Tinnitus-inducing noise trauma and D-cycloserine alter amydalo-hippocampal excitatory biomarkers


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Introduction

Tinnitus, a perception of sound affecting 1 in 5 people, is a pathology most commonly caused by noise trauma. Patients with chronic tinnitus are difficult to treat, with poor characterization of the mechanisms initiating and maintaining the condition. The lab observed dorsal hippocampal plasticity in the early stages of tinnitus (Goble et al., 2009), showing a strong causal linkage between the amygdala and hippocampus in auditory-likelinked plasticity (Farmer & Thompson, 2012; Donzis & Thompson, 2014). The current project investigates the initial plasticity mechanisms leading to this disorder and to determine if D-cycloserine (DCS), a partial NMDAR agonist, can reduce this plasticity. Specifically, our study utilized amygalo-hippocampal circuitry in the early stages of tinnitus and looked at DCS as a potential pharmacological intervention for this disorder in an experimental rat model. To assess excitatory and inhibitory signaling in these limbic regions, Arc and GAD 65+67 protein expression were evaluated in male rats (n = 20) after bilateral exposure to acute high-intensity noise (115 dB, for 1 hr). Western blot analysis and immunohistochemistry confirmed Arc expression, an activity-related IEG protein, was significantly up-regulated in both the amygalo complex and dorsal hippocampus post-noise trauma. The results especially changes in expression of either of these IEGs, the biophysical enzymes required for GABAergic inhibition, occurred post-noise trauma. DCS (5 mg/kg, p. o.; to pre-contract pre-treated) prevented up-regulation of Arc expression in the amygdala due to noise trauma, hereby facilitating an exploration of plasticity within the amygdala. However, DCS alone up-regulated Arc expression within the dorsal hippocampus (see also Donzis & Thompson, 2014), and did not reduce Arc expression from noise trauma, suggesting that endogenous hippocampal Arc was not a saturating concentrations post-noise trauma. These regional differences may be further investigated the role of the glutamate-excitatory neurotransmitter, Arc, in noise trauma-induced tinnitus. Our results corroborate other findings that indicate both hippocampal and amygdala, non-classical auditory nuclei, are involved in neural plasticity underlying tinnitus.

Methods

Hypotheses

1. Acute noise trauma, excitatory cell divisions in the amygdala-hippocampal circuitry will exhibit plasticity.
2. D-cycloserine (DCS), an NMDAR partial agonist, will reduce tinnitus-related plasticity within the amygdalo-hippocampal circuitry.

Figure 1. (adapted from Kandratavicius et al., 2012). The metabolic/gene expression of Moraxella (MW) can follow the classical pathway to amygdala, or can branch off and activate corticostriatal pathways more directly, rather than via the entorhinal cortex. These two pathways may be implicated in excitability, with parallel processing occurring between the amygdalo-hippocampal circuits.

Figure 2. Example of place-field stability for control (gray) and DCS (black) groups. The stable map of the rat’s path (dark lines) on the maze is displayed along with the single-unit firing positions (black dots) for each treatment condition, showing the spatial consistency of the robust place fields.

Figure 3. Regions of Interest: Dorsal Hippocampus, Amygdala and Primary Auditory Cortex.

Figure 4 (A1-C2). Evidence of rapid plasticity in Arc and GAD protein expression within the amygdalo-hippocampal circuitry. There were consistent regional similarities, indicating that a simplistic interpretation (e.g., noise trauma induces rapid plasticity throughout the circuit) is not well supported. DCS altered Arc protein expression within these limbic regions. DCS also altered tinnitus-related plasticity within the amygdalo complex, a region of the non-classical auditory pathway, indicating it may have value as a potential treatment for tinnitus. Normalized data are presented as mean ± S.EM.

Figure 5 (A-D). Immunohistochemical analysis of the effect of scale noise trauma on Arc 3.1 protein expression within the dorsal hippocampus, amygdala, and auditory cortex. Acute noise trauma appears to increase Arc 3.1 immunoreactivity within the CA1 and dentate regions of dorsal hippocampus as well as within the amygdalo complex. A. Control and noise-exposed sections of dorsal CA1 imaged at 48 h after trauma. B. Control and noise-exposed sections of the amygdalo complex imaged at 48 h after trauma. C. Control and noise-exposed sections of primary auditory cortex imaged at 48 h after trauma.

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