What you need to know about drug therapies for treating hearing loss

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Overview

• Routes of administration in clinical practice
  • Intratympanic injection
  • Direct Injection into the inner ear
  • Drug elution from devices (cochlear implants)

• Limitations of cochlear diagnostics, and implications for new therapies

• Efforts to improve diagnostics – a dialogue between ENT and Audiology
Intratympanic treatments

Entry into the cochlea depends upon:
• Molecular weight of the drug
• Access to the round/oval windows
• Membrane permeability of drug
• Its consistency: Liquid vs gel
Getting drug into the round window: middle ear variability
Bubbles beneath mucosal folds
Drug properties and cochlear entry/elimination

Drugs that are
- Lipophilic (high WLOGP) i.e. dissolve in fats
- Small
- Non-polar cross membranes readily

The Swiss ADME “Boiled Egg” Decreasing permeability across membranes

Dexamethasone for intratympanic injection

Pro-drug

Cleaved

Active form

Dexamethasone Phosphate

Highly polar
Water soluble (injectable)

Dexamethasone

Water insoluble, lipid soluble
Dexamethasone’s properties & cochlea delivery

• Dexamethasone is hard to get in, and easy to leak out of the cochlea.

A measure of the topological polar surface area
Dexamethasone Phosphate doesn’t reach the apex

Intratympanic Gentamicin for Meniere’s Disease

- Gentamicin does not cross into the cochlea easily.

- But once it does, it “stays there” for a long time, and does not cross the blood-labyrinthine barrier easily.
Liquids

• Readily eliminated via the eustachian tube, or into the mastoid
• Can “sneak” around corners readily
• Good for single-dose applications
• But plagued by variable absorption into the cochlea
• Clinical examples:
  • Intratympanic steroids for Meniere’s Disease, Sudden and Fluctuating sensorineural hearing loss
  • Intratympanic gentamicin for Meniere’s Disease.
Gels

- Liquid at room temperature, and gel at body temperature
- More viscous: more likely to form “bubbles” in the RWM niche
- Can run out of the middle ear before they gel
- Higher dose, more controlled and sustained delivery

Miconised Dexamethasone (base) in Poloxamer 407 gel

For Meniere’s Disease

LPT99 (antioxidant) in a hydrogel

Commencing clinical trials this year

Chemotherapy-induced hearing loss
Targeting hair cell regeneration

- FX-322: a glycogen synthase kinase 3β inhibitor (FX03) and valproic acid in a Poloxamer 407 gel
- Expands Lgr5+ stem cells that transdifferentiate into hair cells
- We led the first-time-in-human’s Phase 1 trial in Melbourne in 2017

Intracochlear delivery: Gene therapy

- Direct injection through the stapes
- Gene therapy (Atoh1) [GCF166]
- To replace missing hair cells
- Injecting 20-60 µl aliquots
- There has been some hearing loss from the drug delivery
- There have been some responders
Intracochlear delivery: Steroid elution from CI

“Combined Device” Trial: Dexamethasone (Melbourne)
Intracochlear delivery: Steroid elution from CI

“Combined Device” Trial: Impedances substantially reduced
Chosing candidates for regenerative therapies

Images from Dan Jagger’s laboratory (with thanks):
Supporting cell expansion after hair cell loss

Dead hair cell remnant being “pushed out” by Deiter’s cells)
End-stage disease - “flat” epithelium

Which patients might have cochleae “permissible” for regeneration?

Definitely not
Streptomycin
Fig 6.2 Schuknecht’s Pathology of the Ear, Ed. 1

Possibly
Gentamicin
Fig 6.20 Shuknecht
Can we predict “permissive” cochleae from hearing?

Schuknecht Fig 6.8, 6.9. Kanamycin toxicity
Idiopathic Sensorineural Hearing Loss

No possibility of regeneration at cochlear base
Strial injury more likely than hair cell loss at 1 kHz
Idiopathic Sensorineural Hearing Loss
Summary: Regenerative capacity can’t be predicted from the audiogram

• Regeneration presumably requires a relatively “normal” architecture of organ of Corti.

• This is more likely to be seen at mild-to-moderate hearing loss, but
  • With mild-moderate loss the cause might be strial (i.e. the “battery”) instead
  • With profound loss, the architecture of the organ of Corti can look either relatively normal or “flat” epithelium.
There is poor correlation between cellular damage and audiograms

Fig 7. Landegger et al, Hear Res 2016
Note that the correlations between hearing loss and cellular injury are moderate at best.

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Cell type</th>
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<tbody>
<tr>
<td></td>
<td>HC</td>
</tr>
<tr>
<td>250</td>
<td>0.38*</td>
</tr>
<tr>
<td>500</td>
<td>0.42*</td>
</tr>
<tr>
<td>1000</td>
<td>0.47*</td>
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<tr>
<td>2000</td>
<td>0.45*</td>
</tr>
<tr>
<td>4000</td>
<td>0.49*</td>
</tr>
<tr>
<td>8000</td>
<td>0.41*</td>
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</tbody>
</table>

Word recognition | 0.37* | 0.38* | 0.23 | 0.10 | 0.27 |

* p<0.05, Table 1, Landegger et al Hear Res 2016
Speech understanding too correlates poorly with cochlear cellular damage

100% hair cell survival, yet 0% word recognition!

Fig 7. Landegger et al, Hear Res 2016
This is presumably why audiograms do not predict speech recognition well.

[Graph showing dB HL vs Frequency kHz with markers for different frequencies]
The diagnostic dilemma

• Audiograms and speech testing do not predict cochlear pathology.
• Specific (Mendelian) genetic lesions seen in <10% adults hearing loss. (~40-50% of children with hearing loss)
• Genetic variation *points towards* neuronal, hair cell or strial dysfunction, but is not specifically diagnostic.
• Accurate diagnostics requires an assessment of the *function of surviving cochlear hair cells, neurons and stria*, but we lack these tools for severe-profound hearing loss.
New approaches to functional assessment

We are using the cochlear implant to assess function of surviving cochlear hair cells, neurons and stria
Cochlear Response telemetry

USB Cochlear Implant Communication Pod

ECochG directly from CI electrodes

Laptop
Sound card (signal generation and recording)
Custom Software

Insert Tube Phone
The Cochlear Microphonic
A frequency-following hair cell response

The Auditory Nerve Neurophonic
A frequency-following neural response
Separating the Hair cell - Cochlear Microphonic (CM) and the Neural - Auditory Nerve Neurophonic responses
CM without Auditory Neurophonic (ANN)

Particpant #5: ANN weak or absent

We analyse the frequency components of the CM response using the Fast Fourier Transform.
CM without Auditory Neurophonic (ANN)

• Hair cell responses: At the first harmonic (fundamental)

• Neural (ANN) response is at the second harmonic

(work pioneered by Doug Fitzpatrick, UNC)
CM with ANN

Participant #5: Late in insertion ANN present

When distortion is synchronous with the fundamental, the second harmonic may be due to hair-cell distortion.
Separation of Hair cell and neural responses

• Contributions from
  **hair cells**: (CM and distortion products) and
  **neurons**: (Auditory neurophonic)
  can be derived by analysis of frequency analysis of the “CM” trace.

• CM & ANN vary between patients,
  and at different places within the cochlea
Biomarker 2: Latency

CM in patient with Auditory neuropathy (good hair cell survival)

Latency increases as electrode advances into the cochlea
Latency: tells us where the response arose from

Campbell et al 2017
Audiol Neurotol, 22:180-189
Hypothesis:
Latency shift is a biomarker for local Outer Hair Cell Survival
Confirmation in animal model of CI

<table>
<thead>
<tr>
<th></th>
<th>Guinea Pig Array</th>
<th>Human Array</th>
</tr>
</thead>
<tbody>
<tr>
<td># Intra-cochlear electrodes</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Typical insertion depth</td>
<td>5mm</td>
<td>20-25mm</td>
</tr>
<tr>
<td>Frequency range covered</td>
<td>32 to 16 kHz</td>
<td>20 to 1 kHz</td>
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<tr>
<td>Histology possible</td>
<td>YES</td>
<td></td>
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</table>

8 noise trauma guinea pigs  
16-24 kHz, 124 dB HL for 2 h  

8 normal hearing guinea pigs
Outer hair cell loss at 16 kHz after noise

ND08
4 kHz

No hair cell loss

ND08
16 kHz

Inner Hair Cells present

OHC Loss
Latency shift when OHC present

There is a latency shift when there is no hearing loss and good OHC survival.
No latency shift when few OHC survive

No latency shift when there is hearing loss and OHC loss
New diagnostics from CI derived ECochG

We can determine when there are functioning hair cells and auditory neurons.

Latency:
We can tell where in the cochlea these are located.

Latency-shift:
Appears to be a specific “biomarker” for outer hair cell function above the electrode.
Treatment of hearing now, and in the future

Hearing loss

Genetic testing

Site-of-lesion Diagnostics

Inflammation (MRI)
Neural function
Strial function

Disease modifying drugs
Regenerative therapies
Prognostics for CI

Hearing aids

Gene found (40% children, few adults)

Prognostics
Targeted gene therapy

Cochlear Implants
Therapeutics
Diagnostics
The future?

- Cochlear Implants
- Regeneration
- Drug delivery
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