Tinnitus: Risk factors from noise trauma

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Tinnitus Prevalence in the General Population

- Tinnitus in adults is estimated to range from 10-15% (Hoffman and Reed 2004)

- European estimates show that 7-14% of the population have talked to their physician about tinnitus and 1-4% suffer from disabling tinnitus (Vesterager, 1997)

- Tinnitus affects 35-50 million people in the US and seriously afflicts 12 million individuals. For 2-3 million, tinnitus is debilitating (American Journal of Medicine 2010)

- 49% of US military personnel exposed to blast trauma experience tinnitus (Kara, et al 2007)
Hearing loss and the VA Population

- 50% soldiers exposed to blast develop hearing loss and tinnitus
- Hearing loss and tinnitus top VA disabilities
- VA will spend over 1 Billion on compensation related to hearing loss/tinnitus
- Costs will exceed 2 billion by 2014
Debilitating Tinnitus: Case 1

- Adult male with normal hearing
- Severely injured when a wheel rim separated
- Family described a sound similar to a cannon
- Result was permanent hearing loss and tinnitus in the exposed ear
Debilitating Tinnitus: Case 2

- Adult male at construction site
- Hit in head with 20,000 pound container
- Skull and temporal bone fracture
- Result: permanent unilateral tinnitus, chronic dizziness, and headaches
Debilitating Tinnitus: Case 3

- Adult male
- Automobile accident front and side airbag deployed
- No serious injury reported other than face going numb at time of accident
- Result: permanent unilateral tinnitus and collapsed sound tolerance
Tinnitus not new

• Ancient Egyptians
  • believed tinnitus was a symptom of a bewitched ear and developed medicinal oils and herbs that were infused into the outer ear canal as a treatment

• Aristotle and Hippocrates
  • Fathers of Masking: In 400 BC realized that a “greater” sound could drive out the lesser sound of tinnitus and suggested it as a potential treatment

• Babylonian Talmud
  • Ancient Hebrew Text describes the curse of “Titus” as a buzzing in the brain that responds to sound therapy to aid in habituation
Why does the problem of tinnitus persist?

- Tinnitus is a symptom with often unknown etiology
- Tinnitus is strongly associated with hearing loss but not all individuals with hearing loss have tinnitus
- Tinnitus definition unclear because of discrepancy between percept and disability
- Two competing viewpoints
  1. The reaction to the sound
  2. The tinnitus sound signal itself
What can we learn about Tinnitus from animals?

• The biological mechanisms of tinnitus are likely to be present in other species

• Drug induced tinnitus can be applied to animals

• Animals can be used to study the role of hearing loss on tinnitus

• Therapies can be evaluated in animals to test efficacy and safety
Animal Models of Tinnitus

- **Lick Suppression**
  - Jastreboff (shock suppression 1988)

- **Operant**
  - Heffner (Shock Avoidance, Reinforced Licking 2002)
  - Bauer-Brozoski (Suppression, food reinforcement 2003)
  - Ruttiger (Liquid food reinforcement 2003)
  - Guitton (shock avoidance, 2003)

- **Startle Reflex**
  - Turner (2006)
Is Salicylate Induced Tinnitus a Central Phenomenon?
3 Dimensional Rat Scan in Quiet vs Drug Treatment

- Nose
- Orbit
- Brain
- Cerebellum
- Forelimb

Images showing the scan results in different areas of the rat brain.
MicroPET inferior Colliculus and Auditory Cortex

Paul, Lobarinas et al 2009
Quantification

Mean Metabolic Change in IC relative to Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percent Baseline Change</th>
</tr>
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<tbody>
<tr>
<td>Real Sound</td>
<td>2.5% IC right, 3.0% IC left</td>
</tr>
<tr>
<td>Salicylate 250 mg/kg + Quiet</td>
<td>7.5% IC right, 8.0% IC left</td>
</tr>
<tr>
<td>Salicylate 250 mg/kg + Real Sound</td>
<td>0.5% IC right, 1.0% IC left</td>
</tr>
</tbody>
</table>
Sound, Salicylate and Brain Activity

- Quiet
- Real Sound
- Aspirin
- Left Damaged
MicroPet Studies

- Salicylate increased activity in the IC and AC under quiet conditions to levels similar to those under real sound.

- Under Salicylate no behavioral or DPOAE evidence of hearing loss was found.

- Unilateral noise trauma alone caused a decrease of activity under sound contralateral to the hearing loss.
What about Noise?
Gap Prepulse Inhibition of the Acoustic Startle (GPIAS)
Schematic of GPIAS

No gap condition

Carrier Noise (6, 12, 16, or 24 kHz NBN)

Startle Stimulus

Startle Response

50 ms silent gap

Tinnitus

Startle Stimulus

Startle Response

Carrier Noise (6, 12, 16, or 24 kHz NBN)
Gap Prepulse Inhibition

- No Gap = Large Startle
- Gap = Small Startle
- Gap + Tinnitus = Large Startle
Chronic Unilateral Tinnitus from 126 dB NBN centered at 16 kHz
Cyclobenzaprine from clinical observation to systematic evaluation

- **Uses**: muscle relaxant sleep aid and treatment for fibromyalgia
- **Mechanism**: structured like tricyclic antidepressant, shown in rats to activate the Locus Coeruleus in the brainstem (stress and panic)

Supported by a grant from the Tinnitus Research Initiative
Effect on the Startle Reflex and Hearing
Effect on GPIAS

Effect of Cyclobenzaprine on Noise Induced Tinnitus

- Baseline
- 20 days post noise
- Cyclobenzaprine .5 mg/kg

Percent GPIAS

Frequency (Hz): 6k, 12k, 16k, 20k, 24k
Blast Injury
Blast Tube

- Custom blast wave generator constructed from standard PVC piping rated at 250 PSI and covered with a metal shield

- Generator is sealed at one end with a threaded PVC cap and the other end with custom fabricated multilayered aluminum diaphragms

- A solenoid driven arrow was housed inside the tube and used to pierce the diaphragm at the desired pressure

- Using house air, blasts of 187-192 dB pSPL could be reliably produced (measured with a dedicated high-pressure probe)
Blast Trauma: Anatomy and Effects on Hearing

Effect of Blast Trauma on Startle Amplitude

- Baseline Bandpass
- Post Blast Bandpass

Startle Response Amplitude (mV)

Startle dB SPL

OHC

IHC

OHC

IHC
Tinnitus and Blast Trauma

Blast Induced Tinnitus (GPIAS)

- Baseline
- Post Blast (15d)

Percent GPIAS

Carrier Frequency (kHz)

- 6
- 12
- 16
- 20
- 24
Tinnitus Susceptibility

- Regardless of magnitude of hearing loss some animals do not show evidence of tinnitus

- Patients with chronic debilitating tinnitus report major life events before the onset of tinnitus

- Is there some other factor that predisposes individuals to tinnitus?

- Can modulating the state of the animal prior to the noise exposure change tinnitus susceptibility?
Summary

• Measures of tinnitus reaction do not appear to be correlated with perceptual characteristics of tinnitus

• Hearing loss is strongly correlated with tinnitus

• Animals exposed to noise develop similar hearing loss and tinnitus patterns as humans

• Animal models can provide a reliable alternative to study novel drug therapies for tinnitus and can help identify neural correlates
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Questions?