane molecules in the lateral plasma membrane of the outer hair cells [13, 22, 27].

The subsurface cisternea make up the innermost layer of the lateral cell wall. These flattened sacks, enveloped in elementary membranes, are connected with the tubular reticulum. The cisternae are made up of one or multiple layers. Mitochondria are associated with the innermost layer. Structurally, subsurface cisternae resemble endoplasmic reticulum but possess properties of both endoplasmic reticulum and Golgi complex. The molecular composition of the subsurface cisternae membranes and their content are unidentified. These sacks divide the cytoplasm of the inner hair cells into two regions: external, which contains an axial core; and external, where the cortical cytoskeleton is located [17, 34, 35].

The elements of the lateral wall develop in a sequential order. Initially, motor proteins incorporate in the plasma membrane. This is followed by the development of the cortical reticulum along with its connections with the plasma membrane (radial pillars), which allow motors to effect cochlear mechanisms. Outer hair cells may be regarded as a hydrostat, capable to withstand elevated intracellular pressure. Most cells get destroyed when intracellular pressure increases, even to a small degree. Maintenance of high cell turgor results from the low water membrane permeability and the fortified trilaminar structure of the lateral wall. The morphologic features of outer hair cells surprisingly resemble gliding bacteria in terms of structure and function. Outer hair cell movement involves neither flagella nor pseudopodia: they move around by rotation without bending or changing form. Bacterial cells, similarly to outer hair cells in vertebrates, have increased intracellular turgor, undeveloped central cytoskeleton, trilaminar wall structure, and invaginated external membrane. Gliding bacteria movement occurs by the transduction of the electrochemical gradient into mechanical force in the absence of ATP [36, 37, 38, 39, 40].

The molecular mechanism of the electro-motility is unknown. Among the various models proposed, the area-motor model and the flexoelectricity models have been endorsed. Models, related to the change of motor area, assume that motor molecules exist in the plasma membrane in two stable states: extended and compact. The likelihood of a motor to exist in either state depends on the membrane potential. When the membrane potential fluctuates, molecules change their state and surface. Conformational changes are accompanied by the transfer of electric charge across the membrane. Changes in the surface are expressed in axial elongation or shortening of the cell. This model explains the existence of intramembranous particles, and why motility of the outer hair cells remains intact after the trypsin destruction of the intracellular structures. The recent discovery of prestin also supports this theory [6, 8, 41, 42, 43].

Raphael (2000a) has proposed an alternative flexoelectrical type of electromotility mechanism. According to his model, motility of the outer hair cells is carried out by the changes in the plasma membrane curvature in response to electrically induced reorientation of the dipoles

in it. On the basis of the lateral wall structure, he has defined the term "motile unit," which includes part of the plasma membrane along with the cytoskeleton attached to it and limited by adjacent pillars. The elevated turgor pressure in the extracisternal space of the cell bends the plasma membrane outward in the region between the pillars. The membrane curvatures, formed in this manner, are determined not only by turgor pressure, but also occur spontaneously, as an internal trend of the building blocks of proteins and lipid molecules in the absence of external forces. This phenomenon explains the remaining motility, observed in the outer hair cells after trypsinization. The decrease of curvature radius results in shortening of the cell; and the increase - in its lengthening. Curvature changes in the plasma membrane lead to changes in the space between the spectrin and actin filaments. In this model, the cell plasma membrane is regarded as a liquid crystal, composed of dipoles. Solid crystals are characterized by positional and orientational arrangement, whereas liquid crystals are characterized only by orientational arrangement.

In biological membranes, phospholipids and protein molecules are in state of lateral diffusion. They have no positional arrangement - they are forced to orient their long axis according to the size of their dipole moment. In this way, dipoles create an internal electrical field, which polarizes membranes. When an external electrical field is applied, the dipoles rotate and reorient their direction toward the field. When the external electrical field increases, more molecules are likely to line up toward the field until saturation. Unlike the area-motor model, according to which a molecule possesses only two structural states, the flexoelectrical model has suggested that each molecule can take up multiple positions of orientation. There is no concrete standpoint whether the dipoles are connected with protein or lipid molecules - two self-contradictory alternatives. Conformational models of the protein molecules can change the membrane curvature as result of their large dipole moments. Another possibility is for the electric field to induce aggregation of membrane proteins and easily bring about curvature deformation. Voltage-dependant insertion of amino acids and formation of lateral chains, which extend one of the bilayers and triggering curvature deformation, is also possible [10, 14, 21, 34].

The high membrane resistance limits the electric conductivity of the liquid compartments, resulting in the separation of electric charges in the electric field. Such separation of charges in the outer hair cells may cause depolarization and contraction on one side of the cell membrane, and hyperpolarization and elongation on the opposite side [7, 28, 35, 44].

This description is an attempt to take into account recent discoveries of ultrastructure of the outer hair cells lateral wall and mechanisms that compensate acoustic impedance and contribute to precise tuning.

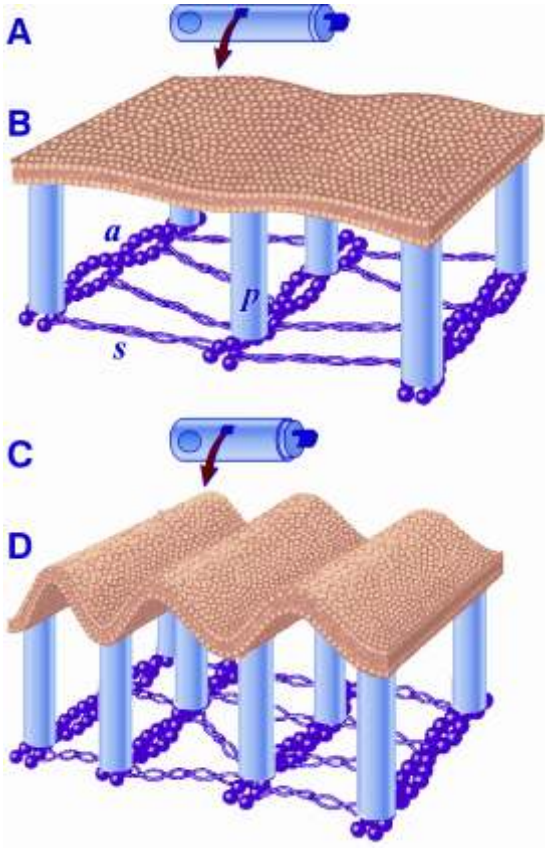

Figure 1. Illustration of the membrane bending model. The plasma membrane is tethered to a subplasmalemmal cytoskeleton by 30-nm-long "pillar" (p). The molecular composition of the pillars is unknown. The pillars bond to parallel actin filaments (a) that run circumferentially around the cell. The actin filaments are spaced about 40 nm apart and cross-linked with molecules of spectrin (s), that run longitudinally along the cell. (A, C) The OHC, when hyperpolarized and depolarized, respectively. Depolarization makes the OHC shorter and wider. (B, D) Potential alterations in membrane curvature resulting from electromotile length changes. Note the increased membrane crenulations in (D). From Oghalai et al. (2000)

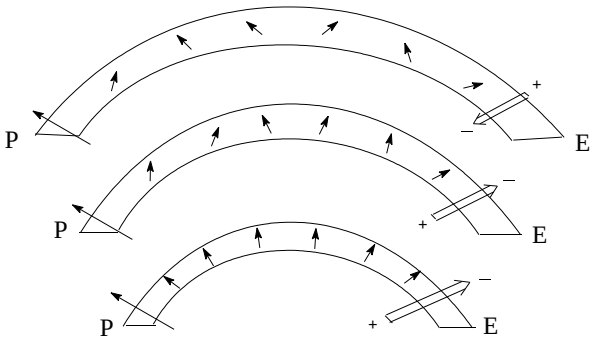

Figure 2. This figure displays the effect of altering the external electric field on the molecular dipoles and, consequently, the curvature and polarization of the membrane. The magnitude and direction of the polarization vector (P) and electric field vector (E) are illustrated as arrows at the left and the right of a curved element of the membrane. The top panel illustrates a hyperpolarized membrane, in which the molecular dipoles have rotated to minimize the polarization opposed to the applied field. This corresponds to the largest radius of curvature. The middle panel represents a slightly depolarized membrane, at which more of the dipoles are aligned with the field and the polarization is increased. The bottom panel represents a maximally depolarized membrane, in which all the dipoles are aligned with the applied field. This corresponds to the largest curvature and the shortest length of the motile unit. From Robert M. Raphael (2000)

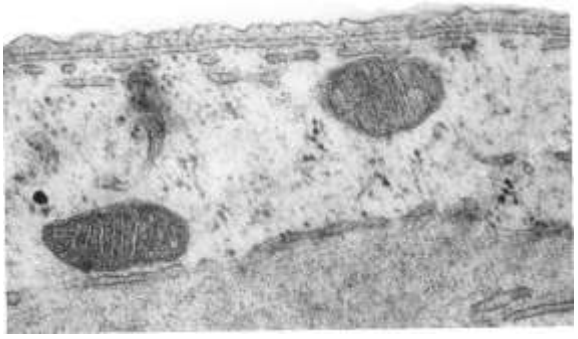

Figure 3. Lateral wall of outer hair cells. Beneath the plasma membrane is the continuous sheet of subsurface cisternae. Mag. 16 000 x

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