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The cochlear amplifier: augmentation of the traveling wave within the inner ear

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Abstract

Purpose of review—There have been many recent advancements in our understanding of cochlear function within the past ten years. In particular, several mechanisms that underlie the sensitivity and sharpness of mammalian tuning have been discovered. This review focuses on these issues.

Recent findings—The cochlear amplifier is essentially a positive feedback loop within the cochlea that amplifies the traveling wave. Thus, vibrations within the organ of Corti are sensed and then force is generated in synchrony to increase the vibrations. Mechanisms that generate force within the cochlea include outer hair cell electromotility and stereociliary active bundle movements. These processes can be modulated by the intracellular ionic composition, the lipid constituents of the outer hair cell plasma membrane, and the structure of the outer hair cell cytoskeleton.

Summary—A thorough understanding of the cochlear amplifier has tremendous implications to improve human hearing. Sensorineural hearing loss is a common clinical problem and a common site of initial pathology is the outer hair cell. Loss of outer hair cells causes loss of the cochlear amplifier, resulting in progressive sensorineural hearing loss.

Keywords

cochlea; cochlear amplifier; outer hair cell; hearing; hearing loss; otoacoustic emissions

Introduction

One important survival advantage mammals have over other vertebrates is a better sense of hearing. This includes an improved sensitivity to quiet sounds, the ability to hear higher frequency sounds, and better frequency discrimination to distinguish between two tones of nearly the same frequency. These advancements enhance the ability of mammals to hear important environmental cues, such as the sound of an approaching predator. Additionally, they underlie the ability of humans to hear nuances associated with speech. While many of the fundamental mechanisms function similarly between the mammalian and the nonmammalian cochlea, mammalian hearing is better because of the cochlear amplifier. The cochlear amplifier is essentially a positive feedback loop within the cochlea that amplifies the traveling wave. Thus, vibrations within the organ of Corti are sensed and then force is generated in synchrony to increase the vibrations. In this review, the role of force production within the cochlea to produce cochlear amplification and the micromechanical mechanisms that underlie it are discussed.

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Organ of Corti

The organ of Corti (Fig. 1) is a highly organized sensory structure. There is a single row of inner hair cells and three rows of outer hair cells that are positioned on top of the basilar membrane by various supporting cells. There are tight junctions between the apex of the hair cells and the surrounding supporting cells. This forms a barrier between the endolymph and the perilymph called the reticular lamina. Outer hair cell stereocilia insert into the overlying tectorial membrane whereas inner hair cell stereocilia do not.

The entire organ of Corti vibrates up and down in response to sound pressure waves. However, because the insertion points of the basilar membrane and the tectorial membrane onto the osseous spiral lamina are at slightly different radial positions, a transverse shearing movement develops between the reticular lamina and the tectorial membrane. This directly deflects outer hair cell stereocilia, whereas the fluid movement in the space between the tectorial membrane and the reticular lamina is believed to indirectly deflect inner hair cell stereocilia [1].

Passive cochlear mechanics

The cochlea has both passive and active mechanical properties. The passive properties are found even in a postmortem cochlea, and define its tonotopic organization. Mechanically, the cochlea can be modeled as a series of radial sections ranging from the base to the apex. The resonant frequency of each section is based on the average mass, stiffness, and damping of the basilar membrane at that section. There are systematic differences in these physical properties along the length of the cochlea that determine the frequency response at any specific location [2]. Thus, the basilar membrane at the base of the cochlea has a lower mass and a higher stiffness and vibrates maximally in response to high-frequency sounds. In contrast, the basilar membrane at the apex of the cochlea has a higher mass and a lower stiffness and vibrates maximally in response to low-frequency sounds.

Sound pressure waves are transmitted to the perilymph of scala vestibuli by the stapes footplate at the base of the cochlea. The pressure waves then begin propagating up the length of the cochlear duct towards the apex (Fig. 2A). Basilar membrane vibration is maximal at the point where the frequency of the incoming sound matches the characteristic frequency of the basilar membrane. At that point, the pressure wave crosses the organ of Corti, enters scala tympani, and travels back down scala tympani to the round window.

Cochlear amplifier

Experimental measurements of basilar membrane vibrations within the postmortem cochlea (*ie*, without a cochlear amplifier) demonstrate that increasing sound pressure level linearly increases basilar membrane motion. However, these passive mechanical properties can not explain the exquisite sensitivity and frequency selectivity of mammalian hearing. An active mechanism within the cochlea was first proposed by Thomas Gold [3]. The concept that a source of mechanical energy exists in the cochlea appeared validated when it was discovered that sounds can be produced by the inner ear, called otoacoustic emissions [4]. Now, it has been well proven that mammalian hearing is enhanced by some type of amplification process within the cochlea.

Measurements of basilar membrane vibration in the living cochlea demonstrate dramatically improved sensitivity and sharpness of tuning [5–8] (Fig. 2B). In other words, the basilar membrane vibrates more in a living cochlea than in a dead cochlea, particularly in response to quiet sounds. This property is called the cochlear amplifier. Positive feedback occurs locally along the length of the cochlea, to amplify vibrations of the basilar membrane on a cycle-by-

cycle basis. These precise cochlear tuning characteristics are conveyed to auditory nerve fibers via synaptic transmission from the inner hair cells [9–11].

Force of the cochlear amplifier is generated by outer hair cells

Differential movements between the tectorial membrane and basilar membrane deflect hair cell stereocilia. Mechanoelectrical transduction channels are present at the tips of the stereocilia (Fig. 3). Deflecting the stereocilia bundle one way opens the channels and deflecting the bundle the other way closes the channels [12]. Because of the positive endolymphatic potential (approximately +80 mV) and the high cation (K^+ and Ca^{+2}) concentrations in the endolymph, opening the transduction channels causes an influx of current, depolarizing the hair cell. While the normal resting potential of a hair cell is around −60 mV, it can vary by up to several millivolts with high-intensity sound stimuli [13,14]. This variation of the intracellular voltage caused by mechanoelectrical transduction is called the receptor potential.

Current influx triggers processes within the outer hair cell (OHC) to generate force and amplify the sound pressure wave. A low endolymphatic potential diminishes the cochlear amplifier [15•]. The force produced by the cochlear amplifier does not act to amplify sounds equally at all frequencies. It is tuned to generate maximal force only at the characteristic frequency [16•]. This provides a sharpening of the tuning curve and improves frequency selectivity, the ability to distinguish between two tones of nearly the same frequency. If there was no frequency dependence of the cochlear amplifier, frequency sensitivity (the ability to hear quiet sounds) would be improved, but not frequency selectivity.

The relative contributions of the passive and the active properties of the organ of Corti in defining the tonotopic frequency map of the cochlea are poorly understood. In nonmammalian species, frequency specificity occurs at the level of the hair cell, and some phylogenetic remnant of this property probably remains in the mammalian cochlea. Certainly, hair cell morphology changes along the length of the cochlear duct, with longer OHCs at the base and shorter OHCs at the apex. Additionally, there are spatial variations in the mechanosensitive stereociliary bundles that might determine frequency selectivity. However, a distinct role for hair cell tuning within the mammalian cochlea has not been identified.

It is possible that hair cells at any position along the length of the mammalian cochlea could be made to function at any frequency simply by changing the passive properties of the basilar membrane. One hypothesis of how the cochlear amplifier is tuned is based upon the angle of the OHCs relative to the basilar membrane. The stereocilia are closer to the stapes than is the base of the cell. Thus, the force created by an OHC in response to having its stereocilia deflected acts in a “feed-forward” mechanism to deliver energy to a more apical section of the cochlea, slightly ahead of the traveling wave [17–19].

Outer hair cell electromotility

The cellular basis behind the cochlear amplifier is thought to be OHC electromotility [20–23•]. Electromotility is a process unique to the OHC in which its length changes with intracellular voltage (Fig. 4). Electromotility can occur at frequencies up to 100 kHz and does not require ATP or calcium. Thus, OHCs elongate and contract at acoustic frequencies, acting to amplify the natural vibrations of the traveling wave. No other hair cell (nor any other kind of cell) is able to change its length so rapidly in response to electrical stimulation. Human OHC electromotility functions similarly to that of other mammals [24,25].

Outer hair cells have a cylindrical shape. They vary in length from approximately 12 μm at the basal end of the cochlea to approximately 90 μm at the apical end. Their diameter is approximately 9 μm. Each region of the OHC has a specific function. The stereocilia at the

apex of the cell are responsible for converting the mechanical energy of the traveling wave into electrical energy. Synaptic structures are found at the base of the hair cell and they are responsible for converting electrical energy into chemical energy by modulating the release of neurotransmitters. These two regions provide functions that are common to all hair cells (inner, outer, and vestibular).

The central portion of the OHC is different than all other cells because this is where electrical energy is converted into mechanical energy (electromotility). Most cells have a central cytoskeleton to maintain their shape. Because such an internal skeleton would impede electromotility, a specialized cytoskeleton is found just inside the plasma membrane, which acts to permit electromotile cell length changes (Fig. 5) [26]. The lateral wall has a unique trilaminate structure composed of a plasma membrane, a cytoskeleton, and a membranous organelle called the subsurface cisternae. The plasma membrane is a phospholipid bilayer that holds many particles between the inner and outer leaflets. The cytoskeleton contains parallel actin filaments crosslinked with spectrin, associated with Protein 4.1 [27–29]. Pillars of unknown composition tether the actin filaments to the plasma membrane [28,30]. The subsurface cisterna is an intracellular organelle, similar to endoplasmic reticulum or Golgi apparatus, which lines the inside of the cytoskeleton.

Electromotility originates within the lateral wall of the OHC. A complete understanding of the mechanisms behind force generation within the lateral wall is lacking. However, the prestin protein within the plasma membrane is clearly central to this process [31–35]. This protein is not expressed in other hair cells, and likely works in concert with associated proteins and lipids of the lateral wall to form “motor complexes.” Each motor complex senses the intracellular voltage and individually generates force by changing its surface area [36–44]. The motor mechanism is a biologic form of piezoelectricity [45–49•]. Intracellular anions can modulate prestin function [50,51•]. Changing the intracellular anion content inhibits electromotility and decreases the longitudinal stiffness of OHCs [52••].

The lipid component of the OHC lateral wall plasma membrane is important to the generation of electromotility. The fluidity of the plasma membrane of the OHC lateral wall is similar to that of other eukaryotic cells [53]. But, changing the voltage across the membrane changes the ability of lipids to diffuse within the membrane [54]. This may be due to membrane curvature changes or interactions with prestin proteins. Further evidence supporting the importance of the lipid component of the plasma membrane for normal electromotility is that chlorpromazine, a drug that modulates membrane curvature, affects OHC electromotility and reduces cochlear function [55,56•].

The forces generated by each of the individual motors are coupled together through the lateral wall plasma membrane and cytoskeleton to achieve a net change in cell length. Because the OHC is fixed apically to the reticular lamina and basally to the cup of a Deiter’s cell, electromotile shape changes can modify the vibration of the cochlear partition [57]. The OHC is pressurized to be strong enough to transmit force to the rest of the organ of Corti. Calcium may modulate OHC stiffness as well [58•]. Recently a prestin knockout mouse has been generated that has been found to have sensorineural hearing loss, supporting the importance of prestin protein for normal hearing [59].

Active stereociliary bundle movements

Electromotility might not be the only force generating process within the OHC. Recently, a negative stiffness has been identified in the mechanoelectrical transduction process that is probably responsible for otoacoustic emissions found in nonmammalian species. In simple terms, this means that after deflecting the stereocilia a certain distance, a force produced within the stereocilia causes them to deflect further. This process may also be important for normal

functioning of the mammalian cochlear amplifier [60–62]. Active bundle movements, called fast adaptation, are triggered by the entry of cations through the mechanoelectrical transducer channel [63••–67].

Other, active processes within the stereocilia associated with mechanoelectrical transduction also produce nonlinearities that might modulate the cochlear amplifier. These processes are thought to be much slower than either electromotility or active bundle movements, and can not function at the higher frequency range of mammalian hearing. This includes slow adaptation of mechanoelectrical transduction, a process by which actin-myosin interactions function to tighten tip links between adjacent stereocilia to bias the mechanoelectrical transduction channels in an operating region of maximal sensitivity [68,69]. Also, in the nonmammalian cochlea, electrical resonance is derived from the interplay between voltage-dependent ion channels within an individual hair cell [70,71]. Although electrical resonance has not been identified in mammalian cochlear hair cells, voltage-gated ion channels are certainly important in shaping the receptor potential [72]. In the OHC, this directly impacts the electromotile response.

Efferent modulation of the cochlear amplifier

The gain of the cochlear amplifier appears to be regulated by the medial olivocochlear bundle. These efferent nerve fibers originate within the brainstem and project to the OHCs, releasing acetylcholine as their neurotransmitter. OHCs have a specialized α9 acetylcholine receptor on their synaptic pole that permits calcium influx from outside the cells and calcium release from intracellular stores [73]. This triggers the opening of potassium channels and causes cell hyperpolarization. There is also a slow effect of acetylcholine, which may produce changes in the OHC cytoskeleton via second messenger systems [74–76•]. Acetylcholine has been shown to increase the amplitude of electromotility in isolated OHCs by decreasing cell stiffness [77]. In vivo, stimulation of the efferent nerve bundle elevates cochlear thresholds [78,79] and reduces motion of the cochlear partition, protecting the cochlea from acoustic overstimulation [80]. Thus, the central nervous system actively controls cochlear function by changing OHC electromotility. This may be important clinically as an innate mechanism that reduces hair cell damage from loud noise exposure [81,82]. Additionally, the efferent system may play a role in filtering out background noise, improving the ability of humans to understand speech in noisy environments [1].

Otoacoustic emissions

One consequence of having an active system is that oscillations can occur even when no energy is coming into the system from the outside. In the cochlea, these are called spontaneous otoacoustic emissions. Other types of otoacoustic emissions can be measured as well, including distortion product otoacoustic emissions and transient evoked otoacoustic emissions. These can be triggered by playing certain types of sound stimuli into the ear, and so are more useful clinically than the measurement of spontaneous otoacoustic emissions. For otoacoustic emissions to be generated, most of the peripheral auditory pathway must be functioning, with the exception of inner hair cells and the auditory nerve. Specifically, otoacoustic emissions test for nonlinearities caused by OHC force production, and thus test the cochlear amplifier [83•]. The measurement of otoacoustic emissions has become an important nondiagnostic tool to test cochlear function, particularly in newborn hearing screening.

Conclusion

A thorough understanding of the cochlear amplifier has tremendous implications to improve human hearing. Sensorineural hearing loss is a common clinical problem, and can be caused by many different etiologies including noise exposure, ototoxicity, and age-related hearing loss

(presbyacusis). The common site of pathology for all of these conditions within the inner ear is the OHC. The attachments of OHC stereocilia to the tectorial membrane can be broken even with mild noise exposure. This reduces the ability of electromotility to provide positive feedback, leading to a temporary hearing loss. With further damage, the actin core of the stereocilia can fracture. With enough trauma, hair cell death occurs and a permanent hearing loss results because mammalian cochlear hair cells do not regenerate. The inner ear sensory epithelia are among the smallest organs in the body, containing less than 20,000 sensory cells. The small number of cells in the hearing organ means that the loss of even a small number affects hearing. After OHCs begin to degenerate, additional structures within the cochlea begin to sustain damage as well, including inner hair cells, supporting cells, and auditory nerve cells.

Sensorineural hearing loss is a common disease and there are no effective treatments. Clinically, it is heartbreakingly common to see a small elevation in high-frequency thresholds lead to a dramatic worsening of a patient's speech discrimination ability, particularly in the presence of background noise. This occurs because frequencies above 2 kHz contain the formants of consonants. Also, a significant amount of information regarding sound source directionality is contained within these higher frequencies. While hearing aid technology continues to improve, they function basically to compress and amplify incoming sounds. A hearing aid cannot make up for loss of the cochlear amplifier because it cannot improve frequency discrimination. New techniques of treating sensorineural hearing loss will likely need to recreate the mechanical properties of the cochlear amplifier. This may require the development of technologies based on implantable micro- and/or nano-scale machines.

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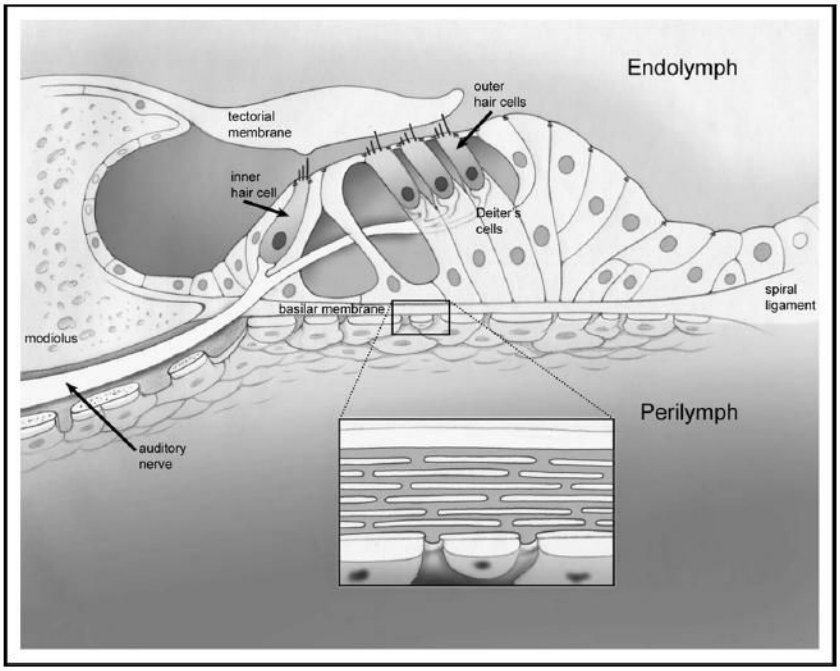

Figure 1. Organ of Corti

There is a single row of inner hair cells and three parallel rows of outer hair cells. Outer hair cells are supported by Deiter cells. The hair cells and all supporting cells sit on the basilar membrane. A section of the basilar membrane is enlarged to demonstrate the radial arrays of collagen filaments within it. The basilar membrane and the tectorial membrane are fixed at different locations to the modiolus. When sound vibrations cause the organ of Corti to move up and down, a shearing force is created, which deflects the hair cell stereocilia.

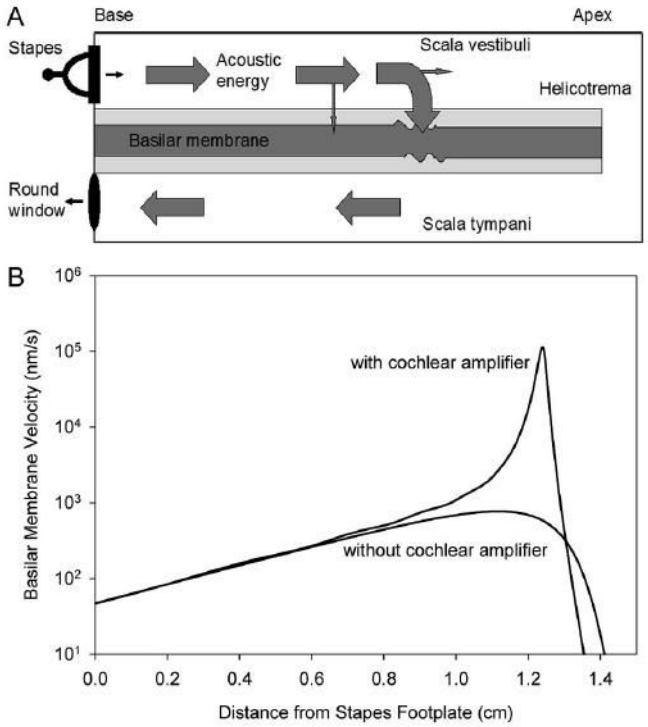

Figure 2. Pressure waves begin propagating up the length of the cochlear duct towards the apex

(A) Acoustic energy propagation down the cochlea. Sound pressure waves enter the scala vestibuli through movement of the stapes footplate. The acoustic energy propagates down the perilymph, traversing the basilar membrane predominantly at the region of its characteristic frequency. This creates the classical “traveling wave” motion of the basilar membrane. The region of the characteristic frequency is the area of maximal vibrations of the basilar membrane. The energy then propagates back to the round window through scala tympani. **(B)** Peak amplitudes of basilar membrane motion with and without the cochlear amplifier. These plots are based on simulations of the cochlear traveling wave as it propagates down the cochlea from the stapes to the helicotrema when a single frequency tone is played into the ear. The peak amplitude of the traveling wave is plotted. Without the cochlear amplifier, the traveling wave gradually reaches a peak, and then rapidly declines. With the cochlear amplifier, there is a large increase in basilar membrane motion. Also, note that there is sharpening of the peak with the cochlear amplifier. This permits improved frequency discrimination.

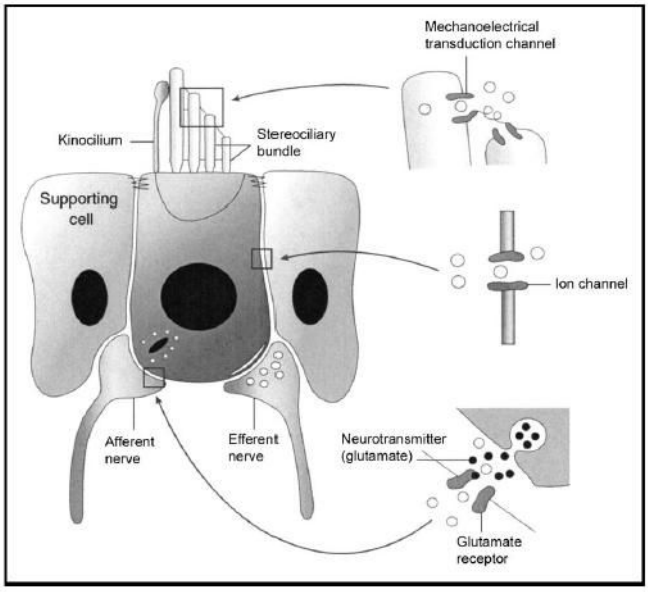

Figure 3. Stereotypical hair cell

The boundary between the endolymph and the perilymph is the apical tight junctions between hair cells and supporting cells (the reticular lamina). There are three major functions within all hair cells. (1) Mechanoelectrical transduction occurs at the tips of the stereocilia, allowing ions from the endolymph to enter the cell. (2) Efferent nerve terminals and other ion channels modulate the intracellular voltage inside the hair cell and permit potassium exit from the cell for recycling. (3) Depolarization of the hair cell causes synaptic transmission of the afferent auditory nerve terminals. The neurotransmitter is glutamate. Figure derived from Eatock (1997) [84].

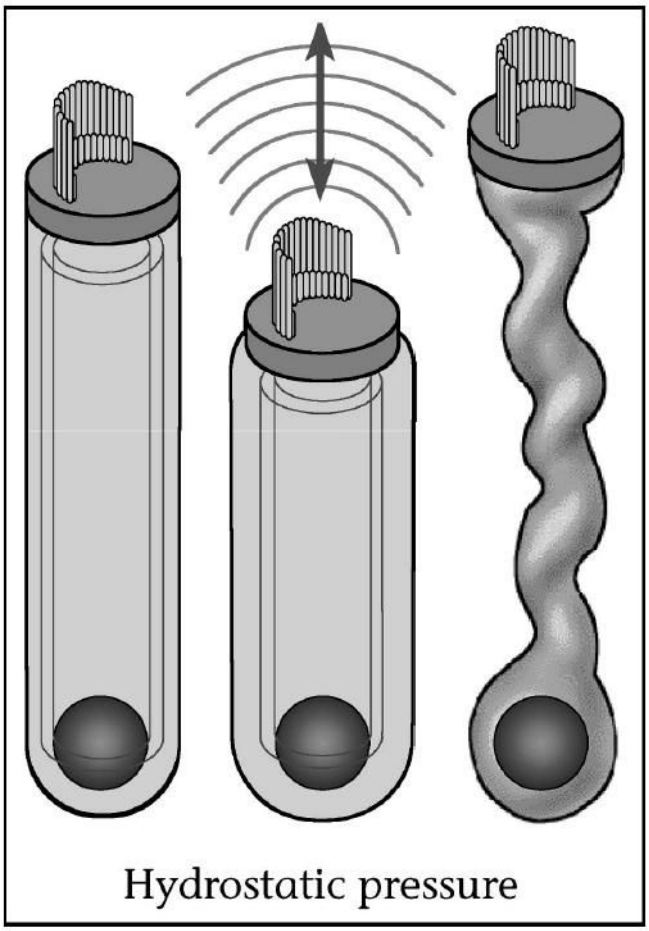

Figure 4. Outer hair cell electromotility

Outer hair cell electromotility. Outer hair cells contract and elongate with each cycle of sound as their intracellular voltage changes. This amplifies the vibration of the organ of Corti, permitting exquisite hearing sensitivity and frequency selectivity. OHCs have an intracellular turgor pressure to help maintain their shape. Loss of OHC turgor pressure causes the cell to constrict so that it can no longer produce electromotile force. Figure derived from Brownell (1999) [85].

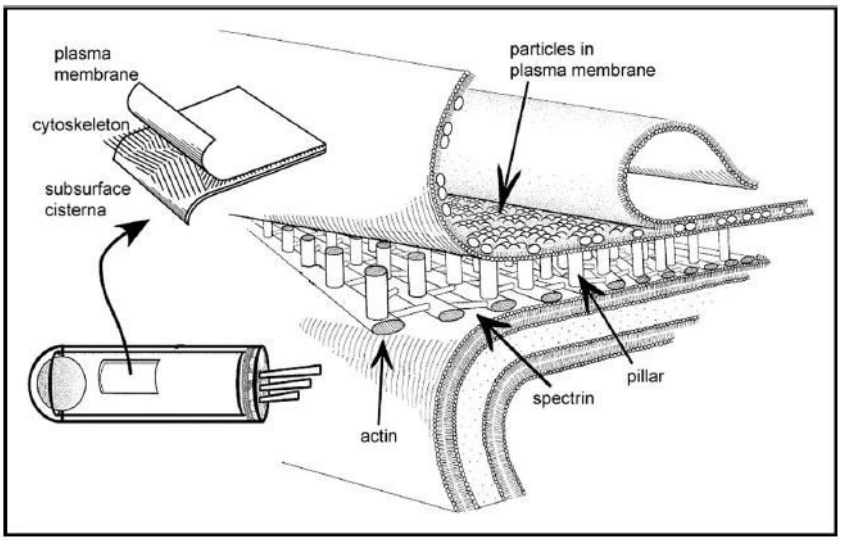

Figure 5. Diagram of OHC with detail of lateral wall components

The lateral wall is composed of the plasma membrane, the cytoskeleton, and the subsurface cisterna. The cytoskeleton contains actin, spectrin, and pillar molecules. Some (perhaps most) of the particles in the plasma membrane are prestin proteins. Figure derived from Oghalai *et al.* (1998) [26].