Hearing, Ribbon Synapses and Noise Induced Hearing Loss

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SPEAKERS: DR KEVIN SLEIGH
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Learning Aims

- Be aware of current epidemiology and criteria of NIHL as per Victorian work cover claims
- Understand recent advances regarding ribbon synapses in hearing and their importance in noise induced hearing loss (NIHL)
- Consider the potential implications of these advances for noise control including audiometric testing
- Be aware of the potential to medically treat patients with early detected NIHL
Outline

- My credentials
- The classic view of noise-induced hearing loss
- Synaptic injury – the new paradigm
- Evidence in animals
- Expected consequences in people
- Clinical evidence for hidden hearing loss
- Implications for hearing assessment
- Potential therapeutic approaches
The William Gibson Chair of Otolaryngology
The University of Melbourne

The Hon. Peter Howson
A long interest in neurotrophins and the ear
Neurotrophins and CI

Tycocinski et al, Hear CRC
Neurotrophins and regenerative surgery for Cochlear Implants

Big electrode

Few surviving neurons
Die-back of nerve ending
Neurotrophins and regenerative surgery for Cochlear Implants

Neurotrophins

Preserve Neurons

Many small electrodes

Regenerate nerve endings to connect with electrode
Normal

Deafened

Regeneration

OHCs

IHCs

Habenula Perforata

Wise et al, J Comp Neurol, 2006
NT Polymers to coat the CI: Polypyrrole

Richardson et al Biomaterials 2007
NT and Electrical stimulation augment neurite outgrowth

Thompson et al, J Controlled Release 2010
Noise exposure - the classic view

http://nanobio.snu.ac.kr/?mid=a_04
Audiogram

Hearing and hair cell loss
Hair cells - stereocilia
Endocochlear potential

(A) Stria vascularis

Perilymph (Scala vestibuli)
~0 mV 5 mM [K⁺]

Endolympth (Scala media)
~80 mV 150 mM [K⁺]

(B) Fibrocytes

2K⁺

Low K⁺ ~0 mV

Capillary

Na⁺,K⁺-ATPase

3Na⁺

2K⁺

K⁺

Na⁺

2Cl⁻

NKCC

KCNQ1/KCNE1

Perilymph

Stria vascularis

Endolympth

www.pnas.org
Travelling wave
Travelling wave: role of OHC - active mechanics
Noise exposure - the classic view

http://nanobio.snu.ac.kr/?mid=a_04
Noise and Synaptic injury-the new paradigm

Hocking et al, NEJM, 2015
“Synaptopathy” - the main features

- The effect is like a neuropathy, deafferenting the cochlea
- Thresholds are unaffected
- Amplitude growth is reduced
- This occurs at low noise levels, that were previously thought not to be very harmful
- The injury is permanent
- It is not detected on an audiogram, so has until now gone “undetected”
Thresholds unaffected
Amplitude growth reduced

Kujawa and Liberman, J Neurosci, 2009

Unaffected region

Affected region

Kujawa & Liberman
J Neurosci, 2009
Pathology: Reduced ribbon synapses on inner hair cells

Kujawa and Liberman, J. Neurosci, 2009
Inner hair cells
Kujawa and Liberman, J Neurosci, 2009
But why are thresholds not affected?

Auditory neurons with High Spontaneous Rate Low thresholds

Liberman et al, JARO, 2015
The “penumbra” effect

- Synaptopathy can occur in ears that also experience classical noise exposure.
- The region of synaptopathy surrounds the region with hair cell loss.
Perceptual Effects

- Clarity of supra-threshold sounds are compromised, particularly in the presence of competing noise.
- Translates to difficulty hearing speech in background noise.
- Tinnitus?
HLL risk anticipated at noise levels above recommended limits

- Typical stimulation paradigm to induce these changes are 95-100 dB noise for 2 hr
  (Guinea Pig: band-pass filtered 4-8 kHz – our group)

- 100 dB band pass filtered 8-16 kHz for 2 hours
  (Mouse, Kujawa and Liberman)
### Table 1. Estimates of noise exposure from plant and equipment

<table>
<thead>
<tr>
<th>Noise source</th>
<th>Range (dB)</th>
<th>Mid point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutting machines</td>
<td>83–93</td>
<td>88</td>
</tr>
<tr>
<td>Locomotives (electrical)</td>
<td>85–95</td>
<td>90</td>
</tr>
<tr>
<td>Haulage truck</td>
<td>90–100</td>
<td>95</td>
</tr>
<tr>
<td>Loaders</td>
<td>95–100</td>
<td>98</td>
</tr>
<tr>
<td>Long-wall shearers</td>
<td>96–101</td>
<td>99</td>
</tr>
<tr>
<td>Chain conveyors</td>
<td>97–100</td>
<td>99</td>
</tr>
<tr>
<td>Continuous miners</td>
<td>97–103</td>
<td>100</td>
</tr>
<tr>
<td>Loader-dumper</td>
<td>97–102</td>
<td>100</td>
</tr>
<tr>
<td>Fans</td>
<td>90–110</td>
<td>100</td>
</tr>
<tr>
<td>Pneumatic percussion tools</td>
<td>114–120</td>
<td>117</td>
</tr>
</tbody>
</table>

McBride, Occupational Medicine, 2004
How does this relate to the National Standards?

4. INTERPRETATION

4.1 In this National Standard for Occupational Noise [NOHSC: 1007(2000)]:

- $L_{Aeq,8h}$ (eight-hour equivalent continuous A-weighted sound pressure level in dB(A) referenced to 20 micropascals) means that steady noise level which would, in the course of an eight-hour period, cause the same A-weighted sound energy as that due to the actual noise over an actual working day. $L_{Aeq,8h}$ is to be determined in accordance with Part 1 of Australian/New Zealand Standard AS/NZS 1269\(^1\).

- $L_{C,\text{peak}}$ (peak noise level) means C-weighted peak sound pressure level in decibels measured by a sound level meter with a peak detector-indicator characteristic complying with Australian Standard AS 1259.1\(^2\).
Time-intensity trade-offs

3 dB time-halving rule

<table>
<thead>
<tr>
<th>Continuous dB</th>
<th>Permissible Exposure Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>85 dB</td>
<td>8 Hours</td>
</tr>
<tr>
<td>88 dB</td>
<td>4 hours</td>
</tr>
<tr>
<td>91 dB</td>
<td>2 hours</td>
</tr>
<tr>
<td>94 dB</td>
<td>1 hour</td>
</tr>
<tr>
<td>97 dB</td>
<td>30 minutes</td>
</tr>
<tr>
<td>100 dB</td>
<td>15 minutes</td>
</tr>
<tr>
<td>103 dB</td>
<td>7.5 minutes</td>
</tr>
<tr>
<td>106 dB</td>
<td>3.75 minutes (&lt; 4 min)</td>
</tr>
<tr>
<td>109 dB</td>
<td>1.875 minutes (&lt; 2 min)</td>
</tr>
<tr>
<td>112 dB</td>
<td>.9375 min (~ 1 min)</td>
</tr>
<tr>
<td>115 dB</td>
<td>.46875 min (~ 30 sec)</td>
</tr>
</tbody>
</table>


Centre for Disease Control Prevention (USA)
Conclusions - noise levels

- Hidden Hearing Loss has been observed at low "at risk" noise levels by occupation standards.
- But HHL can occur after a single exposure (≈ 2 hr).
- And it is permanent.
Detection of HHL

- **Gold standard - Physiological**
  - **Reduced amplitude:** Compound action potential amplitude of auditory nerve
- **Inferred - “Auditory processing”**
  - Signal (e.g. speech) in noise
Auditory brainstem response

Electrocochleography

http://www.hindawi.com/journals/ijoto/2012/852714/fig2/
Physiological Evidence - None published yet, but..

There is evidence that tinnitus may be associated with reduced N1 amplitude

Schaette and McAlpine (2011), replotted in Plack et al, Trend Hear 2014
Human perception consistent with HHL emerging

Effects of chronic noise exposure on speech-in-noise perception in the presence of normal audiometry

A J HOPE\textsuperscript{1}, L M LUXON\textsuperscript{2,3}, D-E BAMIOU\textsuperscript{2,3}

Air crews vs Airforce office staff
Audiometry normal
Speech-in-noise degraded in air crews
Diagnosis - summary

- **Definitive** requires ABR or ECochG (N1 amplitude)
- Difficult and time consuming
- Inferred can look like auditory neuropathy or processing disorders
Proposal on symptoms for persons at risk of HHL

- Temporary threshold shift after noise exposure
- Tinnitus after noise exposure
- More likely from a constant loud exposure (rock concert, Grand Prix) than impulse noise?
Therapeutic Possibilities: Neurotrophins?

Hocking et al, NEJM, 2015
Neurotrophin-3

- NT-3 is main neurotrophin in the adult cochlea
- It is produced by hair cells and supporting cells within the organ of Corti
- NT-3 provides both trophic support to spiral ganglion cells, and also promotes dendritic regeneration after injury
NT-3 controls dendritic regrow and directional

courtesy of Allen Ryan
NT-3 over-expression prevents HHL in the mouse

Proteolipid protein 1 promoter (Plp1) that targets cochlear supporting cells

Fig 7, WAN et al, ELife, 2014
Topical NT-3 diffuses into the inner ear

Richardson et al, Hear Res, 2005
Topical NT-3 to the inner ear has a physiological effect

Noushi et al, Otol Neurotol 2005
Topical Neurotrophins to cochlea modulate hearing

Sly et al, JARO, 2012. Chronic BDNF application to wound window
Will Topical NT-3 treat HHL?

- Unknown to date
- Experiments are underway in my Department, and in Harvard
- If it does work, will need to define therapeutic window, and
determine whether treatment protects or regenerates the peripheral dendrites
HHL is deafferentation of cochlear inner hair cells.

If affects clarity of sound but not audiometric thresholds.

Noise required (in animals) is within industry recommended levels.
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