The Neuroscience of Tinnitus from Cochlea to Brain

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What neurons in the hearing loss region do generates tinnitus, and stopping what they do suppresses it
Then why do 15% of tinnitus sufferers have normal audiograms?

Hypothesis:
Loss of ribbon synapses on high threshold auditory nerve fibers may predispose to tinnitus

Adapted from Kujawa and Liberman
*J. Neurosci* 2009
Drop correlates with AM detection (r=0.45, p=0.027)

- Severe high-threshold fiber loss at 5 kHz will reproduce the EFRs of control subjects with poor AM coding ability;
- An additional loss of ~30-60% of low-threshold fibers was needed to reproduce the EFRs of tinnitus subjects
- Why are these fibers important for tinnitus? (will return to this topic)
Animal models of Tinnitus

**Gap-Startle Method (GPIAS)**

If tinnitus fills the gap, the startle response returns (gap/no gap ratio = 1)

**Conditioning Methods**

(One example)

- Low-pitched sound (<3 kHz): go to black to avoid foot shock
- High-pitched sound (>4 kHz): go to white to avoid foot shock

After tinnitus induction, test preference in silence; if the animal hears tinnitus (which is a high-pitched sound), it will prefer the white box

Yang & Bao et al. PNAS 2011

Tinnitus neural activity begins in the cochlear nucleus

James Kaltenbach (Wayne State University and the Cleveland Clinic)
Susan Shore (University of Michigan)

Neural Plasticity is strongly expressed in the cochlear nucleus (two examples)
Homeostatic Plasticity in the Ventral Cochlear Nucleus

Normal Hearing

Auditory Inputs
VGULT1

Somatosensory Inputs
VGULT2

Results from the Susan Shore Laboratory
Zeng, Nannapaneni, Zhou, Hughes, & Shore (J. Neurosci, 2009)
(Glutamate transporters are tagged with antibodies for immunolabeling)
Homeostatic Plasticity in the Ventral Cochlear Nucleus

Deafened Ear

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(Glutamate transporters are tagged with antibodies for immunolabeling)
Stimulus timing dependent plasticity (STDP) in the Dorsal Cochlear Nucleus
(Results from the Susan Shore Laboratory)

More bimodal intervals are potentiating than depressing in animals with tinnitus

Spontaneous and synchronous neural activity is increased in tinnitus animals

Fusiform cell excitability is increased or decreased depending on the order and timing of bimodal inputs

Wu, Martel and Shore (J. Neurosci 2016)
Koehler and Shore (J Neurosci 2013)
Why is the loss of low threshold fibers important for tinnitus?

*LT fibers have much higher rates of spontaneous firing in quiet (50-90 spikes/sec) than do HT fibers (1-10 spikes/sec)*

This attribute of LT fibers may preserve the balance of excitation and inhibition in the cochlear nucleus

When such fibers are lost:

Homeostatic plasticity may downregulate inhibition to compensate for decreased ANF activity*
Decreased feedforward inhibition may unleash STDP on apical dendrites of DCN fusiform cells
Other inhibitory cell types or circuits in the DCN may be involved
Further changes occur at higher levels of the auditory pathway

*Sound-driven responses also increase: “Central gain”*
A PUZZLE:

Decreased GABAergic and glycinergic inhibition in the VCN, DCN, and IC should be expressed in the thalamus; Consistent with this, some neurons in the auditory thalamus (MGB) show increased excitability in tinnitus animals.

But Sametsky et al (2016) found:

(1) *Increased tonic inhibition* in a *subset* of MGB neurons, mediated by extrasynaptic GABA$_A$ receptors;

(2) These neurons switched to a burst firing mode

Low frequency oscillatory activity is distributed over the cortex in tinnitus:

Delta oscillations (< 4 Hz) recorded over auditory, temporal, parietal, sensorimotor, and limbic cortex of human tinnitus patients

One *hypothesis* is that bursting firing in MGB neurons may drive this activity

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Synaptic rescaling:

Salient features of sensory information are represented in interlaminar (layer to layer) interactions. Sensory codes of lesser salience activate these interactions weakly and are thus "deleted" by inhibition ascending from neurons in deep layers bursting at delta frequencies.

(Paraphrase of Carracedo et al 2013)

Applied to Tinnitus:

Low frequency oscillations distribute over several brain regions, disinhibiting local networks and integrating the tinnitus signal within these networks.

Neuromodulation affects whether one sees interlaminar interactions and delta rhythms

Rat and human slice preparations

Oscillation in layer 5
(Somatosensory/parietal slice)
Changes in Primary Auditory Cortex

Tinnitus neural changes affect electrocortical responses evoked by sound

(1) Frequency organization of the 40-Hz ASSR is modified in tinnitus


(2) Changes in the 40-Hz ASSR track residual inhibition depth

Roberts et al 2015 *Hearing Research*

(3) Modulation of ASSR and N1 responses by attention is attenuated in tinnitus

Paul Bruce and Roberts 2014 *Neural Plasticity*
Is this all there is to tinnitus?

Alters the balance of excitation and inhibition in the CN

Hi-spont fiber loss

Sergeyenko et al 2013
Alters the balance of excitation and inhibition in the CN

Is this all there is to tinnitus?

Hi-spont fiber loss

Neuromodulatory systems (example: PMT cholinergic system)

Auditory Cortex

Thalamus

Other Omissions:
Olivocochlear Pathway
Centralization

Sergeyenko et al 2013
Why is hidden hearing loss important?

May be sufficient to explain tinnitus without audiometric threshold shift

*Might also* explain cases of threshold shift without tinnitus

*JARO* 9:417-435
Tinnitus in adolescents

28.8 % of 170 adolescents in a private school in São Paulo Brazil experienced a psychoacoustically verified persistent tinnitus

High Prevalence of risky listening habits (~90%) in all adolescents

Audiograms (0.25 – 16 kHz) and otoacoustic emissions (to 12 kHz) were normal

Sound Level Tolerance was reduced by 11.3 dB in adolescent with tinnitus

Sanchez, Moraes, Casseb, Cota, Freire & Roberts (2016) Scientific Reports

Loss of inhibition in auditory pathways?
Increased central gain triggered by hidden hearing loss?
Fear of sound?
One-year follow-up (n = 54)
(Sanchez & Roberts ARO 2018 Submitted)

Study 2 parties and raves:
- 42.3% (Groups 2,3)
- 62.5% (Groups 1,4)
  (n.s.)

How do we explain tinnitus persistence and remission?

1. Intracochlear changes?
   - Suprathreshold ABRs
   - EFRs
   - Other temporal processing

2. Risk Behaviors?

Study 1 vs 2 parties and raves:
- 82.1% Study 1
- 53.7% Study 2
  (p = 0.001)

Study 2 parties and raves:
- 42.3% (Groups 2,3)
- 62.5% (Groups 1,4)
  (n.s.)

1 = repeaters (6/14, 42.9%)
2 = no tinnitus either test
3 = recovered tinnitus (8/14, 57.1%)
4 = new tinnitus

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Some take home messages

1. Loss of high-SR auditory nerve fibers may be crucial for tinnitus;

2. Such losses appear to add tinnitus to deficient temporal processing putatively caused by Low-SR fiber synaptopathy;

3. Eliminating the tinnitus sound by neuroplastic remodeling will be difficult, because deafferentation is its initiating condition;

4. Neuromodulation plays an undetermined role;

5. Reactions to having tinnitus are modifiable;

6. Pharmaceutical shotguns not bullets;

7. Prevention of hearing injuries is the key to the problem of tinnitus
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