Neural Mechanisms and Models of Tinnitus Generation

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ABSTRACT

Tinnitus is an auditory phantom sensation; it is the false perception of sound in the absence of an external source. Tinnitus can be managed, but there is no cure. Tinnitus affects approximately 10–20% of the population and is often accompanied by hearing loss. The hearing loss causes reorganization of the central auditory processing pathways and associated areas in the brain, possibly leading to tinnitus. However, the underlying neural mechanisms are poorly understood. This paper reviews possible regions exhibiting activity related to tinnitus, from the cochlea to the primary auditory cortex, and the mechanisms that may underlie tinnitus generation. However, tinnitus is a complex phenomenon and no single mechanism or brain region can account for all tinnitus subtypes or symptoms. In addition, somatosensory system and limbic system, with their strong connections to the central auditory processing pathways, may be involved in tinnitus generation and persistence. Although, there have been advances in understanding neural mechanisms of tinnitus, particularly due to brain imaging studies in humans, there is still a paucity of data linking objective measures of tinnitus, obtained using brain imaging techniques, to subjective behavioral measures.

KEY WORDS: Tinnitus · Tinnitus model · Neural mechanism of tinnitus · Tinnitus generator · Auditory system · Somatosensory system · Limbic system.

INTRODUCTION

Imagine that someone is in a quiet room after coming back from a loud rock concert. A few individuals in that quiet room may hear sounds or noises ringing in their ears or head for a while. This phenomenon is called tinnitus.48 Tinnitus is, in general, a conscious expression of the sound that originates in an involuntary manner in the head and lasts five minutes or more,8,33 yet that varies in severity. According to Dauman and Tyler,7 there are two types of tinnitus: normal tinnitus that lasts less than five minutes and occurs less than once a week, and pathological tinnitus that lasts more than five minutes and occurs more than once a week. The latter is often accompanied by some degrees of hearing loss. Tinnitus is also classified by severity (i.e., tolerable or intolerable) and by duration (i.e., temporary or permanent).

Tinnitus is one of the most difficult hearing disorders to cure because of its elusive causes and complex neurophysiological mechanisms. Furthermore, there are inherent differences in patients’ ability to cope with the stress of tinnitus.48 By location, tinnitus is categorized as middle ear, peripheral neural (cochlear, auditory nerve) and central neural (cochlear nucleus, inferior colliculus, thalamus, auditory cortex) systems. Noise-induced hearing loss, Meniere’s disease, ototoxicity, presbyacusis, and ‘unknown etiology’ are some of the major etiologies of tinnitus.7

In order to diagnose and treat the symptoms associated with tinnitus, audiology and tinnitus clinics have used several assessment techniques and therapeutic approaches. A questionnaire is one of most popular assessments for tinnitus. Eight questionnaires have been widely used: Tinnitus Questionnaire (TQ),16 Tinnitus Handicap Questionnaire (THQ),27 Tinnitus Severity Scale (TSS),45 Subjective Tinnitus Severity Scale (STSS),15 Tinnitus Reaction Questionnaire (TRQ),50 Tinnitus Severity Grading (TSG),6 Tinnitus Handicap Inventory (THI),41 and Intake Interview for Tinnitus Retraining Therapy.21 However, no single questionnaire covers every dimension and it is difficult to compare treatment effects due to many differences in format, scaling, and even in the words that are used on these questionnaires. Moreover, typical audiological evaluations, including pure-tone audiometry (especially with extended high-frequency test up to 12
Mechanisms of tinnitus generation along auditory pathway and neurophysiological theories

Is cochlear damage a possible tinnitus generator?

Many theories have attempted to link cochlear damage to tinnitus. In 1981, Tonndorf proposed that dysfunctional stereocilia in OHC could result in tinnitus. The functional loss of stereocilia would lead to a partial or complete decoupling of the hair cells from the tectorial membrane, which divides the two chambers of scala media and scala transacti. Such decoupling could create internal noise at the hair cell synapse up to 55 dB, and create either a tone or a hissing sound. Further, excessive and intense noise or ototoxic drugs can damage OHCs first in the basal part (i.e., high-frequency regions) of the cochlea and continue to lose IHCs located in the same part to OHC if the noise is sustained or repeated. This idea is supported by clinical observations: some patients with tinnitus and high-frequency hearing loss matched their tinnitus frequency to the point at which the loss began, but it is difficult to make a generalization with other patients who have either low- or middle-frequency hearing loss or who have broad-band perception instead of a tonal perception.

Bauer and colleagues used an animal experiment to examine the relation between cochlear loss by acoustic trauma and behavioral evidence of tinnitus. They found that rats who had been exposed to high intense noise for a period of time experienced a loss in both OHC and IHC and that the loss was highly correlated with the behavioral test for tinnitus. The rat with cochlear hearing loss and tinnitus seemed to hear sounds in the absence of an external source. The authors argue that undamaged area bordering the damaged IHC might have reduced efferent inhibition, giving rise to a highly active area of the basilar membrane and thus resulting in the tonal tinnitus. Although the animal studies could explain this phenomenon, they need to be confirmed by human studies.

Other research has pointed to an alternative mechanism by which an area of the basilar membrane with damaged OHC but intact IHC might contribute to tinnitus generation. Although this theory, tinnitus generated from unbalanced loss in OHC and IHC, seems persuasive in that a loss of motility in OHC might reduce the ability to set the operating point of the IHC resulting in the tinnitus, there is a difficulty in separating OHC from IHC loss. Another aspect of cochlear damage is that in most sensorineural hearing-impaired listeners, both IHC and OHC are equ-
ally damaged.

One way to test the theory of the imbalance of OHC and IHC is to investigate cochlear function clinically in patients with hearing loss and tinnitus. This is accomplished by measuring distortion-product otoacoustic emission (DPOAE) and psychophysical turning curve, thus testing for dysfunction of OHC and normal function of IHC, respectively. Expecting results, which are absent DPOAE responses and sharply turned normal curves, may give details in separated functioning of the cochlea and some tinnitus-related patterns. Nevertheless, since the separated function in OHC and IHC can explain only patients having hearing loss of less than 40–45 dB HL due to a restricted normal response range in DPOAE, the theory has weakness. A good correlation between the tinnitus patients with either high frequency or notch-like hearing loss and their cochlear functions from DPOAE was observed, but only in cases where hearing loss was less than 40 dB HL.42) Tinnitus patient who has normal hearing showed reduced DPOAE responses when compared to non-tinnitus with normal hearing. However, as age increased, the DPOAE functions were ambiguous due to a combination with presbyacusis.42)

Many theories and animal models simulated in cochlea, OHC and/or IHC, have shown a logical correlation between cochlear hearing loss and tinnitus, but there is a risk in stating that the cochlea is a tinnitus generator. Support for the central nature of tinnitus comes from studies that report persistence of tinnitus in patients with acoustic neuromas after transection of the auditory nerve32) and from brain imaging studies of tinnitus in humans showing widespread involvement of cortical structures in tinnitus.30)31)35) In animal studies, where tinnitus is caused by either pharmacologically or noise-induced trauma, abnormal activity in the inferior colliculus and other brainstem nuclei has been reported.44)49) Additionally, the abnormal involvement of non-classical auditory pathways, which receive input from the emotion-processing, somatosensory and visual pathways, may modulate tinnitus.

**Does the auditory nerve play a role in generating a tinnitus signal?**

Some researchers have suggested that an altered spontaneous activity within the auditory nerve might have a role in generating a tinnitus.26)47) Based on the experiment with cats deafened by kanamycin, which is used to treat a wide variety of infections, deviation from the normal random activity within the auditory nerve toward more synchronous spontaneous activity may be interpreted by higher auditory stages as cochlear stimulation. However, the animal experiments are not consistent with results of human studies because tinnitus-inducing events in humans are as likely to increase spontaneous activity as reduce it.41) There is also limited support for the assumption that tinnitus results from increased spontaneous activity in auditory nerve fibers because high doses of salicylate and not small doses seem to result in tinnitus.1) Thus, recent animal studies have focused on the higher level (i.e., the retro-cochlear region) of the auditory system.

**Is the dorsal cochlear nucleus a possible site of tinnitus generation?**

Increased neural activity may occur at one or more levels of the auditory system, resulting from peripheral damage or altered function elsewhere in the system. In other words, the increased neural activity beyond the auditory nerve may be implicated in tinnitus generation. Many studies have reported elevated spontaneous activity in the cochlear nucleus, primarily in the DCN. For instance, Kaltenbach and Afman have shown increased burst-firing in the DCN of rats after exposure to intense sounds, as arguing for a link between such bursting activity and tinnitus perception. They suggested not only the increasing in bursting spontaneous activity but also a decrease in regular spontaneous activity.23) Such imbalance between bursting and regular spontaneous activity may represent increased auditory efferent modulation from the IC or AC and connecting to the DCN, or a lack of inhibition from other cochlear nucleus units. In either case, it may result in the false perception of sound, or tinnitus. Others have found similar burst-firings in the auditory nerve of cats after some exposure to kanamycin and in the rats’ inferior colliculus after being injected with salicylate, and showed results that were similar to those of Kaltenbach and Afman. This model of tinnitus, based on altered firing patterns in the DCN, is principally based on data from animal experiments.

Baguley pointed out some weakness on animal model. He has argued that any possible amplification of spontaneous activity within this feedback loop (DCN to either IC or AC), which could be influenced by processes of attention, emotion, and anxiety in the limbic structures, might be a potential cause of tinnitus perception.1) Still different results between animal and human tinnitus at the auditory nerve stage were shown due to a lack of data on limbic system involvement in animal studies of tinnitus. Thus, it is possible that two or more interconnected systems may mediate tinnitus generation. We will discuss this point later in the paper.

**Is the inferior colliculus a possible site for tinnitus generation?**

Most of the evidence regarding altered spontaneous
firing rate as a possible mechanism of tinnitus has been recorded form the IC. Reduced output from the damaged cochlear region causes diminished inhibition in the central auditory structures as well as excessive excitability of the central auditory system, leading to some degree of tinnitus.\textsuperscript{11)} Melcher and her colleagues used fMRI for quantifying tinnitus-related abnormality in IC of humans. Compared to a control group having normal hearing and without tinnitus, patients with lateralized tinnitus showed abnormally high neural activity in the contralateral IC.\textsuperscript{34)} Like other human studies using brain imaging, this study had the drawback of having small number of subjects and did not include a tinnitus population that had hearing loss. Collective evidence from human brain imaging studies do not show simply a relation to one central structure (e.g., IC) to tinnitus, but a network of cortical and subcortical regions are implicated. Additionally, an interaction with the limbic system may exist possibly correlated with the tinnitus patient’s anxiety or fear about the tinnitus.\textsuperscript{11)}

**How does activity in thalamus affect tinnitus?**

The medial geniculate body (MGB) in the thalamus may play an important role in tinnitus due to descending cortico-thalamic pathways, but little interest has been focused on this level of processing.\textsuperscript{38)} The MRI results from Muhlau’s study found that tinnitus patients had significant decreases in gray-matter size in the subcallosal frontal cortex and increased gray-matter size in the auditory thalamus, primarily the right MGB region, compared to non-tinnitus controls.\textsuperscript{39)} Because of the involvement of subcallosal frontal cortex in the emotion processing network, these findings suggest that effect of tinnitus is not limited to one area and may show a correlation with emotions. Such implication brings us that the generation of tinnitus is reciprocal relation of auditory sensory and emotional regions.

**How does activity in primary auditory cortex affect tinnitus?**

Several plausible hypotheses about the role of the primary auditory cortex (AC) in tinnitus have been offered. They include an increased spontaneous activity and change in the temporal pattern of neural activity such as bursting, resulting in alterations of tonotopic representation that lead to enhanced synchrony. The altered tonotopicity in the central auditory region indicates that deafferentation of specific parts of the cochlea, in the short-term, may lead to a reduced activity in the cortical area corresponding to characteristic frequencies of the damaged region. Some time later, however, excessive neurons may be produced in the frequency regions adjacent (more sensitivity in upper and lower boundaries) to the lesioned areas, resulting in ‘tonotopic reorganization’. Mulnickel et al. proved that the reorganization of AC could be a mechanism of tinnitus generation in human using a 37-channel whole-head neuromagnetometer system. Patients with tinnitus reconstructed the tonotopic map, resulting from a shift of the tinnitus frequency representation into the both sides of frequency boundary within the tonotopic map. They also reported a strong relation between severity of the tinnitus and the amount of cortical reorganization.\textsuperscript{40)} In addition, several neuroimaging studies of humans have identified tinnitus in AC and linked activity on the limbic system; a strong positive correlation between activity on anterior cingulated cortex in both sides of the hemisphere and the level of anxiety related to AC tinnitus.\textsuperscript{13,35,36)

Animal studies have demonstrated altered neural activity and hyperactivity of the primary and secondary AC after auditory damage similar to that causing tinnitus in human.\textsuperscript{10,24)} However, although these studies of cortical neurophysiology have directly measured tinnitus in their animal subjects, we still need to know how the animal experiences tinnitus and how such experiences are related to that perceived by humans because tinnitus is a subjective percept. Therefore, additional measures such as test-retest reliability of behavioral experiments or including various forms of tinnitus (i.e., intermittent and chronic tinnitus) are needed to make animal models more robust.\textsuperscript{3)}

**How can some people have normal hearing and tinnitus?**

Although cochlear processes such as damage or dysfunction might be involved in tinnitus-related activity, some people with normal hearing have tinnitus. This is not explained within the context of previously described models and theories.

Somatic tinnitus, which arises directly from a disorder of the head and upper neck after events such as a car accident, can be one explanation for tinnitus which is not accompanied by hearing loss. For instance, damaged cranial nerves (e.g., V, VII, IX, and X) of head and spinal nerve of neck might affect medullary somatosensory nucleus in the brain, resulting in disinhibition of DCN (see Fig. 1: the somatosensory system projecting to IC and DCN). Levine’s group\textsuperscript{20)} has studied non-auditory factors to tinnitus by somatic tests consisting of jaw contraction, head and neck constriction, or pressure on muscle insertions. They found that forceful contractions of the head and neck might modulate the tinnitus without any disturbance to the ear in a majority of tinnitus patients.

**From models of tinnitus**
A schematic of the regions affected by tinnitus and which, in turn, may modulate tinnitus is shown in Fig. 1. The auditory system has interconnections with the somatosensory and limbic systems. Somatosensory system, with its connection to IC and DCN, may modulate tinnitus. Limbic system projects from thalamus and AC and back to thalamus and IC; this feedback loop is associated with emotional processing and may play a role in tinnitus.

According to Jastreboff’s influential neuropsychological model, tinnitus involves auditory perceptual, emotional, and reactive systems.21) In particular, negative emotional reinforcement such as fear, anxiety, and tension may affect the limbic system and autonomic activation, causing persistent tinnitus even in people with normal hearing. Georgiewa also described the reinforcement of tinnitus and its subjective assessment with having de-compensation, which is associated with the accompanying physical as well as psychological symptoms: patients with de-compensated tinnitus generally undergo a complex somatic and psychological disorder. Interactive processes involving emotions, behaviors, symptoms, and a high co-morbidity with affective and psychosomatic illnesses and the important influence of psychosocial factors are associated with tinnitus, consequently suggesting significance in stage-appropriate interdisciplinary treatments.14)

Neural network modeling has been used by neuroscientists to better understand the neural mechanisms of tinnitus and the functional connections between regions within the networks mediating tinnitus (for a review see Husain, 2007). Modeling has several advantages: derive new hypotheses, data reduction of a complex phenomenon, make predictions that result in new experiments, instantiating and verifying new therapies. Moreover, the modeling allows behavioral, electrical, and neuroimaging data to be simultaneously compared. Extending theoretical models of early 1990’s, lateral-inhibition network (or LIN) models were introduced. The main concept of LIN modeling is that a neuronal element affects its adjacent elements within the same level by means of inhibitory connections. However, if a certain disturbed LIN in central auditory system exists, it will lead to reduced inhibition and hyper-excitation of the system, leading to a trigger of tinnitus.19) Although we do not describe modeling of tinnitus in detail, the approach allows us to described neural mechanisms in greater detail and lead to focused experiments and better verification of tinnitus treatment methods.

DISCUSSIONS AND CONCLUSIONS

According to epidemiological studies, tinnitus is prevalent at a rate of 5–15% in the general population. Prevalence of tinnitus increases with age, peaking at almost 40% after the age of 65 years.9) The American Tinnitus Association (ATA) estimates that more than 50 million American experience tinnitus and about one-third of them have it severely enough to seek medical help. Thus, tinnitus can interfere with activities of daily living for millions of people, yet the possibility of treating or curing tinnitus is very limited.

In this review, we discussed possible locations and mechanisms of tinnitus generation. Activity related to tinnitus may occur anywhere from the cochlea to the cortex and may involve the limbic and somatosensory systems. Tinnitus associated with hearing loss is frequently localized toward the pathological ears. However, tinnitus sensations often persist even when input from the ear is removed by resection of the auditory nerve.11) Tinnitus generation possibly involves multiple mechanisms. For example, increased spontaneous neural activity in IC and consequently altered tonotopic organization in AC may result from some damaged outer hair cells. Combined with altered input from the limbic system, tinnitus may be generated and persist. Additionally, tinnitus is associated with both physical and psychological manifestations, and thus is hard to quantify if only one approach is applied. Current tinnitus research using animal or human subjects provide evidence from different perspectives - animal studies can better control for etiology, whereas human studies allow us to link objective brain imaging measures with subjective behavioral data. For that reason, audiologists, otologists, or specialists who work in tinnitus clinic need
to know various aspects related to tinnitus for better diagnosis and treatment; physical as well as psychological examination including counseling should be considered when screening for tinnitus.

We still need to know how the auditory system produces a sensation that is similar to that of a sound in the absence of an external source. Regardless of the heterogeneity within the tinnitus population, there are common mechanisms by which tinnitus can occur. Both objective and subjective measures of tinnitus should be used to help patients with effective clinical treatments. Recent research using brain imaging in humans and behavioral models of tinnitus in animals is finally beginning to bear fruit and it will lead to better therapies and management techniques.

REFERENCES