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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] effects 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, adrenocorticotropic 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.

Contents

1. Introduction . . . 81
2. The lateral efferent olivocochlear (LEOC) system . . . 82
3. Endogenous opioid peptides: Dynorphins . . . 84
3.1. Endogenous dynorphins: Central nervous system (CNS) . . . 84
3.2. Endogenous dynorphins: Mammalian cochlea . . . 84
3.2.1. Dynorphin receptor/binding site interactions within the mammalian cochlea . . . 84
4. Stress and depression: Relation to tinnitus severity . . . 85
4.1. Endogenous dynorphins: Relation to stress . . . 85
4.2. Endogenous dynorphins: Relation to depression . . . 86
4.3. Endogenous dynorphins: Stress and tinnitus exacerbation . . . 87
4.3.1. Possible role of the nucleus locus coeruleus (LC) . . . 88
4.3.2. Locus coeruleus (LC): Modulation of Type-I auditory responses to sound . . . 88
4.3.3. Locus coeruleus (LC): Modulation of Type-I spontaneous discharge . . . 88
4.3.4. The locus coeruleus (LC): Stress and cochlear dynorphins . . . 89
5. Ionotropic glutamate-sensitive receptors . . . 90
5.1. Ionotropic glutamate-sensitive receptors in the mammalian cochlea . . . 90
5.2. Some properties of NMDA receptors . . . 90
5.2.1. Allosteric modulation at NMDA receptors . . . 90
6. LEOC interactions with Type-I auditory dendrites: NMDA receptors . . . 91
7. Dynorphins and κ-opioid agonists interact with glutamate-sensitive NMDA receptors . . . 92
7.1. Deleterious properties of excess glutamate in the nervous system . . . 92
7.1.1. Reactive oxygen species, oxidative damage and glutamate . . . 92
7.2. Deleterious effects of excess glutamate in the cochlea . . . 93
7.2.1. Dynorphins, NMDA receptors, glutamate and inflammation . . . 94
8. Hyperacusis . . . 95
9. Sodium salicylate, cochlear glutamate, NMDA receptors and tinnitus . . . 95
9.1. Summary: Dynorphins, glutamate, NMDA receptors, inflammation and tinnitus . . . 96
9.2. Predictions: Dynorphins and tinnitus . . . 97
9.2.1. The healthy inner ear . . . 97
9.2.2. The damaged inner ear . . . 97
10. Conclusions . . . 97
11. Proposed pharmacotherapy for tinnitus . . . 98
11.1. Lidocaine . . . 98
11.2. NMDA receptor antagonists . . . 98
11.3. Antioxidant therapy . . . 99
11.4. Proposed opioid antagonist therapy . . . 99
11.4.1. Naloxone . . . 99
11.4.2. Naltrexone . . . 100
Acknowledgment . . . 100
References . . . 100

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