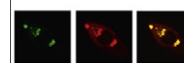


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Review

Endogenous dynorphins, glutamate and N-methyl-D-aspartate (NMDA) receptors may participate in a stress-mediated Type-I auditory neural exacerbation of tinnitus

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ABSTRACT

Tinnitus is the phantom perception of sounds occurring in the absence of an external auditory stimulus. Tinnitus: [1] affects 50 million individuals, [2] often results from acoustic trauma and, [3] is very often exacerbated under stressful conditions. Tinnitus may result from lesions occurring at any location in the auditory system, but its mechanisms are poorly understood. Evidence is provided supporting an endogenous dynorphin-mediated potentiation of glutamate excitotoxicity at cochlear Type-I auditory dendrites that may well exacerbate chronic subjective neural-generated tinnitus during periods of heightened stress. The proposed mechanism is based on the following: [1] lateral efferent olivocochlear (LEOC) axon terminals contain endogenous dynorphin neuromodulators and are presynaptic to cochlear Type-I auditory dendrites that bear both κ -opioid and N-methyl-D-aspartate (NMDA) receptors/binding sites; [2] the release of presynaptic LEOC dynorphins is likely to be triggered by sympathetic stress via the locus coeruleus; [3] sodium salicylate induces an acute excitotoxicity by potentiating glutamate neurotransmitter effects at cochlear NMDA receptors, resulting in a Type-I auditory neural-generated tinnitus; [4] dynorphins participate in central NMDA-receptor-mediated excitotoxic inflammation; and [5] κ -opioid receptor ligands also modulate Type-I auditory neural activity by potentiating glutamate at cochlear NMDA receptors. A stress-activated release of dynorphins into the cochlea could potentiate the already excitotoxic effects of glutamate, producing: [1] hyperacusis, together with an acute exacerbation of [2] chronic

Abbreviations: ACTH, adrenocorticotrophic hormone; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CAP, auditory whole nerve compound action potential; CNS, central nervous system; COX-2, cyclooxygenase-2; ESA, ensemble spectrum of spontaneous neural activity; dB, decibel; dBA, decibel A scale (low frequency filtered-SPL); i.c., intracochlear; IHC(s), inner hair cell(s); i.v., intravenous; LEOC, lateral efferent olivocochlear; LC, (nucleus) locus coeruleus; LSO, lateral superior olive; MEOC, medial efferent olivocochlear; NMDA, N-methyl-D-aspartate; Nor-BNI, nor-binaltorphimine; OHC(s), outer hair cell(s); SPL, sound pressure level; SOC, superior olivary complex

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aberrant Type-I neural activity and [3] a worsening of the activity-dependent central auditory neural plasticity changes that must certainly generate the perception of tinnitus. Treatment options are discussed.

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1. Introduction

One goal of our investigations has been to identify relevant neuropharmacologic substrates in the auditory periphery that are likely to exacerbate many of the symptoms of neural-generated forms of tinnitus. Subjective tinnitus often arises from an altered profile of peripheral auditory activity that then leads to subsequent neural plasticity changes in tinnitus generators of the central auditory system (Mulders et al., 2011; Stolzberg et al., 2011). Conceivably,

pharmacological investigations of recognized receptor interactions with known or hypothesized peripheral and/or central neural correlates of tinnitus will lead to the development of new and effective drug treatment methods for the management of subjective tinnitus (Langguth et al., 2009).

First and foremost, what is subjective tinnitus? Subjective tinnitus is a serious clinical disorder, traditionally defined as the perception of sound (a tone, hum or hissing) occurring in the *absence* of an externally evoking auditory stimulus. Because subjective tinnitus occurs without a physical sound

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