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.

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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.

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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

ABSTRACT BOOK

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