speculated that these neuronal activity changes might lead to central plasticity for tinnitus perception. Also, the balance between excitatory neuron activity and inhibitory neuron activity at the AC was thought to be directly related with tinnitus generation and disappearance.

PD 188

Neurochemical Profiles from the Auditory Cortex of Rats with Behavioral Evidence of Tinnitus: Assessment with High Resolution Magic-Angle Spinning Proton Magnetic Resonance Spectroscopy

Avril Genene Holt; Matthew Galloway; Farhad Ghoddoussi; Anthony Cacace
Wayne State University

Based on advancements in tinnitus research over the last 3 decades, it is reasonable to suggest that a prominent theory of tinnitus neuropathology subsumes a neurochemical basis. This view is consistent with converging evidence that partial or complete peripheral deafferentation from acoustic trauma results in a cascade of changes in the peripheral and central nervous system that induces an imbalance between inhibitory and excitatory inputs to auditory neurons at various levels in the auditory pathways.

Male Sprague Dawley rats were divided into noise-exposed and non noise-exposed groups; auditory thresholds and Gap detection assessments were determined for each group both before and after exposure to a tone (16 kHz, 106 dB SPL, 1 hr). Neurochemical profiles were determined one month after noise-exposure with high resolution magic angle spinning proton magnetic resonance spectroscopy (HR-MAS 1 H-MRS) at 11.7T *ex vivo*. Frozen tissue samples (4–7 mg) were placed into a zirconium rotor containing 8 µL of buffer (pH = 7.4), then into a Bruker 11.7T Avance 500 MHz spectrometer maintained at 4°C, spun at 4.2 kHz, at a spatial orientation of 54.7° (the magic angle) relative to the longitudinal magnetic field (B_0). Tissue spectra were acquired with a Carr-Purcell-Meiboom-Gill (CPMG) echo train acquisition sequence. Concentrations of MR visible metabolites were corrected for tissue weight and were expressed as nmol/mg tissue weight.

Using HR-MAS 1H-MRS, we obtained unbiased neurochemical profiles of intact auditory cortex tissue from noise-exposed animals with behavioral evidence of tinnitus. We found significant increases in alanine (ALA, +41%) and glutathione (GSH, +43%) as well a decrease in glycerophosphorylcholine (GPC, -19%) and their corresponding ratios to total creatine. Although the absence of changes in glutamate, glutamine, and GABA argue against putative lesions in the auditory cortex of noise-exposed animals, elevated ALA is consistent with increased transamination of pyruvate (i.e., the end-product of glycolysis) or increased decarboxylation of aspartate. Similarly, increases in GSH, the major antioxidant in the brain, may represent a compensatory response to cellular oxidative stress. Decreases in GPC, generated during the production of inflammatory mediators from membrane phospholipids, may reflect decreased production of inflammatory lipids or increased demand for GPC in membrane phospholipid biosynthesis. Overall, the results suggest neuroplasticity as measured by ^{1}H-MRS in auditory cortex from an animal model of noise-induced tinnitus, possibly associated with disrupted pyruvate metabolism, oxidative stress, and membrane phospholipid turnover. Future studies will focus on neurochemical changes in other brain regions-of-interest.

Funding
Grant 1I01RX001095-01U.S. Dept. of Veterans Affairs to AGH Grant T42 OH008455 from the National Institute of Occupational Safety and Health, Center for Disease Control and Prevention

PD 189

Neuronal Activity in a Model of Noise Induced Tinnitus: A Longitudinal Study

Avril Holt[1]; Farhad Ghoddoussi[1]; **Antonela Muca**[1]; Aaron Apawu[1]; Mirabela Hali[1]; Sharowynn Wilson[1]; Anthony Cacace[2]; Bruce Berkowitz[1]
[1]Wayne State University School of Medicine; [2]Wayne State University

Background

Tinnitus, "ringing in the ears", is the number one service related disability for Veterans. Currently, no objective biomarkers exist for tinnitus. We have previously demonstrated that both noise- and drug-induced tinnitus result in behavioral deficits in Gap inhibition of the acoustic startle reflex (GiASR) 48 hours following tinnitus induction. Manganese-enhanced MRI (MEMRI) uses the paramagnetic manganese (Mn^{2+}) ion, a contrast agent and calcium channel probe, to assess calcium channel linked neuronal activity. Tinnitus has been associated with increases in neuronal activity, and we have previously reported increases in Mn^{2+} uptake in the inferior colliculus (IC) following acute tinnitus induction. We tested the hypothesis that enhanced manganese uptake (MEMRI) will be positively correlated with Gap detection deficits (GiASR) over time.

Methods

In male Sprague Dawley rats, Mn^{2+} uptake was assessed in 12 regions of interest (ROIs) from MEMRI data (n = 10/group) before, and 1, 28, and 84 day(s) following acoustic trauma (16 kHz, 106 dB SPL, 1 hour). ASR testing was performed twice per week in the same animals across six frequencies (4, 8, 12, 16, 20 and 24 kHz). Each animal was administered a non-toxic dose of 66 mg/kg of $MnCl_2$ (i.p) 24 hours prior to each imaging session (7T Clinscan). In a subgroup of rats, Mn^{2+} clearance from ROIs was measured after 1, 14, 28, 42 and 84 day(s).

Results

All animals had unimpaired pre-pulse ASR responses before and after noise exposure. Deficits in Gap detection were evident in noise animals at all time points except the first week after noise exposure (20 kHz, 60 dB). In contrast to our previous findings in acute models of tinnitus, later time points in this study demonstrated supernormal Mn^{2+} uptake in the paraflocculus at 4 (14% greater) and 12 (7% greater) weeks. Twelve weeks following noise exposure the IC and medial

geniculate body also exhibited significant increases in Mn^{2+} uptake. The clearance rate of Mn^{2+} was found to be similar between subdivisions of the IC at all examined time points.

Conclusions

The present data further strengthen our hypothesis that chronic tinnitus without permanent hearing loss is associated with increases in calcium channel linked neuronal activity. Differential uptake in brain regions may have initially been associated with hearing loss and later with tinnitus, paralleling the progression of a temporary threshold shift. These results suggest the need for longitudinal assessment of tinnitus progression using MEMRI and GiASR biomarkers when evaluating therapeutic intervention.

Funding

Grant 1I01RX001095-01 U.S. Dept. of Veterans Affairs Grant T42 OH008455 from the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention

PD 190

Hyperacusis and tinnitus: A challenge for age dependent hearing loss?

Lukas Rüttiger; Dorit Möhrle; Marlies Knipper
University of Tübingen

Progressing loss of auditory sensation is a major problem of aging populations. In humans, loss of hearing function can be observed through increased thresholds, altered sound processing of temporally and spatially modulated auditory stimuli, but also through abnormal perception of above-threshold sounds or phantom perceptions, like hyperacusis and tinnitus (for review see Knipper et al., 2013).

Previous studies on the rodent had already demonstrated the degeneration of auditory fibres following mild auditory trauma (Kujawa and Liberman 2009, Furman et al. 2013, Rüttiger et al., 2013, Singer et al., 2013) and over age (Sergeyenko et al. 2013).

We here challenge the question if a mild auditory trauma induces hyperacusis or tinnitus in differentially aged animals. Hyperacusis and tinnitus sensation were tested using a behavioral approach (Rüttiger et al. 2003), and hearing function was studied using auditory evoked brainstem responses (ABR) and otoacoustic emissions (DPOAE). To gain insight into the central brainstem function above-threshold responses to click and frequency specific stimuli were analysed in detail for fibre recruitment and latencies of ABR wave deflections (wave amplitudes and latencies). Results from behavior studies on differentially aged rats, before and after auditory overstimulation, are presented in correlation with individual hearing functions and morphological specifications of the hair cell molecular phenotype and hair cell ribbon loss.

Funding

Supported by Action on Hearing Loss, RNID G45 (Rü)

PD 191

Reflex-Based Gap Measurement of Tinnitus in Humans: Results of a Preliminary Study

Jeremy Turner[1,2,3]; Deb Larsen[1]
[1]SIU School of Medicine; [2]OtoScience Labs; [3]Illinois College

Since 2006 researchers have been using gap-based startle reflex approaches in the attempt to quantify tinnitus in animal models and humans. This test, referred to as the Gap Test (or gap prepulse inhibition of acoustic startle; GPIAS), makes use of the startle reflex and the fact that stimuli presented approximately 100ms before a startle pulse will inhibit that reflex automatically. Under normal (non-tinnitus) conditions, silent gap cues placed 100ms before a startle will inhibit the reflex as a function of the salience of the silent gap cue. The Gap Test is based on the premise that tinnitus specifically disrupts one's ability to hear silence and that when tinnitus is present the silent gap cue has a reduced signal-to-noise, thereby degrading the capacity for silent gap cues to inhibit the reflex. Human subjects with tinnitus and hearing-matched controls were tested for gap inhibition of eye-blink startle reflex using background sounds that were 5 and 15 dB above threshold. Data from several dozen subjects will be reviewed and we will highlight the relative merits and shortcomings of this reflexive technique for auditory assessments, hearing loss, hyperacusis, and tinnitus.

Funding

Grant support provided primarily by the Tinnitus Research Consortium to Southern Illinois University School of Medicine, but also through a Neurosensory Research Award from the US Department of Defense Psychological Health and Traumatic Brain Injury Program to OtoScience Labs.

PD 192

Towards a Global Consensus on Outcome Measures for Clinical Trials in Tinnitus

Deborah Hall
University of Nottingham

Introduction

In Europe alone, over 70 million people experience tinnitus. Despite its considerable socioeconomic relevance, progress in developing successful treatments has been limited. The European Union has approved funding to create a pan-European tinnitus research collaboration network (2014–2018). The goal of one working group is to establish an international standard for outcome measurements in clinical trials of tinnitus. This is the COMiT initiative (Core Outcome Measures in Tinnitus). Importantly, this would enhance tinnitus research by informing sample-size calculations, enabling meta-analyses and facilitating the identification of tinnitus sub-types, ultimately leading to improved treatments. Clinical effectiveness is judged according to change in primary outcome measures, but because tinnitus is a subjective condition, the definition of outcomes is challenging and it remains unclear which distinct aspects of tinnitus (i.e. 'domains') are most relevant for assessment. The development of a minimum outcome reporting standard would go a long way to addressing these problems. And COMiT is

ABSTRACT BOOK

Association for Research in Otolaryngology

39th Annual MidWinter Meeting

Saturday, February 20-
Wednesday, February 24, 2016

Manchester Grand Hyatt

San Diego, CA