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How to build a cochlea
to work and amplify sounds at high frequencies

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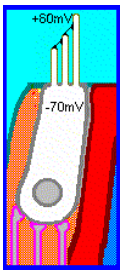
outline

- Cochlear construction
- Cochlear amplification
- The endocochlear potential



A tale of two proteins – pendrin and prestin

Starting points:

The ear is small and relatively inaccessible
The ear works at high frequencies
The structure of the cochlea is critical for function
The inner ear is a protected environment

human hearing range

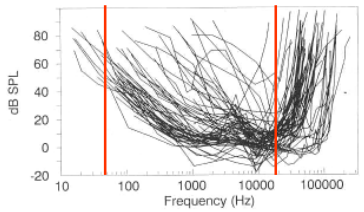
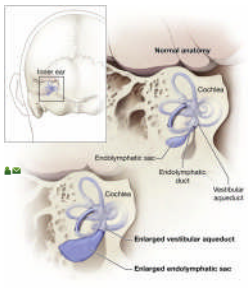


FIGURE 1.1. Behavioral audiograms for over 60 mammals. (Modified after Fay 1988, with permission.)

Mouse models of hearing

Stage E14.5. Endolymphatic compartment filled with dye
D Wu, NIH

Pendred syndrome – enlarged vestibular aqueduct correlates with deafness

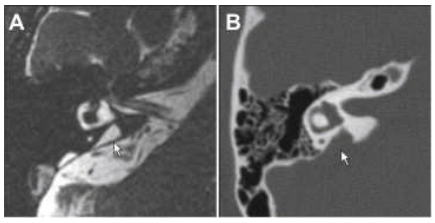


5–15% of children with sensorineural hearing loss have EVA.

Pheips et al, 1998

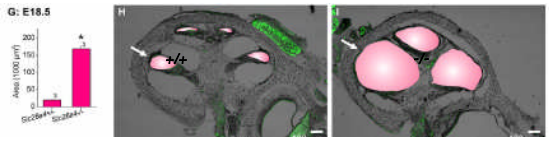
Pendred syndrome – enlarged vestibular aqueduct as correlate of deafness

CT scan MRI



A mouse model of Pendred syndrome: pendrin knockouts

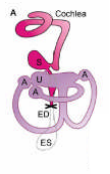
Enlarged scala media in SLC26A4 -/- mice

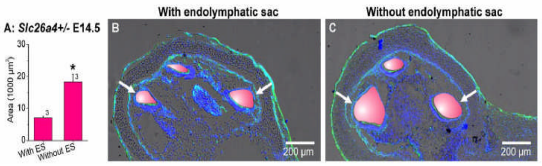


WT SLC26A4 -/-

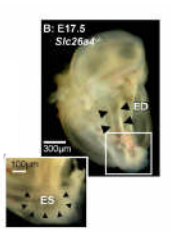
Kim & Wangemann, PLoS, 2010

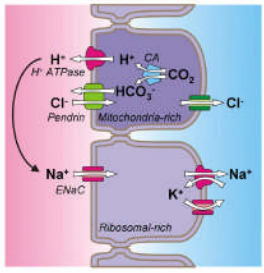
Ligation experiments





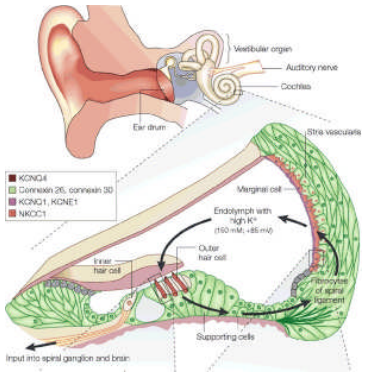
Endolymphatic sac function determines size of vestibular aqueduct



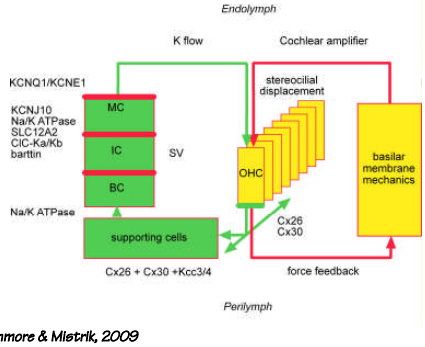


Kim & Wangemann, PLoS, 2010

The potassium circulation hypothesis



Jentsch, Nature Rev Neurosci 2000



Ashmore & Mistrik, 2009

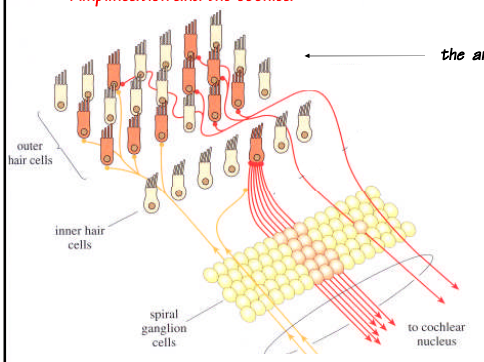
The Cochlear Amplifier is…

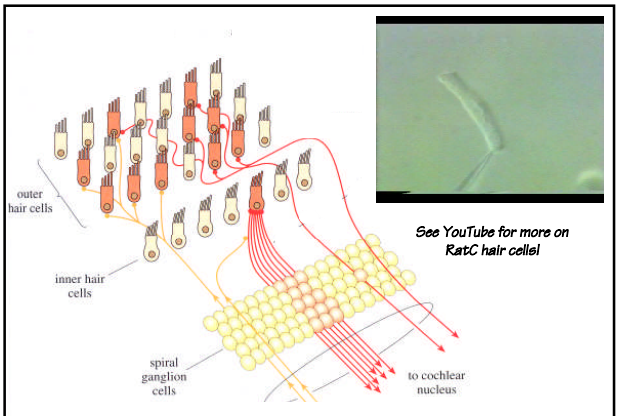
A set of 'processes' which are

1) responsible for >40dB increase in sensitivity at low SPL
2) responsible for otoacoustic emissions
3) responsible for enhanced frequency selectivity
4) dependent on intact physiology of the cochlea
5) labile – disappears post mortem, with noise damage, with ototoxic insult, with age etc etc
6) Something to do with OHCs…

Hallowell Davis
(1896-1992)

Amplification and the cochlea





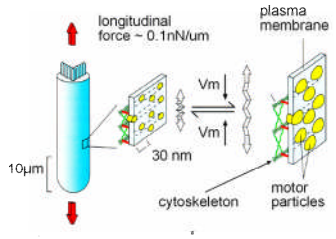
See YouTube for more on RatC hair cells!

The 'motor' occupies most of the OHC lateral membrane

100x magnification:
8nm diameter particles

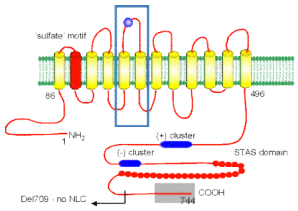
Kachar et al, 1992

The outer hair cell is an ultrafast motor / actuator



an area motor
high copy number (>10^7 /cell)
fast cycle time (> 50 kHz)
cycle associated with a 'gating' charge

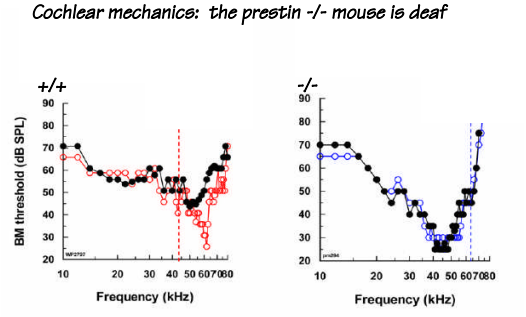
The molecular motor, prestin, is a membrane transporter



Genomic identity: SLC26A5 - a low efficiency Cl-HCO_3 antiporter?
(SLC26 is a superfamily of anion-bicarbonate exchangers)

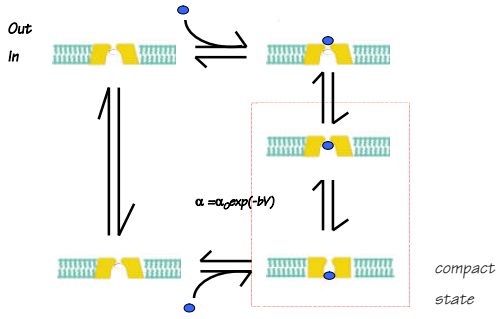
Zheng et al, 2000

Cochlear mechanics: the prestin -/- mouse is deaf



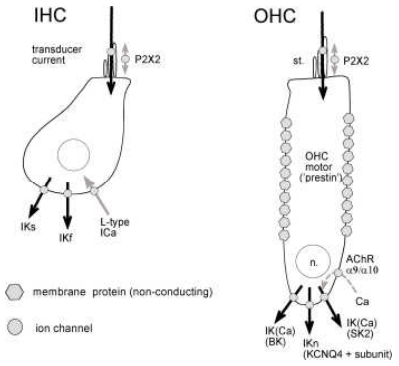
• = post-mortem

Liberman et al., Nature 2002
Mellado Lagarde et al., Curr Biol 2008

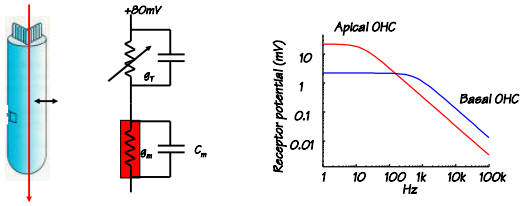


The motor arises from kinetic substates of a conventional carrier; molecular crowding does the rest

Inner and outer hair cells are electrophysiologically distinct



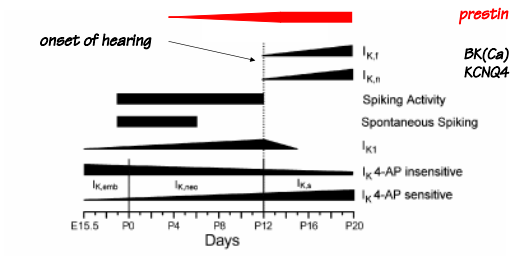
The RC time constant problem:
can outer hair cells work at acoustic frequencies?



Prestin driving force, $\Delta V = Vin - Vout$

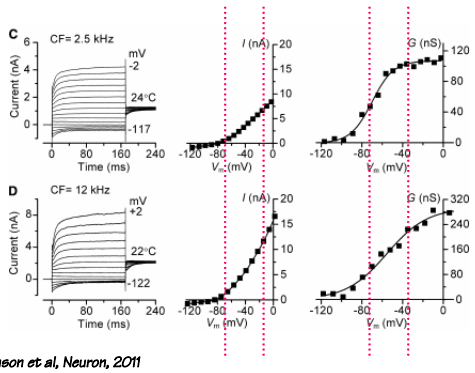
=> All sorts of suggestions, e.g. cochlear amplification due to stereocilia

Beware! Hair cell ionic channels change during development



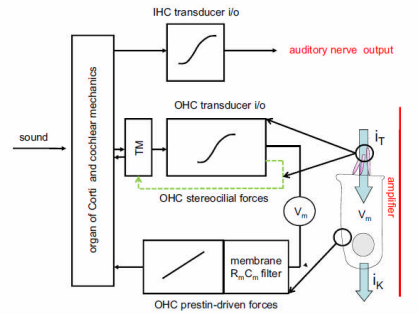
Marcotti et al 2003

Outer hair cells may be more depolarized in vivo than previously thought…



Johnson et al, Neuron, 2011

The cochlear amplifier subsystem – may well be 'fast' enough



Low endolymph Ca^{++}
↑ i_T

↑ V_m
↑ I_k activation
↓ time constant

Conclusions

Pendrin is an efficient Cl-bicarbonate exchanger
critical for cochlear chamber formation

Prestin is an (inefficient) Cl-bicarbonate exchanger
critical for mechanical amplification in the cochlea

Unsolved: At the highest frequencies..?
The molecular structure of prestin

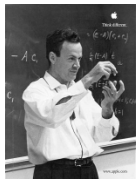
KCNQ4 (underlying DFNA2) is a potassium channel
critical for increasing OHC bandwidth

Unsolved: KCNQ4 cofactors and regulation in OHCs

There's Plenty of Room at the Bottom

..We physicists often look at [biologists] and say: "You should use more mathematics, like we do."

They could answer us---but they're polite, so I'll answer for them: "What you should do for us … is to make the [electron] microscope 100 times better."



Richard Feynman, 1959

With thanks to

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