“Structural and Functional Changes of the Aging Auditory System: An Overview”

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Summary of Cochlear Changes with Age
- Loss of Hair Cells, Usually Starts in Base
- Declines in Spiral Ganglion Cells
- Pathology of Stria Vascularis, Decline in Endocochlear Potential – R. Schmiedt, B. Schulte, M.A. Gratton
- Different Humans, Mammals May have Different Combinations of these Deficits – K. Ohlemiller, J. Willott

Summary of Cochlear Aging Changes
- Sensory Transduction, K+ Cycling, Info To Brain

Summary of Central Auditory System Changes with Age
- Perception of speech and complex sounds in cortical centers

Summary of Central Auditory System Changes with Age
- Structure – Neuroanatomy of Auditory Brainstem
  - Peripheral Deafferentation Results in Central Plasticity and Reorganization
  - Tonotopic reorganization, Inferior colliculus – J. Willott
  - Brainstem Pathways Decline – R. Frisina, J. Walton
  - Neurochemistry, Biochemistry of Neurotransmitters
  - Declines in brainstem inhibitory systems: Glycine and GABA, cochlear nucleus, inferior colliculus – D. Caspary, R. Helfert, J. Milbrandt
Summary of Central Auditory System Changes with Age

Physiology, Functional Changes, Brainstem Levels

- Temporal processing declines are observed at the level of the inferior colliculus – auditory midbrain – J. Walton, J. Ison, P. Allen, R. Frisina
- These are similar to psychoacoustic declines in human listeners with good peripheral sensitivity
- Here more about this, and how it relates to speech, from upcoming presenters: J. Dubno, S. Gordon-Salant, K. Pichora-Fuller, K. Tremblay

Nature of Diabetic Hearing Deficits in Aged Listeners

- Investigated Aged Type 2 Diabetics, relative to Controls who were matched for age, sex and health history
- Performed standard audiometric tests of the periphery, and experimental tests that tap brain function
- Found evidence for accelerated peripheral and central presbycusis
- Induced Type 1 and Type 2 diabetes in middle age CBA mice

Aged Type II Diabetics have Elevated Audiometric Thresholds and Lower DPOAE Amplitudes

<table>
<thead>
<tr>
<th>Test Frequency</th>
<th>Non-Diabetics</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure-Tone Average Thresholds Right Ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Ear DPOAEs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aged Type II Diabetics have Elevated Speech Thresholds in Background Noise

HINT (O, 90, 270 degrees)

<table>
<thead>
<tr>
<th>Noise Location (degrees)</th>
<th>Threshold (dB S/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>270</td>
<td>2</td>
</tr>
</tbody>
</table>

Summary – Diabetes - Human

- Peripheral hearing or audibility, represented by tone, SRT and white noise thresholds, and otoacoustic emissions, showed significant impairment in Type 2 Diabetes vs. Non-diabetics.
- In all hearing tests where impairments are evident in diabetic subjects, the right ear was impaired more than the left ear.
- Hearing measures that are dependent on both central brain and peripheral components of the auditory system, also showed significant differences between diabetics and non-diabetics (HINT, gap detection).

Nature of Diabetic Hearing Deficits in Mice

- Investigated Aging Type 1 Diabetics, relative to Controls, induced by streptozotocin injection into middle age CBA mice
- Type 2 Diabetes induced by high-fat diet
- Performed standard physiological tests of the periphery and auditory midbrain
- Similar to humans, found evidence for accelerated peripheral and central presbycusis
- Discovered cochlear changes in the stria vascularis and type 4 fibrocytes (RAGE)
**Diabetes in Middle Age Mice**

<table>
<thead>
<tr>
<th>Blood glucose level (mg/dl)</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, n=7</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
<td>350</td>
</tr>
<tr>
<td>Type 1 DM, n=6</td>
<td>105</td>
<td>155</td>
<td>205</td>
<td>255</td>
<td>305</td>
<td>355</td>
</tr>
<tr>
<td>Type 2 DM, n=4</td>
<td>110</td>
<td>160</td>
<td>210</td>
<td>260</td>
<td>310</td>
<td>360</td>
</tr>
</tbody>
</table>

**ABR Audiogram Thresholds Increase with Progression of Diabetes**

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Baseline Thresh (dB SPL)</th>
<th>3 kHz Thresh (dB SPL)</th>
<th>12 kHz Thresh (dB SPL)</th>
<th>24 kHz Thresh (dB SPL)</th>
<th>32 kHz Thresh (dB SPL)</th>
<th>48 kHz Thresh (dB SPL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, n=7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 DM, n=4</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Type 2 DM, n=4</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

**Stria vascularis (SV) Area Declines with Progression of Type 2 Diabetes**

<table>
<thead>
<tr>
<th>SV area/brain (µm²/g)</th>
<th>Control, n=4</th>
<th>Type 1 DM, n=4</th>
<th>Type 2 DM, n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>12 kHz</td>
<td>24 kHz</td>
<td>3 kHz</td>
</tr>
<tr>
<td>Middle turn</td>
<td>Baseline</td>
<td>6 Months</td>
<td>4 Months</td>
</tr>
<tr>
<td>Base turn</td>
<td>MT</td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>Apex</td>
<td>MT</td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
</tbody>
</table>

**Receptors for Advanced Glycation End Products (RAGE) are Upregulated with Progression of Diabetes**

<table>
<thead>
<tr>
<th>RAGE+</th>
<th>Control, n=7</th>
<th>Type 1 DM, n=6</th>
<th>Type 2 DM, n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>ROD</td>
<td>ROD</td>
<td>ROD</td>
</tr>
<tr>
<td>Middle turn</td>
<td>0.00</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Base turn</td>
<td>0.15</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>Apex</td>
<td>0.30</td>
<td>0.35</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Summary of Diabetic Hearing Deficits in Mice**

- Aging Type 1 & 2 Diabetics, relative to Controls, show *accelerated* presbycusis.
- Auditory midbrain recordings show *lack of inhibition* in Type 1 diabetics.
- Similar to humans, found evidence for accelerated peripheral and central presbycusis.
- Discovered *decrease* in size of the stria vascularis and RAGE *upregulation* in type 2 fibrocytes – disruption of cochlear K+.
- No change in spiral ganglion cell counts.

**Auditory Efferent Feedback System**

- Maintains health and proper functioning of the inner ear hair cell system.
- For hearing, helps reduce background noise, increasing perception of speech and biologically-relevant sounds.
- Involved in auditory selective attention.
- Present in all vertebrates.
**Structure-Function Changes in the Brain-Ear Feedback System**

![Diagram of the MOC Efferent System](image)

Anatomy of the MOC Efferent System

**Audiometric thresholds averaged for the right and left ears of the young adult (red circles), middle-aged (blue squares) and old (green inverted triangle) human subject groups**

![Pure Tone Audiogram](image)

**Contralateral Suppression Declines With Age in Humans with Normal Hearing**

![Graph showing contralateral suppression declines with age](image)

**Mouse Genetic Strains: Neural Bases of Presbycusis**

- **CBA:** Loses hearing slowly with age
- **Similar time course as human, after correcting for absolute lifespan differences of mice and men**
- **C57, DBA:** Rapid, high-frequency loss
- **Animals are severe-to-profound by one year of age**

**Aims – Age changes in mouse efferent system**

- Determine if mouse genetic strain leads to alterations in:
  - Outer hair cell function
    - Measured by DPOAEs
  - MOC efferent system
    - Measured by contralateral suppression (CS) of DPOAEs
  - Activation of MOC system results in suppression of outputs of the cochlea – DPOAE amplitude
  - Preserves hair cell function
  - Enhances signal perception in noise

**Methods – Mouse Emissions**

![Image of mouse emissions](image)
Decline of Contralateral Suppression (CS) Depends on Age, Genetic Factors Accelerate it

Contralateral Wideband Noise Suppression

0 5 10 15 20 25 30 35 40
-4 -3 -2 -1 0 1 2

CS declines occurred in middle- and old-aged CBA mice relative to young adult mice similar to humans

Kid et al., AudiolNeurotol, 2002
Jacobson et al. Laryngoscope, 2003

Wideband noise CS was lost completely in C57 mice by 10 weeks. The loss equaled that of old-aged CBA mice

Zhu et al., J. Comparative Neurology, 2007

Summary & Conclusions - Efferent Declines with Age

• Outer Hair Cell System Declines with Age in Humans and Mice
• Auditory Efferent Feedback System Diminishes with Age Prior to Outer Hair Cell System Declines
• Extreme Case of this is the C57 Mouse Strain, Rapid Hearing Loss
• C57 Efferent Declines with Age, Structure and Function. Precede this Hearing Loss

Hypothesis: Age-Related CS Declines are Dependent on Anatomical Changes in Central Efferent Regions of the Auditory System

Specific Aims:
• To compare the cell density in regions of the brainstem efferent system in 2 inbred strains of mice (C57 vs. CBA) at young adult ages (6 - 14 week old)
• To compare perikaryal size measurements of neurons of the efferent system (DMPO and VNTB regions) in 2 inbred strains of mice (C57 vs. CBA) with age (6 - 14 week old)

Methods Efferent System Cell Body Measurements

• Mice: Male and female CBA/J, (CBA, 14 weeks old, n=7), and C57BL/6J (C57, 6 weeks old, n=4, and 12 weeks old, n=8); Jackson Laboratories, Bar Harbor, ME
• Tissue Processing: Section series were stained with cresyl violet for Nissl substance allowing visualization of neuronal cell bodies
• Digital Image Analysis System: The measurements of neurons were made using Stereology methodologies
• Statistical Analysis: The statistical analyses were performed with Prism ® 3.0. Multiple comparisons were made among experimental groups by one-way analysis of variance (ANOVA) followed by Bonferroni’s post-hoc tests corrected for multiple pairwise comparisons

Presence of Kv3.1 Channels Declines with Age in CBAs - MOC

Investigate Kv 3.1 Immunostaining in SOC

Physiological Experimental Design - Kv

- Subjects:
  - Kv1.1 and Kv3.1 mice divided into 3 groups of 12, including (-/-), (+/), and (+/+).
- ABR, DPOAEs, and CS of DPOAEs obtained at:
  - young adult state (1-2 months)
  - Older age (7-8 months).

Voltage-Gated K+ Channel

- Kv1.1 and 3.1 knockout mice show deficiencies in the MOC efferent system
- Kv3.1 channels decline with age, starting in middle age, in CBAs who lose their efferent functionality on a similar time course

Significance – Feedback System

- Progression of presbycusis
  - Declines in MOC efferent system (CS of DPOAEs) → declines in outer hair cell function (DPOAEs) → declines in hearing thresholds
  - Alterations in Kv1.1 or Kv3.1 may spark MOC efferent system decline, leading to the above progression of events

Rochester Hearing/Deafness Research Group

Work Supported by NIH: National Institute on Aging, National Institute on Deafness & Communication Disorders

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- Dr. Paul Allen – Behavior, Neurophysiology
- Dr. Robert Frisina – Speech Perception, PET
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- Dr. Robert Frisina, Sr. – Speech Perception, PET
- Dr. David Eddins – Psychoacoustics
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- Dr. Dina Newman – Genetics

Focus Areas:
- Auditory Neurophysiology
- Immunocytochemistry
- Emissions