Animal Models of Tinnitus

Introduction
Pharmacological, cognitive and behavioral approaches are used to treat tinnitus. These have not met with much success due to our poor understanding of its etiology and difficulty to objectively measure it. We developed a behavioral model of animal-induced tinnitus that includes the ability to measure physiological changes induced by tinnitus and reversed by drug treatment.

We are currently exploring a variety of drugs (Lidocaine, Steroids, Anti-Oxidants) as well as a variety of delivery methods (IV, intra-cranial, nanoparticles).

Most human imaging studies (PET, MRI) have implicated the inferior colliculus of the auditory midbrain in the generation of tinnitus. Our preparation consists of an awake rat with a chronic multi-electrode array implanted in the brain. In the same animal, we measure neural activity before, immediately after and several weeks after noise trauma-induced tinnitus, and after intravenous injection with Lidocaine, while simultaneously recording the existence of tinnitus through behavior.

General procedure
- Implanted with electrode array and a permanently implanted carotid catheter
- Measure single neuron activity across the span of auditory midbrain
- Measure extracellular action potential
- Measure intracellular action potential
- Measure high-voltage or low-voltage responses
- Compare neural activity with and without drugs
- Characterize molecular changes in cortex

Materials and methods
- Multi-electrode in plant in central nucleus of inferior colliculus of awake rats
- Catheter in jugular vein to deliver drug, or intra-cranial injection for nanoparticles
- Neural activity recorded with 168 electrodes in an array consisting of 16 kHz (4, 17 kHz)

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Results
Gap detection deficit as evidence of tinnitus
The gap detection ability of rats before and after noise trauma is measured, using a gap detection paradigm similar to Turner et al., 2009. The idea is that if it is hard to hear a silent gap in the continuous pure tone stimulus, from a continuous, frequency-modulated pure tone. A brief burst of a sound will act as a “masker.” The rat's ability to detect another stimulus that follows the masker will reduce the startle reflex (this is called gap-adeptation). In our case, a silent gap is present 50% of the time before the startle stimulus. We compare the startle reflex with and without a gap.

Figure 3. Left: Startle reflex as a function of a silent gap in a tone background, measured before, just after and 1 week post-tinnitus. Right: Just after trauma, the major breaking deficit is at the center of the trauma frequencies, 16 kHz. 3 weeks post-tinnitus, the behavioral evoked response for tinnitus is 16 kHz, with no obvious damage to the cortex.

Auditory Brainstem Response: the animal is not just deaf
The auditory brainstem response (ABR) is correlated with the health of the eardrum part of the auditory pathway. After the measurement of ABR before, just after and 1 week after trauma, the ABR typically recovered to the pre-trauma levels within a few weeks.

Figure 5. Summary ABR thresholds before and after trauma, with no obvious damage to the cortex.

Electrophysiology
Increased excitability
Brain stimulation using electrical stimulation in the contralateral ear for 3 sec before the sound and for 3 sec after the sound stimulation.
Before trauma: 200 ms, post-trauma 60 ms. Just post-trauma: before 45 ms, post-trauma 10 ms. 3 weeks post-trauma: before 113 ms, post-trauma 113 ms.

Response to broadband, complex sounds
Auditory evoked potentials form a basis for the Fourier domain description of sound spectra.
- They are characterized by spectral density and periodicity or angular frequency.

Receptive fields
Before trauma, we found receptive fields from 60 kHz to 35 kHz, about an octave in bandwidth.
- The receptive fields were hyperexcitable (rate of excitation to inhibition), as seen before and after trauma.

Receptive field of collicular cells of the awake rat
Receptive field 3 weeks post-trauma

Immunohistochemistry for CREB and phospho-CREB

Changes in inhibitory neural circuitry

Changes in behavior and molecular expression of drugs