Introduction

Chronic tinnitus is a commonly encountered and inadequately understood pathological condition affecting 15-15% of people, with severe life-altering effects in 1-2%. Current therapeutic strategies largely focus on classical auditory pathways from cochlea to cortex. Tinnitus develops over time, and new evidence indicates interactions of multiple plastic neural systems including, but not limited to bilateral non-sensory and non-auditory auditory pathways of the brain. For example, our lab and others have demonstrated hippocampal plasticity in early and later stages of tinnitus. Studies (Glasco et al., 2009; Jaffe et al., 2008) have shown strong causal linkages between audiogenic and hippocampal auditory information via dentate granule cell activity (Paxinos & Watson, 2019). For example, in a series of planned comparisons were made using Excel software. A series of planned comparisons were made using a planned comparison's methodology. In the current study, male rats were exposed to acute bilateral high-intensity noise (16 kHz, 115 dB, for 1 hr). Western blot analysis was used to assess neural plasticity in multiple brain regions 30 min after exposure. Expression of biomarkers of plasticity included CaMK-dependent protein kinase (CaMK), which was linked to memory consolidation in the hippocampus, amygdala, and corticostriatal (C5, calmodulin-dependent kinase (CaMK), which was linked to activation of transcription factors (CAMK) or the amygdala, and nuclear transcription factors (CaMK) or the amygdala, which was linked to long-term memory in the hippocampus, and the amygdala identified as corresponding to auditory stimuli. Our results confirmed a multi-system modulation in response to the noise trauma in brain regions, including the regions Cb, nAC, Hc, and vertical diagonal band among others with respect to these biomarkers. The region consequently exhibiting plasticity in multiple biomarkers in the medial entorhinal cortex, a critical bridge between cortical and limbic structures. These data indicate that additional regions and additional biomarkers should be strongly considered in the design of new therapeutic interventions.

Behavioral Paradigm

Methods

Subject: 48 animals were used by the UT DVC. Male Long-Evans rats were housed on a 12:12 light-dark cycle in a temperature-controlled room, with food and water available ad libitum.

Behavior: Rats were handled daily for 3 wk while maintaining a constant environment to minimize stressors.

Noise Exposure: Acute noise trauma was induced bilaterally (18 kHz, 115 dB) for 1 hr.

Western Immunoblotting and Analysis for CaMK4, CaMK2β, and PKG-1α: Rats were sacrificed 30 min after time in the sound booth ended, a time point that is important for tinnitus development.

Medial Temporal Lobes: Acute noise trauma significantly down-regulated protein expression in the dorsal hippocampus and the medial entorhinal cortex.

Auditory-linked regions: Acute noise trauma down-regulated protein expression in the nucleus accumbens compared to controls.

Effects of Noise Trauma on PKG-1α

Medial temporal lobes: Acute noise trauma caused a trend for up-regulation of protein expression in the ventral hippocampus compared to controls.

Future Directions

• Follow cortico-striatal circuitry role into tinnitus development.

• Differentiate cells expressing plasticity biomarkers with dual labeling.

• Follow time course of cell death and ablation as potential time points for further molecular assays involving cytokines and trophic factors.

Conclusions

Effects of Noise Trauma on CaMK2β expression

Medial temporal lobes: Acute noise trauma significantly down-regulated protein expression in the ventral hippocampus compared to controls.

Auditory-linked regions: Acute noise trauma had no immediately significant effect on these regions.

Other non-classical regions: Acute noise trauma significantly down-regulated protein expression in the prefrontal cortex.

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Evidence for Multisystem Plasticity in Non-Classical Auditory Regions in Early Stages of Tinnitus


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Conclusions

Effects of Noise Trauma on CaMK4 expression

Medial temporal lobes: Acute noise trauma significantly down-regulated protein expression in the dorsal hippocampus and the medial entorhinal cortex.

Auditory-linked regions: Acute noise trauma induced a trend for up-regulation in the central nucleus of the inferior colliculus, but not the auditory cortex.

Other non-classical regions: Acute noise trauma significantly down-regulated protein expression in the nucleus accumbens compared to controls.

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