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Hidden Hearing Loss: Cochlear Synaptopathy in Noise-Induced and Age-Related Hearing Loss

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The Inner Ear and Sensorineural Hearing Loss

- Auditory Nerve
- Spiral Ganglion
- Sensory Hair Cells
Hair cells & cochlear neurons are key to SNHL

OHCs are biological amplifiers

IHCs send signals to the CNS

Synaptic Connections

Hair cell death causes threshold shifts

Noise or Otoxic Drugs

Threshold Shift
Synapses, not hair cells, are most vulnerable

Synapses die before hair cells, but ganglion cell death is slow

Peripheral axons survive for weeks
Cell body and central axons survive for years/decades
Cochlear synaptopathy is a “Hidden Hearing Loss”

Synapses and nerve terminals are invisible in routine histology

Primary neural degeneration does not elevate thresholds

Schuknecht and Wöllner, 1955
Neuropathy does not elevate thresholds

*Behavioral thresholds in carboplatin-treated chinchillas*

![Image of neural tissue]

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Cochlear Synaptopathy impairs understanding speech in noise

5 - 15 min: TTS
50 - 150 min: PTS

Mammals:
- Chinchilla,
- Guinea Pig,
- Cat and
- Mouse
Outline

1. Cochlear synaptopathy in experimental animals: AHL and NIHL

2. Cochlear synaptopathy in aging humans: analysis of post-mortem inner ears

3. Cochlear synaptopathy in young humans: ECoChG and speech in noise

4. Neurotrophins and the search for a therapy

Quantifying Cochlear Synaptopathy

*Use immunolabeling to see cochlear nerve terminals and synapses*

Pre-Synaptic Ribbon  CIBP2
Post-Synaptic Density  GluA2
Quantifying Cochlear Synaptopathy

In normal ear: every ribbon is opposite a receptor patch and vice versa

Pre-Synaptic ribbons  CIBP2
Post-Synaptic Receptors  GluA2

Maison and Liberman, 2013

Quantifying Cochlear Synaptopathy

In normal ear: synapse counts peak in the middle of the cochlea

Maison and Liberman, 2013
Cochlear Synaptopathy and Temporary Threshold Shift

Mouse: ABR and DPOAE thresholds recover from initial 30-40 dB shift

Kujawa & Liberman, 2009

Cochlear Synaptopathy and Temporary Threshold Shift

ABR Wave 1 does not recover

ABR Wave 1 = auditory nerve

Kujawa & Liberman, 2009
Cochlear Synaptopathy and Temporary Threshold Shift

*Cochlear nerve synapses disappear immediately—hair cells remain intact*

Cochlear Neuropathy after Temporary Threshold Shift

*Spiral ganglion cell death follows—after months to years*
Cochlear Synaptopathy and Temporary Threshold Shift

Noise-induced synaptic loss is observed in other mammalian species

Guinea Pig

Chinchilla

Rat

Cochlear Synaptopathy in Aging Mice

In aging mice, synaptopathy precedes hair cell loss and threshold shifts

Hair Cells

Nerve Terminals

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Cochlear synaptopathy is selective for Low-SR fibers

*Auditory nerve fibers have different threshold sensitivity*

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Cochlear synaptopathy is selective for Low-SR fibers

*L-SR neurons have high thresholds and vice versa*
Cochlear synaptopathy is selective for Low-SR fibers

*High-SR neurons have low-thresholds and vice versa*

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Liberman, 1978

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Cochlear synaptopathy is selective for Low-SR fibers

*Low- and medium-SR fibers comprise 40% of the cochlear nerve*

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Lin, Furman, Kujawa & Liberman, 2011
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Cochlear Synaptopathy in Aging Humans

Dissect the cochlear spiral, measure length and convert to frequency
Cochlear Synaptopathy in Aging Humans

Anti-Neurofilament stains all cochlear axons and terminals

Anti-ChAT stains all cochlear efferent axons and terminals

Cochlear Synaptopathy in Aging Humans

Fiber counts at 0.5 kHz  
Fiber counts at 4 kHz

Viana et al 2015
Cochlear Synaptopathy in Aging Humans

Immunostaining IHC synapses

Viana et al 2015
Cochlear Synaptopathy in Aging Humans

*Hair cell counts in aging humans*

Viana et al. 2015

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Cochlear Synaptopathy in Aging Humans

*Nerve counts in humans with no hair cell loss*

Viana et al. 2015

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**CONTINUED**
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Diagnosing Cochlear Synaptopathy

*SP is from Hair Cells; Wave 1 (AP) is from Cochlear Nerve*

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Shahen et al., 2015
Diagnosing Cochlear Synaptopathy

SP : AP (Wave 1) ratio from tiptrode electrodes in the human ear canal

Liberman et al., 2016

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Diagnosing Cochlear Synaptopathy

College students: High-risk vs. Low-risk based on self report

Liberman et al., 2016

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CONTINUED™
Diagnosing Cochlear Synaptopathy

College students: High-risk vs. Low-risk based on self report

![Graph showing threshold (dB HL) vs. frequency (kHz) for Low Risk (n=12) and High Risk (n=22).]

High-risk group shows reduced word recognition scores

![Bar graph showing speech score (%) for Quiet, Noise, Fast w/ Reverb conditions at 5 dB SNR, 0 dB SNR, 45% 0.3s, 65% 0.3s.]

Liberman et al., 2016
Diagnosing Cochlear Synaptopathy

High-risk group shows pathological SP/AP ratios in ABR

![Graph showing SP/AP ratio for Low Risk and High Risk groups, with mixed gender comparison]

Liberman et al., 2016

Synaptopathy may also cause tinnitus

Signs of Central Hyperactivity

![Diagram showing waveforms for Wave I and Wave V]

Wave I
Auditory Nerve

Wave V
Inferior Colliculus

Time re Peak 1 (ms)
Synaptopathy, Central Hyperactivity & Tinnitus

Tinnitus sufferers have high Wave V : Wave I ratio in ABR

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**Neurotrophins are key to nerve survival**

*NT-3* signaling from supporting cells keeps nerve cells alive

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**Neurotrophin-3 regenerates synapses after noise**

*Transgenic mouse with NT-3 overexpressed in support cells*

**Synapse recovery**

**Functional Recovery**

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Wan et al 2015
Neurotrophin therapy to regenerate nerve fibers?

Direct NT-3 delivery to inner ear via the RW

![Graph showing synapses per IHC over Cochlear Frequency (kHz).]

Neurotrophin therapy to regenerate nerve fibers?

Direct NT-3 delivery to inner ear via the RW

![Graph showing wave I amplitude (μV) over stimulus level (dB SPL).]

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Conclusions

Noise and ototoxic drugs cause rapid synaptic loss and slow cochlear nerve degeneration, even if hair cells recover

Aging causes slow synaptic loss, long before hair cell loss

Initially, synaptic loss is selective for high-threshold, low-SR fibers

Cochlear synaptopathy does not elevate audiometric thresholds but causes deficits in more complex hearing tasks and maybe tinnitus

Slow degeneration of spiral ganglion offers a therapeutic window; NT-3 can regenerate missing synapses

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  human temporal bone work

Jun Suzuki – MEEI; Leslie Shinobu – Decibel Therapeutics
  Round window NT-3 delivery in mouse

Gabriel Corfas & Guoqiang Wan – Kresge Hearing Research
  NT-3 overexpression in mouse models