Endolymphatic Potential (EP)

The endolymphatic potential is a positive standing potential (70-100 mV) that can be measured from the scala media referenced to ground. The EP reflects flux of K+ ions through the stria vascularis into the scala media. From the scala media K+ ions move into hair cells through their stereocilia, carrying their receptor potentials. As K+ ions are expelled basolaterally from hair cells they are taken up by supporting cells from which they move down a concentration gradient towards the spiral ligament through a syncytium of gap junctions to the root cells, which are the distal-most epithelial cells that are in gap junctional connectivity with supporting cells. K+ ions expelled from root cells are taken up by type II fibrocytes, which closely surround root cell processes. From the type II fibrocytes K+ ions move via gap junctions through a syncytium of cells that includes type II fibrocytes, type I fibrocytes, strial basal cells, and strial marginal cells. This intercellular route is a means of passing K+ ions through the tight junction barrier among strial basal cells that prevents extracellular diffusion of ions into the stria from the perilymphatic space.

The EP is generated by the combined action of multiple cells within the stria vascularis. The strial marginal cells are the sites of most of the energy that is consumed by the production of the potential. This consumption is largely in the form of ATP that fuels the action of Na+,K+-ATPase, which is located in the highly amplified basolateral membrane of marginal cells. The stochiometry of the ATPase is 2 K+ ions into the cells and 3 Na+ ions out of the cell for every molecule of ATP that is hydrolyzed. The K+ taken up basolaterally by the marginal cells is expelled apically into the scala media, where is available to the apical surfaces of hair cells to use to carry receptor currents. The ATPase moves Na+ and K+ into the marginal cells' cytoplasm from their extracellular space, the intrastrial space, the volume of which is miniscule. In order for the ATPase to function there must be an inexhaustible supply of Na+ within the marginal cells' cytoplasm. The Na+ ions are supplied by the Na,K,2Cl- co-transporter (NKCC1), which is co-localized within the basolateral membrane of marginal cells, along with the ATPase. The co-transporter is charge neutral, as indicated by its name. For every 3 Na+ ions the ATPase expels from the cell, the co-transporter supplies another 3 into the cell, along with 3 K+ ions and 6 Cl- ions. (The Cl- exits via a basolateral Cl- channel.) The end result of the combined action of the ATPase and the co-transporter is 5 K+ ions into the marginal cell cytoplasm for every molecule of ATP that is consumed, a very efficient system that is utilized in other organs such as the kidney and choroid plexus.

Marginal cells are highly unusual in that they have a positive resting potential that is slightly higher than the endolymphatic potential within the scala media. This means that K+ ions that are expelled apically do not have to be driven into the scala media against an electrochemical gradient. A positive resting potential is highly unusual and probably requires an unusual extracellular environment. The need for an unusual extracellular environment may be the explanation for why the intrastrial space is enclosed within a barrier of tight junctions that isolates the intrastrial space from adjacent perilymphatic and endolymphatic spaces. It is useful to consider the endolymphatic potential as a K+ current. Current is a voltage drop across a resistance. The source of the EP can be found by identifying the resistance in question. Most evidence bearing on this issue indicates that the identity of that resistance is the plasma membrane of strial intermediate cells. (See the review by Wangemann in Hearing Res. 2002, 165:1-9.) Intermediate cells depolarize in the presence of low extracellular K+ ions. This causes their cytoplasmic K+ to move into the intrastrial space via inward rectifying channels (Kir 4.1). The action of the marginal cells avid uptake of K+ from the intrastrial space keeps K+ levels low in that space, and this activates intermediate cells to expel more K+. Intermediate cells have a continuous supply of K+ through their connections via gap junctions to type II fibrocytes of the

spiral ligament. Type II fibrocytes have the same morphological and molecular specializations as strial marginal cells for K+ ion uptake (an amplified plasma membrane and ATPase and Na,K,2Cl co-localization within that membrane). Type II cells take up K+ ions from the perilymphatic space. Some K+ ions may diffuse to the site of type II fibrocytes from where it is expelled from hair cells but most K+ probably gets delivered directly to the type II fibrocytes via the system of gap junctions. Most K+ expelled by the sensory cells is from outer hair cells(OHCs). OHCs utilize far more K+ that IHCs in the process of generating the cochlear microphonic potential. The current candidates for a mechanism of K+ uptake by Deiters cells are the potassium-chloride channels KCC3, KCC4, and the Kir 4.1 channel. Mice engineered to knock out any of these genes are deaf.

The EP is present even when no external sounds activate the ear. Current density analysis has indicated that most of the K+ ions pass through the organ of Corti even in the absence of sound stimulation (Zidanic and Brownell). This notion is strongly supported by the finding that elimination of the EP results in reduction of spontaneous activity in auditory nerve fibers and by the fact that the standing current can be reduced by sound stimulation (strong condensation clicks). The former effect reflects activity of inner hair cells. The latter probably reflects action of the outer hair cells. There is also evidence that K+ ions leave the endolymphatic space by leakage through Reissner's membrane and also through K+ channels located in cells in or near the outer sulcus. Little is known about K+ passage through these routes. It is possible that these routes may act as shunts that help ensure that K+ egress from the stria vascularis into endolymph is matched by K+ egress from the scala media in the absence of acoustic activation of the organ of Corti. Such regulation of ionic content is necessary so that the scala media remains isotonic with surrounding tissue and scalae.

The presence of the EP provides a positive biasing voltage across the apical membrane of sensory cells. The combined presence of a negative resting potential in the hair cells and the positive potential of the EP provides an extra-large electrochemical gradient down which the K+ ions flow when moving from scala media into the hair cells. The fact that the energy consuming tissue that generates EP is located on the lateral wall means that the vasculature that supplies energy and removes metabolic wastes is physically distant from the sensory transducers. This removes pulsations and noise generated by the vasculature from the organ of Corti.

The EP is a critical part of the mechanisms that provide the mammalian cochlea with its unique sensitivity to movement at frequencies above ca. 3 kHz. That sensitivity is manifested in mammalian-specific two part tuning curves. The tips of the tuning curves are at the frequencies to which hair cells are most sensitive (CF). The motion of the basilar membrane has the same tuning properties as is reflected by hair cell output, the responsivity of auditory nerve fibers. This tuning and sensitivity reflects an active process of the organ of Corti in response to sound-induced motion of the basilar membrane. This active process is possible only with the presence of normal levels of EP. High doses of the drug furosemide blocks the Na,K,2Cl co-transporter and results in a transient elimination of the EP. Loss of EP is accompanied by reduction of cochlear microphonic potentials and by elimination of the tips of tuning curves of auditory nerve fibers. Loss of the tips of tuning curves results in as much as a 40-70 dB loss in sensitivity at the CF. EP loss results in the sensitivity of tails of tuning curves being depressed only about 20 dB. The sensitivity loss of auditory nerve fibers tuned to low frequencies (<3 kHz) is also approximately 20-30 dB when EP is eliminated.