

***Hidden Hearing Loss & Brain Changes from Ototoxic Drugs***

***Richard Salvi, Ph.D.***

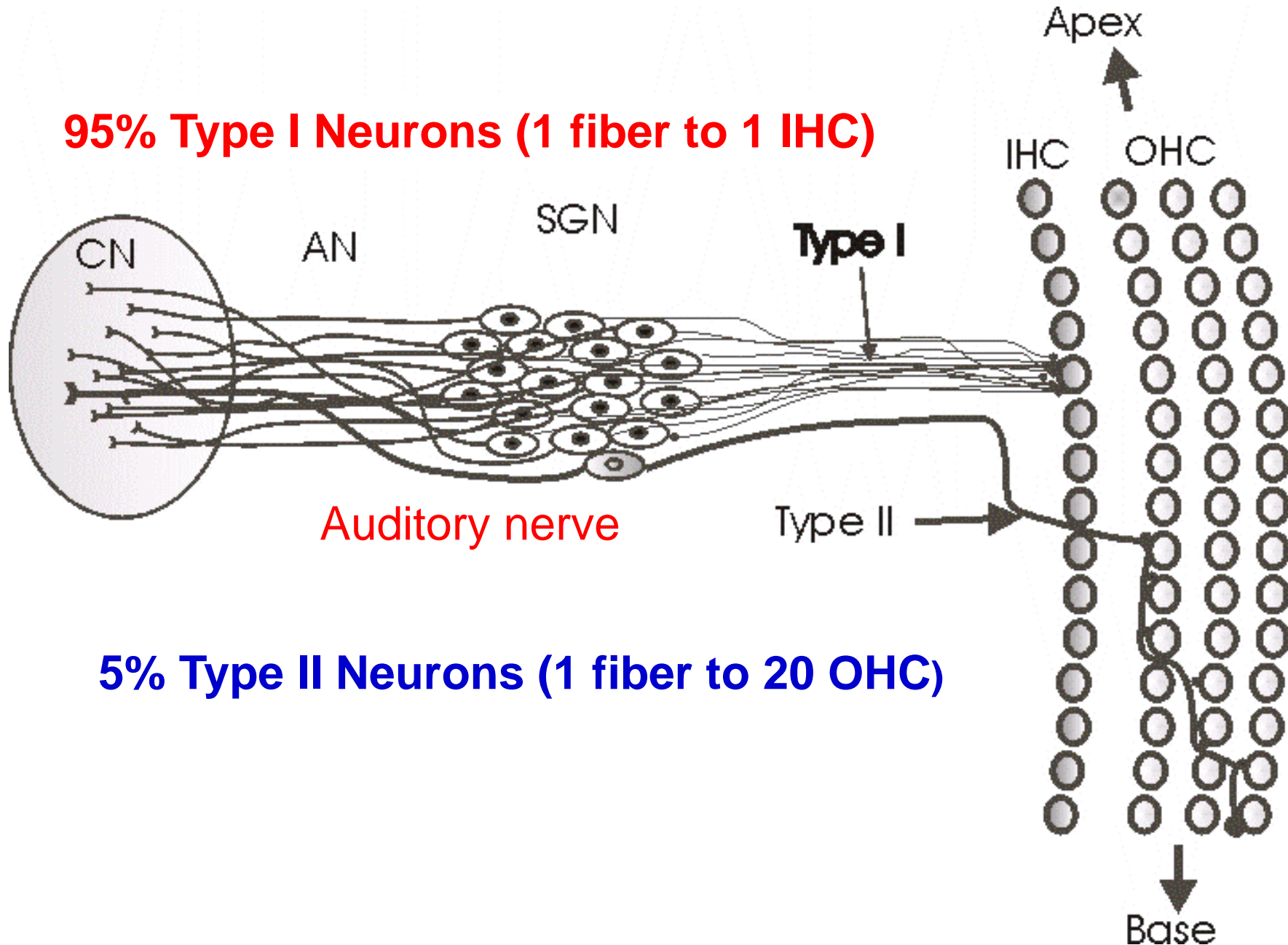
***Center for Hearing & Deafness***

***University at Buffalo***



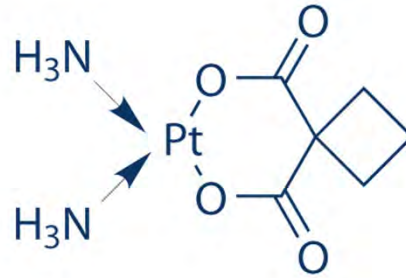
## ***Background: Afferent Innervation of Hair Cells***

**95% Type I Neurons (1 fiber to 1 IHC)**



**5% Type II Neurons (1 fiber to 20 OHC)**

# Carboplatin



- ✓ **2nd Generation Anti-Cancer Drug**
- ✓ **Less Ototoxic than Cisplatin**
- ✓ **Studies in Mice, Guinea Pig, Rats**
  - ✓ **Little hearing loss**
  - ✓ **Little hair cell loss**
- ✓ **Test Carboplatin in Chinchillas**
  - ✓ **Selective Damage to:**
    - ✓ **Inner Hair Cells (IHC)**
    - ✓ **Type I Auditory Nerve Fibers**



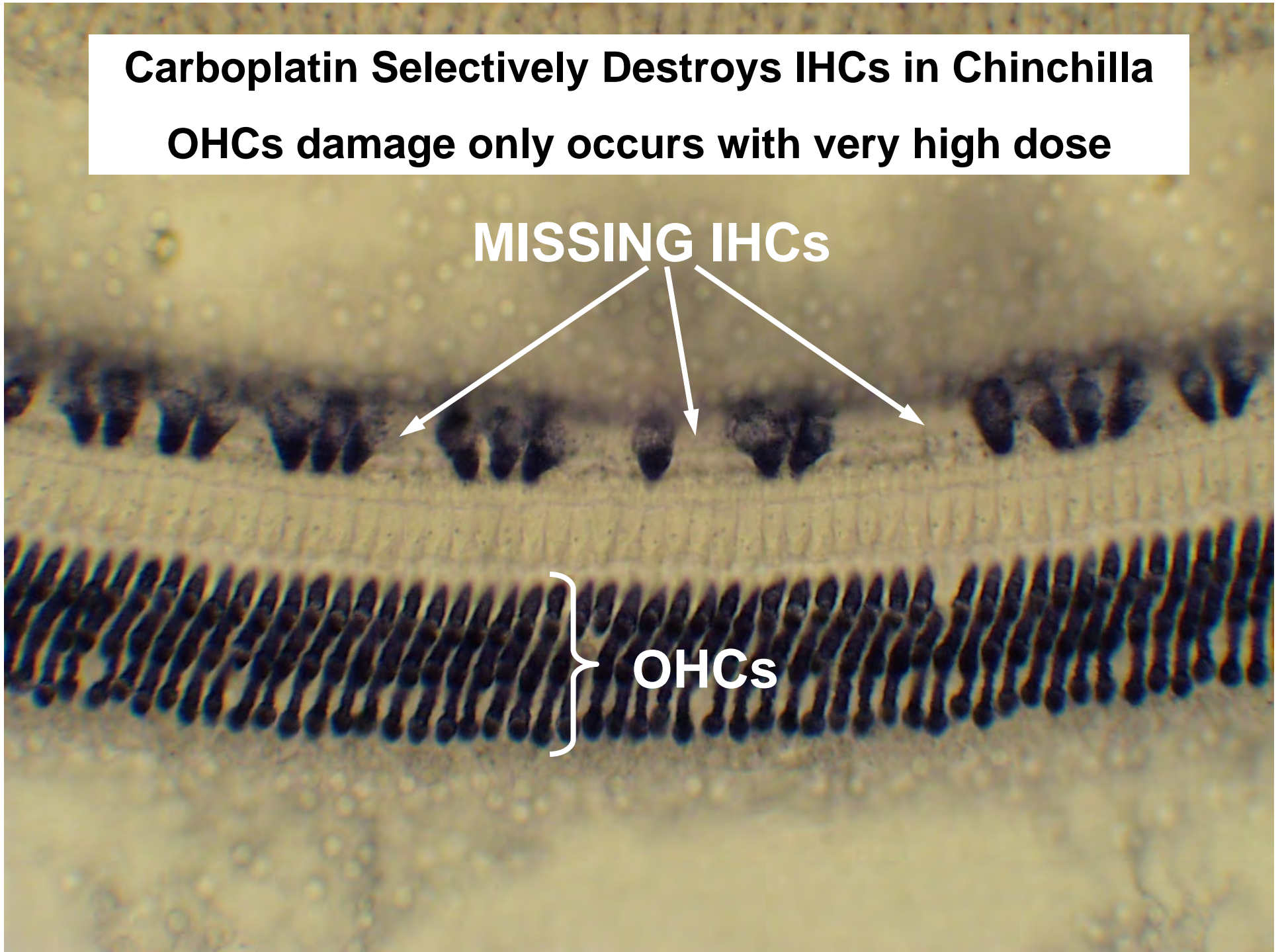


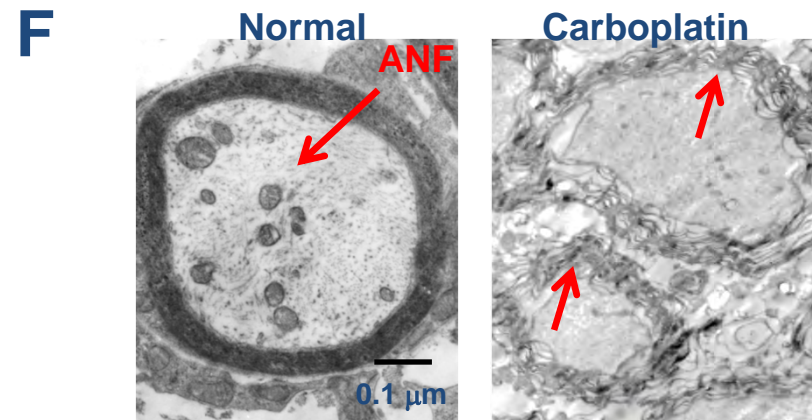
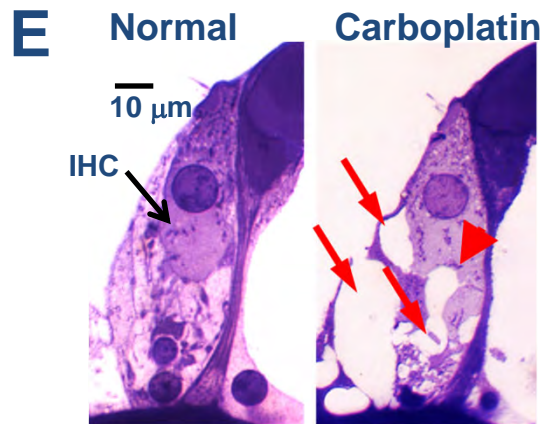
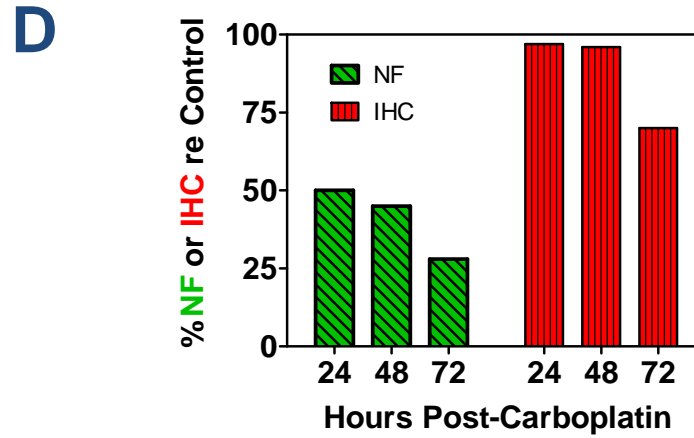
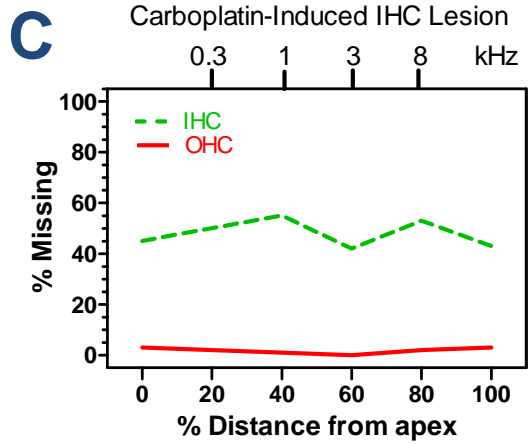
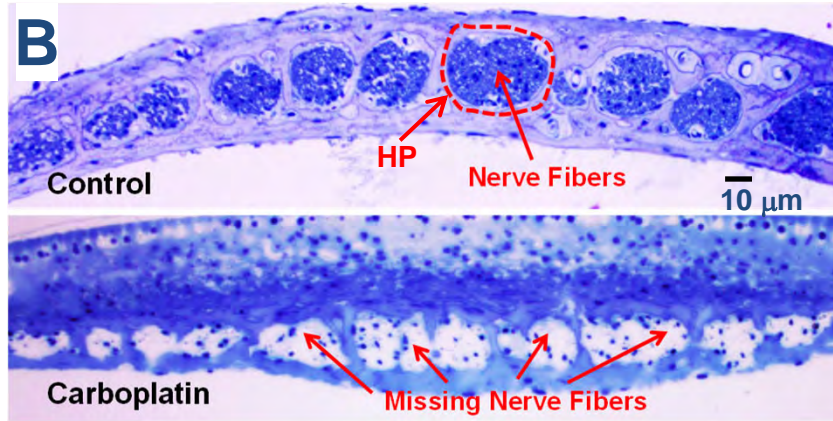
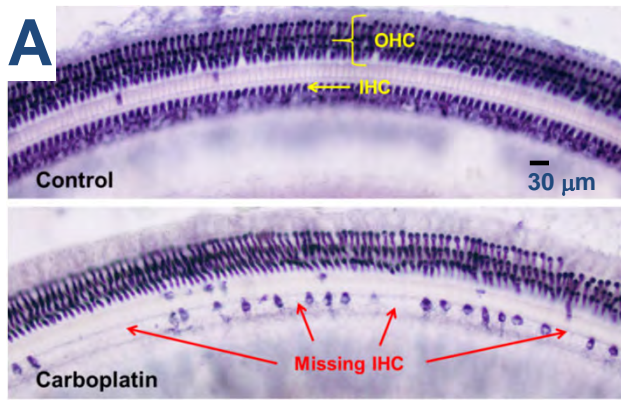
**Carboplatin Selectively Destroys IHCs in Chinchilla**  
**OHCs damage only occurs with very high dose**

**MISSING IHCs**

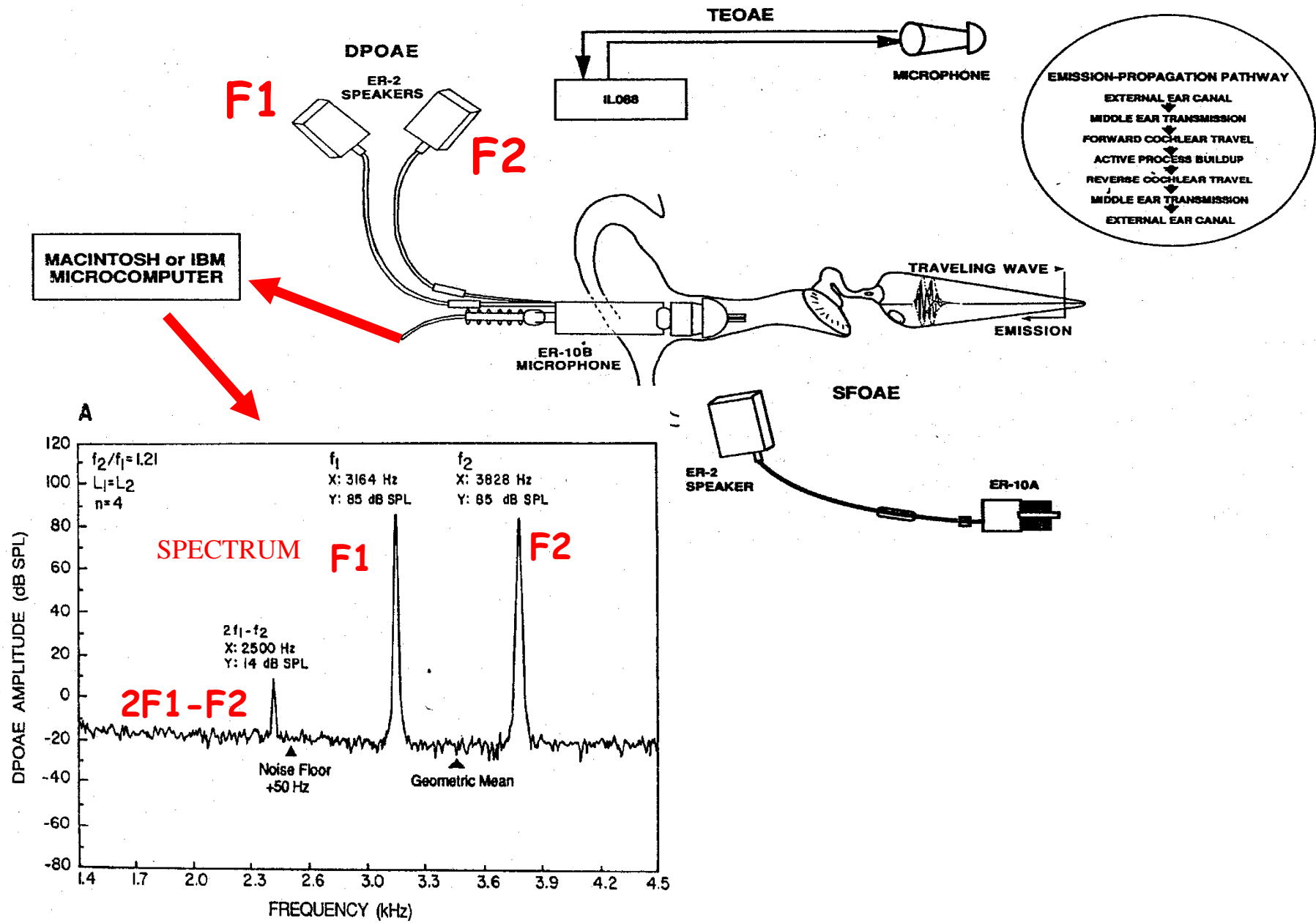


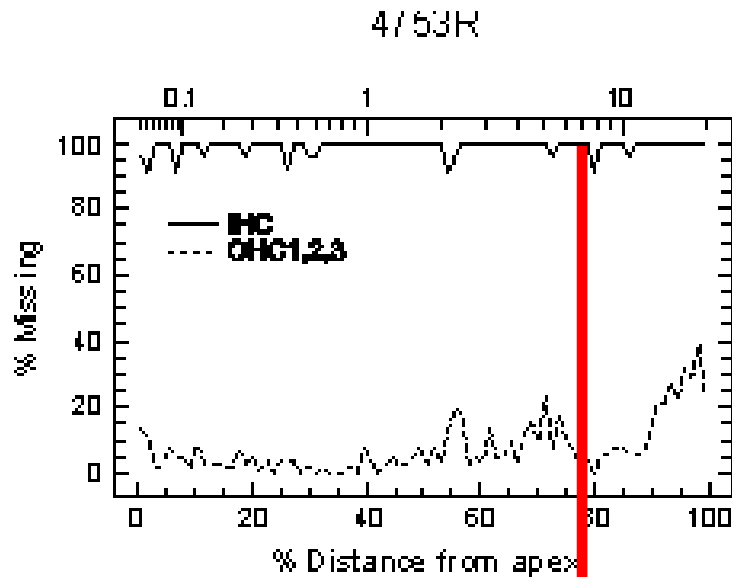
**OHCs**



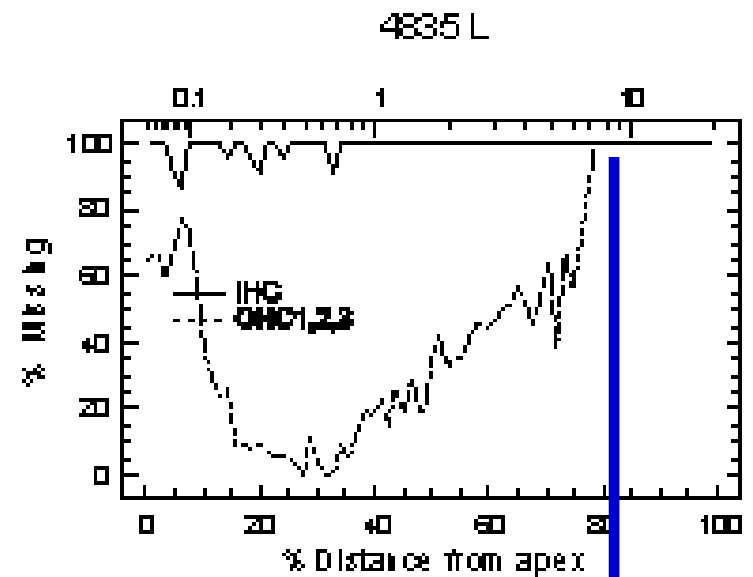
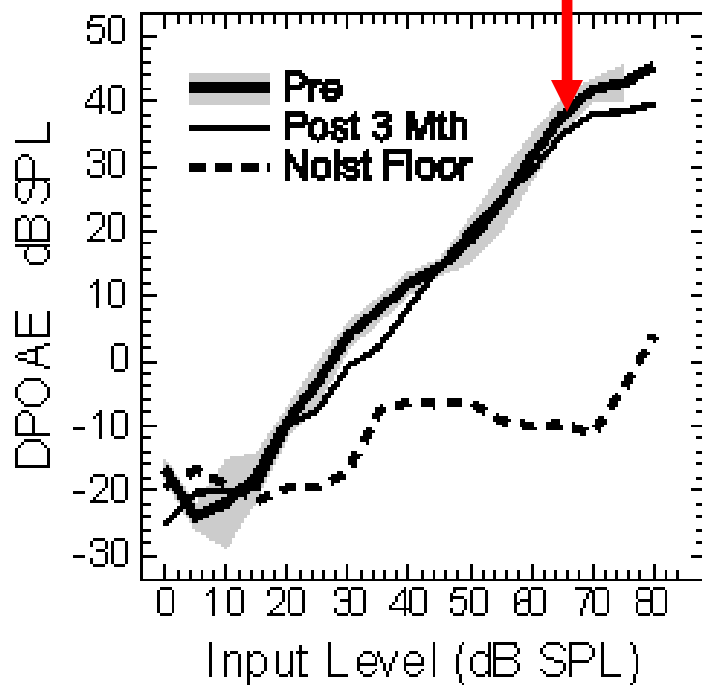


# Distortion Product Otoacoustic Emission (DPOAE) Test of Outer Hair Cell Function

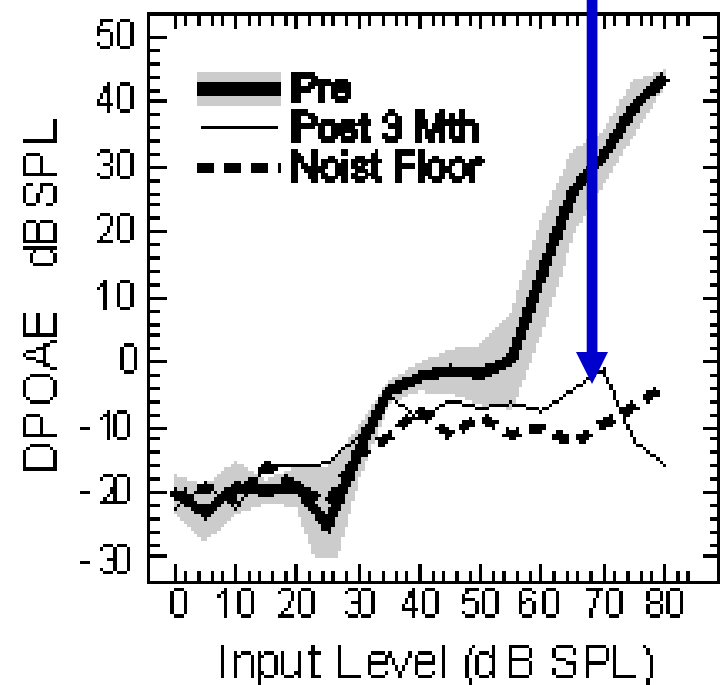




**IHC Loss-No effect On DPOAE**  
7.2 kHz



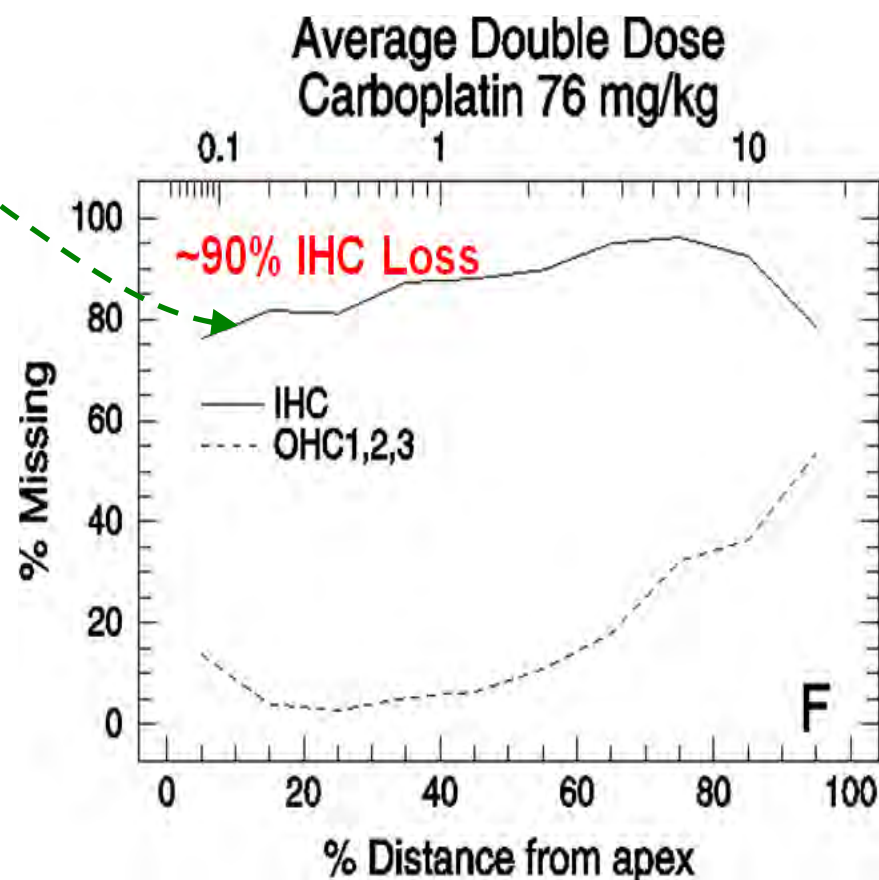
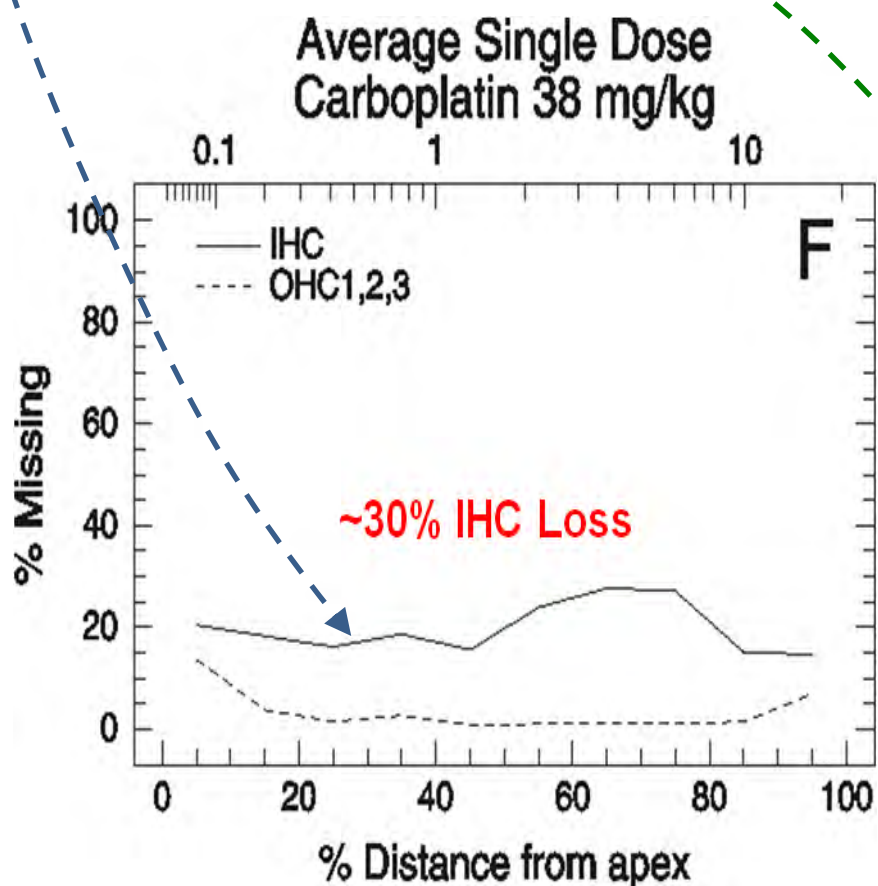
**OHC Loss-Reduces DPOAE**  
9.6 kHz



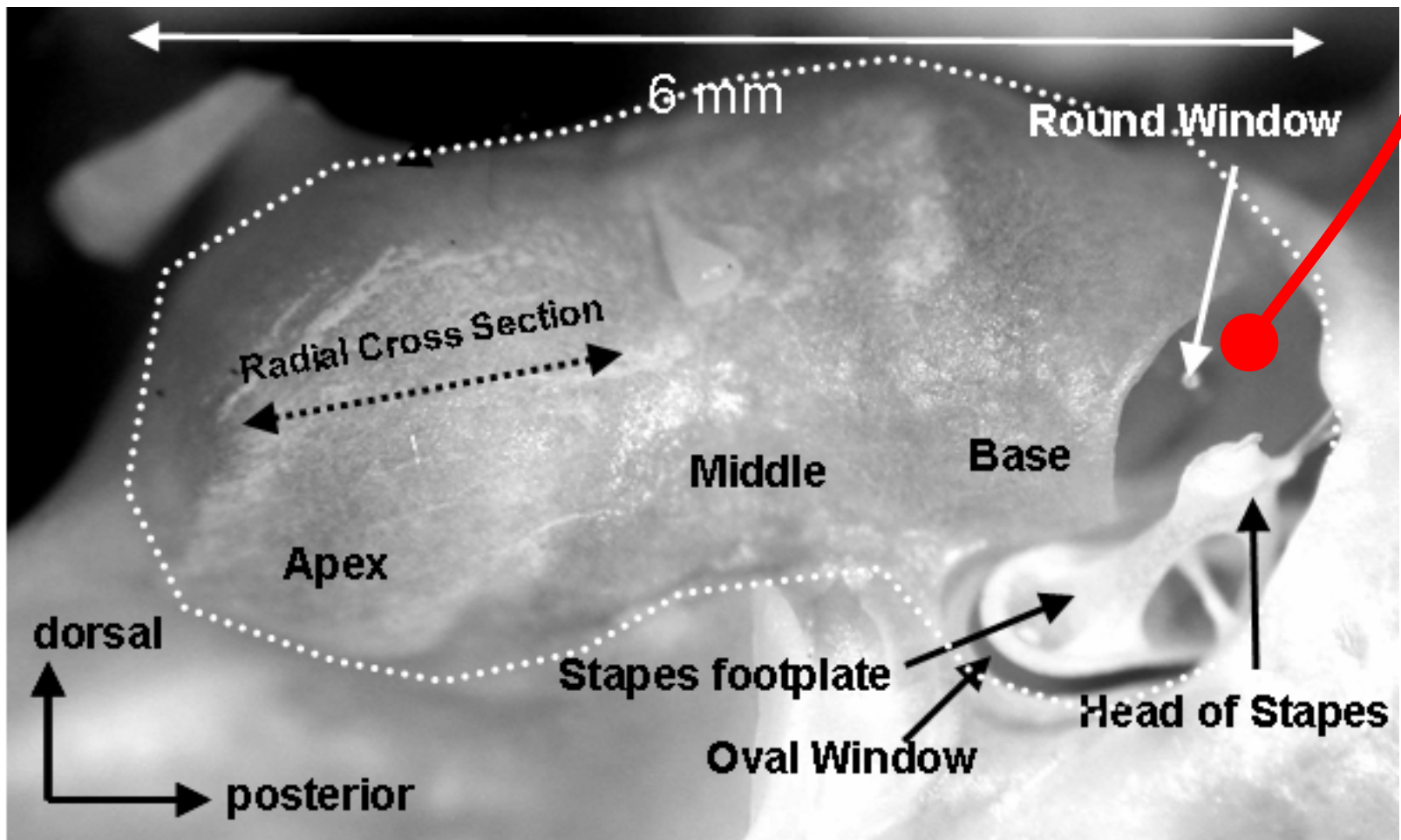
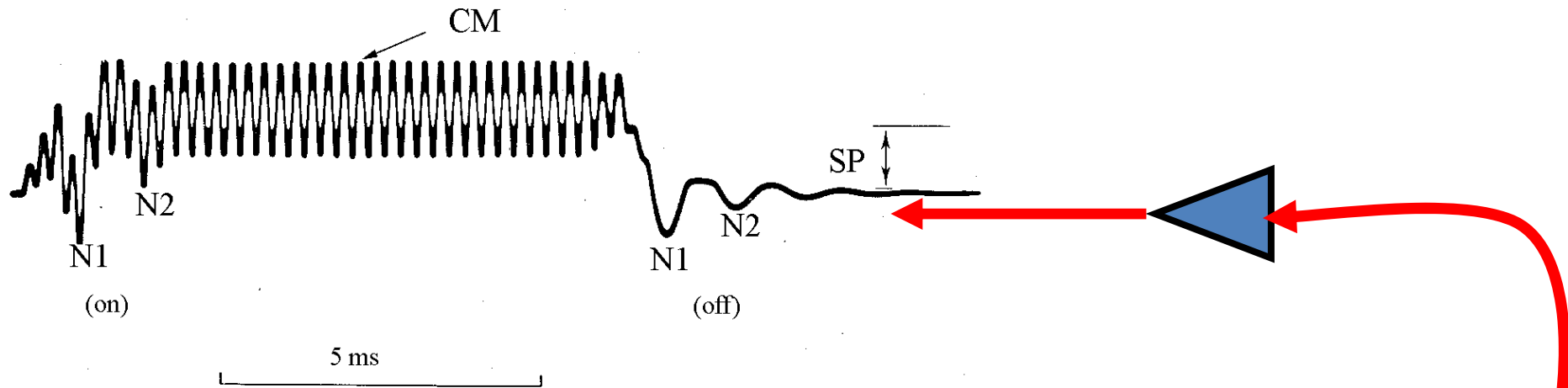


## Effects of IHC/Type I Lesion on Cochlear Potentials

- ✓ **Mean Hair Cell Lesions (Cochleogram)**
- ✓ **Single Dose: 30% IHC Loss (flat lesion)**
- ✓ **Double Dose: 85-90% IHC Loss + OHC Lesion in Base of Cochlea**

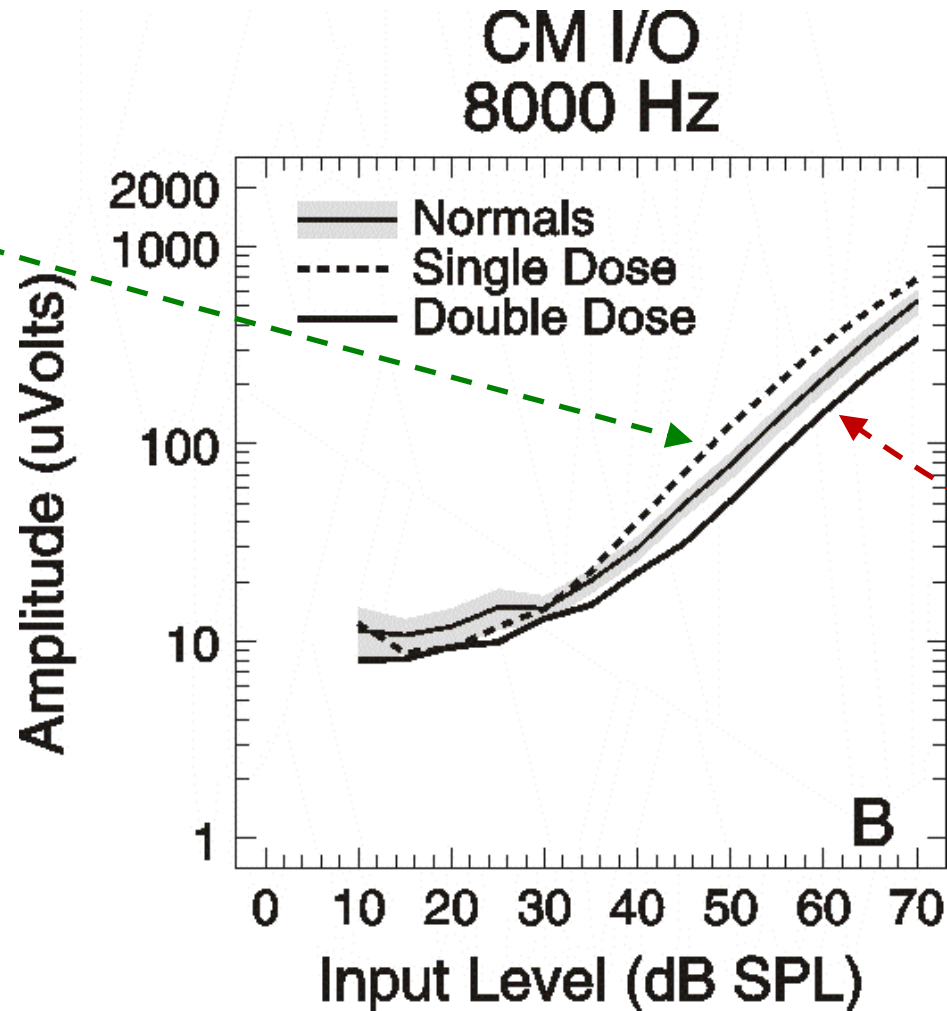






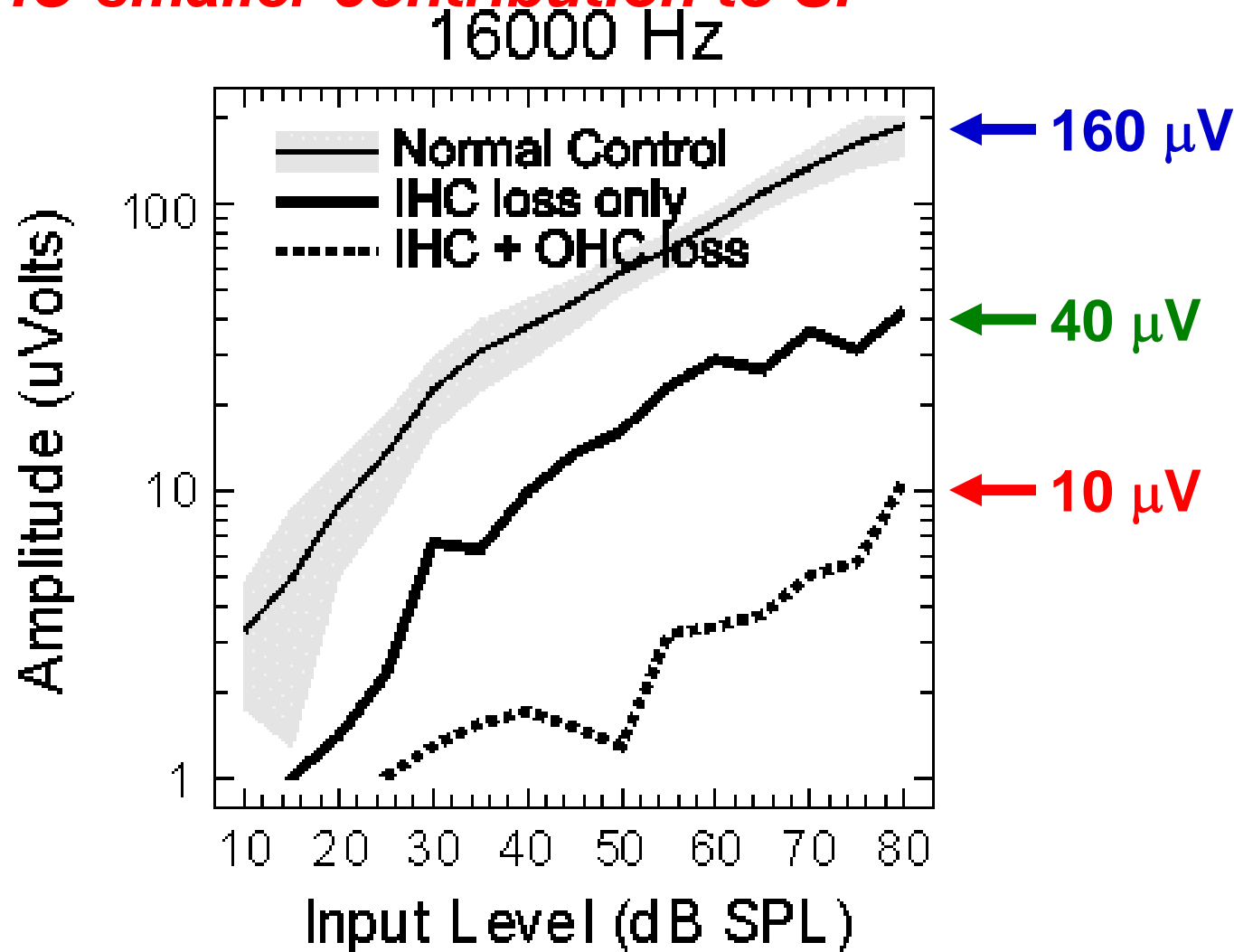
## Cochlear Microphonic (CM)

- ✓ Generated by Outer Hair cells
- ✓ **Single dose: Slight Increase in CM**
- ✓ **Double dose: Slight Decrease in CM**



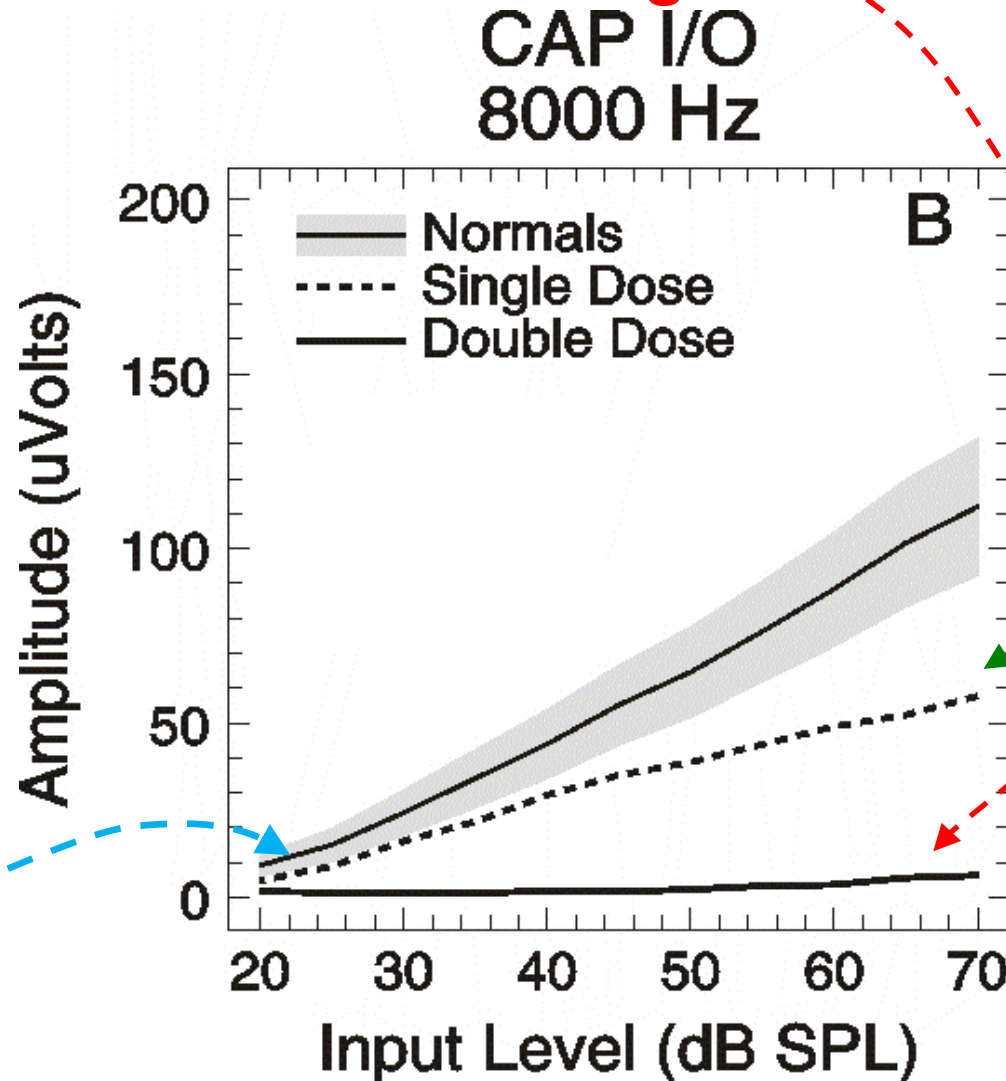
# Summating Potential (SP)-IHC Major Source

- Normal Cochlea: 160  $\mu\text{V}$  SP
- IHC Lesion-Large Decrease SP
- OHC-smaller contribution to SP



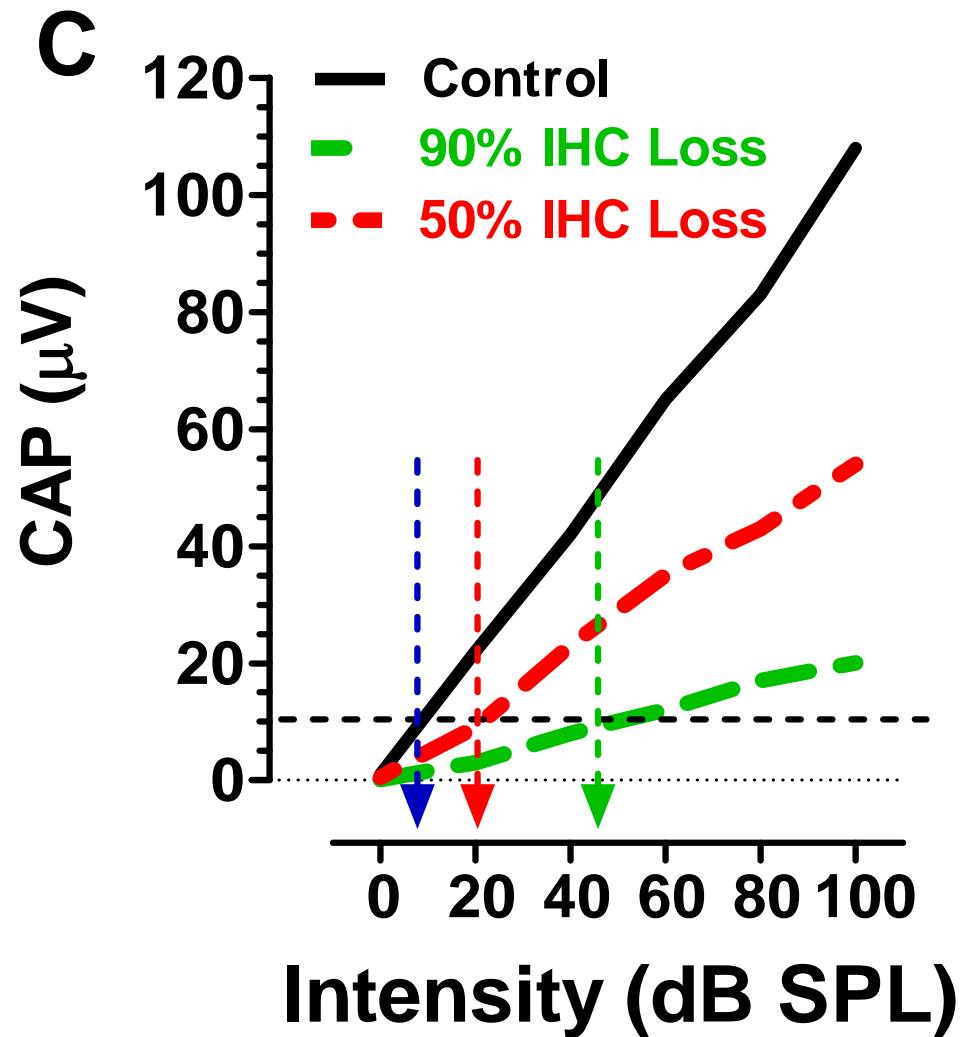
# Compound Action Potential

- ✓ CAP Reduction Roughly Proportional to IHC Loss
- ✓ Little Change in CAP Threshold
- ✓ 90% IHC Loss-CAP almost gone

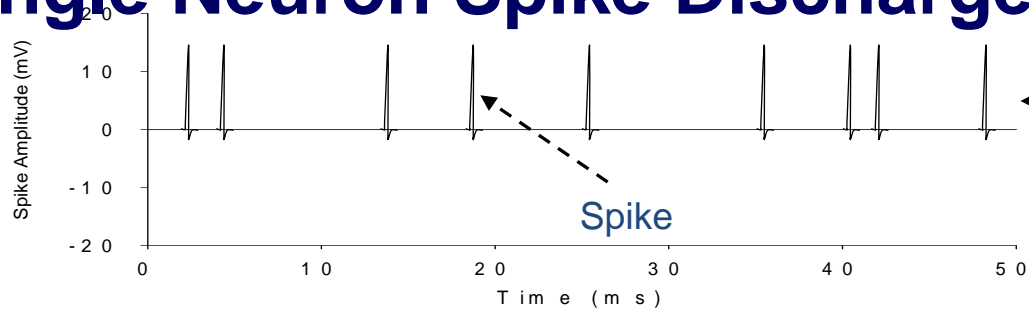




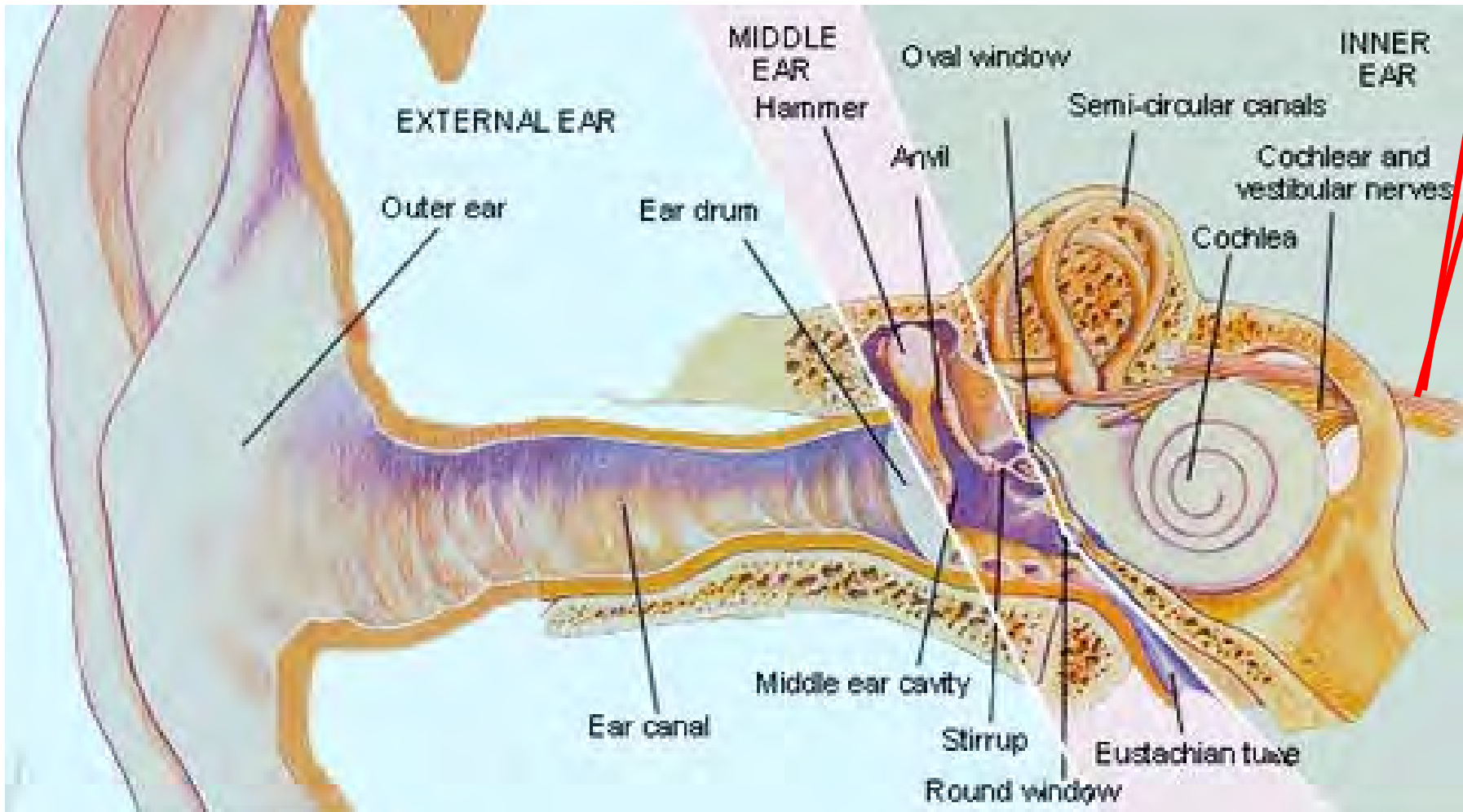
# *CAP Amplitude vs CAP Threshold*



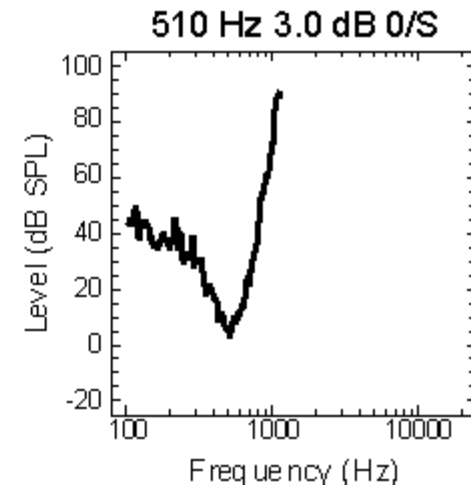
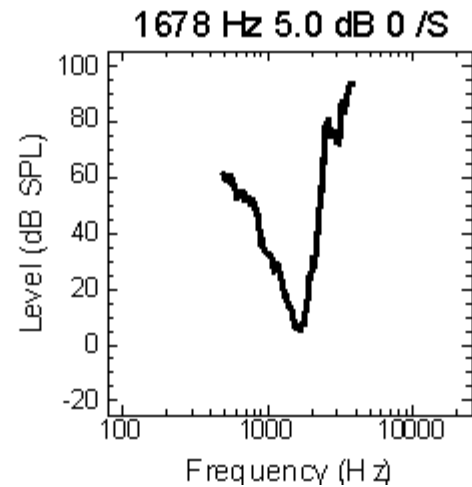
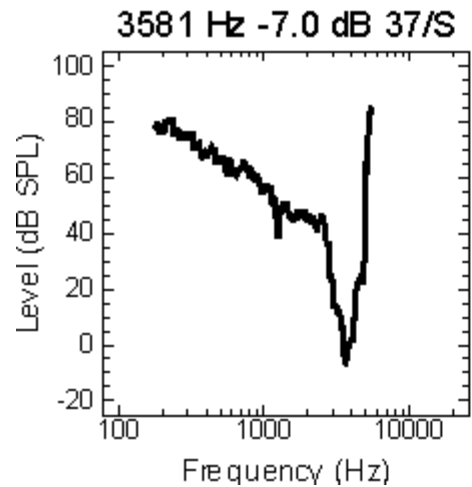
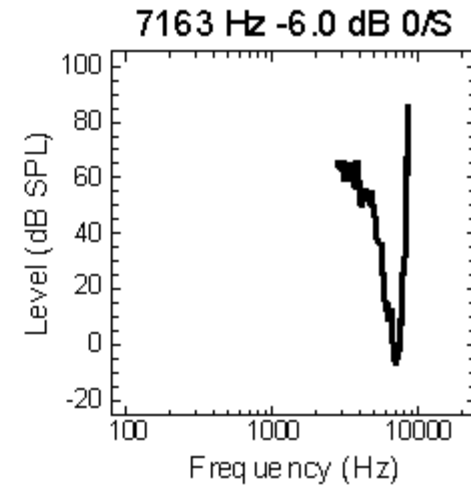
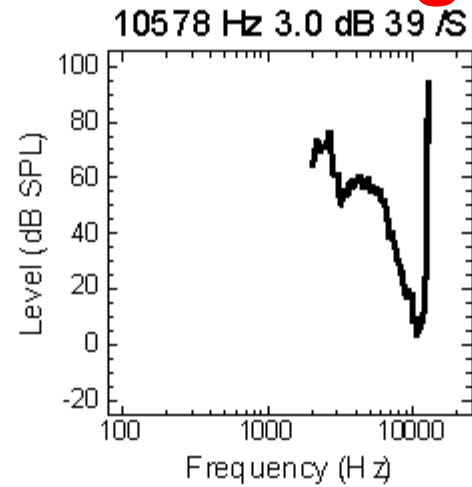
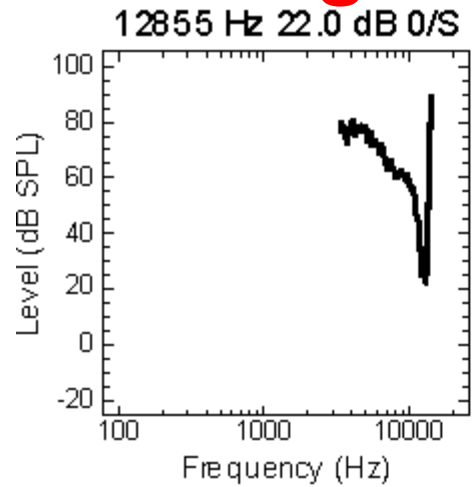
# Single Neuron Spike Discharges from Auditory Nerve



microelectrode



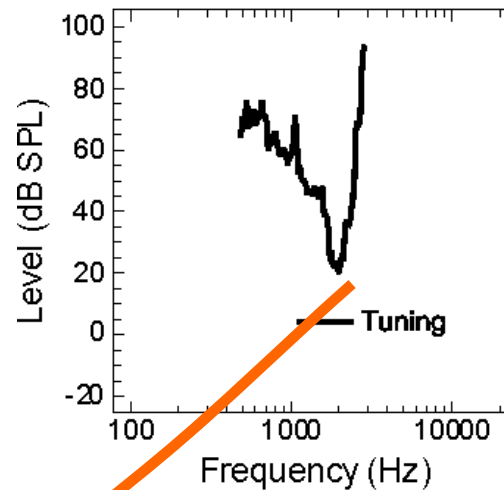
# Normal Single Fiber Tuning



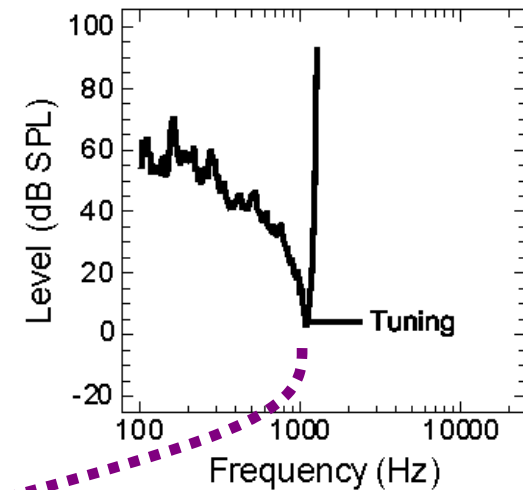
• **Sharp tuning with massive IHC Loss**

• **Normal Threshold**

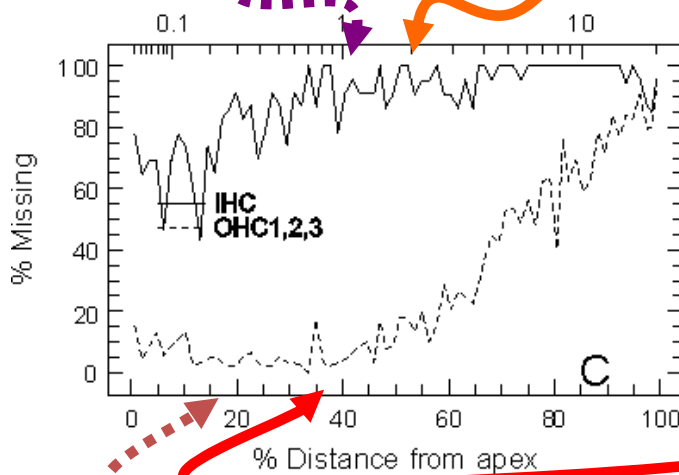
4420 U# 7  
1996 Hz 20.0 dB 50 /S



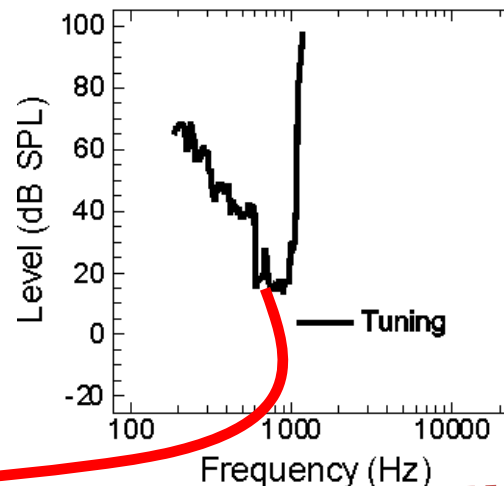
4420 U# 21  
1112 Hz 3.0 dB 100 /S



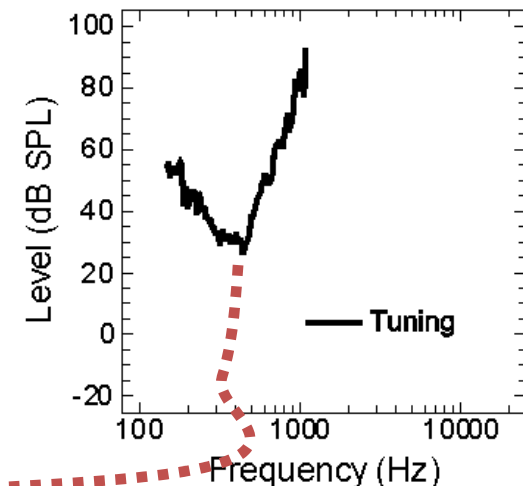
Subject 4420R  
38 mg/kg X2  
Frequency (kHz)



4420 U# 10  
895 Hz 13.0 dB 71 /S



4420 U# 4  
376 Hz 21.0 dB 33 /S



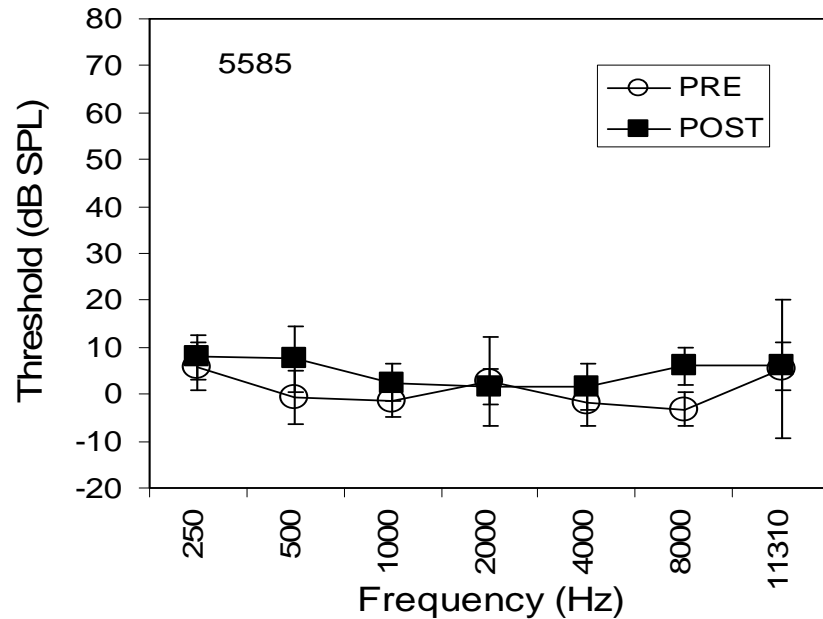


# How Does IHC Loss Affect Threshold?

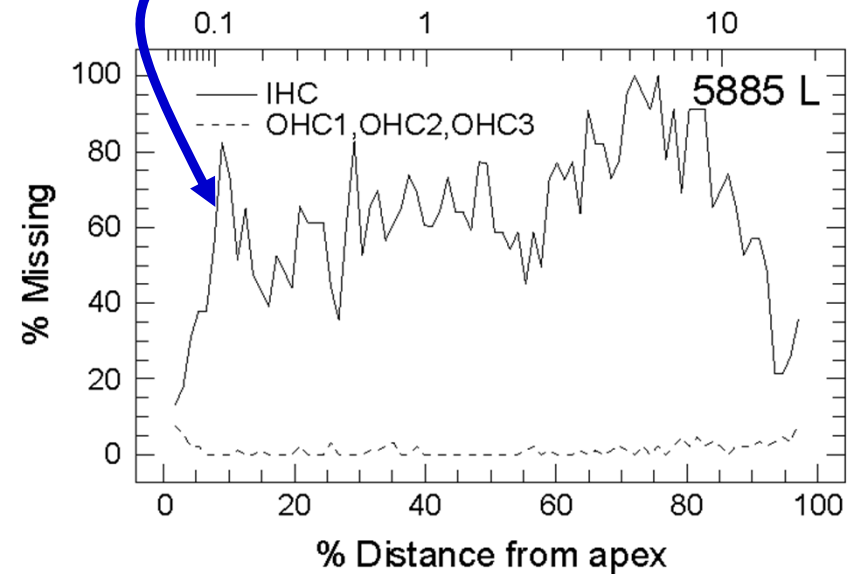
Measure Threshold Pre and Post-Drug

Evaluate Cochlea

- **No Hearing Loss!**



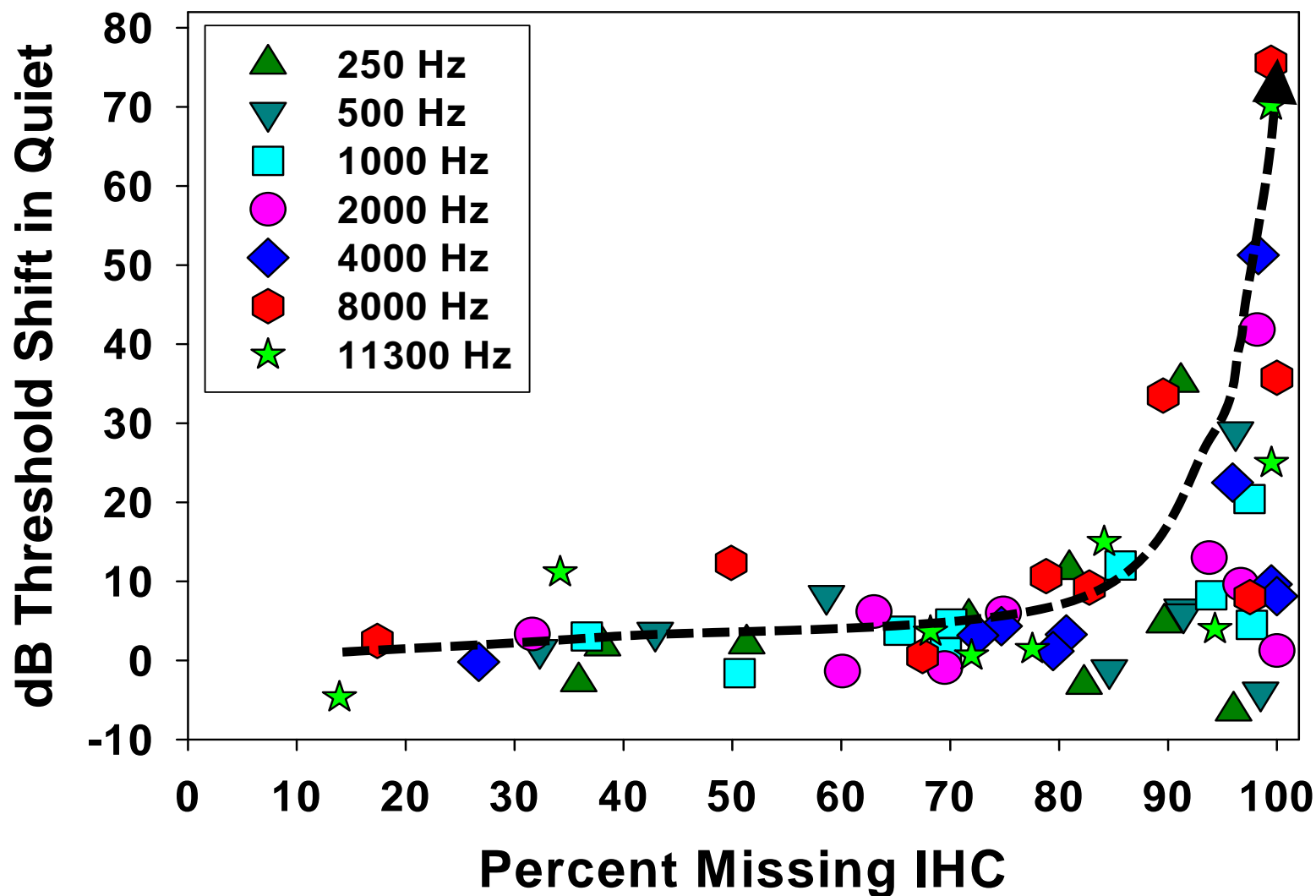
- **Massive IHC Loss**



# How Much IHC Loss Affect Behavioral Thresholds?

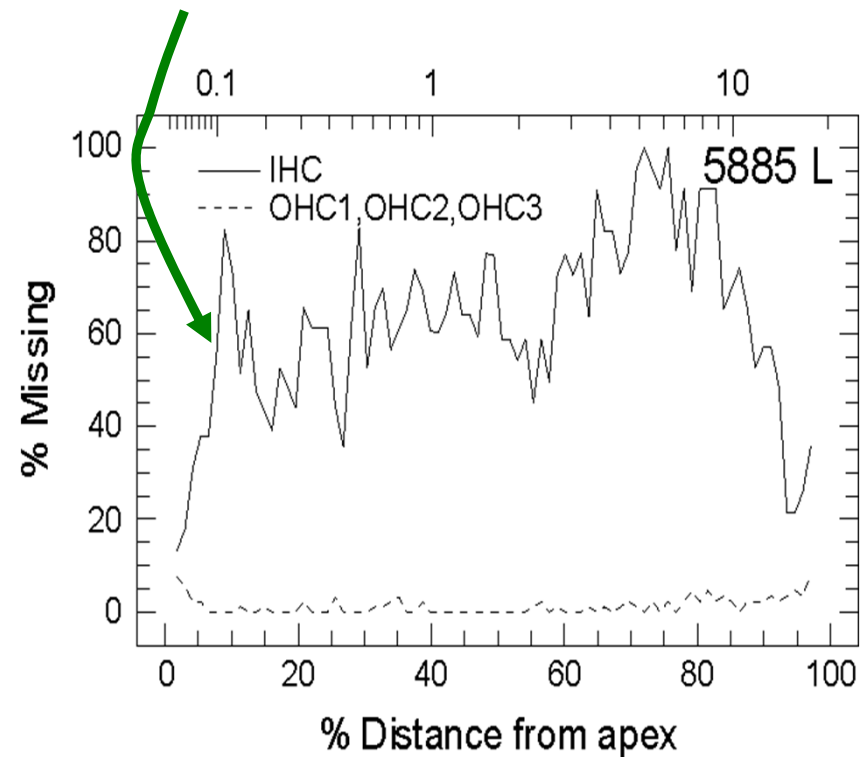
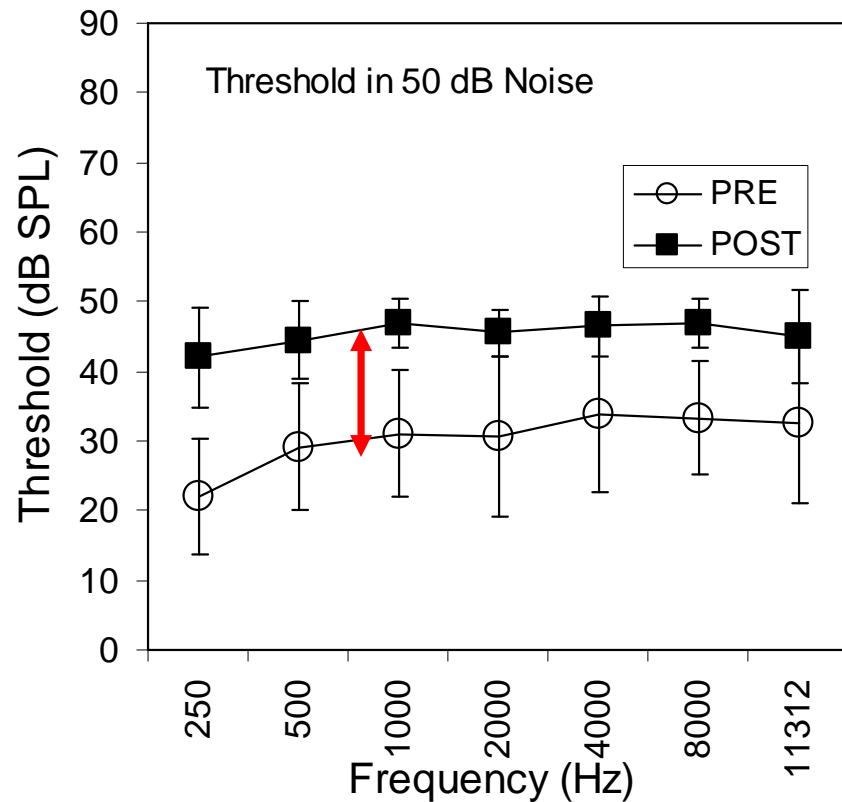
- ✓ Little Change in Threshold Until >85% IHC Loss
- ✓ Few IHC & Auditory Nerve Fibers Needed to Detect Sound

## Threshold Shift in Quiet vs. IHC loss

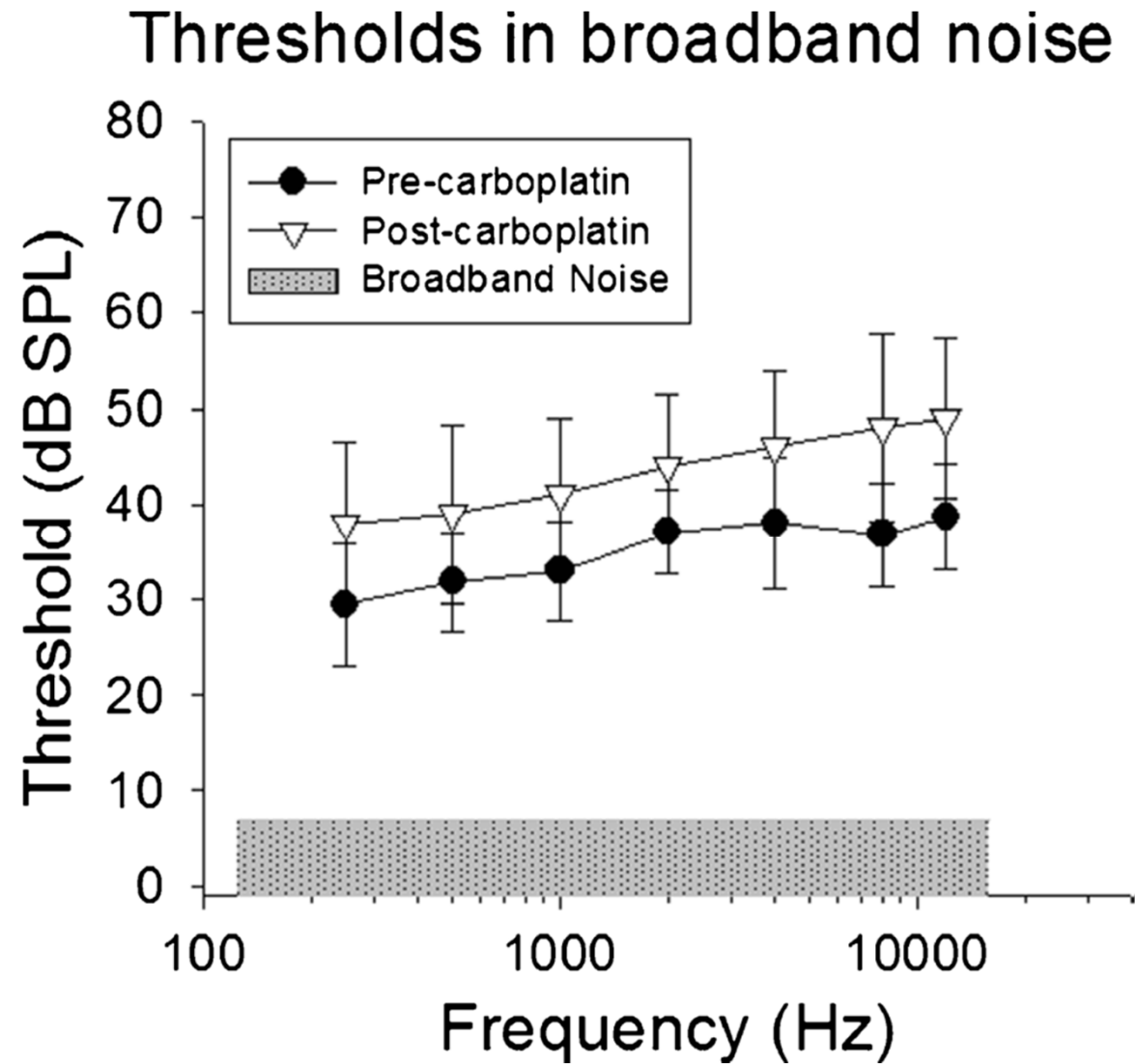


# How Does IHC Loss Affect Threshold in Noise?

- **Thresholds in Noise Increases with IHC Loss**



## Threshold in Noise increases with IHC Loss

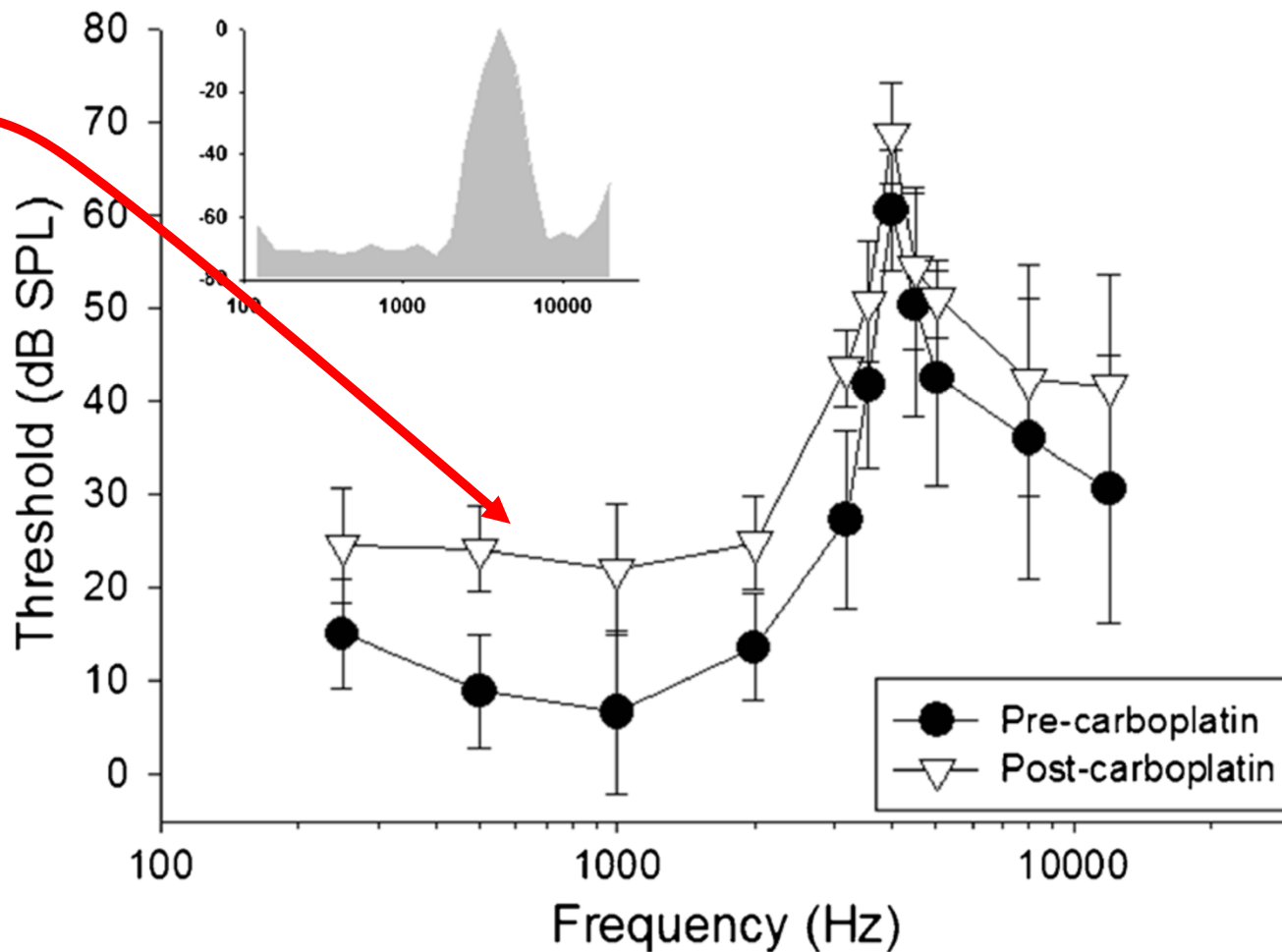




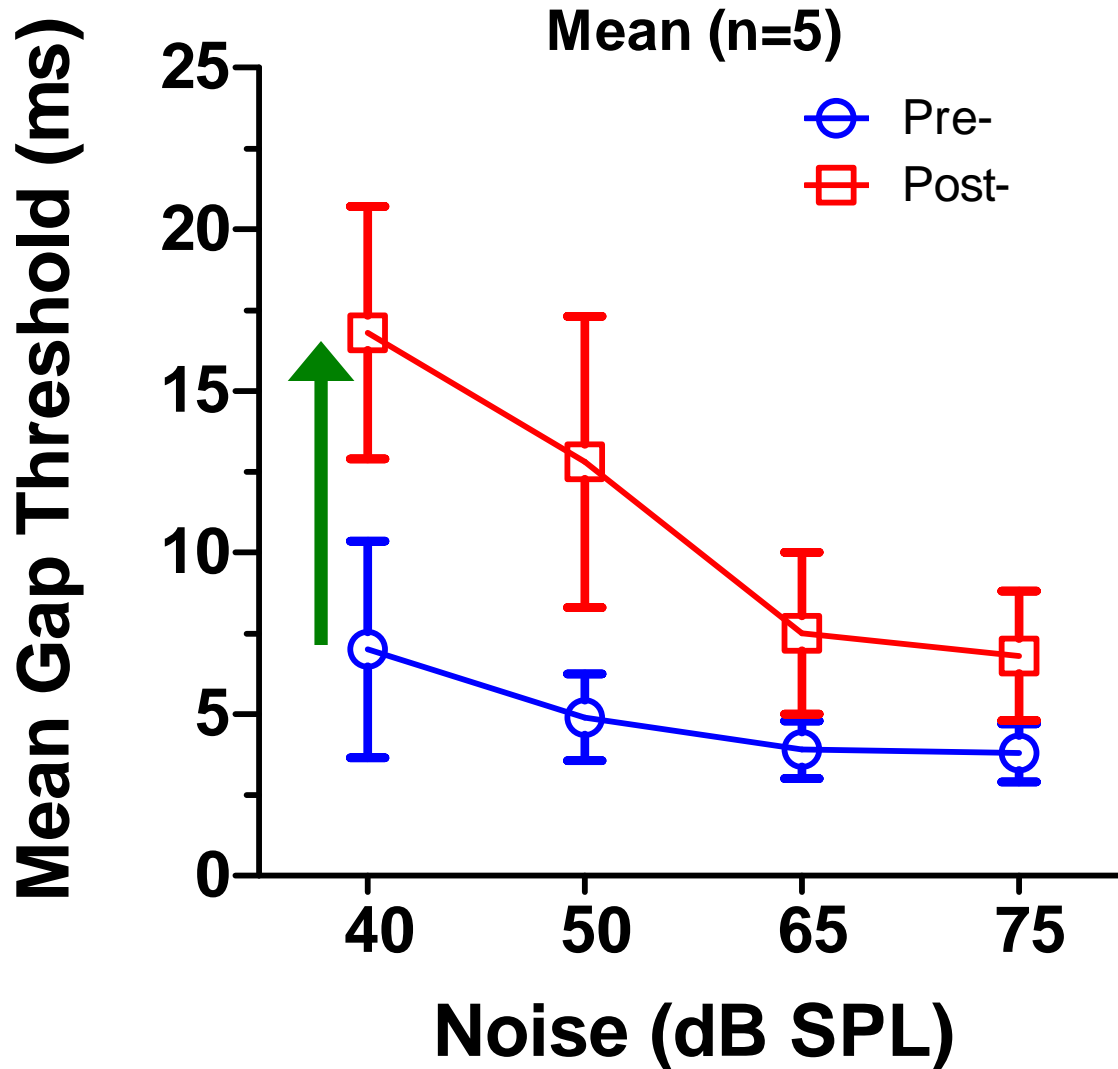
# Threshold of 4000 Hz Tone in Narrow Band Noise Centered at 4000 Hz

## • Thresholds Elevated Above & Below Masker

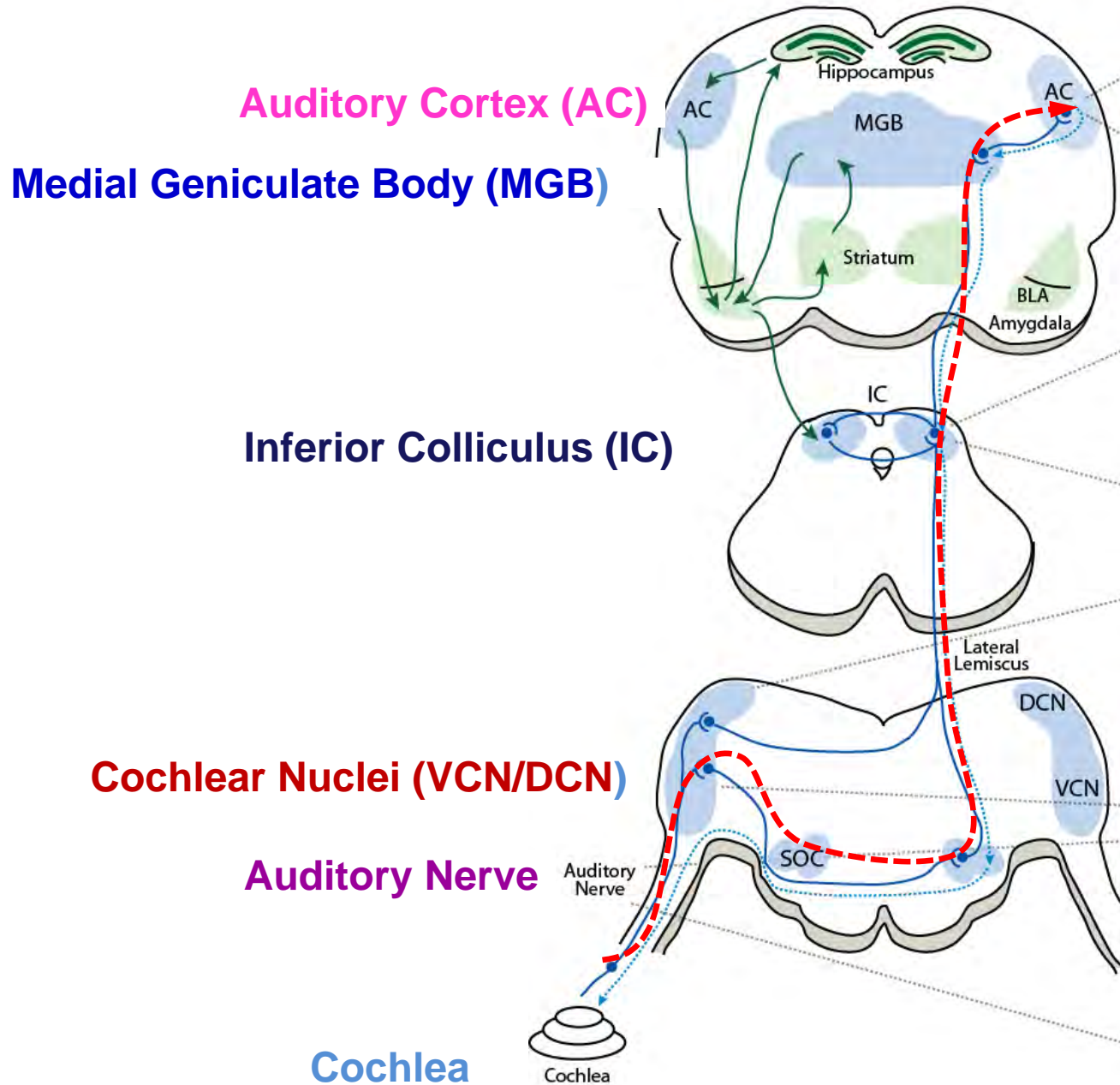
Carboplatin treatment increases off-frequency thresholds in 70 dB SPL narrowband noise centered at 4000 Hz



# Gap Silent Gap in Noise (Gap Detection)



# Auditory Pathway

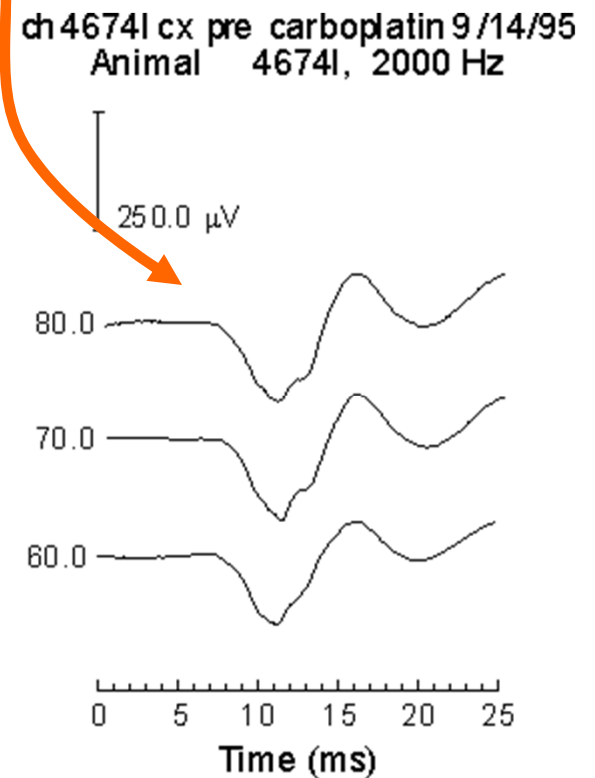
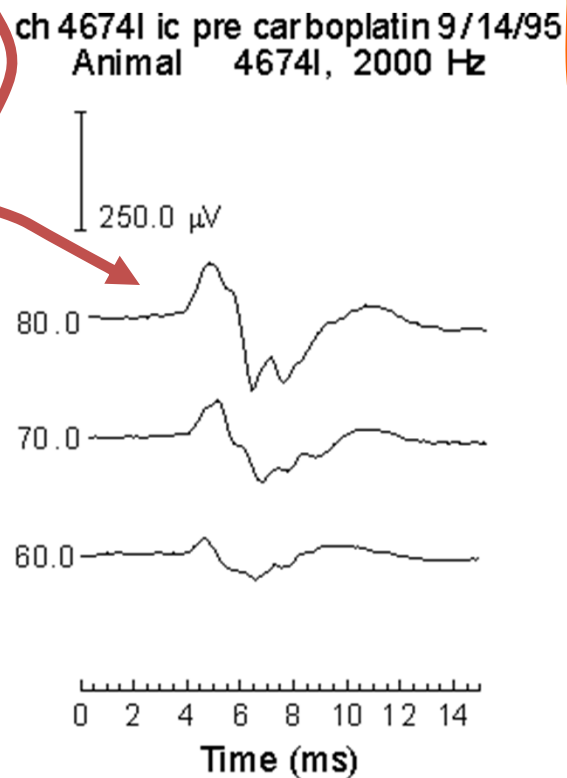
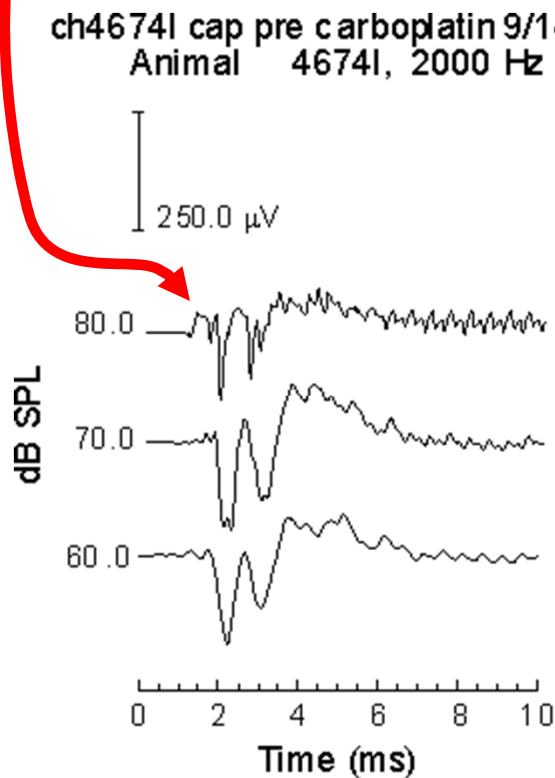


# Chronic Electrodes Record Activity Before & After IHC Loss

•CAP from Round Window

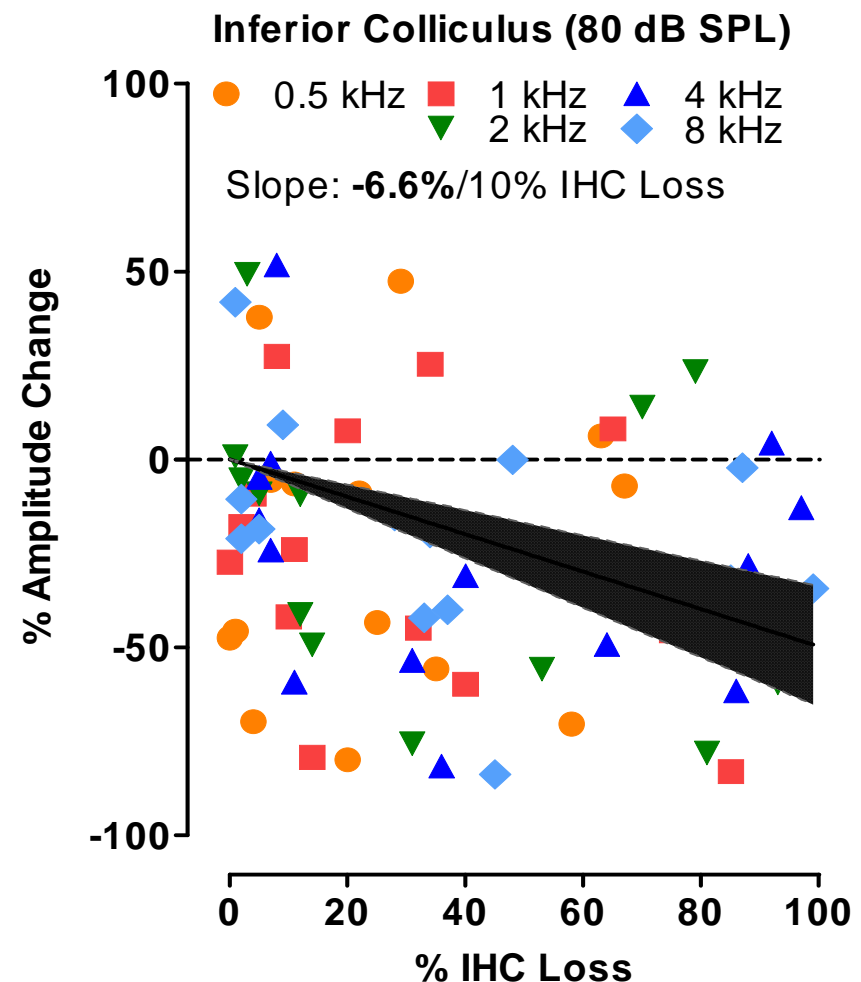
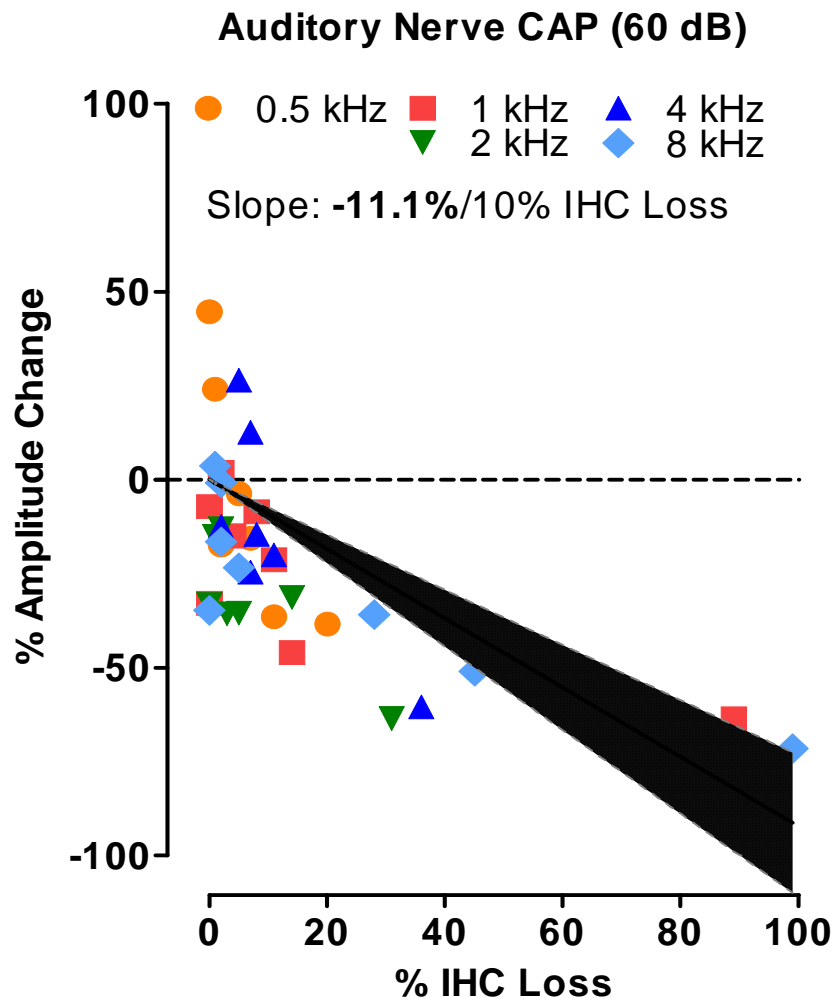
•IC (inferior colliculus)

•AC (auditory cortex)



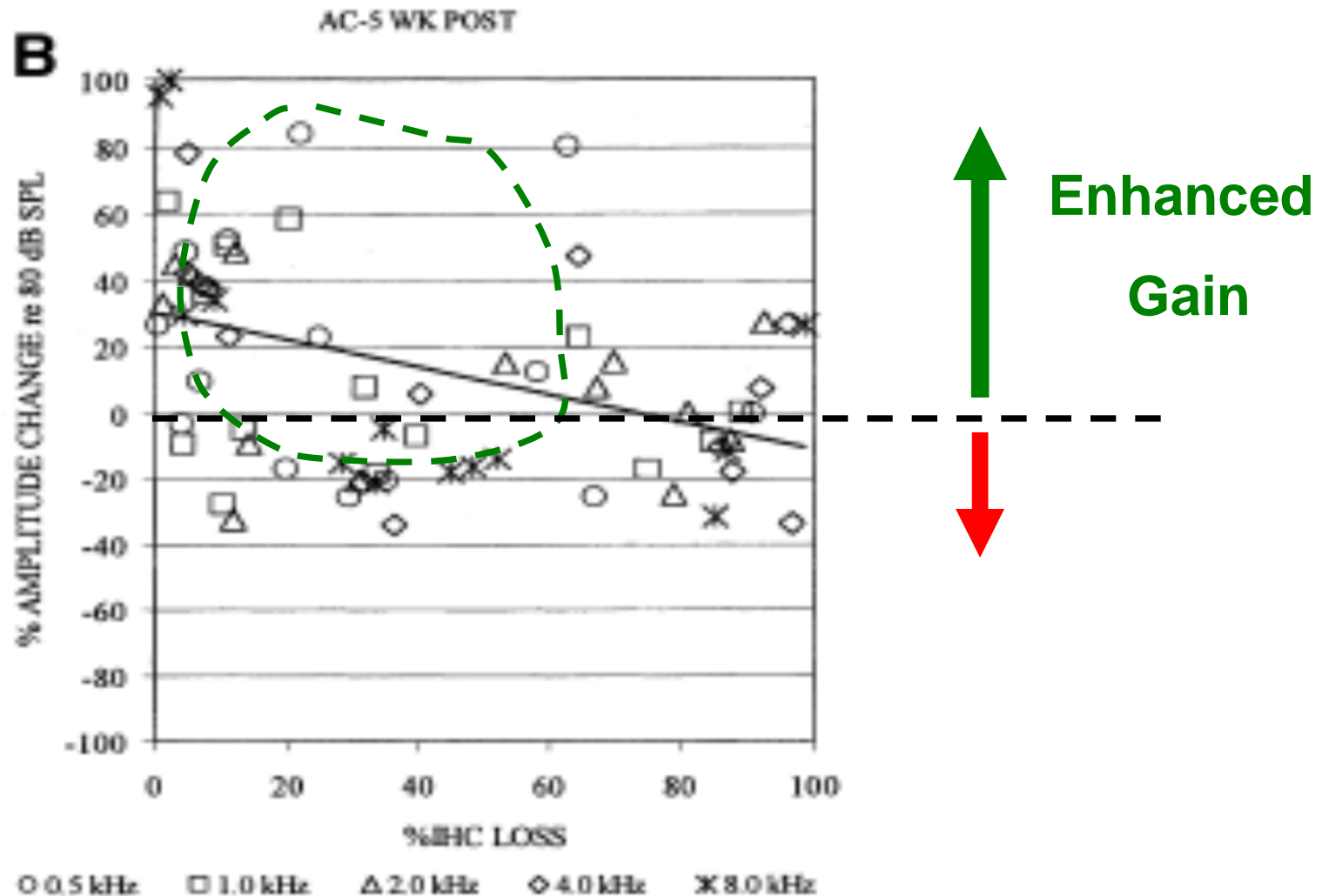
# Effect of IHC Loss on CAP vs. IC Suprathreshold Amplitudes

- CAP Amplitude Decreases 11.1% per 10% Loss of IHC
- IC Amplitude Decreases 6.6% per 10% Loss of IHC
- Increase in Central Gain Partially Compensate for Cochlear Loss
- Additional Increase Seen in Auditory Cortex



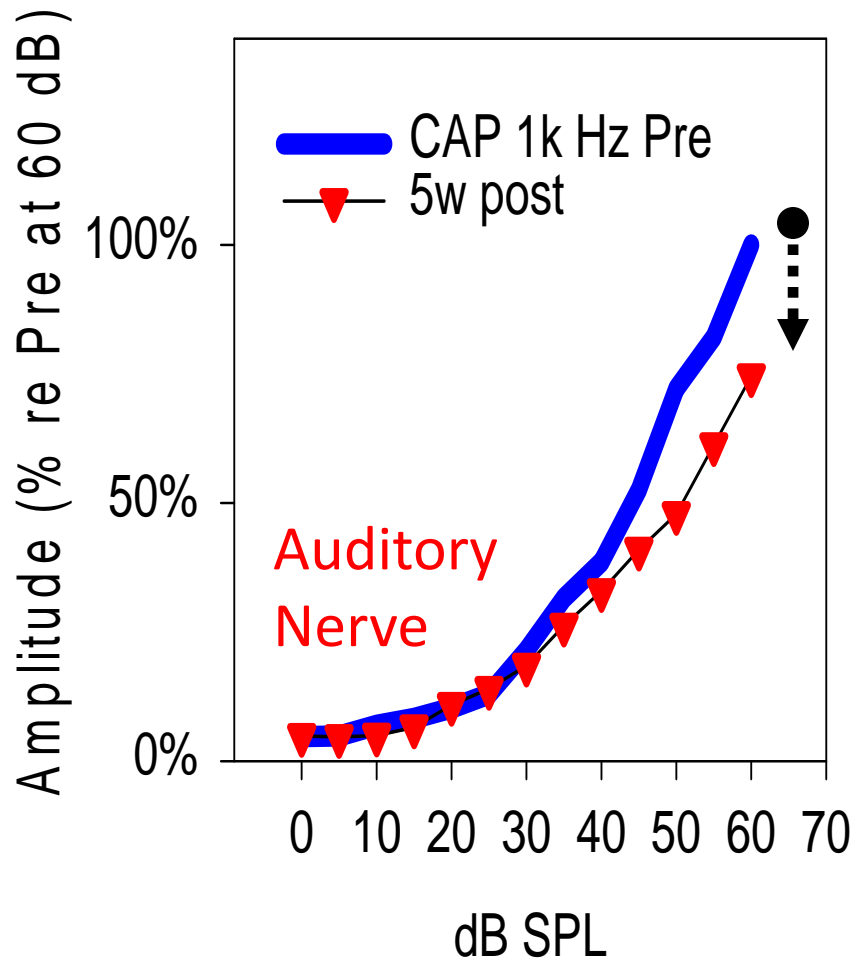
# Effect of IHC Loss on AC Suprathreshold Amplitudes

- ✓ Additional Increase (Gain) Seen in Auditory Cortex
- ✓ AC Amplitudes Larger than Normal with IHC Lesion <60%
- ✓ AC Amplitudes Decrease with IHC Lesions >60%

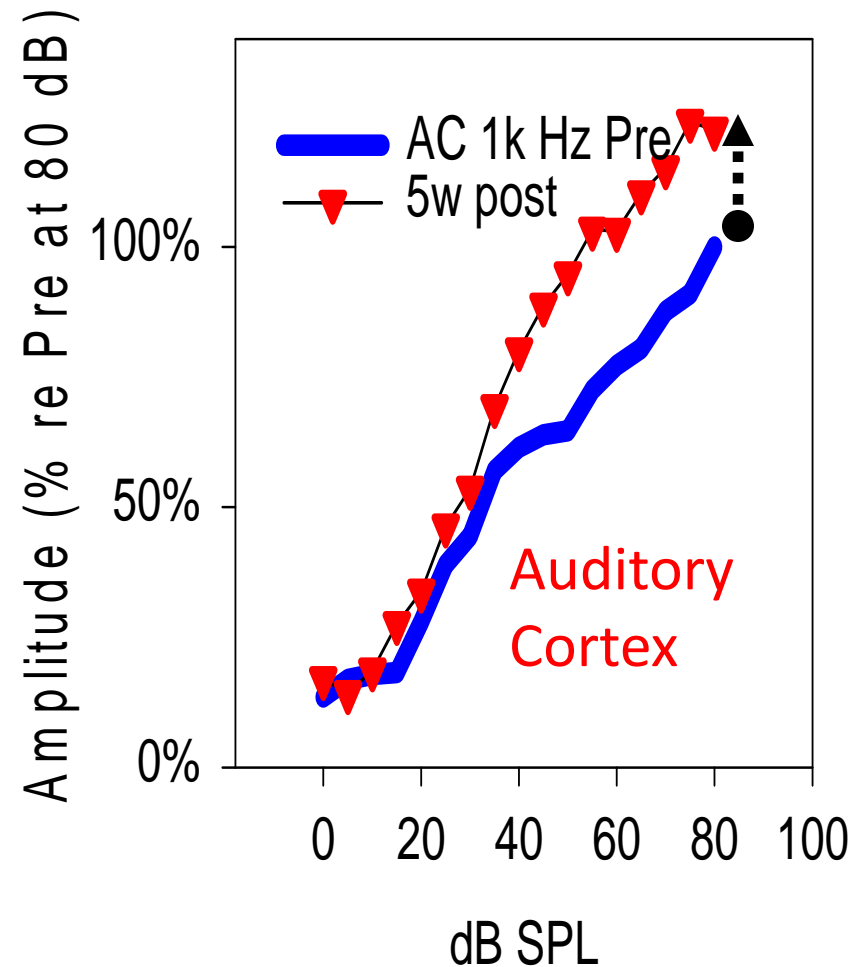


# What Mechanisms Increase Central Gain?

REDUCED CAP  
AMPLITUDE



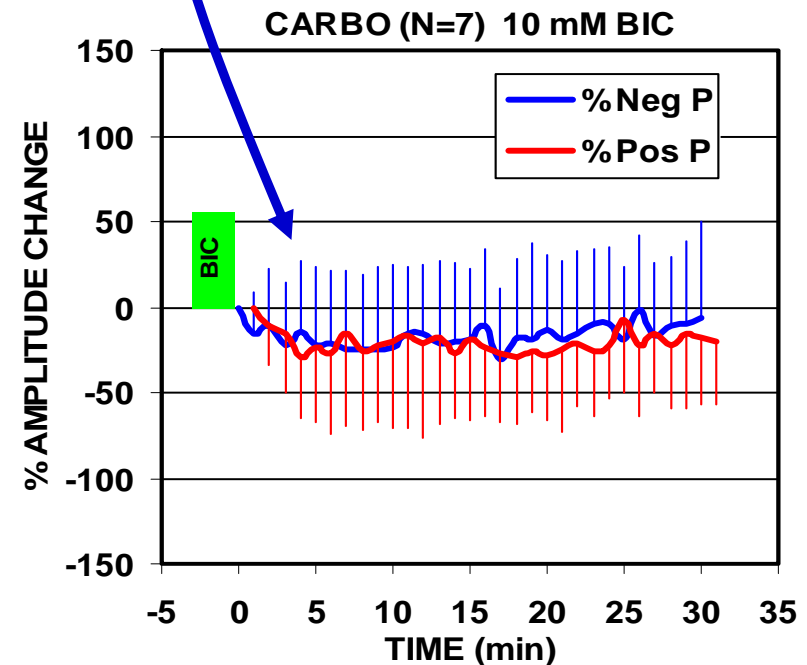
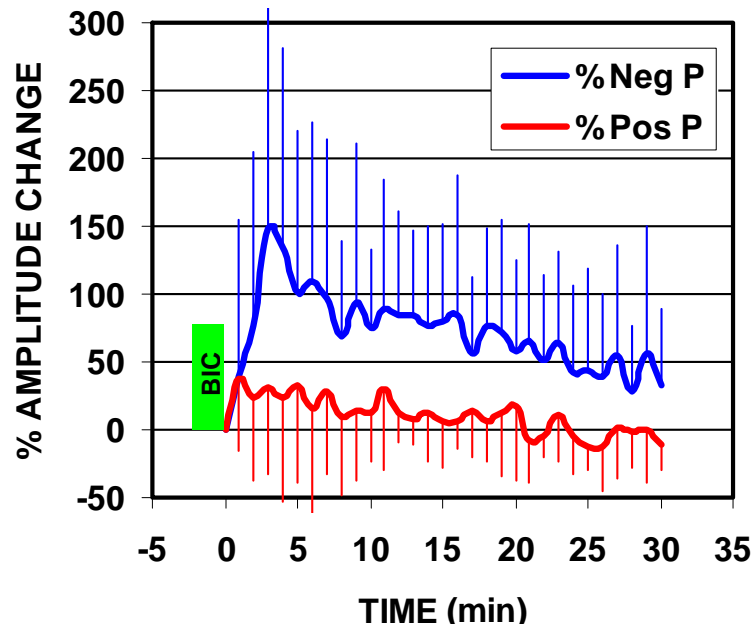
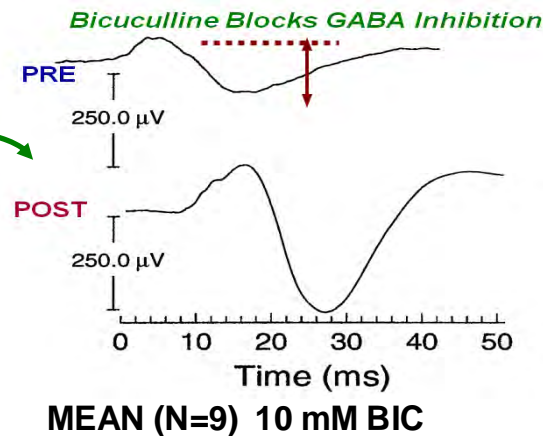
ENHANCED  
AUDITORY CORTEX  
RESPONSE





# Is Inhibition Present after Carboplatin Treatment?

- Apply Bicuculline to Suppress GABA-mediated Inhibition
- Large Increase in Normal Animal
- Almost no change in Carboplatin-Treated Animal



# Interpretation

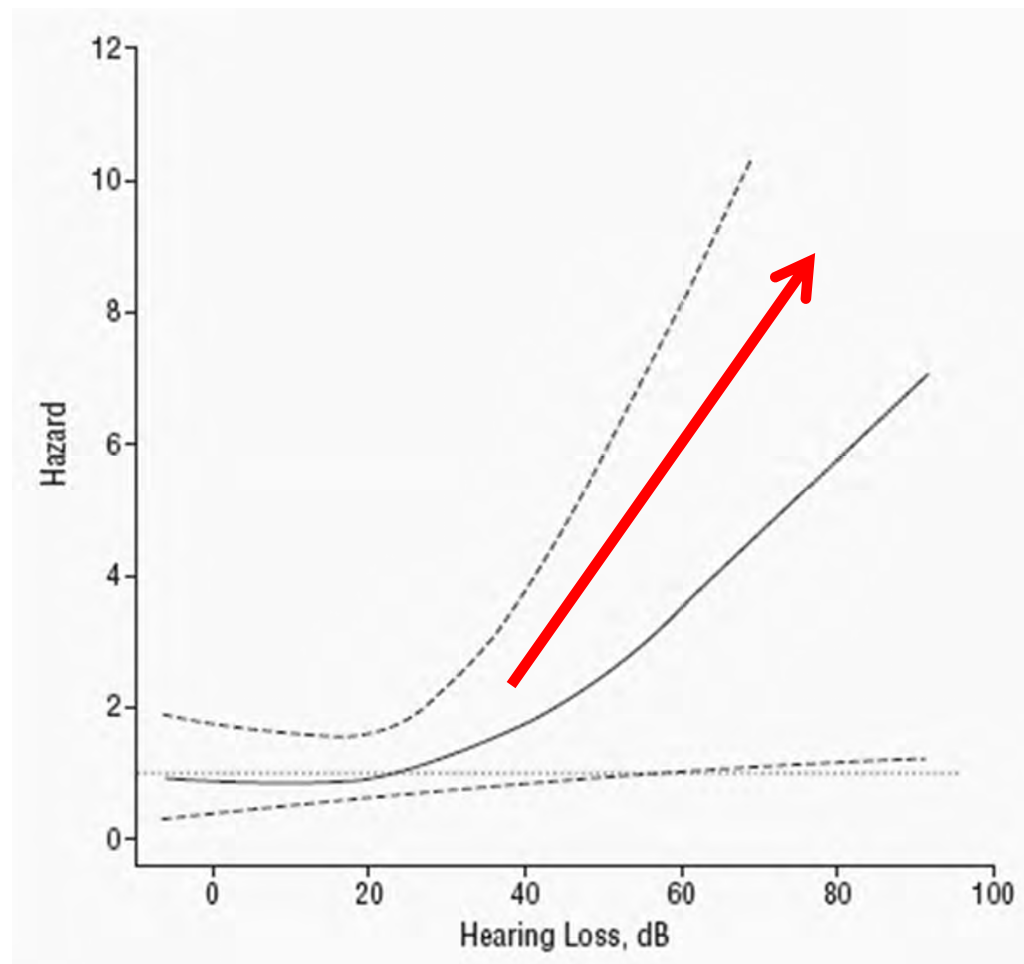
## Carboplatin-induced IHC Loss

- Enhances AC amplitude
- Increased Gain of Central Auditory System  
Compensates for Reduced Peripheral Input

## Enhancement Mechanism

- Loss of GABA<sub>A</sub> receptors
- Reduced GABA release

- **Lin et al. 2011, Arch of Neurology**
- **Prospective study, 639 individuals**
- **Dementia free 1990-1994**
- **12 years later: 58 Dementia**
- **Hearing Loss Risk Factor for Dementia**



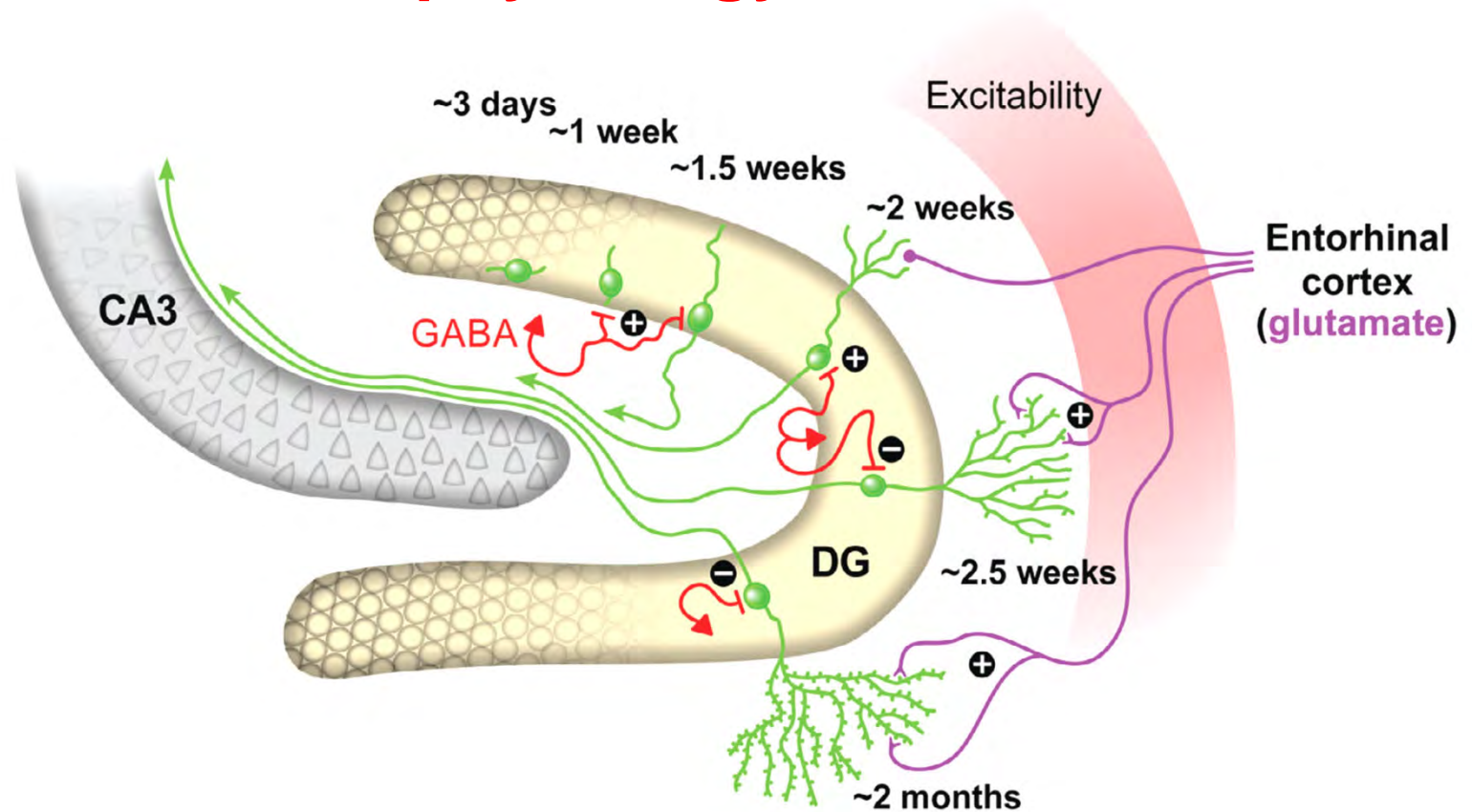
# Cisplatin/Carboplatin/Oxaliplatin

- **Cisplatin Blocks Cell Division**
- **Cisplatin-adverse neurological effects**
- **Chemobrain-cognitive fog**



# Hippocampus -Neurogenesis

- Stem Cells-Dentate Gyrus
- Rat ~9000 newborn neurons per day
- 2 Months-Electrophysiology Mature



# *Hippocampus Function*

- ***Memory-Acquisition & Retention***
- ***Recognition memory-Unifying features (e.g. person's face + auditory sound of name)***
- ***Damage hippocampus-memory impairment***
- ***Suppress neurogenesis-impair memory***
- ***Emotion & Mood***
  - ***Stress-suppresses neurogenesis***
  - ***Depression-suppresses neurogenesis***
- ***Spatial Maps-"Place Cells"***
  - ***Neurons Respond to Specific Locations***

# *Experimental Questions*

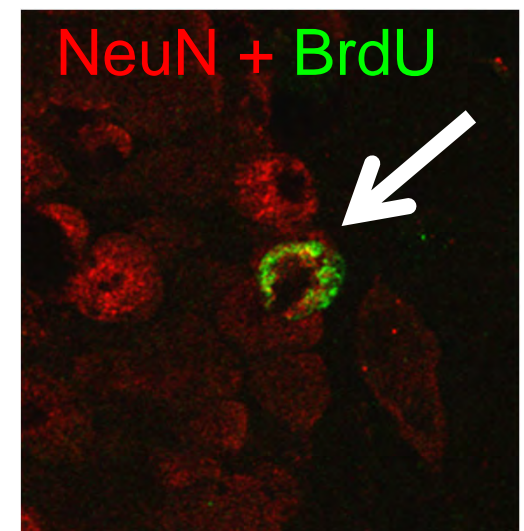
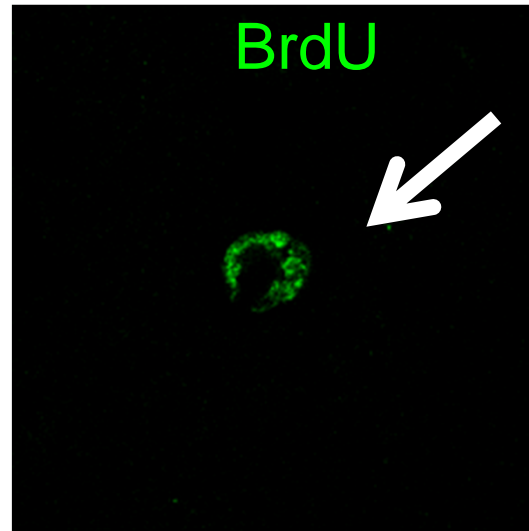
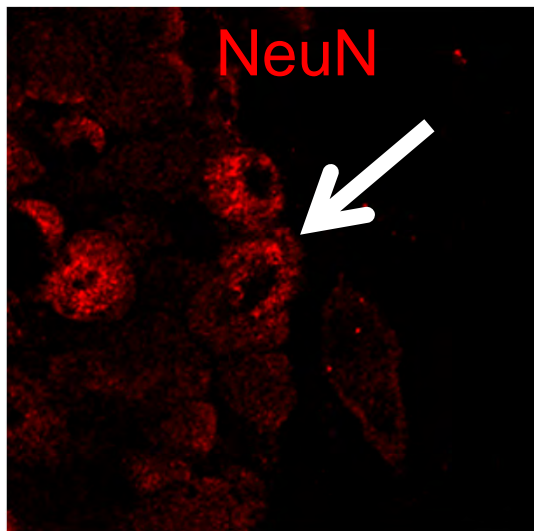
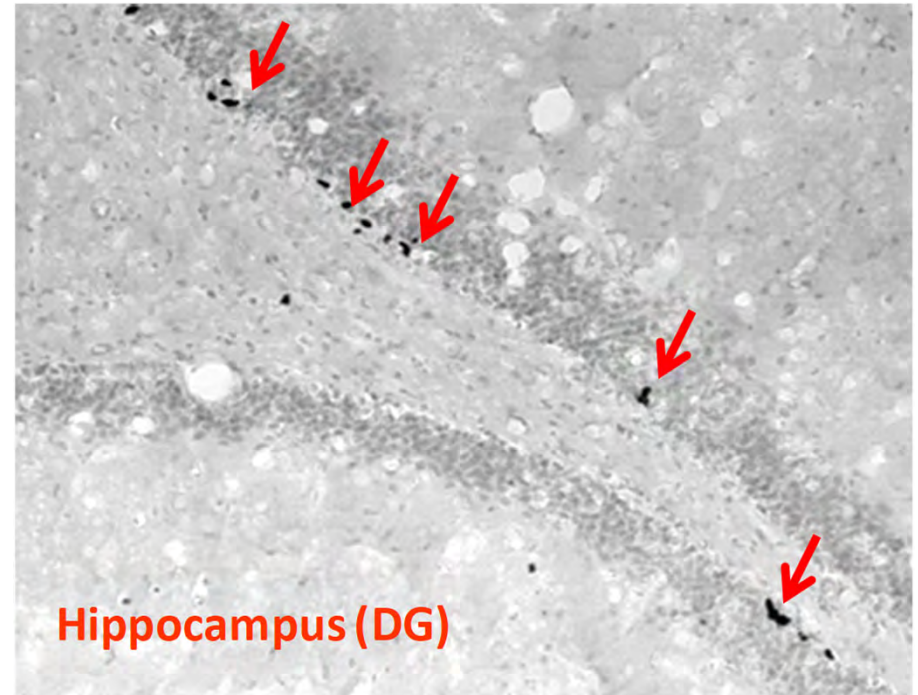
- *Cisplatin-Long Known to be Ototoxic*
- *Cisplatin Blocks Cell Division*
- *Does Cisplatin Affect Cell Proliferation in the Hippocampus?*
- *Can the Toxic Effects of Cisplatin be Prevented?*



# Cell Proliferation

Bromodeoxyuridine  
(BrdU) Incorporated  
into DNA Dividing Cells

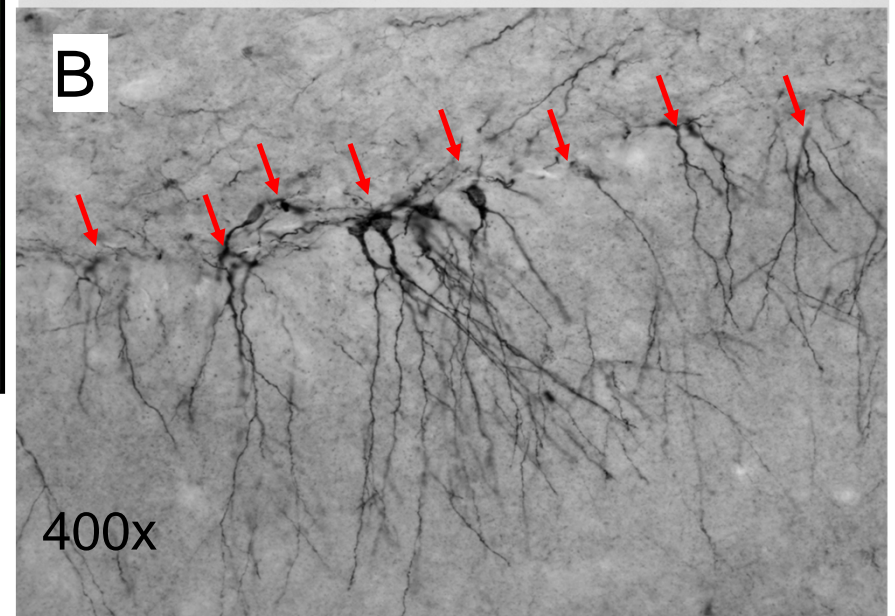
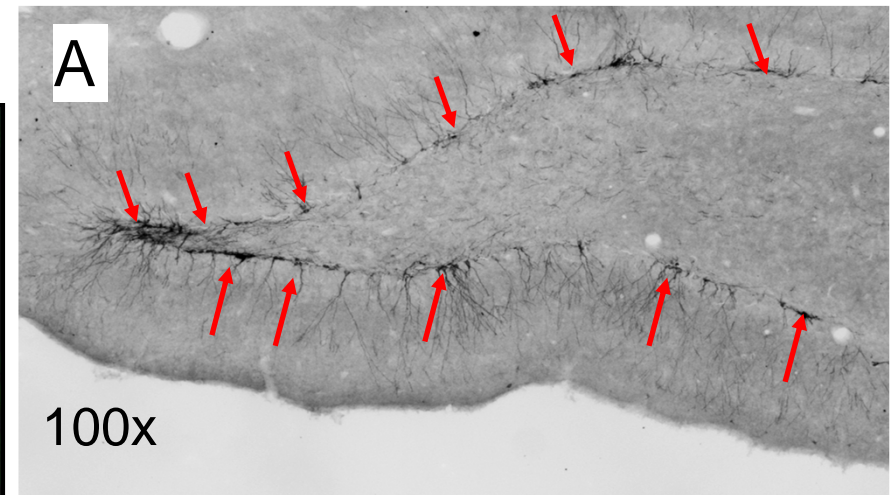
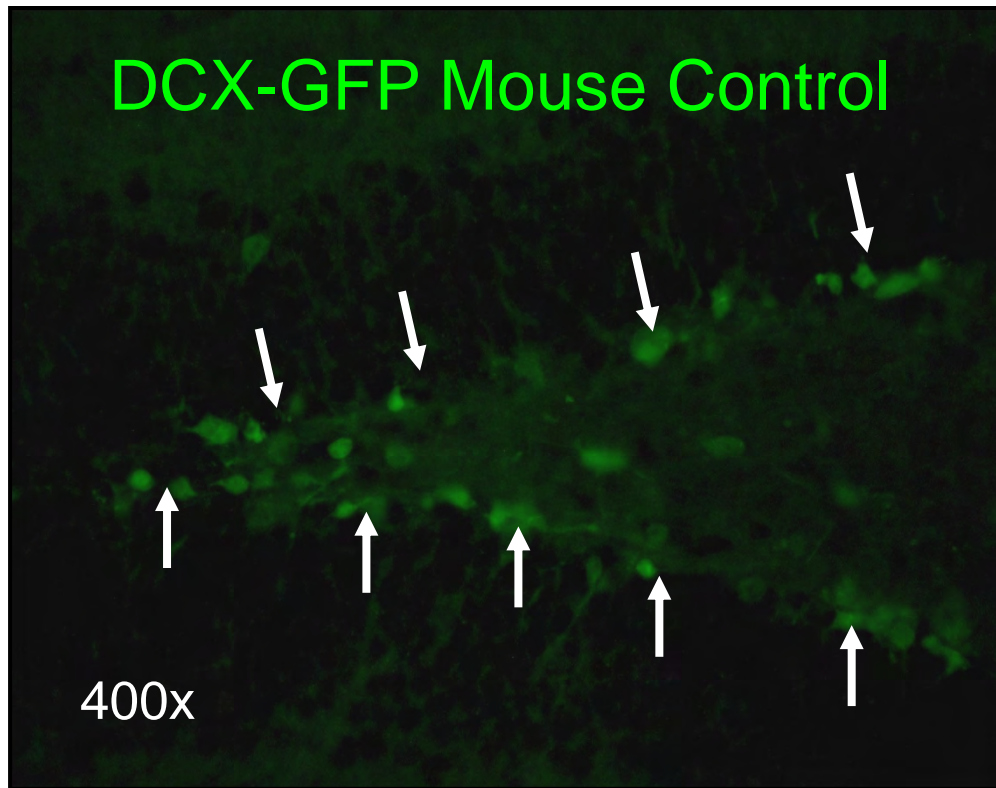
NeuN: Mature Neurons



# Doublecortin (Dcx)-Labels Newborn Neurons

- **Dentate gyrus-lined with Dcx neurons**

**Control Rat**



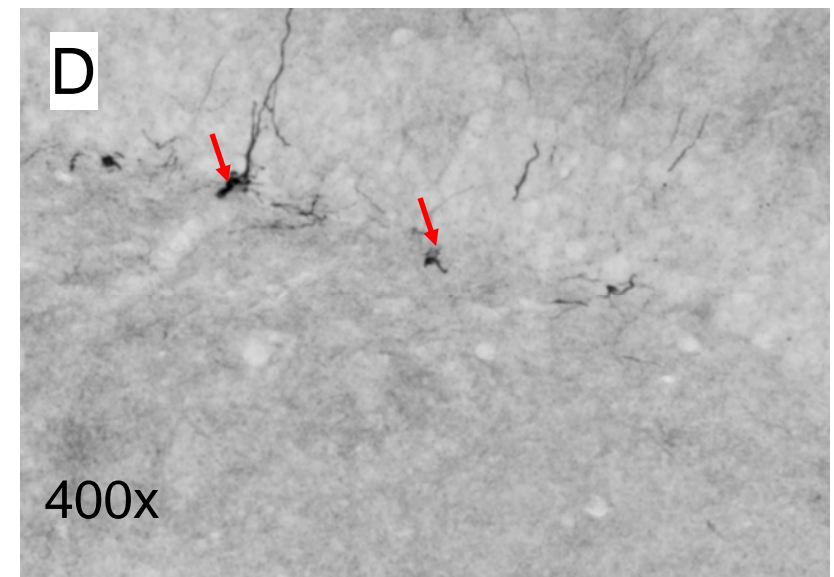
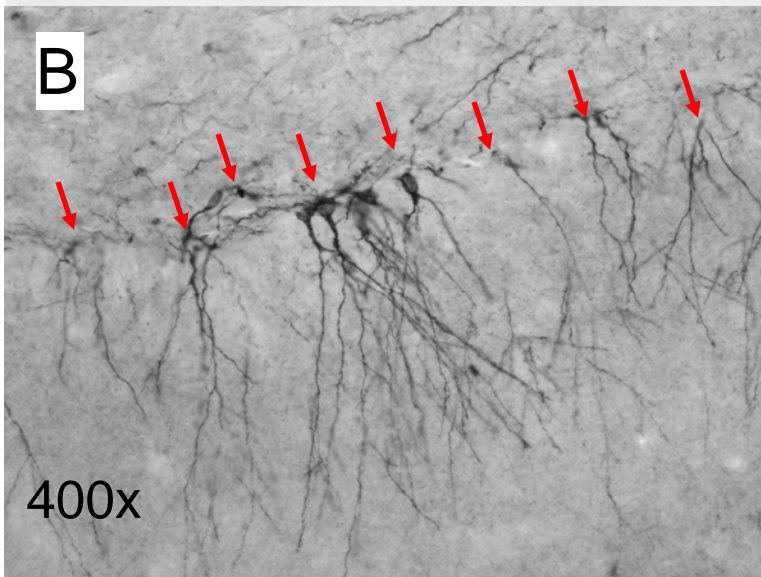
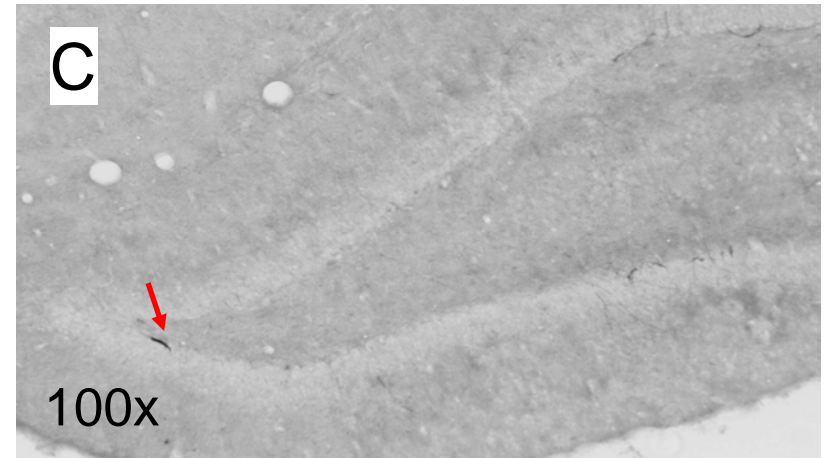
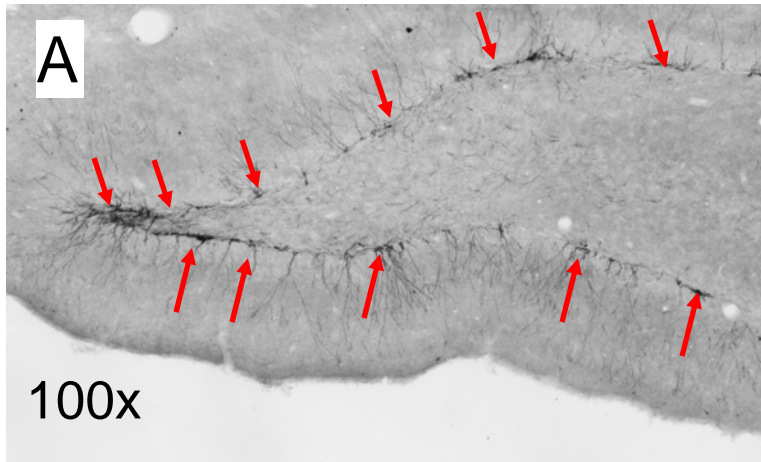


# Cisplatin Suppresses Doublecortin

- **Few doublecortin neurons 7 d post**

Control

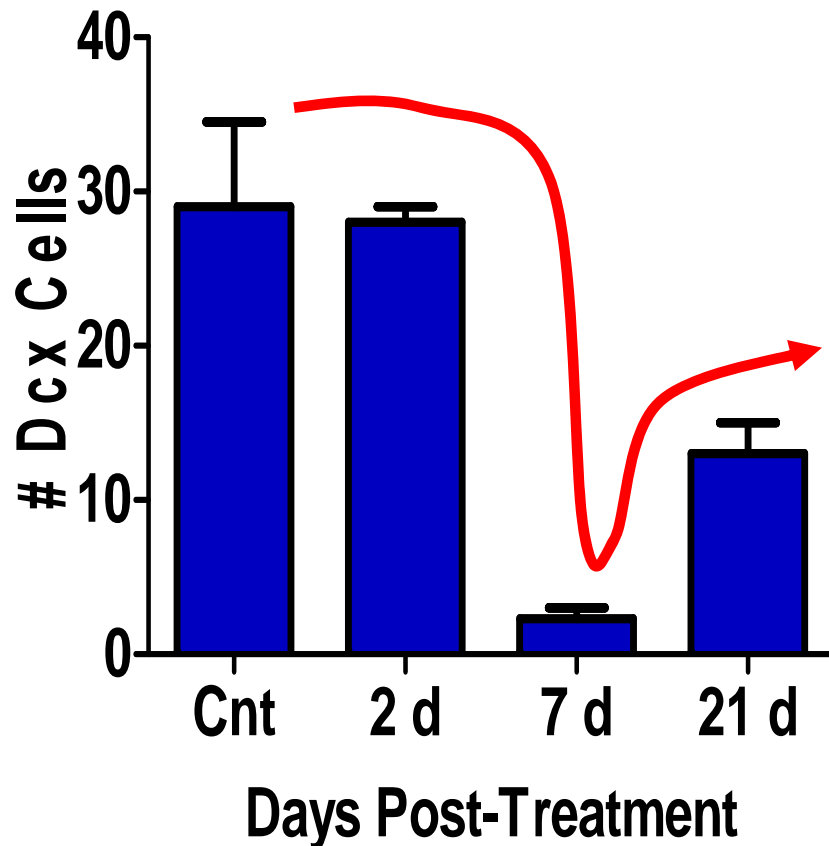
7 day Post-Cisplatin



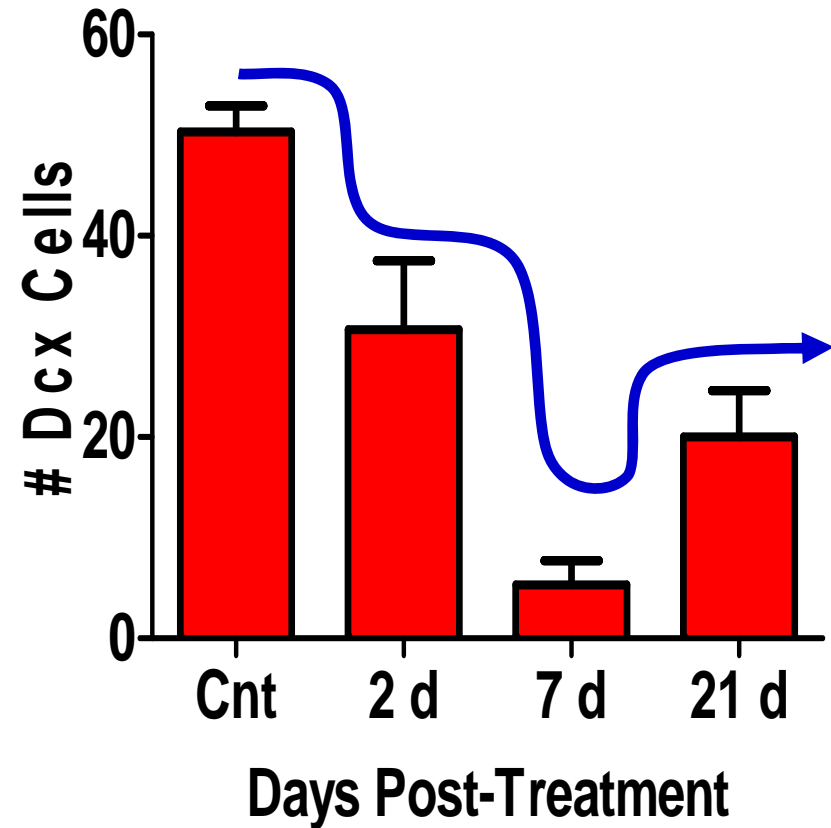
# Cisplatin Suppresses Neurogenesis

- 7 d – Nearly Total Suppression
- 21 d – Suppression ~55%

Rostral Hippocampus

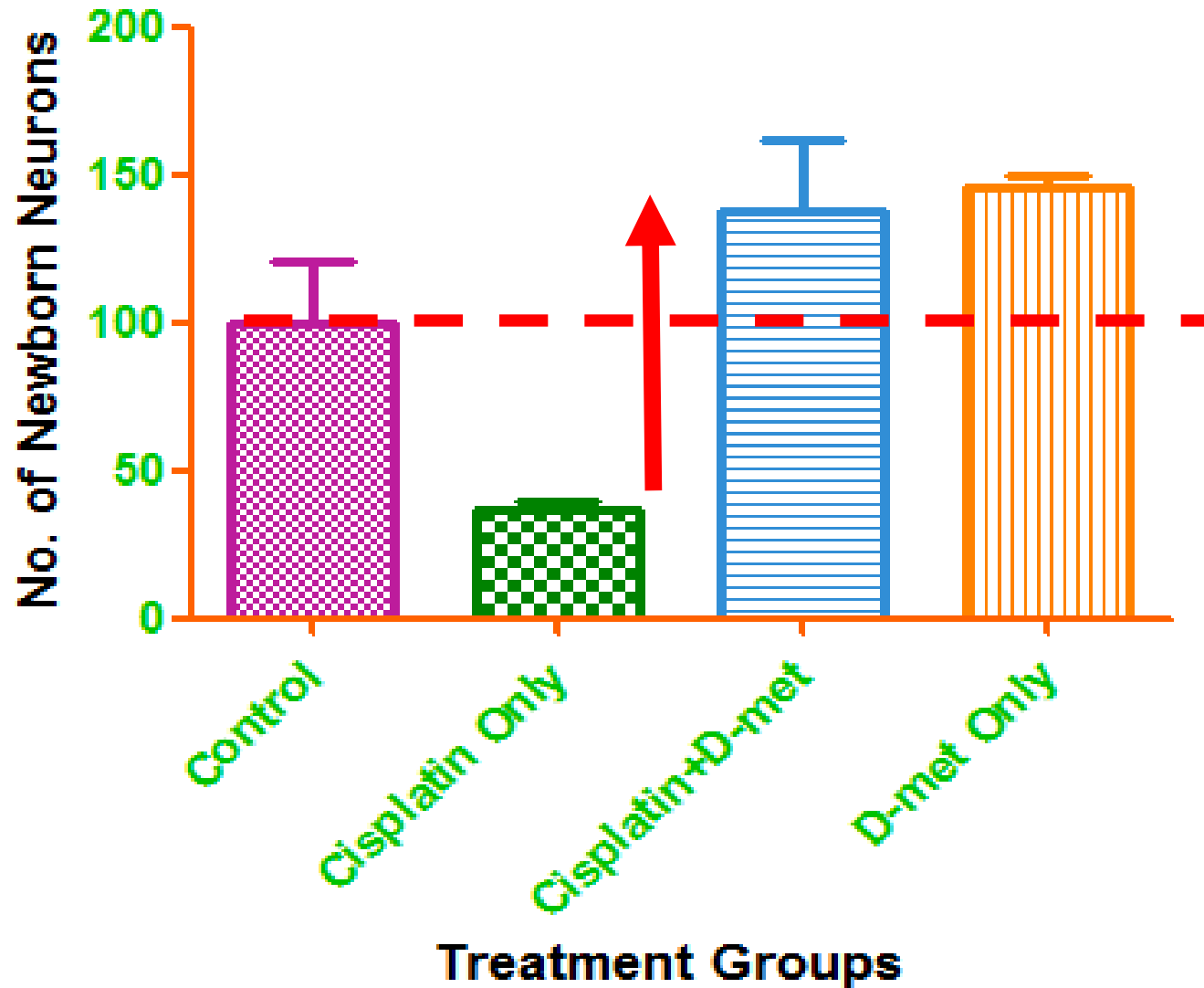


Caudal Hippocampus



# *D-Methionine-Antioxidant Therapy*

- *Blocks Suppressive Effects of Cisplatin*
- *More Newborn Neurons*



# ***Noise Exposure***

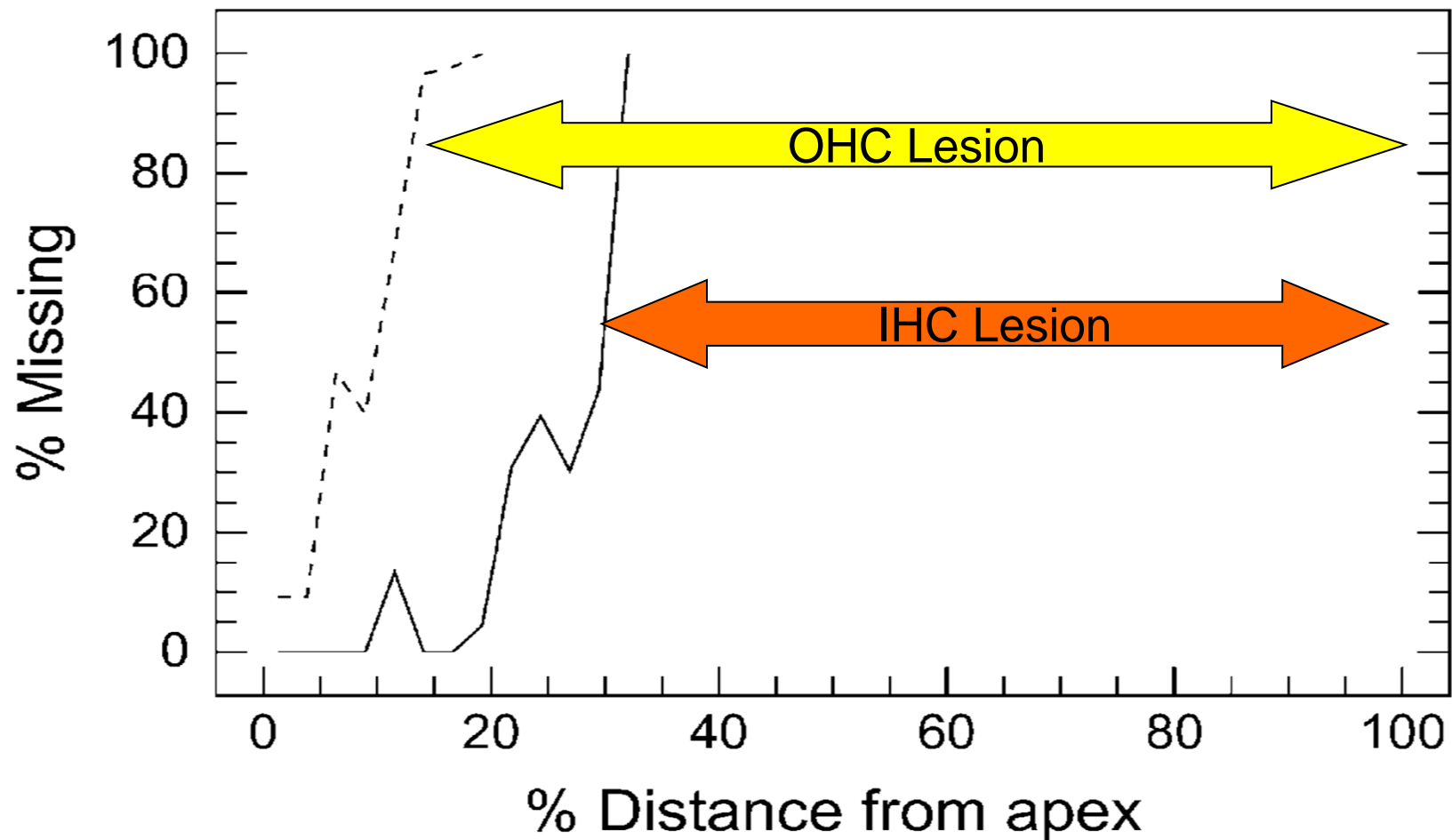
## ***Major Cause of Hearing Loss***

- ***Damages Cochlea***
- ***Induces Tinnitus***
- ***>50% Combat Personnel Iraq & Afghanistan***
- ***Many Combat Personnel PTSD***
  
- ***Does Noise-Induced Hearing Loss Affect Neurogenesis in Hippocampus?***

## Does Noise-Induced Hearing Loss Suppress Neurogenesis

- **Noise Induced Hearing Loss in Left Ear**
- **Retain Normal Hearing in Right Ear**

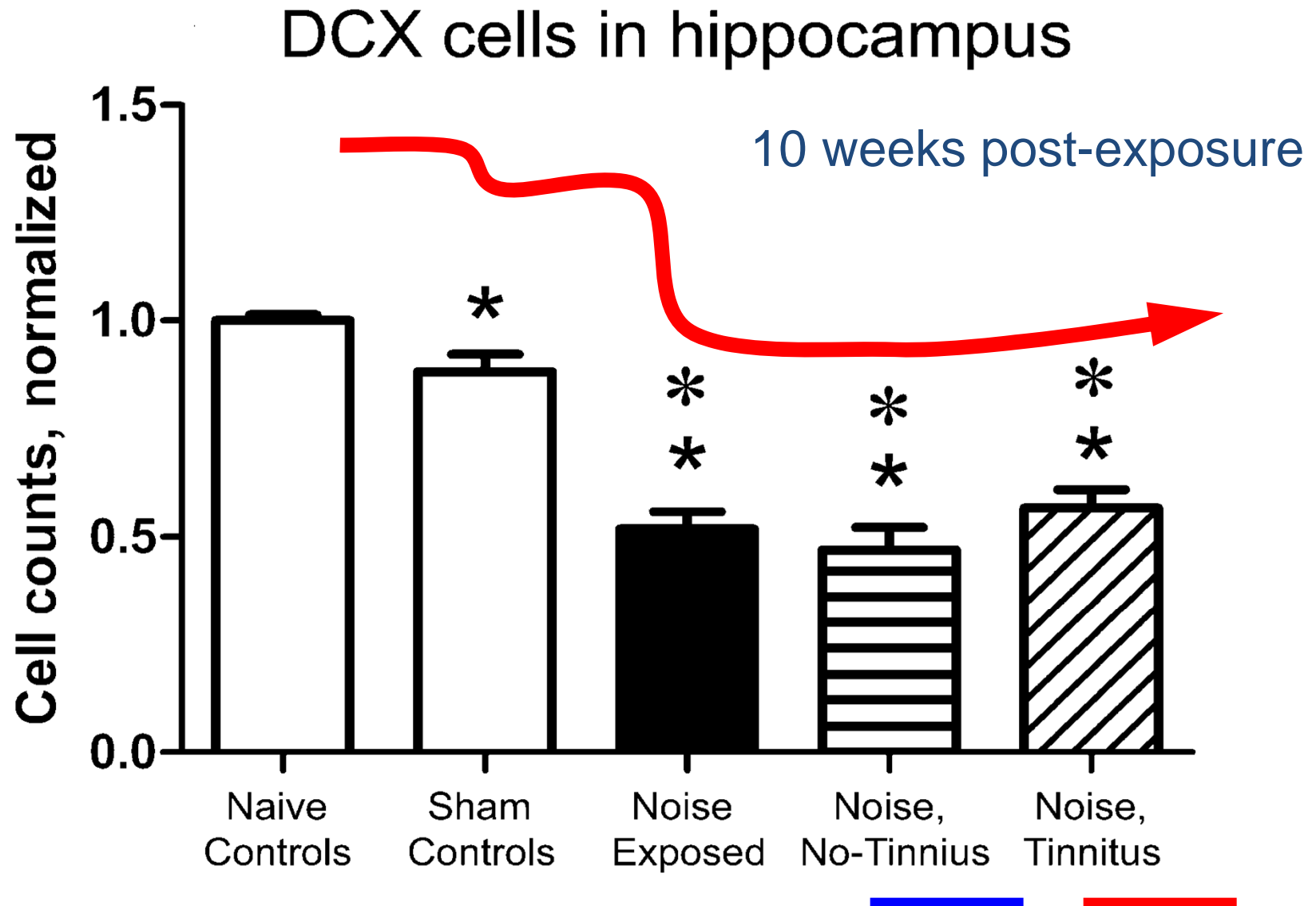
• *Noise: 2 h, 126 dB, 12 kHz Narrow Band Noise*





# Noise Induced Suppression of Neurogenesis

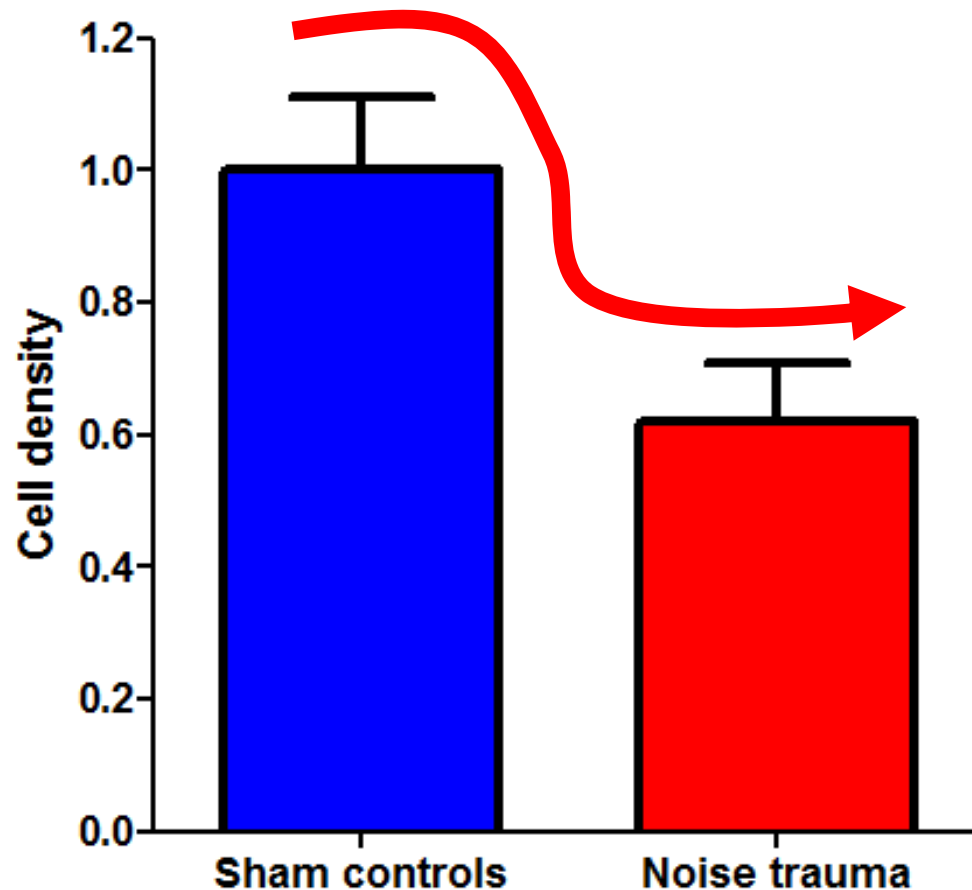
- **Tinnitus vs. No-Tinnitus Rats-No Difference**



# Noise Suppresses Cell Proliferation

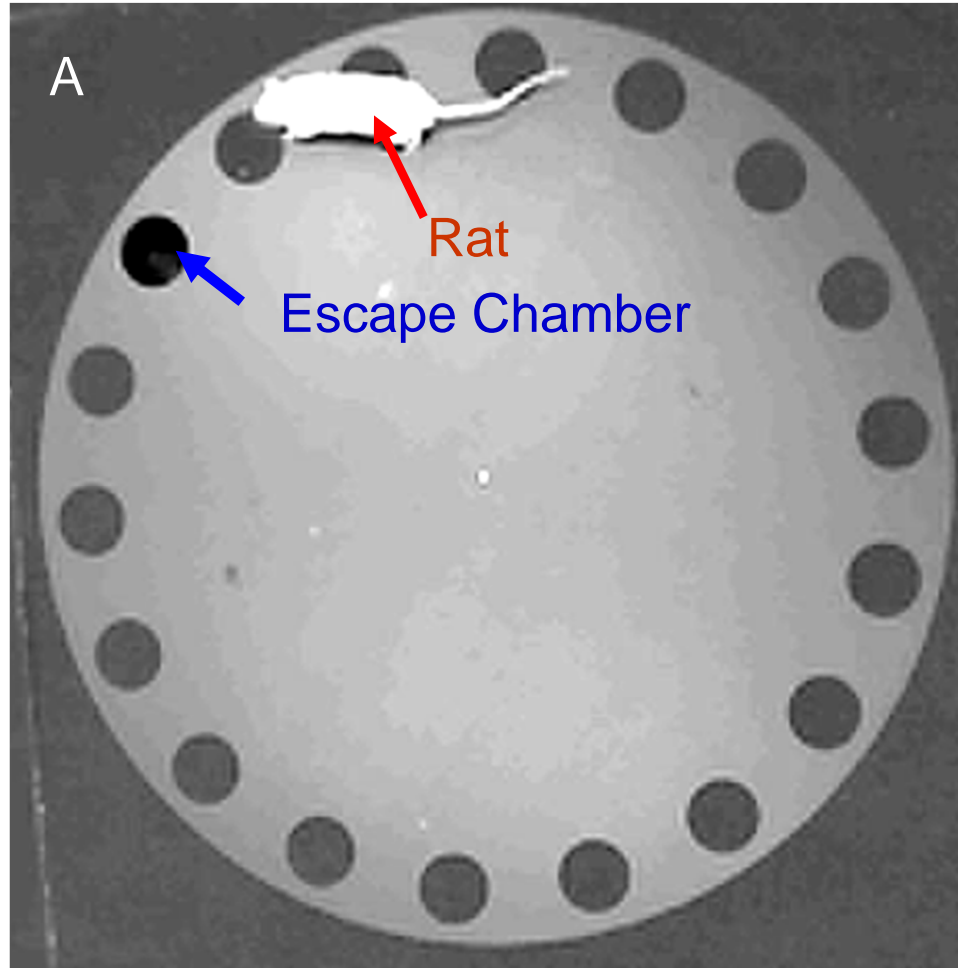
- **Ki67-Proliferation Marker**

**B** Ki67 Cell Density - Sham vs Noise

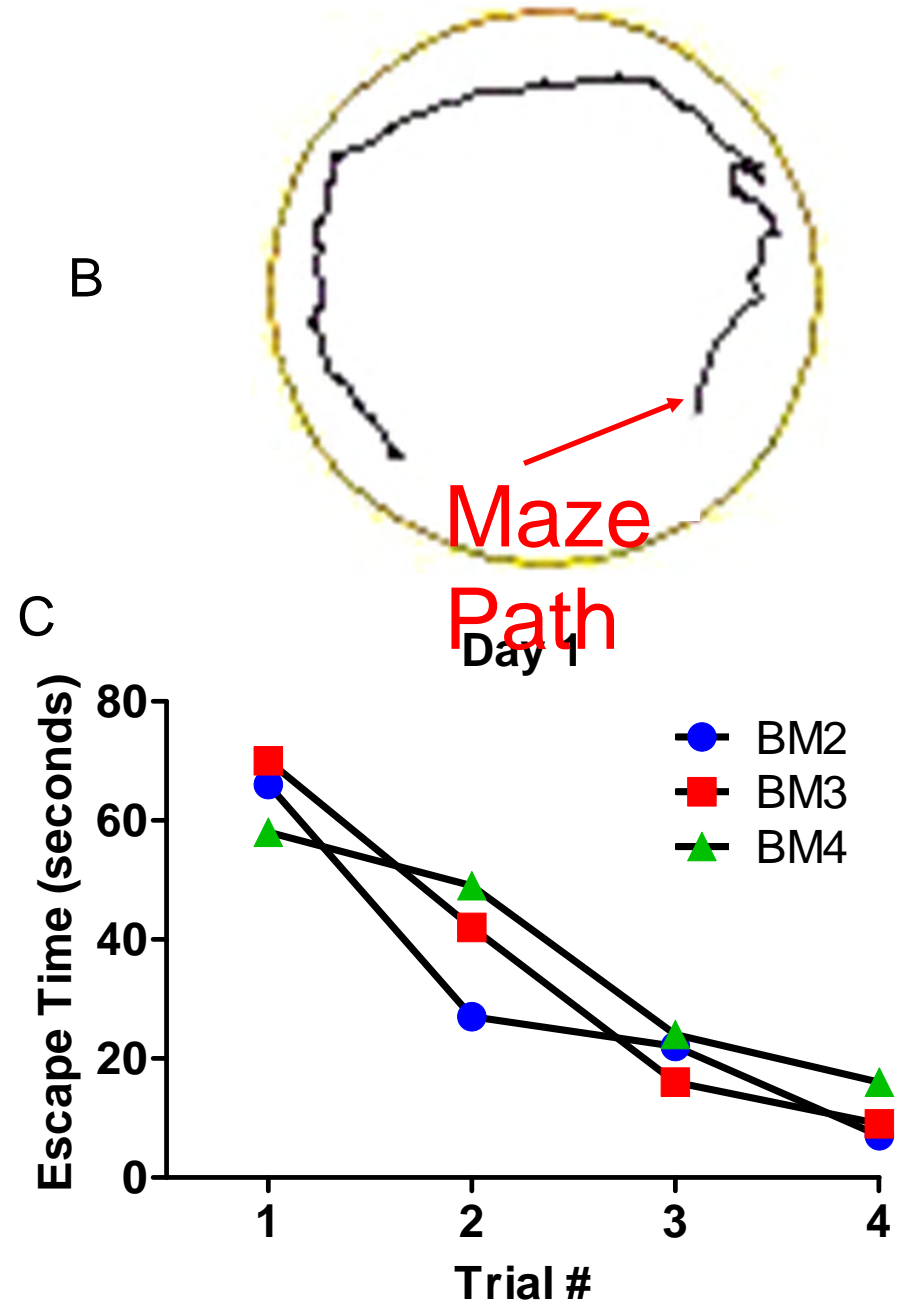


# Barnes Maze Spatial Learning

- Acquisition & Retention
- Find Car in Parking Lot!



Barnes Maze

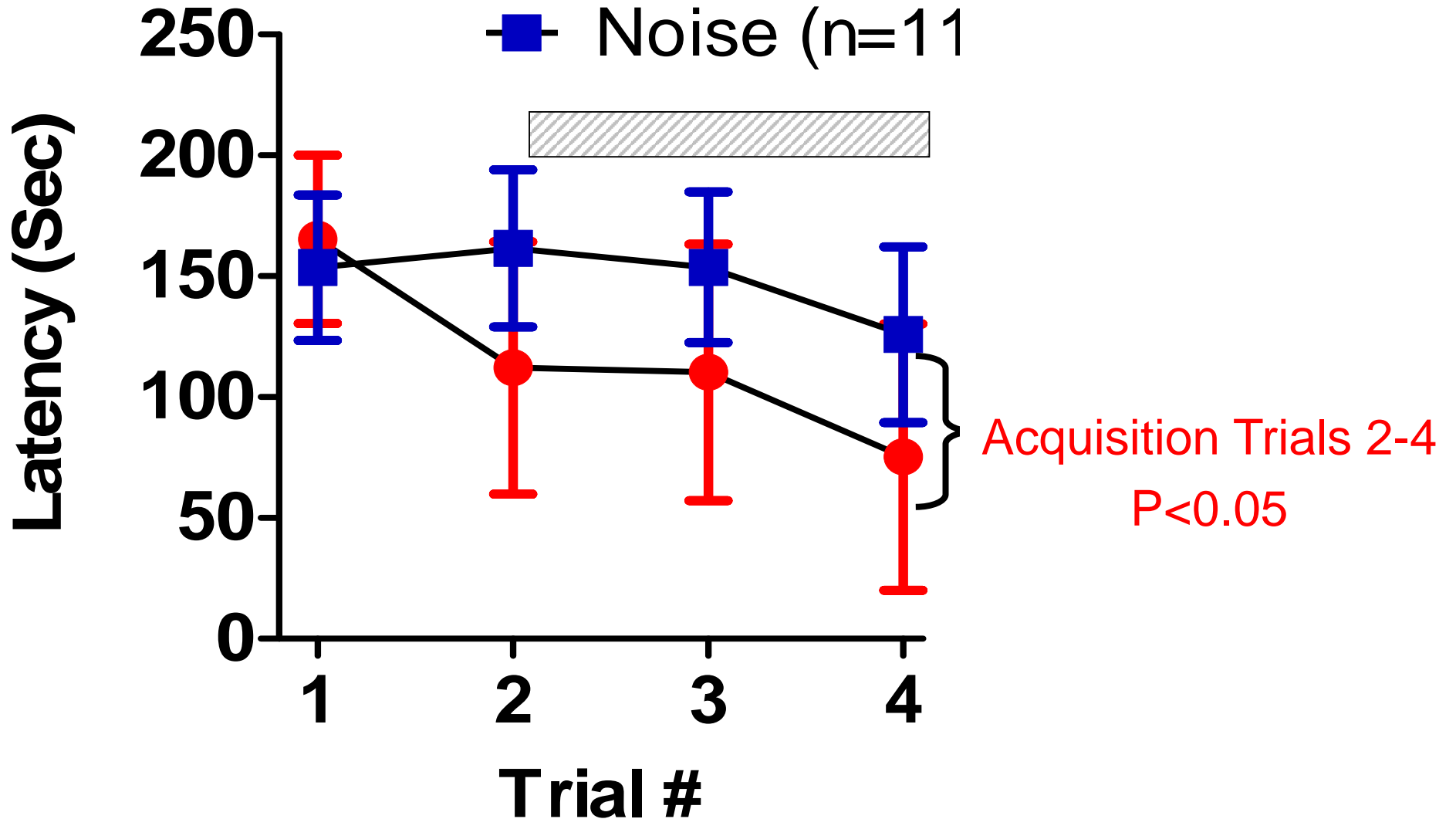


# Barnes Maze Post-Noise Exposure

● Memory Acquisition

● Control (n=5)

■ Noise (n=11)



# Thank You

## Questions & Discussion

