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Tinnitus and underlying brain mechanisms

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Abstract

Purpose Of Review—Tinnitus is the sensation of hearing a sound when no external auditory stimulus is present. Most individuals experience tinnitus for brief, unobtrusive periods. However, chronic sensation of tinnitus affects approximately 17% of the general US population, 44 million people. Tinnitus, usually a benign symptom, can be constant, loud and annoying to the point that it causes significant emotional distress, poor sleep, less efficient activities of daily living, anxiety, depression and suicidal ideation/attempts. Tinnitus remains a major challenge to physicians because its pathophysiology is poorly understood and there are few management options to offer patients. The purpose of this article is to describe the current understanding of central neural mechanisms in tinnitus and to summarize recent developments in clinical approaches to tinnitus patients.

Recent findings—Recently developed animal models of tinnitus provide the possibility to determine neuronal mechanisms of tinnitus generation and to test the effects of various treatments. The latest research using animal models has identified a number of abnormal changes, in both auditory and non-auditory brain regions that underlie tinnitus. Furthermore this research sheds light on cellular mechanisms that are responsible for development of these abnormal changes.

Summary—Tinnitus remains a challenging disorder for patients, physicians, audiologists and scientists studying tinnitus-related brain changes. This article reviews recent findings of brain changes in animal models associated with tinnitus and a brief review of clinical approach to tinnitus patients.

Keywords

Clinical evaluation of tinnitus; brain structures linked to tinnitus; brain mechanisms underlying tinnitus development

Introduction

Tinnitus is a symptom, not a disease, with diverse etiologies most commonly involving the inner ear [1, 2]. It can be triggered by noise-induced hearing loss, presbycusis, otosclerosis, otitis, Meniere's disease, or by ototoxic medications – basically the same conditions that cause hearing loss [3]. Ear wax and conductive hearing loss can also cause tinnitus. Tinnitus is generally classified into two main types; non-pulsatile and pulsatile, also referred to as subjective and objective tinnitus. The non-pulsatile, or subjective, tinnitus is the most

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common and is the type that is discussed in this review. Approximately 20% of individuals experiencing tinnitus report severe associated distress and it is these tinnitus patients that are most likely to visit a physician [4]. Distress of tinnitus has been associated with a range of psychological disorders, including annoyance, sleep problems, anxiety, depression and suicidal ideation and attempts [4]. The following sections review neural correlates and brain changes with tinnitus based on animal studies. In addition, a brief clinical approach to tinnitus patients is also reviewed.

Tinnitus-associated changes in the auditory system

Tinnitus is linked to abnormal changes at one or more levels along the auditory pathway [5-7]. Human brain imaging studies have identified altered tinnitus-related activity in auditory areas, including the inferior colliculus [8] and auditory cortex [9-11]. Magnetic resonance imaging has revealed differences in sound-evoked responses between tinnitus and non-tinnitus groups in cortical [12] and subcortical auditory nuclei [13] and found evidence for structural differences in the thalamus [14], the auditory brainstem [15], and the auditory cortex [16].

Animal models have helped to identify abnormalities in neuronal activity of the auditory brain regions that are linked to tinnitus [17]. More importantly, these studies shed light on the neural mechanisms involved in development of the abnormal activity. Animals with behavioral evidence of tinnitus typically exhibit increased rates of spontaneous firing, abnormally high synchrony and bursting firing, as well as reorganization of tonotopic maps in the auditory cortex [18]. Down-regulation of inhibition in the auditory system is a broadly accepted mechanism responsible for altering activity in the auditory system of animals with behavior evidence of tinnitus [19]. Research into each of these neural correlates is reviewed below.

Hyperactivity

Damage to the cochlea induced by acoustic trauma, ototoxic agents, or other causes that lead to increased spontaneous firing rate of neurons in several auditory structures: the dorsal and ventral cochlear nuclei [20-22], the central nucleus of the inferior colliculus [23-25], the primary (A1) [26] and secondary (A2) [27] auditory cortices, but not necessarily the fibers of the auditory nerve [28].

The most common defect associated with tinnitus is damage to the hair cells or fibers of the auditory nerve, produced by acoustic trauma or ototoxic drugs. The central auditory system appears to increase its gain to compensate for the reduced sensorineural input from the cochlea. As a result, hyperactivity often develops in the cochlear nucleus [29, 30], the inferior colliculus [23-25, 31] and the auditory cortex [32]. Neurons exhibiting tinnitus-related hyperactivity are not uniformly distributed within a single auditory structure. After an acoustic trauma, laboratory animals develop abnormally high spontaneous activity, predominantly in the regions that have neurons tuned to the sound frequency of the acoustic trauma [23-25, 31]. Hyperactivity can manifest itself as a phantom sound of tinnitus, as well as hyperacusis or intolerance of loud sounds [28, 33]. The hyperactivity can be enhanced or suppressed by administering lidocaine in the auditory cortex of tinnitus patients [11, 34]. In individuals whose tinnitus is made louder by lidocaine, the auditory cortex shows an increase in the level of activation. Conversely, individuals who experience a decrease in loudness exhibit a corresponding decrease in cortical activation [11]. Brozoski et al., [35] attempted to attenuate tinnitus via suppression of hyperactivity in the auditory system by systemic administration of vigabatrin (a GABA transaminase inhibitor), which is known to enhance inhibition. This drug both successfully suppressed hyperactivity in auditory neurons and completely and reversibly eliminated the psychophysical evidence of tinnitus. Although

vigabatrin has serious side-effects that prevent its clinical use in the US, this study confirmed a link between hyperactivity in the auditory system and tinnitus.

Although many studies report that hyperactivity in the central auditory system is likely to be a neuronal correlate of phantom sound perception, results from other studies are inconclusive. Recordings from the inferior colliculus and auditory cortex after tinnitus induction with salicylate are inconclusive, with different studies showing that spontaneous activity increased, decreased, or showed no significant change [23, 27, 36]. The presence of hyperactivity in the auditory cortex depends on the manner in which tinnitus is induced. Noise trauma is associated with increasing firing [26], but a reduction is seen when tinnitus is elicited by salicylate [27].

Bursting and synchronized activity

Besides hyperactivity, tinnitus-related changes in the auditory system also include increased neural synchrony and bursting activity. Following sound exposure, abnormal bursting activity occurs in the auditory nerve dorsal cochlear nucleus and inferior colliculus [37-40]. Similar bursting activity has been reported for the inferior colliculus after salicylate treatment [39] or cisplatin treatment [40]. Surprisingly, bursting has not been reported in neurons of the auditory cortex following either noise exposure or after salicylate or quinine treatment [26, 41, 42].

The neurophysiological signature of tinnitus might be increased regularity or decreased asynchrony of spiking [43], or increased cross-fiber synchrony [42, 44]. There is some evidence that both acoustic trauma and ototoxic drugs can increase synchronous discharge across different levels of the auditory system. Salicylate treatment increases synchronous firing among auditory nerve fibers [45, 46].

Reorganization of cortical tonotopic maps

Several studies show that abnormal auditory cortex activation is linked with reorganization of cortical tonotopic maps. The extent of reorganization is correlated with the occurrence and severity of tinnitus in both patients and model animals [47-50]. Recent studies, however, suggest that macroscopic tonotopic reorganization of auditory cortex is not required for the emergence of tinnitus and is not typical for tinnitus that accompanies normal hearing or mild hearing loss [51, 52].

Down regulation of inhibition as a potential cellular mechanism underlying tinnitus

The primary hypothesis of cellular mechanisms underlying tinnitus development is that hearing loss leads to a down regulation of inhibition and reorganization of the central auditory system [19, 35, 53].

An emerging pattern associated with tinnitus pathology indicates that intense noise exposure leads to cochlear damage and hearing loss, which often is not subjectively noted and thus not clinically detected. Decreased cochlear input leads to hyperactive and more responsive central auditory circuits, evidenced by functional MRI (fMRI) studies in patients with tinnitus and in vivo recordings in animal models of tinnitus [13, 38, 54, 55]. Increased spontaneous firing rates, increased evoked responses, and reorganization of tonotopic maps are consistent with decreased inhibition (disinhibition) [18, 53, 56]. A recent in-vitro study confirmed that a down regulation of GABAergic inhibition is responsible for development of hyperactivity in the dorsal cochlear nucleus in mice with behavioral evidence of tinnitus [57].

Tinnitus-associated changes in the non-auditory brain regions

Although several non-auditory areas of the brain have been related to tinnitus, the focus here is on studies implicating structures of the limbic system and other forebrain regions in tinnitus. The limbic system is a rather loosely defined set of brain structures, both cortical and subcortical, that contributes to memory, motivation, and emotion, and attention. Limbic system interconnections with the auditory system occur in both directions: from auditory to limbic structures and from limbic to auditory structures [58-61]. These interconnections have been related to a wide variety of brain functions and behaviors, from auditory fear conditioning [62] to plasticity in auditory cortical responses to sounds [63, 64] to emotional responses to vocal stimuli [65-70].

Given its association with emotional responses to acoustic and other sensory input, the limbic system was an early focus of models of the brain mechanisms underlying the distress component of tinnitus [5, 6, 71]. The amygdala, a limbic system structure that coordinates emotional expression, shows increased tinnitus-related activity in both salicylate and acoustic-trauma animal models of tinnitus [72, 73] and in humans experiencing tinnitus [74, 75]. The amygdala is often associated with aversive responses, and its involvement can be viewed as a kind of “final common pathway” for the expression of the distress of tinnitus. More broadly, there is evidence that several limbic structures, including the amygdala, anterior cingulate cortex, hippocampus, orbitofrontal cortex, and anterior insular cortex, contribute to a generalized “distress circuit” that can be activated by real or phantom stimuli associated with hearing, with pain, or with other sensation [76, 77]. The plasticity associated with these circuits may be critical for the transition to a distress response evoked by the tinnitus percept [78].

Generation and persistence of tinnitus

The plasticity in limbic circuits and the roles of limbic regions in evaluating the salience of acoustic signals are now considered by several researchers to contribute more fundamentally to the generation and persistence of chronic tinnitus. This view, initially proposed several years ago [5, 6, 9, 71], has been further developed in recent work. Work on animal models shows that both acoustic trauma and salicylate cause increased spiking activity and increased expression of immediate early genes in the amygdala [72, 73, 78] The problem with interpreting such studies is that hyperactivity could result from the hearing loss associated with these treatments, from the percept of tinnitus, or from the distress of tinnitus [79].

Several studies in humans have sought to identify limbic system changes associated with the tinnitus percept. Rauschecker and colleagues propose that the ventromedial prefrontal cortex (vmPFC) and the nucleus accumbens are closely involved in the generation and maintenance of tinnitus [7, 14, 77, 80]. The core of this proposal is that hearing-loss induced hyperactivity in auditory circuits is normally suppressed by limbic structures. One such substrate involves projections to the thalamic reticular nucleus, a region that has a direct inhibitory input on neurons of the auditory thalamus. The vmPFC and nucleus accumbens are integral to evaluations of the significance of sounds, and would normally suppress the inappropriate hyperactivity following acoustic trauma. However, they hypothesize, in a subset of individuals the vmPFC does not properly regulate the inappropriate neural activity in the thalamus, leading to tinnitus. Evidence in favor of this hypothesis is that tinnitus sufferers have reduced cortical thickness of the vmPFC and hyperactivity in nucleus accumbens. In this view, limbic dysfunction is seen as a necessary prerequisite for chronic tinnitus, rather than as a sequel to the initiation of tinnitus.

Other research supports the involvement of the limbic system in the generation and maintenance of tinnitus, but differs in the manner in which this occurs and the brain regions that contribute. de Ridder and Langguth and their colleagues [76, 81] propose a process that involves several forebrain circuits and includes both the auditory system and limbic related structures. Thus, phantom percepts arise from sensory deafferentation, and subsequently reach awareness only when the hyperactivity in auditory cortex is linked to a larger network that supports perception (including parietal and frontal cortical areas). The perception does not occur without involvement of a "salience" network that includes the anterior cingulate cortex and anterior insular cortex. The hippocampus, as a limbic region underlying memory, also appears to play a role [9, 15]. These regions, interacting with the amygdala through a learning process, form the basis for the distress of tinnitus or other phantom percepts such as phantom pain.

Overall view of limbic system role

In understanding the role of the limbic system in tinnitus, a major challenge has been to separate the roles associated with generation, maintenance, and distress associated with the phantom auditory percept. There is strong support for roles of the anterior cingulate cortex, insular cortex, and amygdala in the distress associated with tinnitus [77, 82, 83]. How these brain regions contribute to the generation and maintenance of tinnitus is less clear, and differs across researchers. The vmPFC, cingulate cortex, and hippocampus have been implicated, but the interconnections among these regions and other limbic and auditory regions are complex. Ultimately, we may gain increased understanding of the mechanisms of tinnitus through the neurotherapeutic approaches that seek to modulate either the occurrence of tinnitus or the distress associated with it [76].

Clinical management of tinnitus

The clinical approach to tinnitus consists of a thorough medical history, ear and neurological examination, audiological evaluation, and imaging before rendering a diagnosis and treatment plan. The focus is to rule out serious causes (e.g., an acoustic tumor) or treatable causes (e.g., wax impaction or otosclerosis). The focus should be on the physical and psychological aspects of tinnitus. The clinician should reassure patients about the benign nature of tinnitus while counseling them to the available modalities of tinnitus management. The consulting physician should allow adequate time during the initial tinnitus evaluation, usually 45-60 min. Such time is well spent as it will enhance the physician patient relationship, encourage patient compliance with management options and indeed will save a significant time and energy during subsequent visits.

The initial tinnitus history should focus on the nature of tinnitus, particularly its laterality and loudness, factors that increase or decrease it, and interference with activities of daily living especially sleep. The psychological impact of tinnitus must also be assessed, including anxiety, depression and suicidal ideation or attempts. The physician should inquire about patient's coping mechanisms and strategies to reduce stressful and emotional situations. The medical history typically includes ear disease, noise exposure or trauma, use of ototoxic medications, thyroid disease and migraine. History should also include allergies, smoking, use of illicit drugs and alcohol as most of these components can lead to increase in tinnitus loudness.

Physical examination of the tinnitus patient should include microscopic ear examination, especially if there is a history of chronic otitis media and or prior ear surgery. A head and neck exam should focus on evident allergic signs, thyroid lesions and temporomandibular joint disorders (TMJ). Although literature discusses TMJ association with tinnitus [84] the mechanism is unclear. The author of this review [MH] explanation of this relationship is that

TMJ patients tend to clinch jaw more frequently than normal which increases the middle ear stiffness resulting in pseudo conductive hearing loss and subsequent lower threshold of hearing inner ear tinnitus.

Audiological, chemical, and imaging studies are important in the evaluation of tinnitus. Comprehensive audiometry, otoacoustic emission, tinnitus pitch and loudness matching, tinnitus masking level and residual inhibition are commonly performed, particularly at tinnitus clinics. These hearing tests provide important information about the extent of hearing loss, outer hair cell function, perceived tinnitus loudness, and tinnitus suppression [masking] with external sounds. Subjective loudness of less than 10dBSL and low interest variability [less than 3dBSL] are frequently seen in chronic tinnitus. Elevated, or exaggerated, subjective tinnitus loudness in dBSL is [a good measure of exaggerated perception of tinnitus] an. Chemistry typically includes blood chemistry, metabolic profile and thyroid function.. MRI Imaging of the posterior fossa with internal auditory canals views is commonly obtained with unilateral tinnitus and asymmetric high frequency sensorineural hearing loss to rule out an acoustic tumor or brainstem lesions affecting the auditory pathway [MH, Meniere's].

The management of tinnitus hinges upon sympathetic, compassionate care by the treating physician. Unfortunately, tinnitus patients worldwide have to contend with a general attitude that “nothing can be done about tinnitus and you have to learn to live with it”. While there is some truth in this attitude, it will negatively affect any management option that can lessen the impact of tinnitus. To be objective, that attitude stemmed from real frustration on the part of physicians that they had little to offer in terms of knowledge about tinnitus pathophysiology or about specific treatments. The intense interest in the auditory neuroscience of tinnitus provides better understanding of tinnitus pathophysiology and hopefully additional management options for tinnitus patients.

The management of tinnitus usually requires a multidisciplinary approach by physicians [ENT, Otologists, Neurotologists, Neurologists and psychiatrists] and allied health providers such as Audiologists, Psychologists, physical therapists and hearing aids dispensers [Audiologist or non Audiologists]. Central to the management of tinnitus is a complete medical evaluation by a physician trained in the field. These usually are ENT, Otologists and neurologists. It is absolutely critical that physicians spent the needed time to discuss tinnitus, reassure patients and offer sympathetic approach to management. Once a specific disease process has been ruled out, the two main options for managing tinnitus are masking using hearing aids or other masking devices and medications to address tinnitus major secondary symptoms; mainly poor sleep, anxiety or depression. Sound therapy, masking and hearing aids are best handled by qualified Audiologists. It is prudent that cost effective and proven modalities of sound generators are employed to minimize expenses that are not covered by insurance.

Pharmacological management of tinnitus is best handled by neurologists or psychiatrist. First line therapy using medications such as Nortryptiline [typical of tricyclic antidepressants class] and Alprazolam [typical of benzodiazepine class] can be provided by ENT as long as they are comfortable monitoring patients' progress and potential serious adverse reactions while taking these medications. Several recent studies have shown positive response with using melatonin [85-87].

Literature and internet are filled with studies and many herbal and non-herbal supplements claiming efficacy that has not been proven by rigorous randomized studies. It is the responsibility of the treating physician to become familiar with these supplements and their efficacy to help guide patients to save then unrealistic expectations and cost of unproven

treatment. Recently over the past decade, repetitive trans-magnetic cortical stimulation [rTMS] has been used, primarily in Europe, for tinnitus management [88-93]. Most of these studies while supporting this approach emphasize the fact that further work needs to be done in this field.

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Summary

Despite the best efforts of physicians to help tinnitus patients and of researchers to identify the underlying brain mechanisms, we are still far away from understanding the keys to successful treatment of tinnitus. Tinnitus, which often results from an insult to the peripheral auditory system, is associated with changes in structure and function of many brain regions. These include multiple levels of the auditory system as well as regions of the limbic system associated with memory and emotions. Given the broad extent of brain regions affected, it is unlikely that there will be a “single” drug or treatment modality that can effectively reduce or eliminate tinnitus. A multidisciplinary approach to the management of tinnitus patients is clearly needed.

Key points

- We are still far from understanding the keys to successful treatment of tinnitus.
- Current research suggests that tinnitus is associated with abnormal changes in the auditory system and the limbic system.
- Given the broad involvement of brain structures linked to tinnitus, it is unlikely that there will be a “single” drug or treatment modality to cure tinnitus.
- Current tinnitus management requires a multidisciplinary approach by physicians, including sound therapy and use of medications to control secondary tinnitus symptoms such as poor sleep, anxiety or depression.