Neurobiology of Hearing

Salamanca, 22nd May 2019

3. Cochlear amplification: outer hair cells

Jonathan Ashmore
Neuroscience, Physiology and Pharmacology
University College London

j.ashmore@ucl.ac.uk

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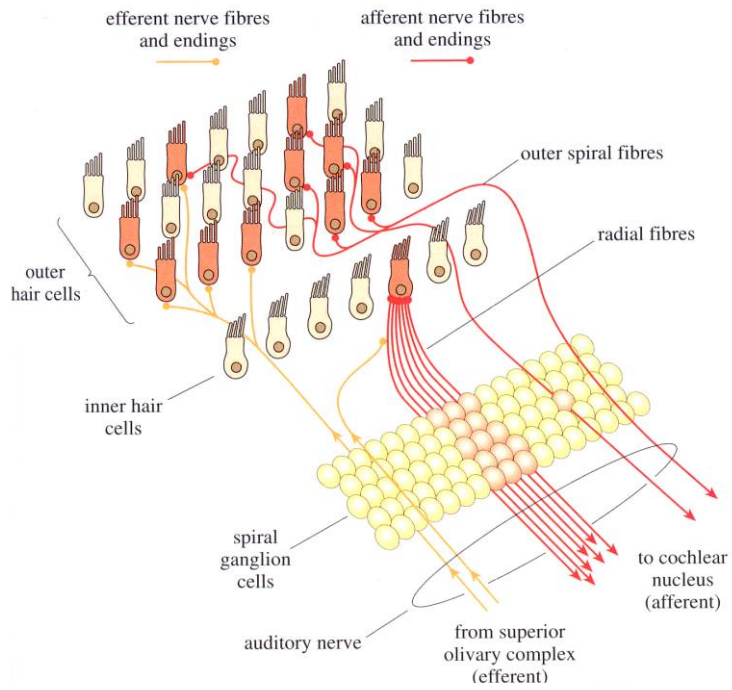
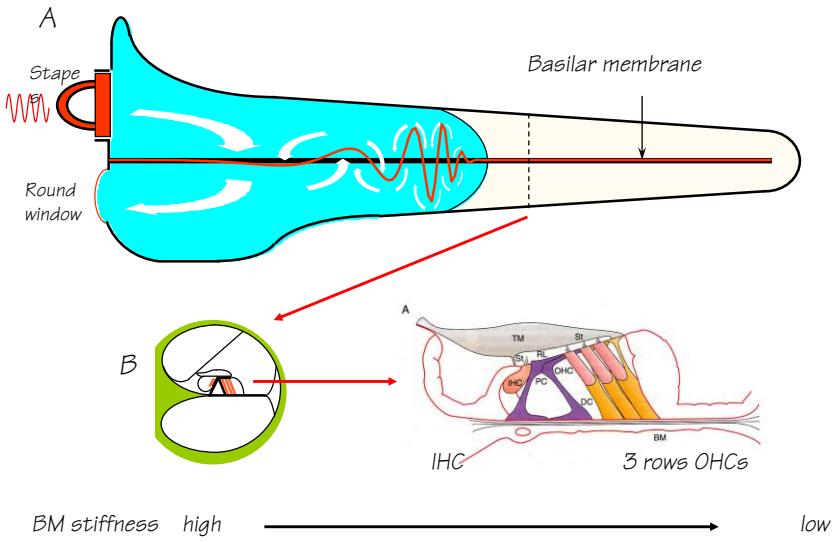


2

The mammalian cochlea is a mechanical spectrum analyser



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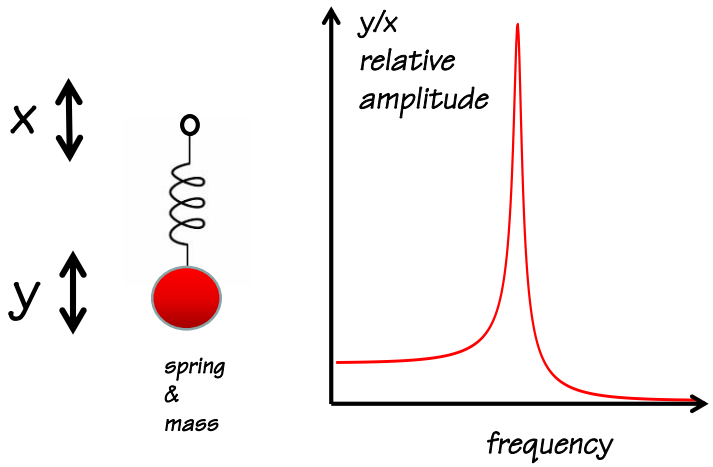

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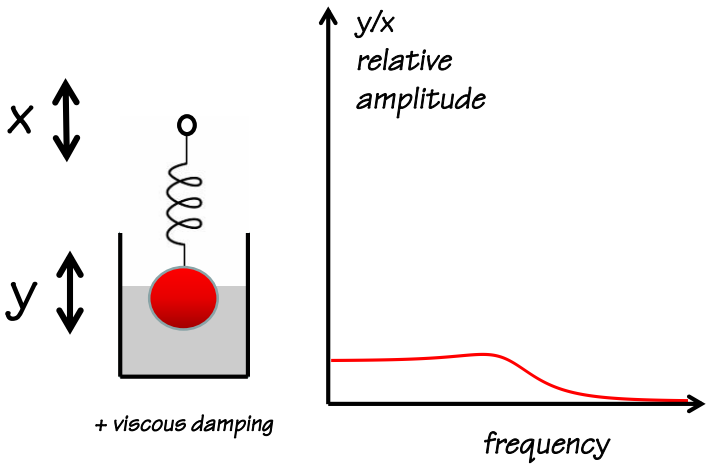

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We can use this idea to make an in-silico model of the cochlea

See:

http://147.162.36.50/cochlea/cochleapages/theory/index.htm

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Problem: cochlear bandwidths are narrow..

Solution: a 'cochlear amplifier' to counteract viscosity effects
(Gold 1948, Davis 1983)

responsible for sound amplification (100 x)

responsible for frequency selectivity

'linked' to otoacoustic emissions

Use the outer hair cells to compensate for fluid viscosity

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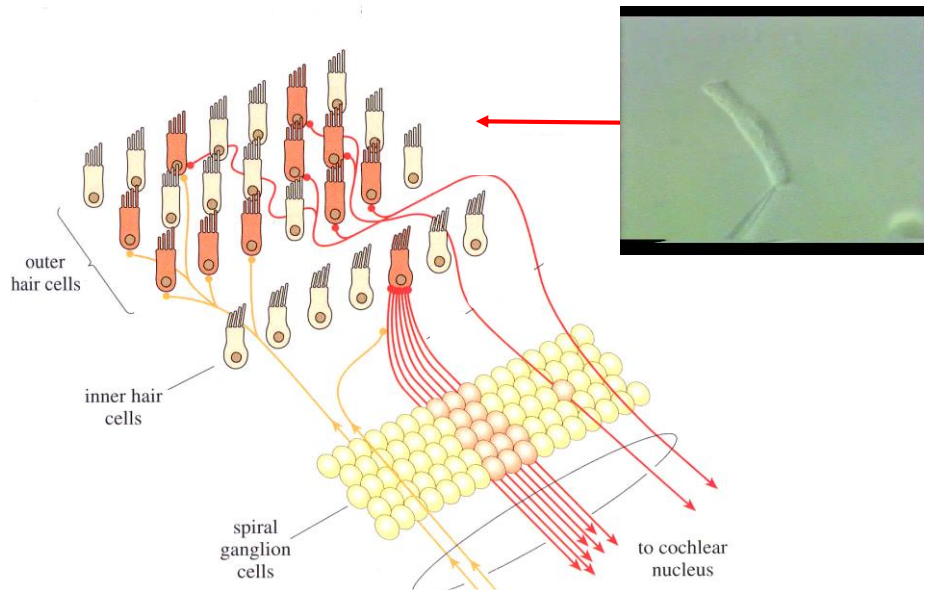

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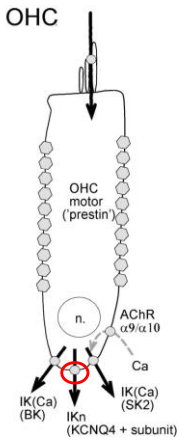
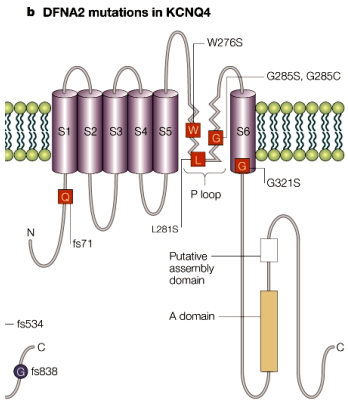
Kv7.4 / KCNQ4 – one of the main K channels in OHCs





Mutations in the gene define a deafness locus DFNA2

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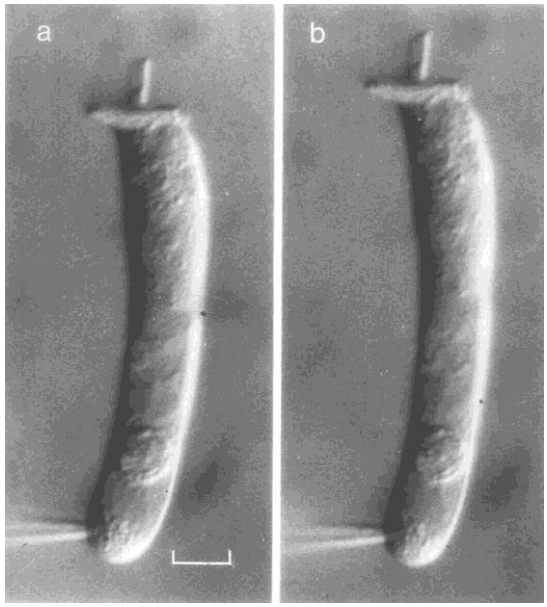
Outer hair cells have an additional property: they change length



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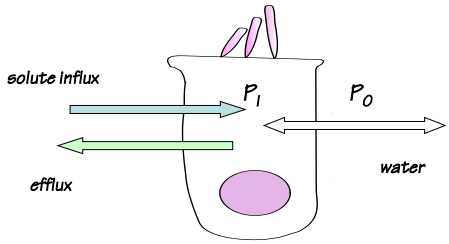
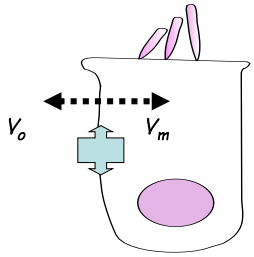
Two ways to make a cylindrical cell change length

Area constant



Volume constant

(The cochlear motor)



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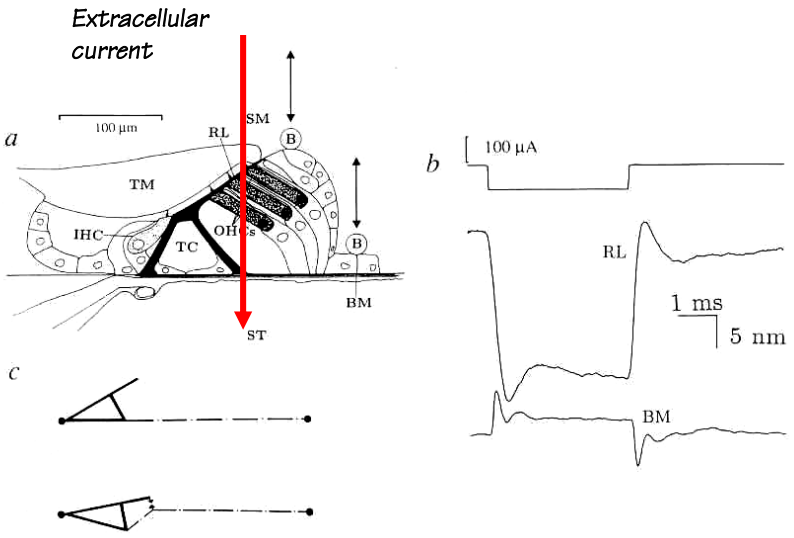
Outer hair cells in situ distort the cochlear partition



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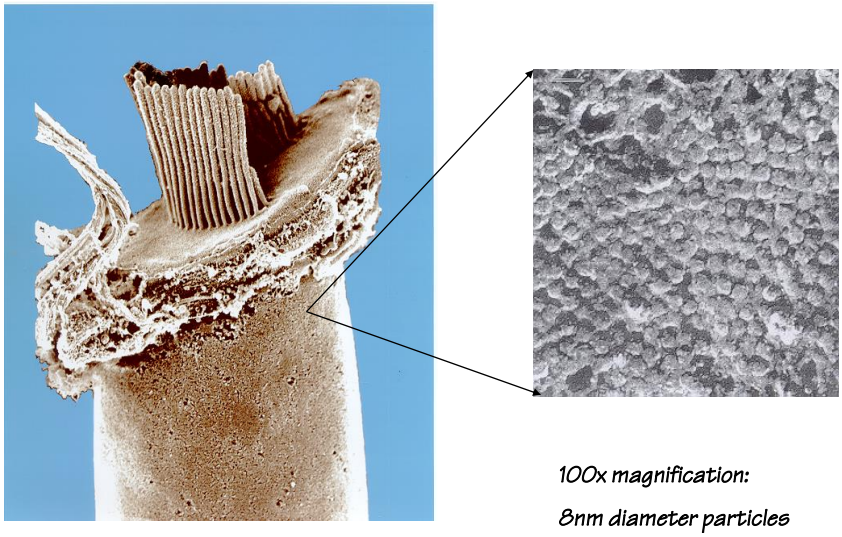
The 'motor' occupies most of the OHC lateral membrane



100x magnification:

8nm diameter particles

B Kachar - NIDCD

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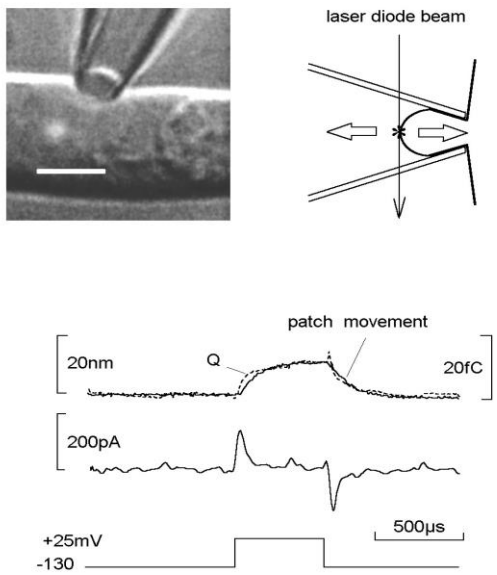
The motor is local and has an electrical 'fingerprint'



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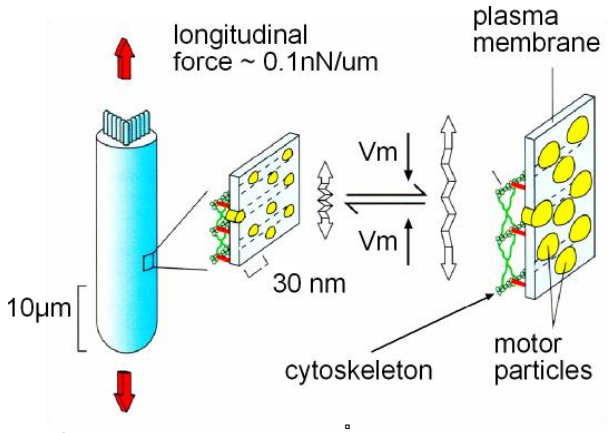
The outer hair cell is an ultrafast motor / actuator



an area motor
high copy number (>107 /cell)
fast cycle time if driven (> 50 kHz)
operation associated with a gating charge

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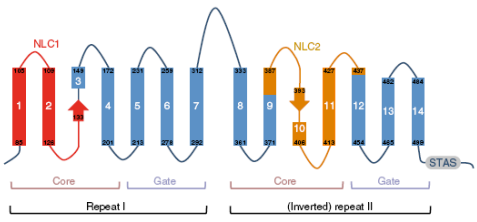
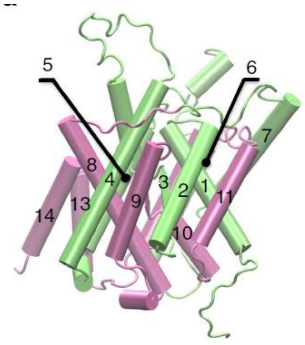
The molecular motor, prestin, is a membrane transporter

Homology model: Gorbunov et al., 2014





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

Originally reported by Zheng et al, 2000

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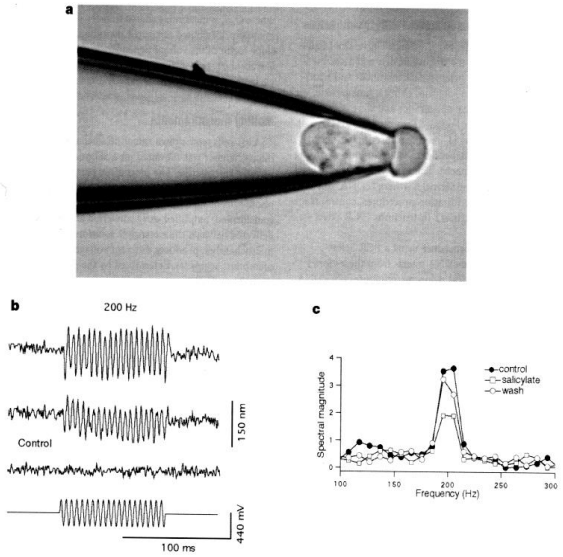
Prestin transfected HEK cells



Zheng et al,. 2000

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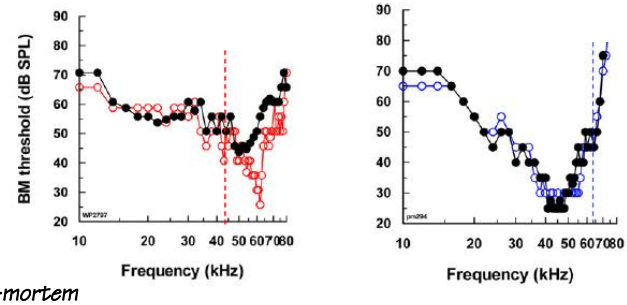
Prestin KO mouse does not have amplification

WT

prestin KO



• = post-mortem

Liberman et al., Nature 2002

Mellado Lagarde et al., Curr Biol 2008

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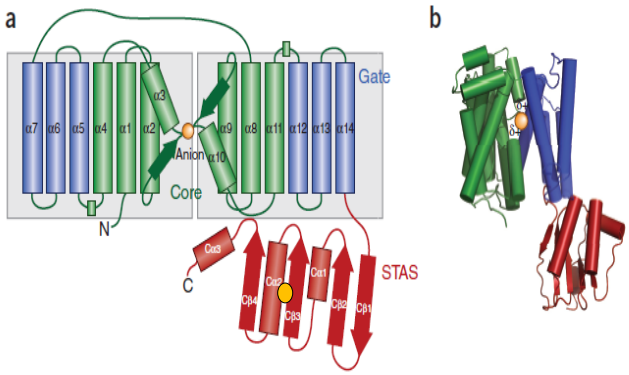
2015: crystal structure: of a bacterial SLC26

(from a thermophilic bacterium, Deinococcus geothermalis)



Geertsma, et al., Nat. Struct. Mol. Biol. 2015

From Reithmeier & Moreas with permission

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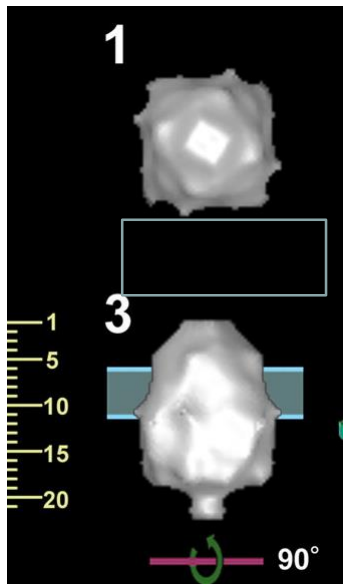
Mammalian prestin (SLC26A5) is a tetramer = dimer of dimers



nanometres

outside

membrane

cytoplasm

Mio et al, J Cell Biol. 2008

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The SLC26 superfamily and relatives in Drosophila & C. elegans

They are bicarbonate exchangers

(Red blood cells have bicarbonate exchangers in the SLC2 family)

Mount and Romero Eur J Physiol (2004)

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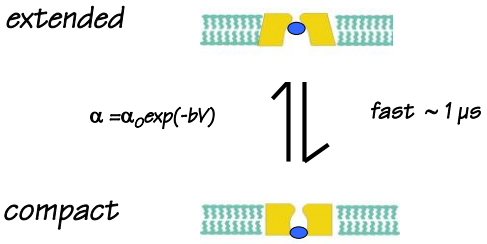
A simple model for prestin action



● = intracellular anion (Cl^- or HCO_3^-)

'Molecular crowding' leads to macroscopic effects.

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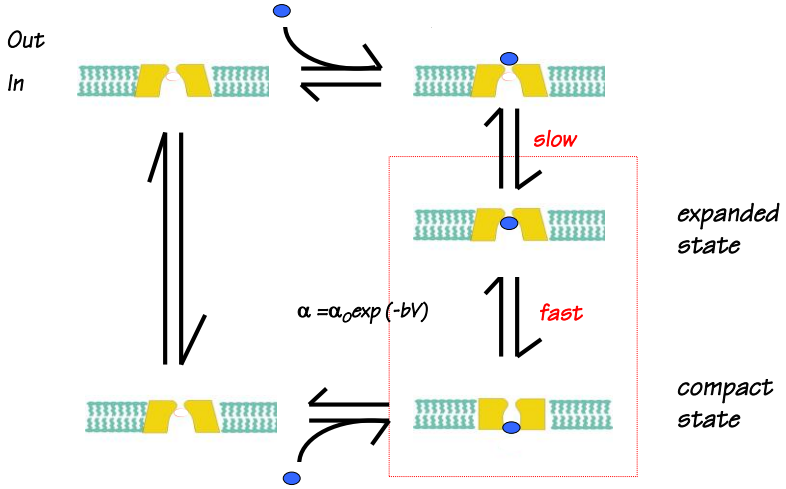

conventional 4 state carrier model

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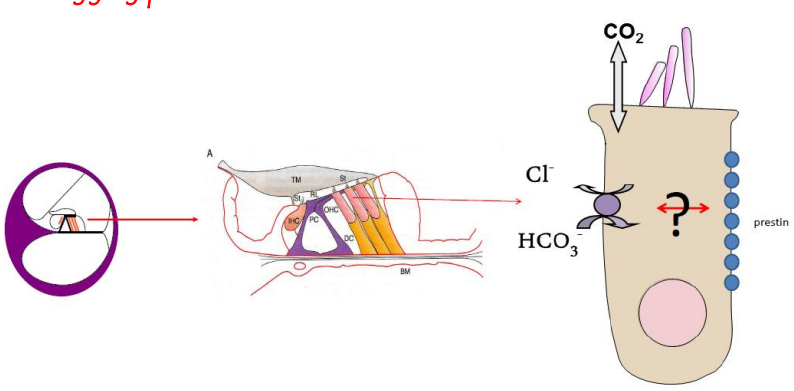
A nagging problem



Ikeda et al, 1991: OHCs regulate their intracellular pH
Prestin is a member of the SLC26A anion-bicarbonate family of transporters

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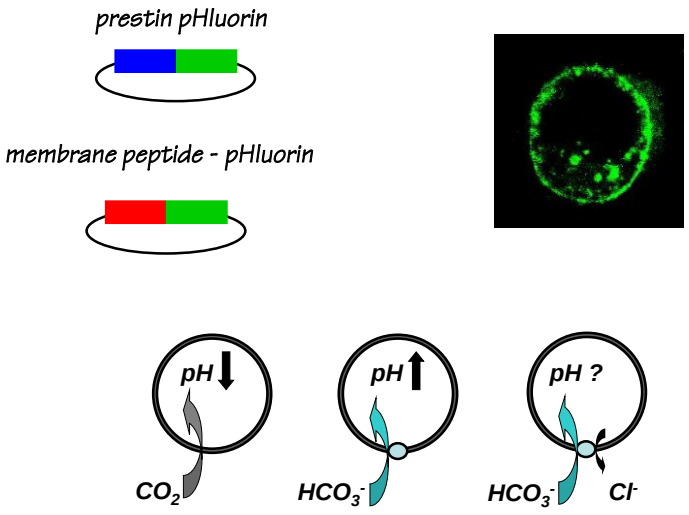
Cl^- controls HCO_3^- loading in prestin expression systems



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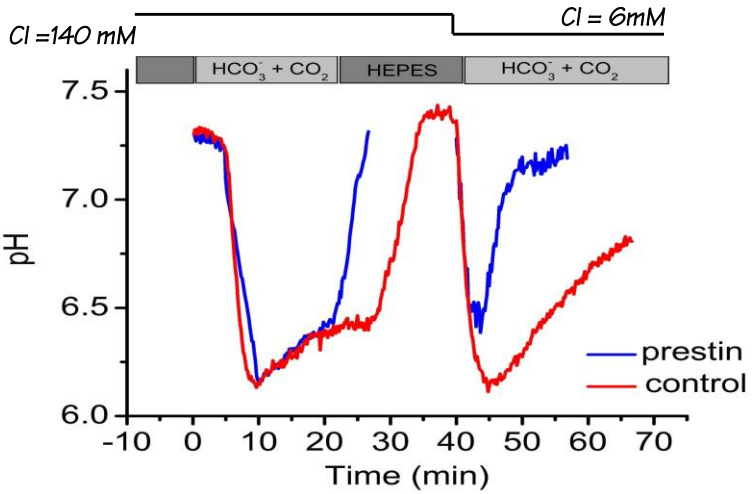
HCO_3 is transported by prestin under Cl control



Mistrik et al, 2012

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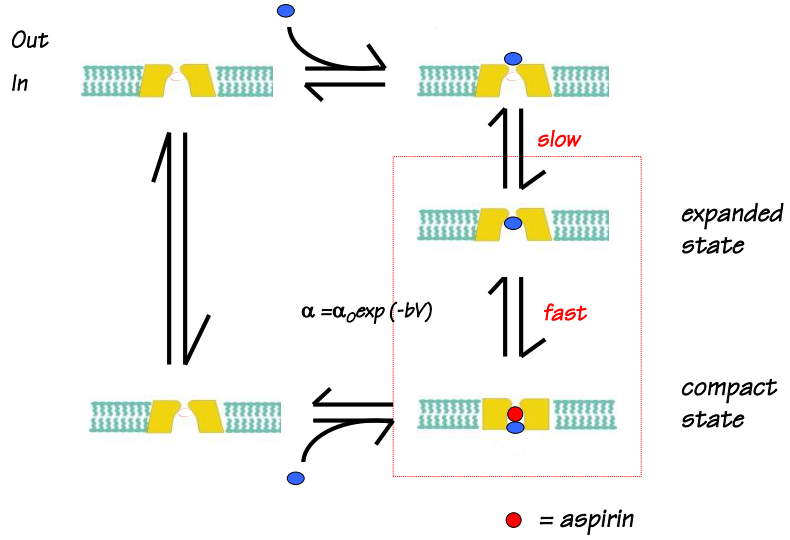

conventional 4 state carrier model
low turnover rate ~900 s^{-1} (=0.1% of other Cl-HCO_3 transporters)

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Conclusions

1) The mammalian OHC is an ultrafast actuator

2) The 'motor' molecule is also low efficiency Cl -HCO_3 exchanger

3) The 'motor' arises from part of a transport cycle and creates a 'cochlear amplifier'

Unresolved:
how is it inserted and (?) is there turnover ?
what is the mechano-enzyme structure of prestin?
how is it coupled into the cell cytoskeleton?

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