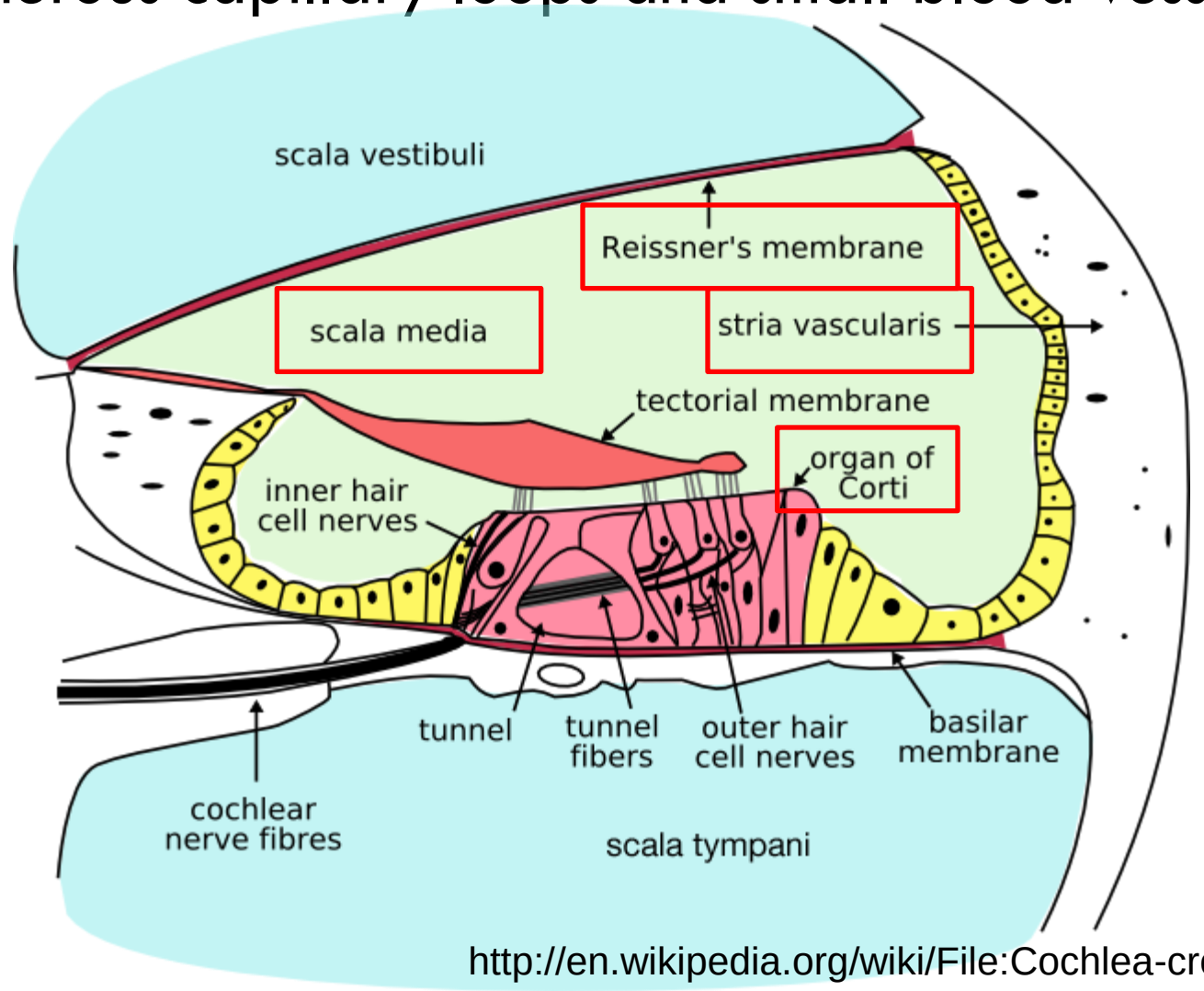
POTASSIUM RECIRCULATION AND STRIA VASCULARIS

201403

Reporter: R樊樂遠
Supervisor: VS黃啟原

Anatomy

- numerous capillary loops and small blood vessels



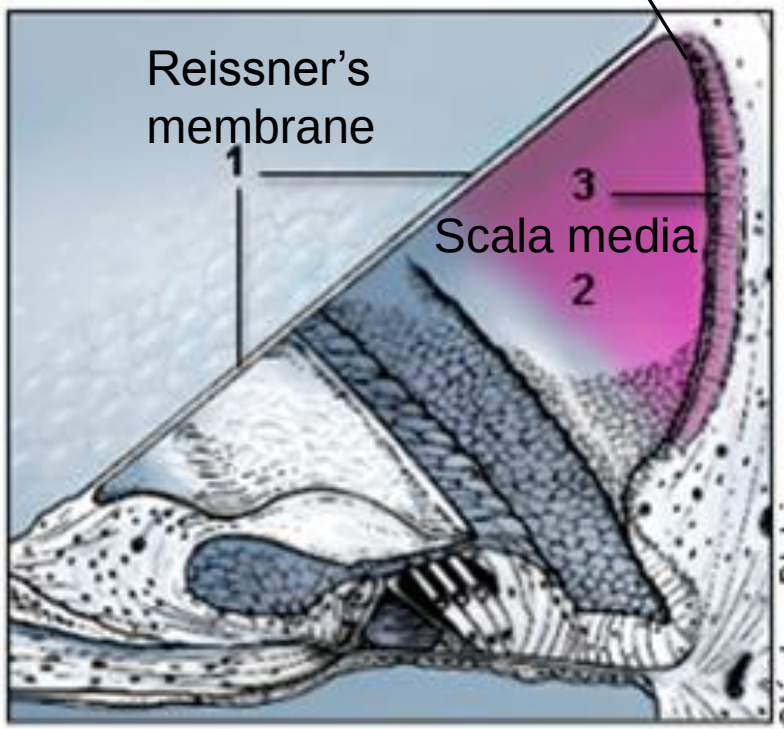
http://en.wikipedia.org/wiki/File:Cochlea-crosssection.png

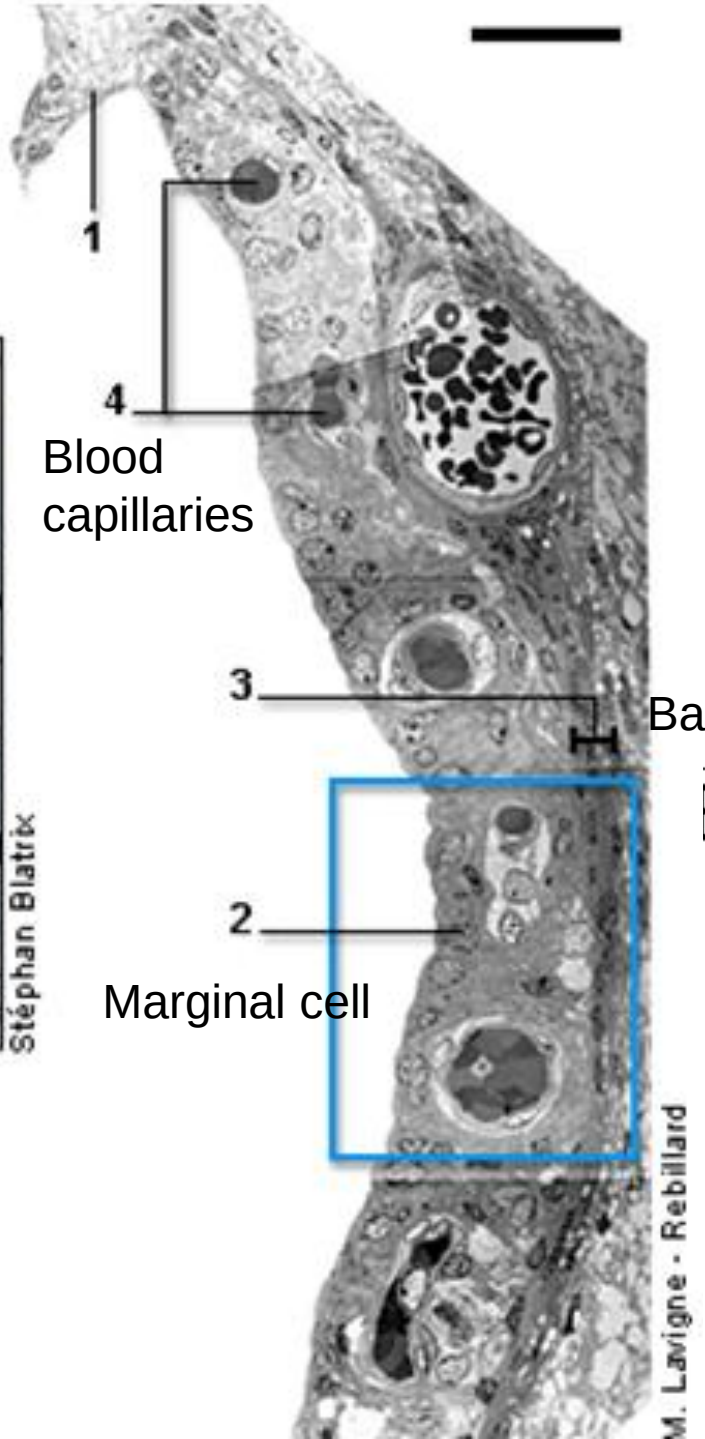
Stria vascularis

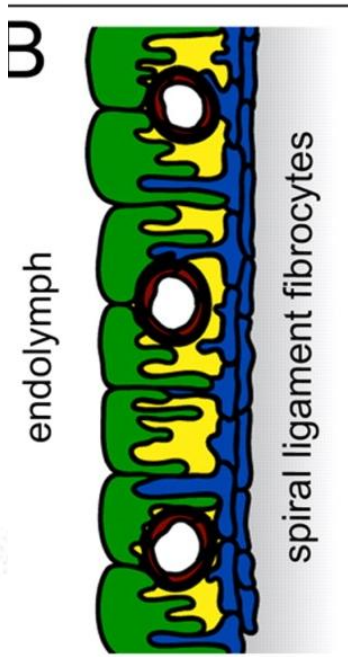
- It produces endolymph for the scala media
- The stria is a stratified epithelium containing primarily three cell types and intra-epithelial capillaries.

- **Marginal cells** : K+ transport and line the endolymphatic space of the scala media.
- **Intermediate cells** : scattered among capillaries.
- **Basal cells** : separate stria vascularis from the underlying spiral ligament.

Stria vascularis







- The scala media is filled with endolymph, which has a high potassium concentration and a low sodium concentration
- The stria vascularis participates in maintaining the ion concentrations in the endolymph.
- Stria vascularis pumps ions to the endolymph via Na-K-ATPase pumps, which is an energy-consuming process. It is essential for the normal function of hair cells.

The role of potassium recirculation in cochlear amplification

Pavel Mistrik[a] and Jonathan Ashmore[a,b]

[a]UCL Ear Institute and [b]Department of Neuroscience, Physiology and Pharmacology, UCL, London, UK

Correspondence to Jonathan Ashmore, Department of Neuroscience, Physiology and Pharmacology, UCL, Gower Street, London WC1E 6BT, UK
Tel: +44 20 7679 8937; fax: +44 20 7679 8990;
e-mail: j.ashmore@ucl.ac.uk

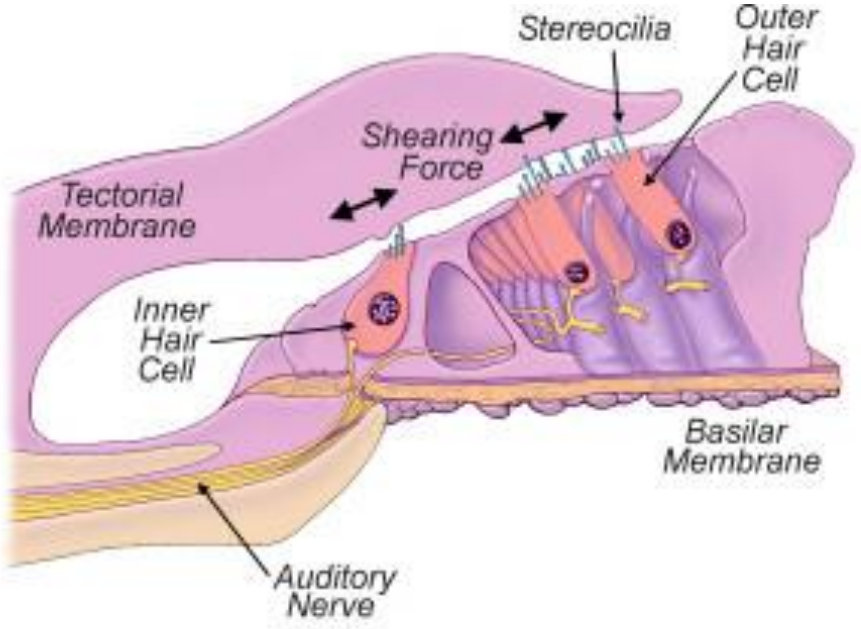
Current Opinion in Otolaryngology & Head and Neck Surgery 2009, 17:394–399

- Potassium (K+) is the major ion of the inner ear endolymph and fills scala media.
- Why does scala media contain high K+? With low levels of sodium and calcium, endolymph resembles intracellular medium.
- Its composition is maintained by the correct operation of the stria vascularis along the full length of the cochlea.

Hair cells and cochlear amplification

- During sound stimulation, K+ becomes the charge carrier entering through the transducer channels.
- A partial explanation for a high endolymphatic K+ is that transduction does not thereby place a high metabolic load on the hair cells. Energy demands are made on stria vascularis instead.
- The great diversity of potassium channel proteins means that hair cells can employ multiple strategies to extrude K+. K+ channels are certainly used in ionic pathways in hair cells.

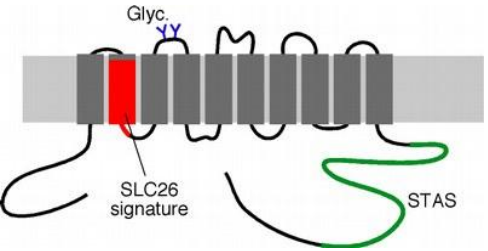
- When K+ does enter the cell, the resulting depolarization leads to force generation by the outer hair cells (OHCs) and activates transmitter release from inner hair cells onto the afferent nerve.

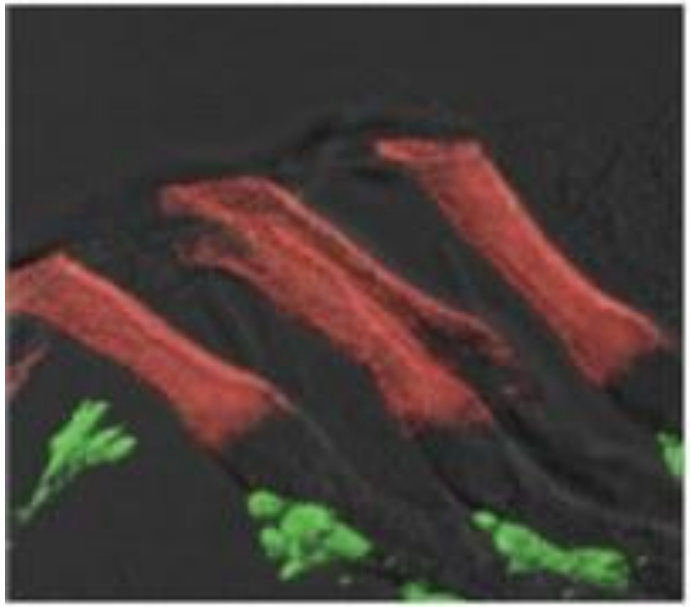


The Organ of Corti

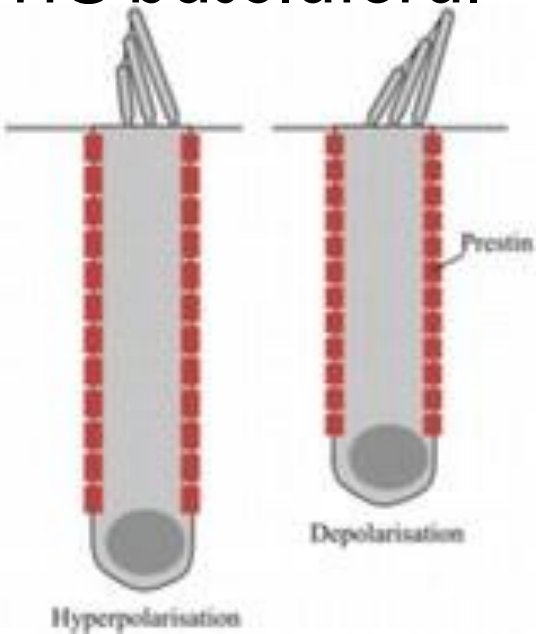
http://www.neurophys.wisc.edu/auditory/johc.html

- Cochlear amplification can be traced to the correct operation of the OHCs, the OHC basolateral membrane of multiple copies of a protein SLC26A5 (prestin).
- Prestin, acting as a voltage-gated mechanoenzyme, depends on the potentials across the OHC basolateral membrane.

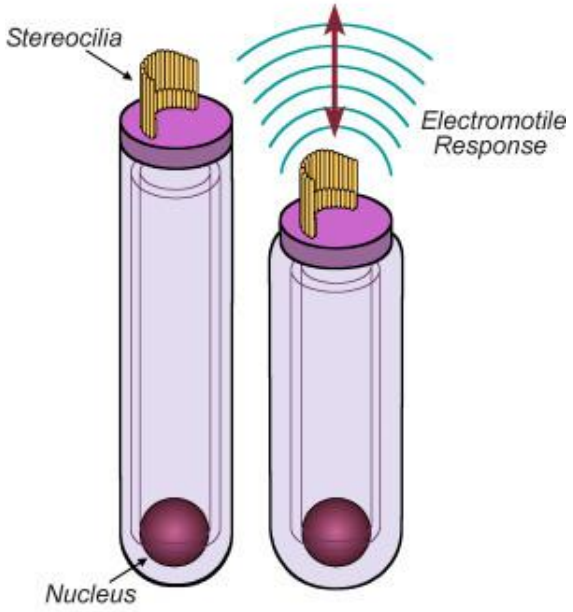




http://www.uni-marburg.de/fb20/physiologie/ags/oliver/research



- There are arguments that these forces could originate from the stereociliary bundle itself, but such mechanisms depend primarily on the entry of calcium, rather than K+, through the transducer channels.



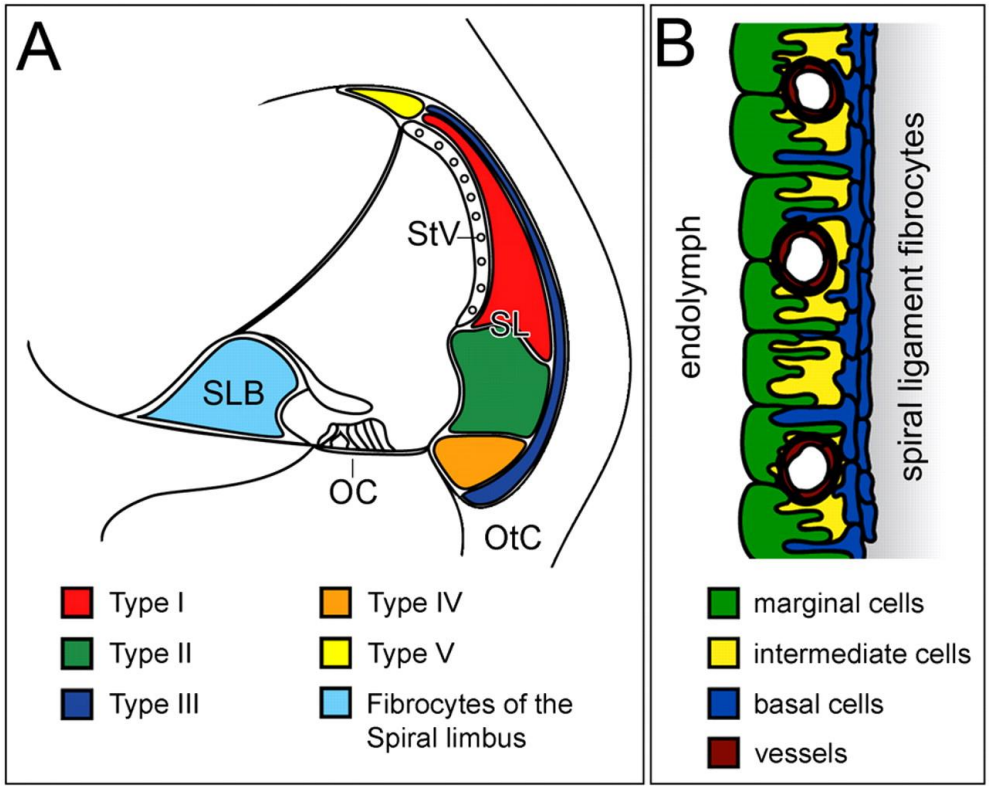
The Outer Hair Cell

http://www.neurophys.wisc.edu/auditory/johc.html

- There is agreement that amplification depends on feedback operating close to instability regimes. In these cases, the precise parameters and regulation of the parameters become critical. K+ recirculation plays a significant part in this homeostasis.
- Much of what we understand of the amplification process is informed by computer models of the cochlea.

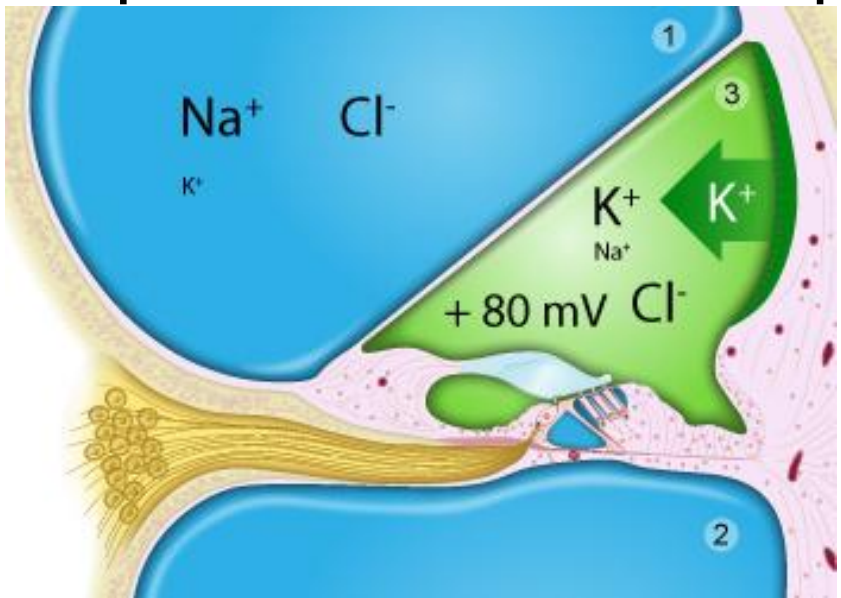
Molecular recycling pathways for K+ in the cochlea

- Several crucial potassium transport-related molecules
- hair cells and supporting cells in the organ of Corti, type II fibrocytes in the spiral ligament, and the intermediate and marginal cells of stria vascularis.



http://dev.biologists.org/content/135/9/1725.figures-only

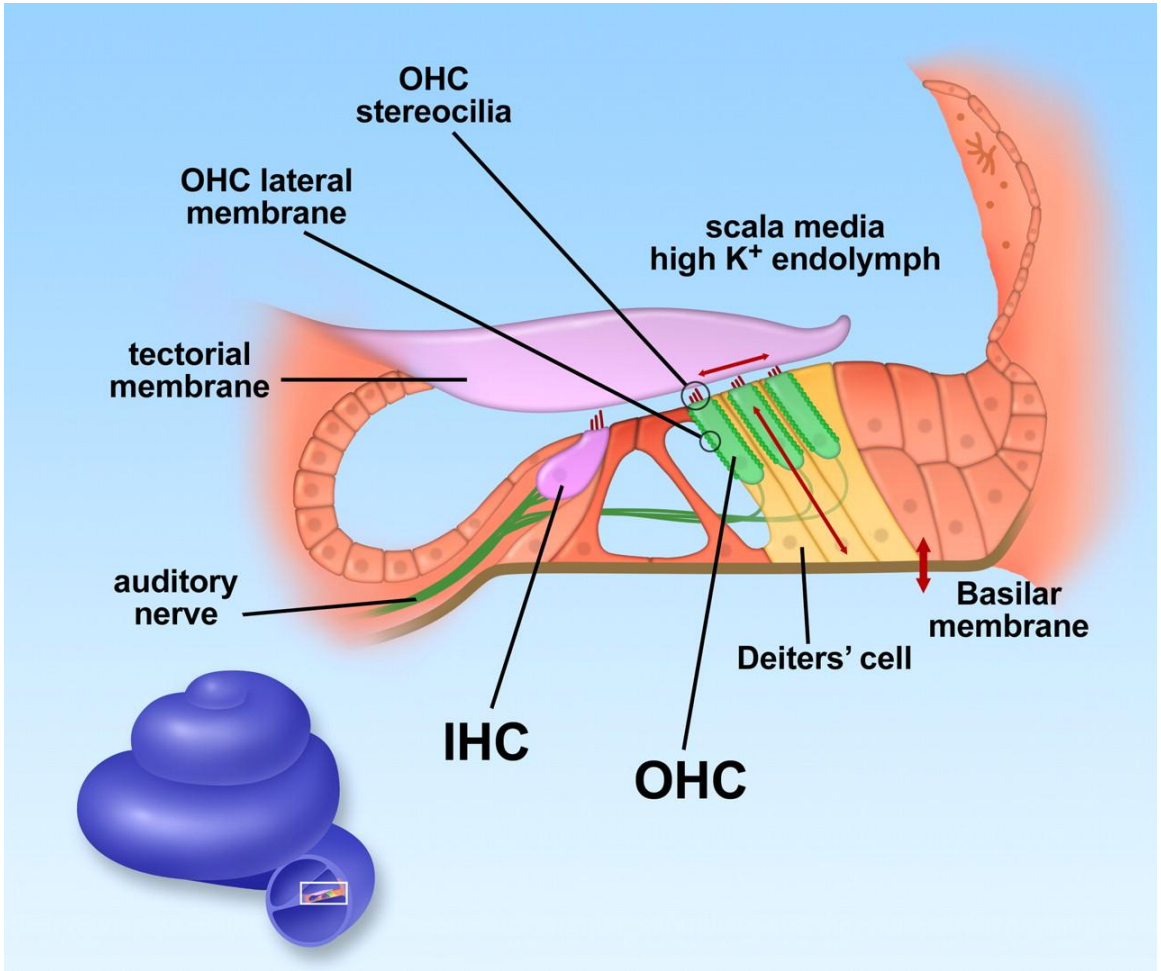
- The recycling hypothesis proposes that K+ enters the OHCs and IHCs through the apical mechanotransducer channels.
- In one classical scenario, K+ ions diffuse extracellularly through the tunnel of Corti to reach perilymph. (low-impedance extracellular pathway)



limited to the scala media (= cochlear duct; 3), is very rich in potassium, secreted by the stria vascularis, and has a positive potential (+80mV)

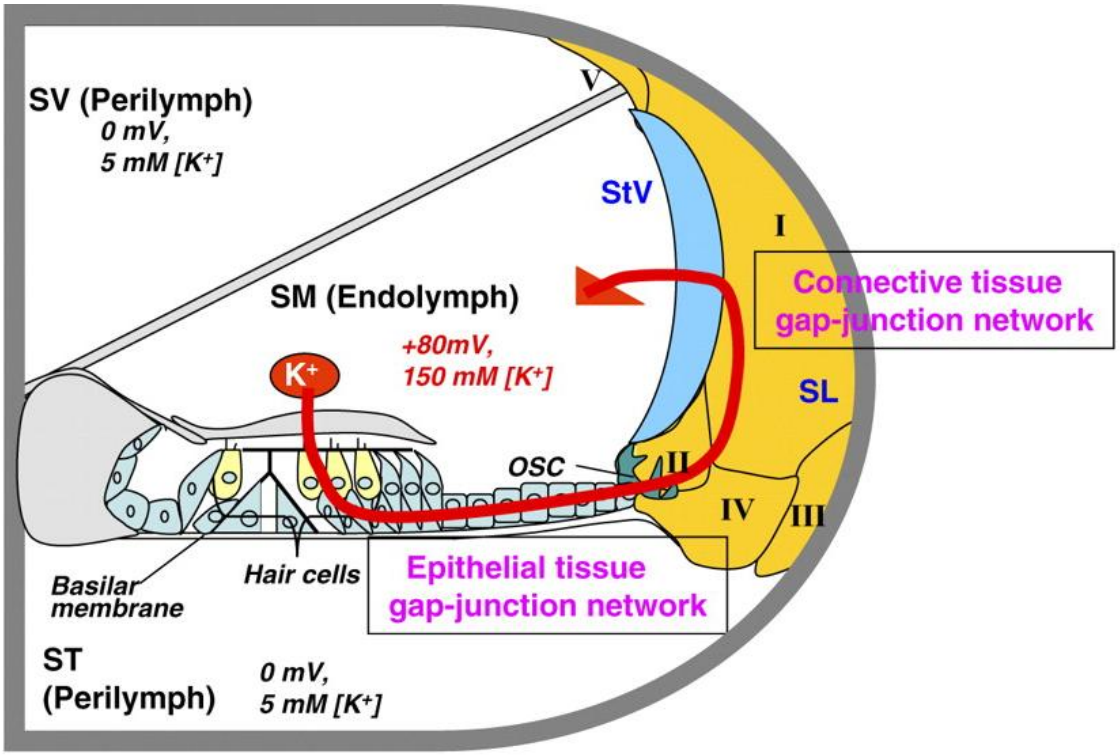
http://www.cochlea.eu/en/cochlea/cochlear-fluids

- An alternative proposal is that K+ ions are taken up by neighboring Deiters' cells.
- Mice lacking the K-Cl cotransporters Kcc4 or Kcc3, both normally expressed in Deiters' cells, are deaf.

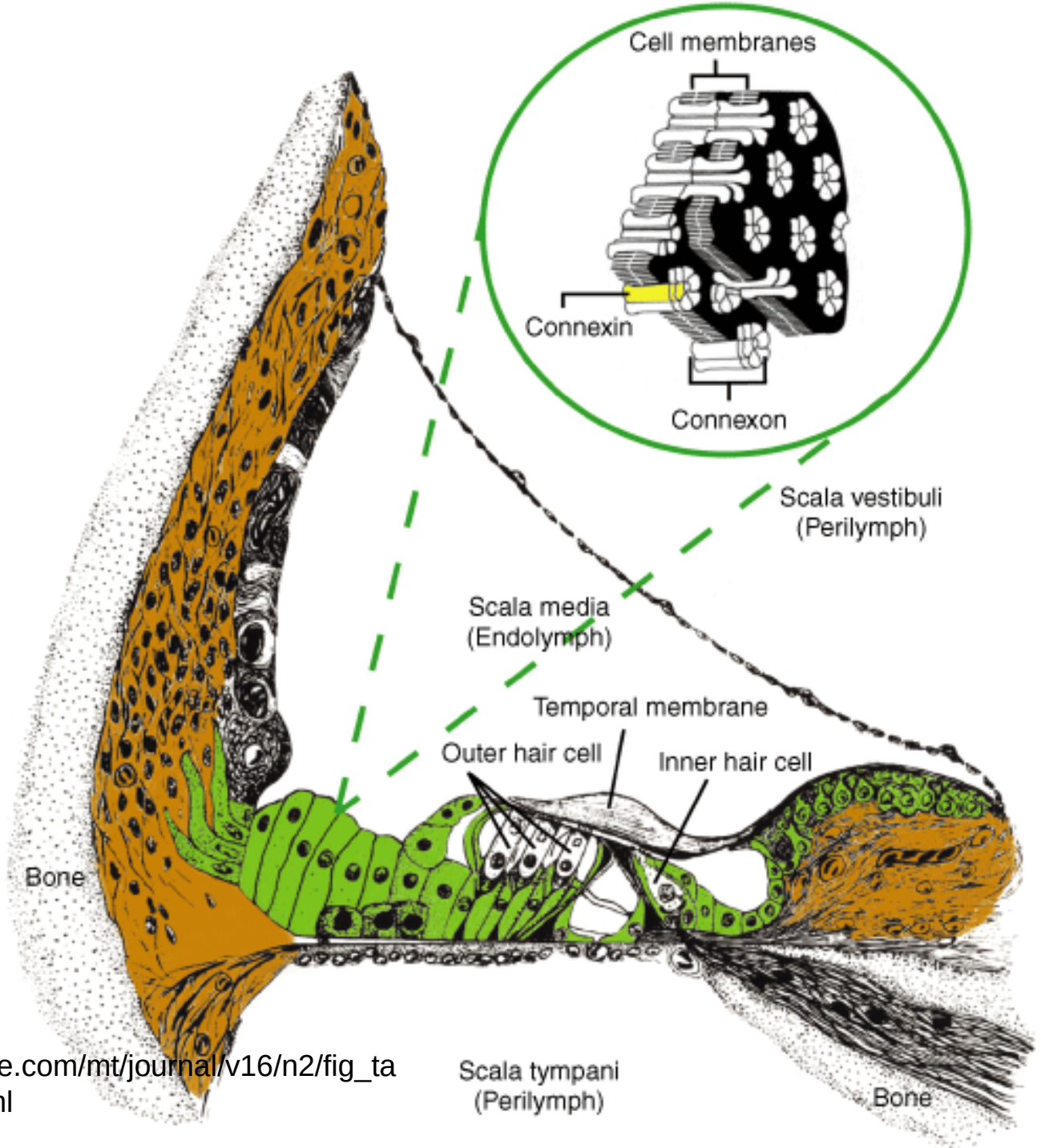


http://physrev.physiology.org/content/88/1/173

- From the Deiters' cells, K+ ions pass through the epithelial tissue gap junction system coupling supporting cells in the organ of Corti.
- This gap junction system is implicated by the extensive evidence from GJB gene mutations and in mouse models in which targeted ablation of connexin 26 (Cx26) in the organ of Corti leads to deafness



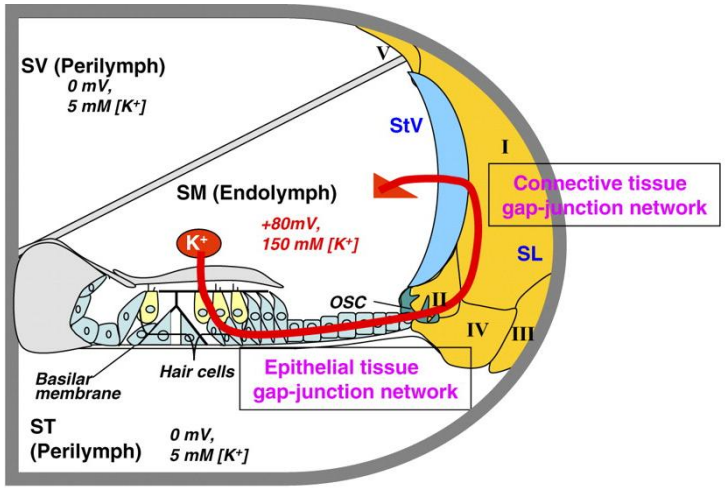
http://ajpcell.physiology.org/content/291/5/C1038



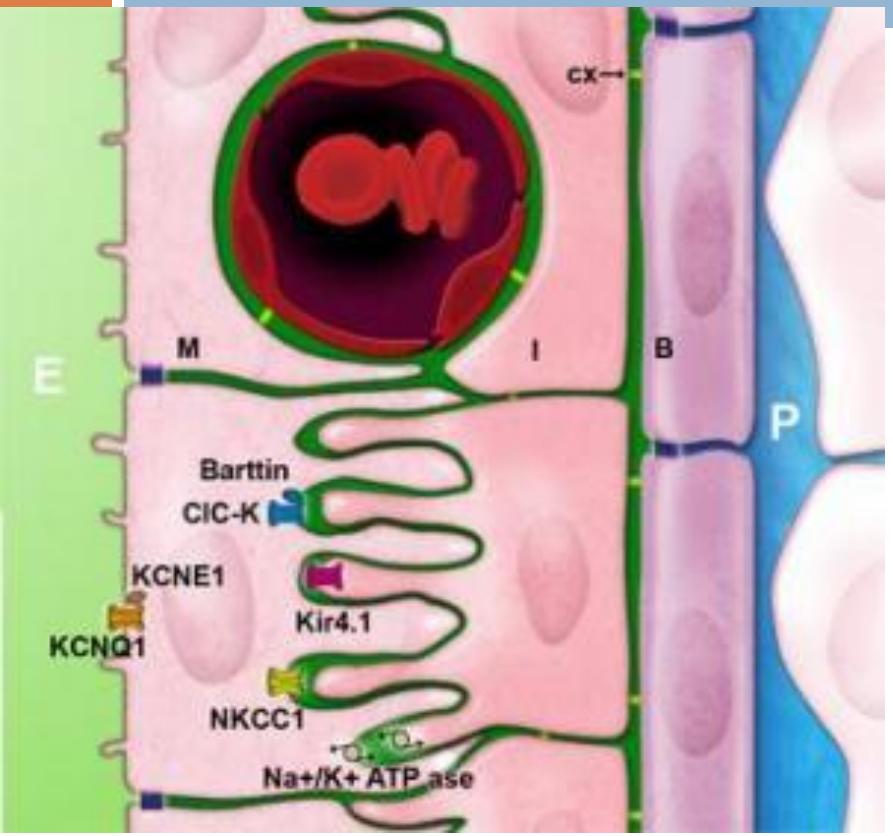
http://www.nature.com/mt/journal/v16/n2/fig_tab/6300351f3.html

- The gap junction system represents a potentially high-impedance pathway between cells' in contrast to the low-impedance extracellular pathway through the tunnel of Corti.
- It is also not known how K+ ions are released from the gap junction system into perilymph, although connexin hemichannels may form one route.

- The candidates for K+ transport into stria vascularis are poorly understood. The presence of K+/Na+ ATPase activity and a K+/Na+/2Cl co-transporter in type II fibrocytes of the spiral ligament suggests that K+ is actively transported.
- Gap junctional proteins (Cx30) between II fibrocytes with basal and intermediate cells of stria vascularis suggests that K+ diffusion occurs through the connective tissue gap junction system into stria vascularis.



http://ajpcell.physiology.org/content/291/5/C1038

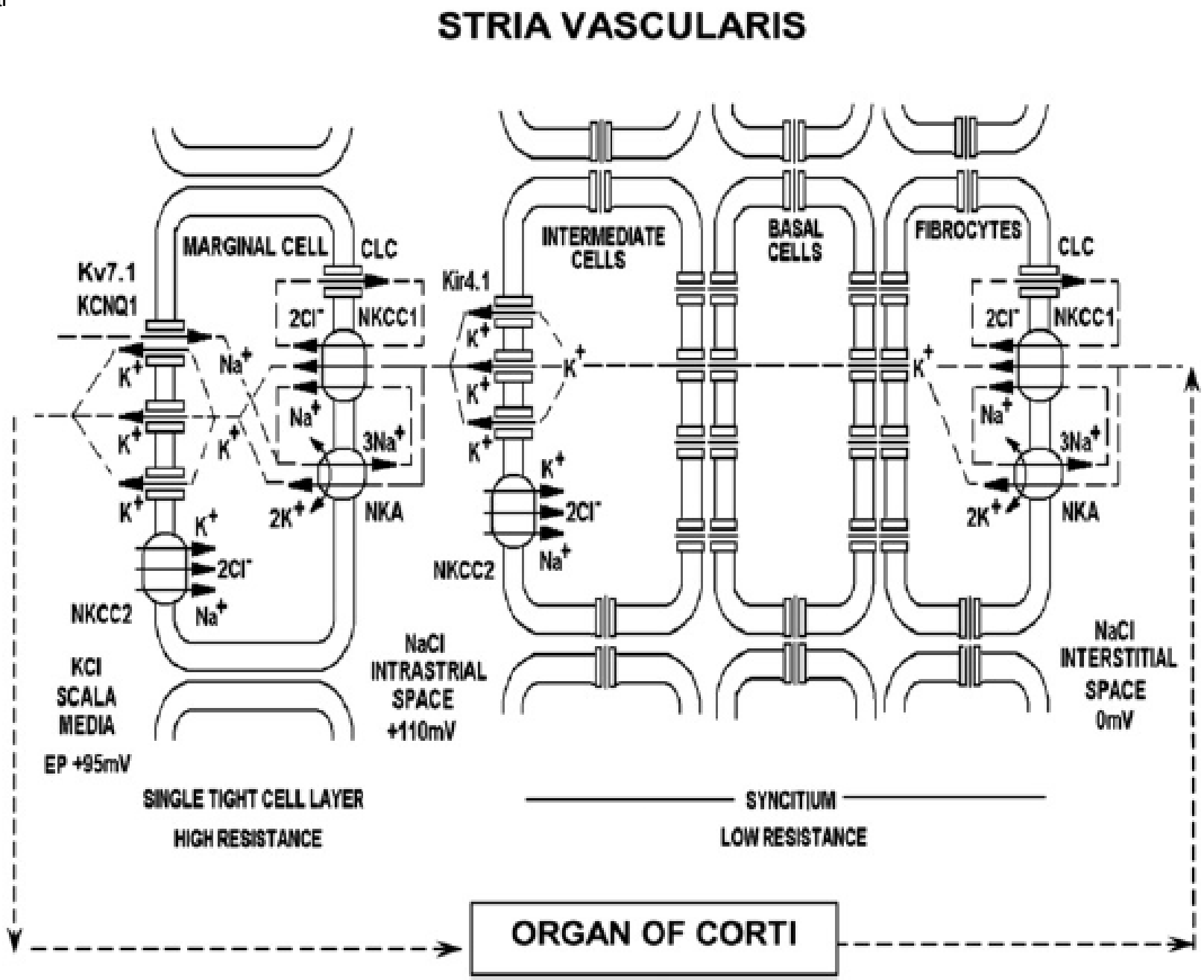


- The potassium flow originating from the fibrocytes of the spiral ligament penetrates into the basal cells via a connective tissue gap junctions system composed of connexins. lateral wall of the cochlea and in the stria vascularis.

In this system, the absence of the underlying transport proteins can be responsible for a hereditary hearing loss.

- The endolymphatic compartment is held at a positive potential of at least +80 mV. (large K+-diffusion potential)
- The low K+ levels (5mmol/l) in the intrastrial space between the marginal and intermediate cells is maintained by the action of a K+/Na+ ATPase, a K+/Na+/2Cl co-transporter (SLC12A2) and a Cl return path at the base of the marginal cells.
- Finally, K+ permeates into scala media through a further potassium channel complex, KCNQ1/KCNE1 in the apical membrane of marginal cells

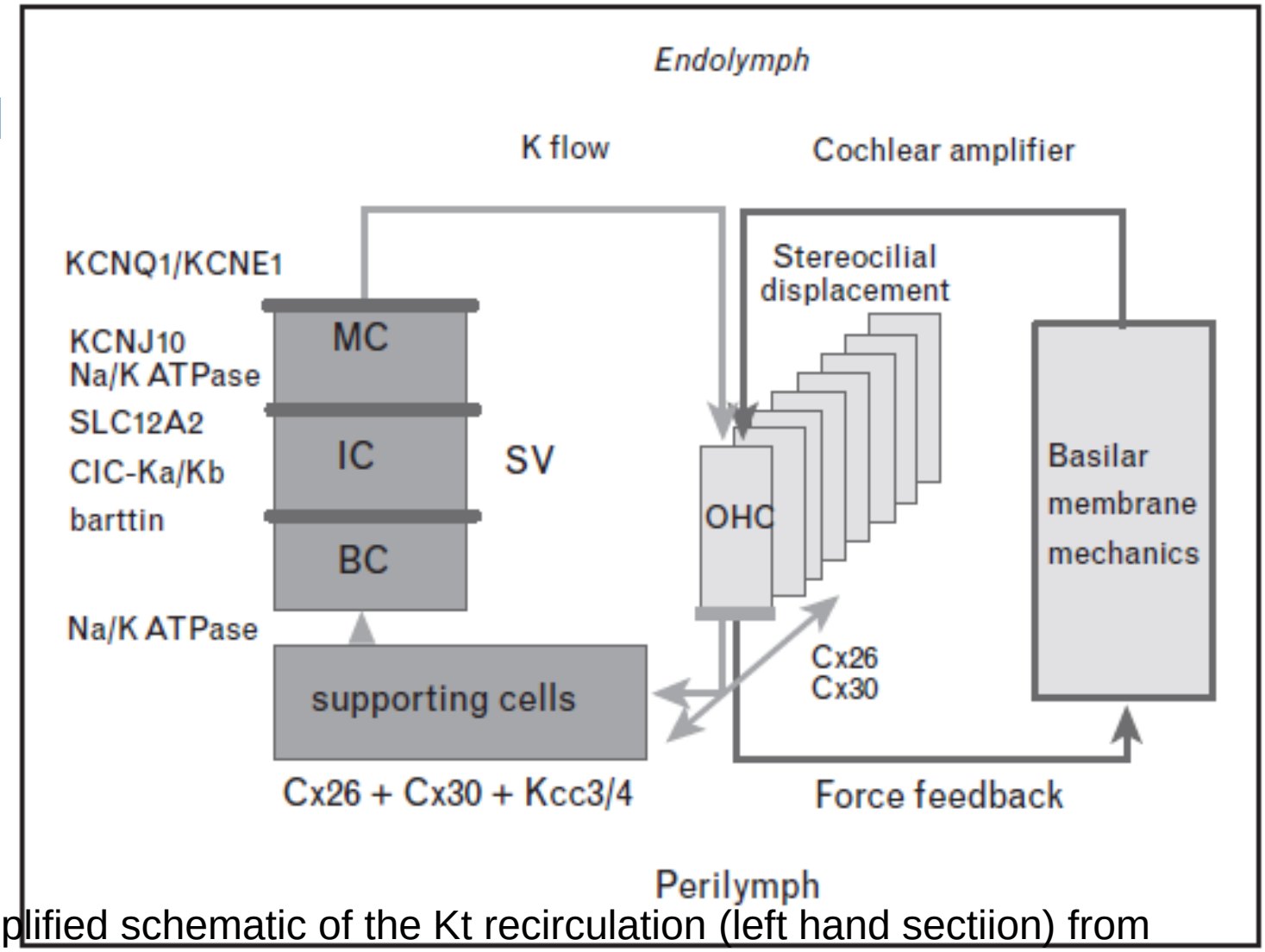
2011 - Ion flow in stria vascularis and the production and regulation of cochlear endolymph and the endolymphatic potential



K+ recycling and cochlear amplification

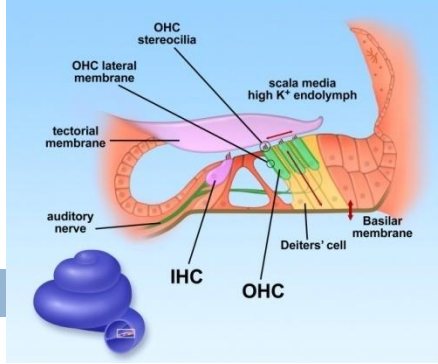
- Although the components for K+ recycling are in place, direct evidence for this proposal is still missing (absence of high-resolution imaging methods sensitive to ion fluxes)
- However, assuming K+ recycling hypothesis does open alternative ways for thinking about how K+ flow affects the cochlear amplification mechanism.

Figure 1 Cochlear K^+ flow and amplification interlock



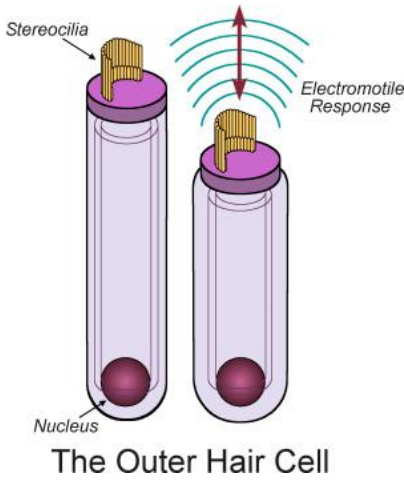
A simplified schematic of the Kt recirculation (left hand sectiion) from endolymph through the outer hair cells (OHCs) to perilymph. Displacement of the OHC hair bundle gates current flow and generates force feedback (right hand section) to the cochlear partition.

Cochlear amplification



- Sound waves enter the scala vestibuli of the cochlea and travel throughout it, carrying with them various sound frequencies. These waves exert a pressure on the basilar and tectorial membranes of the cochlea which vibrate in response to sound waves of different frequencies.
- When these membranes vibrate and are deflected upward, the stereocilia of the OHCs are deflected toward the tallest stereocilia. This causes the tip links of the OHC hair bundle to open allowing inflow of Na+ and K+ which depolarize the OHC.

- Upon depolarization, the OHC can then begin its process of amplification through positive feedback.
- This positive feedback mechanism is achieved through a somatic motor and a hair bundle motor which operate independently of one another.
- Both the somatic motor and the hair bundle motor produce significant displacements of the basilar membrane. This, in turn, leads to augmentation of bundle movement and signal amplification



The Outer Hair Cell

K+ recycling hypothesis

- First, any reduction in endocochlear potential would affect the magnitude of the electrical driving force of the OHC mechanotransducer. The consequent reduction in OHC depolarization and forces during a sound stimulus would affect cochlear amplification.
- Such reductions in endocochlear potential should arise from mutations in any of the genes encoding K+ transportrelated proteins in stria vascularis, or equally from reduction in the energy supply for the pumps in stria vascularis (as occurs in anoxia).

- The magnitude of the effect is difficult to predict. It is known that relatively short (2–3 min) periods of anoxia can reduce endocochlear potential by over 30mV and affect cochlear tuning. There are no significant falls of endolymphatic K+ during these short experimental periods.

- Second, recent evidence indicates that endocochlear potential can also be reduced when chloride ion flow in stria vascularis is altered.
- To counteract Cl transport into the marginal cells of stria vascularis through the SLC12A1 co-transporter, a small *b-subunit protein, barttin,* is required to permit anion exit from the marginal cells.

- In some mouse models of Bartter syndrome, mutations of barttin compromise both Cl re-exit and the positive endocochlear potential, but the high endolymph K+ is not affected.
- The barttin-deficient mouse has no distortion product otoacoustic emission (DPOAE). →intact OHC function.
- The driving force for K+ entry through the mechanotransducer channel in the absence of endocochlear potential is reduced by less than half.

- Third, irrespective of the K+ concentration in scala media, the outflow of K+ from the hair cells is likely to be a critical determinant of OHC function and longterm survival.
- Loss of OHCs may arise from
  - intracellular potassium accumulation, in which case, the cells would swell to maintain osmotic balance
  - the depolarization when K+ channels are lost, intracellular calcium would rise, producing a loss of transduction sensitivity and cell death.

- Fourth, clearance of K+ from around OHCs is likely to be critical. Often described as 'K+ intoxication' of the organ of Corti, K+ buildup would depolarize the OHCs.
- The clearance mechanisms for K+, however, may also involve other permeable ions.
- Some forms of deafness and sensitivity loss could result from altered intercellular flow of metabolites and secondary messengers between cells during the embryogenesis of the cochlea.

Modeling K+ circulation in the cochlea

- The picture painted of global potassium recirculation in the cochlea is difficult to investigate experimentally due to complexity of the underlying molecular network.
- However, it can be approached by computational biology using in-silico cochlear models. The first attempt to model a 3D ionic circulation between distinct cochlear compartments was made >30 years ago
- The computational power now available is much greater. This allows the consideration of relatively complex circuits with reactive elements.

- Such models are sufficiently detailed, allowing the physiological effects of selected mutations of transport and gap junction proteins on the K+ currents to be studied.
- However, there remain disagreements about how outer hair cell forces affect cochlear mechanics

Conclusion

- The idea of recycling of K+ in the cochlea is based on the cellular localization of critical K+ transport-related molecules in different cochlear compartments.
- This recycling is almost certainly critical for the efficiency of cochlear amplification based on OHC somatic electromotility but still lacking are dynamic measurements of this flow.

- OHC operation can be seen as a sensitive functional indicator of
  - mutations in K+ transport-related molecules in the cochlear
  - the absence of endocochlear potential
  - K+ buildup in the organ of Corti itself.

Thank you for your attention!

Reference

- http://www.ncbi.nlm.nih.gov/pubmed/24480364
- http://www.ncbi.nlm.nih.gov/pubmed/23422312
- http://www.ncbi.nlm.nih.gov/pubmed/23151402
- http://www.ncbi.nlm.nih.gov/pubmed/21523631
- http://www.ncbi.nlm.nih.gov/pubmed/21329750
- http://www.ncbi.nlm.nih.gov/pubmed/19741536

- http://www.ncbi.nlm.nih.gov/pubmed/10478593
- http://www.ncbi.nlm.nih.gov/pubmed/9925027
- http://www.ncbi.nlm.nih.gov/pubmed/9745959
- http://www.ncbi.nlm.nih.gov/pubmed/7737927