Age-Related Hearing Loss: From Animal Models to Human Hearing

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Outline

• What we have learned from animal models of presbyacusis (age-related hearing loss)
  • Neural presbyacusis
  • Sensory presbyacusis
  • Metabolic presbyacusis
• How we may use this information to understand potential mechanisms of hearing loss in older humans
• Analysis of “audiometric phenotypes”
Animal models of presbyacusis

- Hearing loss in older adults results from accumulated effects of noise, drugs, disease...
- In older humans, difficult to determine:
  - which portion of hearing loss relates to each risk factor?
  - which portion of hearing loss relates to aging alone?

Gerbil animal model of presbyacusis

- Gerbils raised for 3+ years in controlled environment ("quiet aged")
  - Noise exposure
  - Drugs
  - Nutrition/diet
  - Humidity
- In quiet-aged gerbils, pathological changes and hearing loss relate only to the aging process
Three Cochlear Systems

- Inner hair cells and primary auditory neurons (transduction)
- Outer hair cells and micromechanics (cochlear amplifier)
- Lateral wall and stria vascularis (power supply)
Neural Presbyacusis

Spiral ganglion cells are reduced in size and number along the entire cochlear duct.

Primary neural degeneration, not related to sensory cell loss.

Mills et al. (2006)

Neural Presbyacusis

- Least understood
- Appropriate animal model?
  - Ouabain treatment (Lang & Schmiedt)
  - Early noise trauma (Kujawa & Liberman)
  - Mouse mutants
- Causes of neural shrinkage and loss with age?
- Significance for older humans?

Kujawa and Liberman (2009)
Neural Presbyacusis

- Evidence in humans (archival temporal bones)
- Spiral ganglion cells decline with age, even without hair cell loss

Otte et al. (1978)  
Mackary et al. (2011)

Neural Presbyacusis

- How to assess in humans
  - ABR Wave I amplitudes?
  - Synchrony?
  - Recovery of forward masking?
  - Hearing in noise?
- Functional effects for older adults
  - Normal hearing
  - Hearing loss
  - Clinical significance?
Three Cochlear Systems

- Inner hair cells and primary auditory neurons (transduction)
- Outer hair cells and micromechanics (cochlear amplifier)
- Lateral wall and stria vascularis (power supply)

Sensory Presbyacusis

Tarnowski et al. (1991)
Sensory Presbyacusis

- Outer hair cell (OHC) loss results in:
  - Threshold shift of ~50-70 dB (complete OHC loss)
  - Loss of cochlear amplifier
  - Broadened tuning
  - Loss of compression and other nonlinearities, such as otoacoustic emissions
- Not seen in quiet-aged gerbils
- Sensory presbyacusis is due to noise or ototoxic drug exposure, not aging

Three Cochlear Systems

- Inner hair cells and primary auditory neurons (transduction)
- Outer hair cells and micromechanics (cochlear amplifier)
- Lateral wall and stria vascularis (power supply)
Metabolic Presbyacusis

- Lateral wall responsible for production and maintenance of endocochlear potential (EP)

- Positive voltage of 80-100 mV present in the endolymph of scala media
- Battery that provides voltage to outer hair cells (cochlear amplifier)

- In quiet-aged gerbils, a systematic degeneration of lateral wall and reduced EP

Atrophy of the cochlear lateral wall (quiet-aged gerbil)
Metabolic Presbyacusis

Young Gerbil

Old Gerbil

Schmiedt and Schulte, 1992

Metabolic Presbyacusis

27mV

5mV

Human

74 year old

Schmiedt and Schulte, 1992
Metabolic Presbyacusis

- Neural threshold loss not associated with OHC loss
- Hearing loss correlated with EP loss
- Does EP loss alone result in hearing loss in older gerbils?
- Model EP loss in a young ear


Metabolic Presbyacusis

- Chronic application of furosemide (diuretic) to the round window of young gerbil
- Hair cell and neural systems intact and functioning
- Chronic decrease of EP can be controlled by dose and duration

Metabolic Presbyacusis

- Decline in endocochlear potential (EP)
  - Deprives the cochlear amplifier of its essential power supply
  - Reduces cochlear amplifier gain
    - Low frequencies: as much as 20 dB
    - High frequencies: as much as 60 dB
  - Reduces but maintains nonlinearities
  - Can entirely explain the characteristic audiogram of older gerbils

- Is this the case for older humans?
• Schematic boundaries of human audiograms
• 5 audiometric phenotypes
• Based on 5 hypothesized conditions of cochlear pathology
• Predicted from animal models
• Audiograms in MUSC human subject database searched for “exemplars” of each phenotype

MUSC Human Subject Database

• Longitudinal study of age-related hearing loss
• Enrollment began in 1987 (24+ years)
• Inclusion and Exclusion Criteria
  • 60 years or older (now 18 and older)
  • Hearing ability to provide measurable results
  • In good general health
  • No evidence of conductive hearing loss
  • No evidence of active otologic disease
  • No evidence of significant cognitive decline
Human Subject Protocol

• Audiometric Measures
  • Hearing for pure tones, including extended high frequencies
  • Ability to understand speech in quiet and in noise
  • Otoacoustic emissions
  • Upward and downward spread of masking
  • Middle ear function
  • Auditory brainstem responses

• Current Analysis: Audiograms (N=1,728)

Human Subject Protocol

• Questionnaires
  • Medical history
  • Prescription and over-the-counter drugs
  • Noise history
  • Hearing aid history
  • Self-assessed hearing handicap (HHIE)
  • Tinnitus
  • Smoking
  • Handedness
  • Family pedigree for hearing loss

• Otologic examination
Human Subject Protocol

• Cognitive Measures
  • Attention
  • Working memory
  • Processing speed
  • Perceived workload

• Brain imaging while listening to and understanding:
  • Low-pass filtered speech
  • Speech in background noise

Human Subject Protocol

• Blood measures
  • Clinical chemistries
    • Lipid profile
    • Hematology panel
    • Hormones (Estradiol, Progesterone - Females)
    • C-reactive protein
  • DNA extracted
    • To identify and characterize genes that are under- or over-expressed with age

• Temporal bone donation
Human Participants

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<th>Age Range</th>
<th>Total with any data</th>
<th>Total with longitudinal data</th>
<th>Currently Active</th>
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<tr>
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<td>18-59</td>
<td>60-98</td>
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<tr>
<td>Female</td>
<td>163</td>
<td>555</td>
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<tr>
<td>Male</td>
<td>149</td>
<td>425</td>
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<tr>
<td>Total</td>
<td>312</td>
<td>980</td>
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<tr>
<td>Grand Total</td>
<td>1,292</td>
<td>494</td>
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</table>

- Measures are made yearly or every 2-3 years

![Initial Audiogram](image)
• 5 audiometric phenotypes

• 1,728 audiograms from MUSC human subject database searched for “exemplars” of each phenotype

• 385 exemplars (22%)
Pre-Metabolic (3%)
Predictions: Older-Normal and Pre-Metabolic

- Younger
- Mostly female
- Negative noise history
- Relatively sharp tuning
- Nonlinearities intact (e.g., OAEs, compression)
- Neural thresholds?

Metabolic

Schematic

Examples

Threshold (dB HL) vs. Frequency (kHz)
Predictions: Metabolic

- Older
- Predominately female
- Negative noise history
- Tuning intact, but higher thresholds (reduced gain)
- Nonlinearities present but reduced (e.g., OAEs, compression)
Predictions: Sensory

- Younger
- Predominately male
- Positive noise history
- In regions of OHC loss (with intact IHCs)
  - 50-70 dB hearing loss
  - Broadened tuning
  - Nonlinearities absent

Metabolic + Sensory
Metabolic + Sensory (34%)

Predictions: Metabolic + Sensory

- Older
- Predominately male
- Positive noise history
- Hearing loss and nonlinearities affected by both OHC and EP loss
Audiometric Phenotypes - Exemplars

- Older-Normal phenotype is youngest
- Metabolic phenotype is oldest

Age - Exemplars

- Older-Normal phenotype is youngest
- Metabolic phenotype is oldest
Gender - Exemplars

- **Sensory** phenotypes are primarily male
- **Older-Normal** and **Metabolic** phenotypes are primarily female

Noise History - Exemplars

- **Sensory** phenotypes are more likely to have positive noise exposure histories
- **Older-Normal** and **Metabolic** phenotypes are less likely to have positive noise histories
Noise History - Exemplars

- **Sensory** phenotypes are more likely to have positive noise exposure histories.
- **Older-Normal** and **Metabolic** phenotypes are less likely to have positive noise histories.

Metabolic vs. Sensory

The graph shows a comparison of metabolic vs. sensory traits. The y-axis represents the threshold (dB HL), and the x-axis represents frequency (kHz). The different lines and markers indicate various groups and their thresholds at different frequencies.
Metabolic vs. Sensory

- Controlled for differences in age and higher frequency hearing
- Thresholds at 0.25-2.0 kHz average 16.5 dB better for Sensory than Metabolic phenotypes
- For Sensory, transduction currents reduced by OHC loss, preserving EP with aging?
Next Steps

- Validate approach by predicting phenotypes of non-exemplar audiograms (N=1,354)
  - Machine learning tools (Support Vector Machines, Random Forests)
  - Statistical tool (Quadratic Discriminant Analysis)
  - How well do phenotypes for non-exemplars correspond to predicted demographics?
- Near completion - High consistency of threshold, age, gender, and noise history within groups

Age - Exemplars vs. Non-Exemplars

- Age distribution similar for exemplars and non-exemplars
- **Older-Normal** phenotype is youngest
- **Metabolic** phenotype is oldest
Gender - Exemplars vs. Non-Exemplars

- Gender relationships similar for exemplars and non-exemplars
- **Sensory** phenotypes are primarily male
- **Older-Normal** and **Metabolic** phenotypes are primarily female

Next Steps

- Assess predictions with additional measures of auditory function from older human subjects
  - Otoacoustic emissions
  - Upward and downward spread of masking
  - Auditory brainstem responses
  - Ability to understand speech in quiet and in noise
  - Hearing handicap/hearing aid benefit
  - Neuroimaging (selected subjects)
- Assess predictions by examining longitudinal changes in auditory function
Longitudinal Analyses

- Older-Normal
  ↓
  Metabolic?

- Pre-Metabolic
  ↓
  Metabolic

- Sensory
  ↓
  Metabolic + Sensory

Next Steps

- Confirm with biological markers
- Genetics - Provides framework beyond affected vs. non-affected
- Otopathology from human temporal bones
Conclusions

• Results from animal models can be used to predict human cochlear pathology using audiograms and more sensitive measures of auditory function
• Human audiometric phenotypes appear consistent with predictions from animal findings associated with sensory and strial pathology
• Approach may be applied to understanding neural presybaclesis

Conclusions

• Audiometric phenotypes are consistent with the view of age-related hearing loss as a metabolic, vascular, neural disorder rather than a sensory disorder
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