Noise

Acoustic Trauma to the Inner Ear

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KEYWORDS

• Tinnitus • Noise trauma • Hearing loss • Hidden hearing loss
• Temporary threshold shift • Permanent threshold shift

KEY POINTS

- There are different types of hearing loss: temporary, hidden, and permanent hearing loss.
- All types of hearing loss are associated with tinnitus. It is likely that all tinnitus are associated with some form of hearing loss.
- Predicting the severity of noise-induced hearing loss from the noise exposure (whether sudden or lifelong) is complex.
- Furthermore, the relationship between the tinnitus perceived by the patient and the characteristics of the hearing loss is currently poorly understood.

INTRODUCTION

Hearing Loss and Tinnitus are Closely Associated

(Subjective) Tinnitus is a symptom of many possible underlying causes (Claudia Barros Coelho and colleagues' article, "Classification of Tinnitus: Multiple Etiologies with the Same Name," in this issue), with the generative source of tinnitus (if there is a localized one) serving as an active topic of fundamental animal research.[1] In humans, particularly those with distressing tinnitus, the heterogeneity observed indicates that in all likelihood, there are a variety of mechanisms that give rise to the percept of tinnitus.[2,3] Indeed, multiple mechanisms are likely at work within one individual, and if a specific event such as trauma led to tinnitus, it is plausible that the mechanisms giving rise to the tinnitus acutely following the initial traumatic event differ from the ones responsible for the chronic percept of tinnitus.[4]

Tinnitus itself is not a disease but rather a symptom of an underlying condition that can be classified into subtypes based on its many causes. For nonchemically induced

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tinnitus associated with exposure to loud noises, blast wave injury, Ménière disease, or simply aging, sensorineural hearing loss is a common denominator. Tinnitus is also often associated with conductive hearing loss resulting from recurrent ear infections, chronic serous otitis media, otosclerosis, perforated tympanic membranes, or even cerumen impaction (ear wax build-up). Less commonly, tinnitus develops following head injury, circulatory system changes such as anemia and high blood pressure, vestibular schwannoma, diabetes, thyroid disorders, and many other conditions.

Chemical induction is equally prevalent, with tinnitus being the most commonly reported side effect mentioned in response to prescribed medicine, arising when patients start (eg, nonsteroidal anti-inflammatory drugs) or even stop taking a medication (benzodiazepines). In cases of particularly ototoxic medications such as cisplatin, more than 90% of patients will acquire hearing loss over some frequency range (typically the higher frequencies) and develop the associated tinnitus by the third round of chemotherapy treatment.[5–8] As detailed in a later article (Fatima T. Husain's article, "Perception of, and Reaction to, Tinnitus: The depression factor," in this issue), certain factors such as stress and anxiety negatively enhance the reaction to the tinnitus, with this tinnitus reaction being exacerbated by exposure to certain medications, head injury, and particularly in those with depression.[9]

In this article, the authors focus primarily on trauma-induced tinnitus, and in particular noise-induced tinnitus, whether acute or chronic. Indeed, "tinnitus induction by acoustic trauma is most likely the most common form observed in the human patient."[10] As the presence of tinnitus is associated with hearing loss, with age being the main predictor of its prevalence in the adult population in the United States,[11] age-related hearing loss and tinnitus go hand-in-hand. The earliest well-established theory considers tinnitus to be the perceptual consequence of neuronal hyperactivity in the central auditory system, emerging after loss of the neural input from the ear to the brain that would be expected from a healthy inner ear.

Although we do not yet understand the neural origins of tinnitus, it is clear that tinnitus often develops in multiple phases. In the case of trauma to the inner ear resulting from noise exposure, the early phase of tinnitus may be directly related to damage sustained by the structures of the inner ear itself, whereas over a period of a few days, the main correlate of the tinnitus might shift to a locus in the central nervous system (CNS).[12–15] In animals, evidence for changes in neural activity associated with tinnitus immediately following noise trauma can be seen within an hour of trauma in cats[3] and a few hours in hamsters.[16]

Therapeutic developments for tinnitus would greatly benefit from a comprehensive understanding of the neural origins and pathologic evolution of tinnitus. However, this goal has been confounded by evidence suggesting that patients could have tinnitus in the absence of hearing deficits as measured by standard audiogram.[17,18] This challenges the widely accepted view of tinnitus as being initiated via impairment in cochlear function, which leads to hyperactivity in the relevant CNS structures.[19–22] Because cochlear damage is usually thought to result in an initial elevation of hearing thresholds, as measured through the standard audiogram, absence of any clear deficit in cochlear function was believed to indicate that hearing loss of peripheral origin and tinnitus, while often comorbid, could arise independently from each other.[17,18] More recent research has indicated that in fact, all subjective tinnitus are likely associated with hearing loss, although not always apparent from the standard audiogram. Data have shown that normal hearing thresholds do not necessarily indicate absence of cochlear damage. Following mild acoustic trauma, mice can exhibit only a temporary threshold shift in hearing together with a permanent deafferentation of approximately 50% of the auditory nerve fibers (albeit in the high-frequency region of the cochlea[23]).

Thus, if a sufficient population of low-threshold auditory nerve fibers remains responsive to sound, the audiogram can present as normal, even when hearing is not. Conversely, impaired function of efferent fibers (from brainstem to cochlea) can still be associated with normal thresholds.[24,25]

Further investigation by Schaette and McAlpine showed that humans with tinnitus and otherwise normal audiograms, extended to 16 kHz, indeed had a deficit in auditory nerve function manifested as a reduction in nerve output at high sound levels, indicating deafferentation of high-threshold auditory nerve fibers.[26] This deficit seems to be compensated for at the level of the brainstem, supporting the view that tinnitus is promoted by homeostatic mechanisms that act to normalize levels of neural activity in the central auditory system.

DIFFERENT TYPES OF HEARING LOSS

Mounting evidence implicates tinnitus as an indicator of underlying auditory deficits, however mild these deficits might be. It has become appreciated that certain types of hearing deficits not revealed by a standard audiogram might be compensated for by a maladaptive mechanism within the central auditory pathways leading to the perception of tinnitus.[27,28] This takes us from the former concept of "some form of hearing loss is associated with tinnitus" to a picture in which "tinnitus is a symptom of a form of hearing loss." As such, the authors briefly summarize their understanding of hearing loss, in particular noise-induced hearing loss (NIHL), the most commonly studied form of hearing loss in animal models.

In animals, NIHL presents as a continuum of 3 main forms of damage with escalating severity, where the transition from one type to another can depend on relatively small changes in the duration and the intensity of the sound exposure, as well as the structure of the sound (eg, gaussian vs nongaussian).

- The mildest form of NIHL is defined by a temporary decrease in the sensitivity to sound, referred to as temporary threshold shift (TTS). In TTS, the sensitivity to sound is initially impaired within a day, and by definition, returns to baseline within a week from exposure. Research on animal models indicates this type of hearing loss does not result in a loss of the sensory hair cells of the inner ear, although its exact molecular underpinnings are only partially understood.[29,30]
- Next on the continuum is hidden hearing loss (HHL). HHL, in addition to the temporary loss of hearing sensitivity seen in TTS, is characterized by a permanent loss of neural connections from a subgroup of afferent (sensory) neurons located in the center of the cochlea called spiral ganglion type I sensory neurons, which carry information from the inner hair cells to the cochlear nucleus of the brainstem.[31] Although type I sensory neurons relay information from the inner hair cells to the cochlear nucleus, they are divided into at least 3 subgroups based on their spontaneous rate and relative sensitivity to sound (designated as type Ia–Ic). The neurons presumed to be involved in HHL consist primarily of type Ic afferent neurons, characterized by a high threshold of response to sounds and a low spontaneous rate of activity. Noise exposure causes retraction of the neural processes of these neurons from their associated hair cells. In consequence, their loss, while leaving hearing thresholds unchanged, results in significant functional impairment that manifests as a decreased ability to resolve speech in the presence of competing noise, hence the name "hidden" hearing loss.[32] By convention, at least in animal models, no loss of hair cells is seen in noise exposures that result in TTS/HHL. The situation is likely the same in humans, with

evidence of deafferentation of the human inner hair cells, in temporal bones, with aging and noise.[33–35]

- At the end of the NIHL continuum is the permanent threshold shift (PTS)-inducing noise exposure, which results in both the loss of neuronal connections as well as a permanent loss of sensitivity to sound.[29,36] Depending on the severity and structure of the noise exposure, the damage in the cochlea following a PTS-inducing noise exposure may vary considerably, from loss of outer hair cells, to significant disruption in the integrity of the organ of Corti.[37,38]

Note that in addition to the loss of neural connections mentioned earlier, which can result in a reduced transmission of information from the cochlea to the brain, it has been shown that in rats, there can be up to 30% damage to the outer hair cells before any hearing loss is detectable using compound action potential threshold.[39]

NOISE PARAMETERS DO NOT ALWAYS PREDICT PATTERN OF HEARING DEFICITS

The type and severity of the NIHL (TTS/HHL/PTS) depends on a combination of extrinsic and intrinsic factors. Extrinsic factors principally depend on the intensity, frequency, and duration of the exposure to sound, although other poorly understood factors such as sound statistics likely have an impact. Intrinsic factors are more complex and include circadian changes to gene expression,[40] cortisol levels,[41] genetic factors,[42] and sex hormones among others.[36,43,44] Small changes in intrinsic or extrinsic factors can dramatically influence the outcomes of a noise exposure. For example, a difference of 2 dB in the intensity of a long duration sound exposure can determine whether a subject will sustain HHL or PTS (a change of 2 dB corresponds roughly to an increase of sound power by 60%).

It is also worth noting that different areas within the cochlea may sustain different types of damage from a single traumatic noise exposure. For example, a midfrequency high-intensity noise exposure can result in a PTS in the midfrequencies, HHL in the high frequencies, and only a TTS in the lower frequencies. It is therefore impossible to anticipate the type of damage and the associated tinnitus that will result from noise exposure and trauma, as a patient can exhibit a combination of all 3 types of hearing impairment. Thus, any treatment, pharmacologic or otherwise, will need to mitigate the hearing threshold shifts in all forms of NIHL, as well as reverse or prevent the loss of synapses in both HHL and PTS. It is possible that this dual pattern of hearing loss (midfrequencies and high frequencies in response to a midfrequency noise exposure) is at play in aging and partially accounts for the universal loss of high-frequency hearing in all humans' experience.

HYPERACUSIS AND RECRUITMENT

Both hyperacusis and recruitment are often associated with tinnitus and must be considered when developing therapeutic strategies.[45–47] Hyperacusis is defined by a lowered threshold to discomfort from sound, wherein sounds perceived as loud by normal hearing persons are instead perceived as painfully loud by the hyperacusis patient. The comorbidity of tinnitus and hyperacusis seems somewhat paradoxial at first glance, as the patient typically does not perceive the constant subjective tinnitus sound to be painful. However, sounds perceived as tinnitus and the pain related to hyperacusis likely arise from separate pathways,[48] with the perception of pain carried by a small subset of neurons in the auditory nerve.[49]

In contrast, recruitment is characterized as a rapid growth in the perceived loudness of sound that is incongruent with the relatively small increase in sound level that actually occurs. Although the physiologic correlate of these two distinct conditions is unclear, the resulting hypersensitivity to sounds can lead to a challenge in alleviating the associated tinnitus, particularly for patients whose tinnitus is reduced by sound stimulation such as hearing aids or devices that offer different levels of sound therapy (LaGuinn P. Sherlock and David J. Eisenman's article, "Current Device-Based Clinical Treatments for Tinnitus," in this issue) Patients with hyperacusis, recruitment, or other forms of sound sensitivity may encounter some discomfort when using sound amplifying devices.

SYNAPTOPATHY, ENDOCOCHLEAR POTENTIAL LOSS, AND OTHER UNMEASURED DEFICITS

The endocochlear potential is a positive electrical potential present in the central part of the cochlear duct called the scala media. The value of this potential, measured in the endolymphatic fluid that fills the scala media, varies between +80 mV and +120 mV along the length of the cochlear duct. It is an essential driving force within the cochlea, allowing for the initial transduction of the acoustic signals into an electrical/neural signal, via a driving force that generates an electrical gradient between the positive potential of the fluid that bathes the stereociliae of the hair cells (+80 to +120 mV) and the negative potential inside the apical part of the hair cells (−45 mV). The physical acoustic signal propagating along the cochlear duct leads to mechanical oscillations of the stereociliae, which lead to the opening and closing of ionic channels in the stereociliae. The large electric potential across the boundary between endolymph and the inside of the hair cells drives rapid ionic fluxes into the hair cells, eventually leading to the "mechanotransduction" of sounds into neural signals via the hair cells.

Although there is no directly measured correlation between a change in endocochlear potential and the emergence of tinnitus, it is thought that large variations in endocochlear potential might be an important contributing factor: in the healthy inner ear, the highly positive endocochlear potential is achieved by maintaining a high endolymph concentration of potassium (K^+), which is associated with higher auditory nerve spontaneous activity.[50] The outer hair cells of the cochlea can modify the endocochlear potential via mechanoelectrical transduction channel opening. Acute noise trauma reduces the opening probability of these channels, leading to a temporary increase in the endocochlear potential.[51,52] The associated increase in endocochlear potential can depolarize the inner hair cells and, through a somewhat complicated cascade of events, cause a fusion of the synaptic ribbon to the plasmatic membrane, an increased release of glutamate, and depolarization of the associated nerve fibers.[53] This may lead to a subsequent increase in the spontaneous rate of activity of the corresponding auditory nerve fibers lasting a few days. Conversely, a decrease of the endocochlear potential, such as the decrease that may occur weeks after cochlear injury, results in a decreased electromotive driving force and therefore a hearing threshold shift. In PTS, these shifts are associated with chronic tinnitus.

As mentioned earlier, there are indications that tinnitus is always associated with a hearing loss, although in some cases it is an HHL. Noise exposure or aging can lead to a permanent loss of some synapses between the hair cells and the cochlear nerve fibers.[54,55] Following even a relatively mild noise trauma then, a rapid and excessive release of the neurotransmitter glutamate from ribbon synapses in the inner hair cells causes a partial disconnection/retraction of the afferent neurons to the inner hair cells.

Although some neural terminals can re-form a functional connection with the hair cells, thus restoring hearing to a level corresponding to individuals' recovering hearing thresholds[56] and tinnitus disappearing in the days following a comparatively higher level sound exposure, sometimes it is thought that the neural reconnection is incomplete. As mentioned in the description of the different types of hearing loss (particularly HHL), this mechanism seems to preferentially affect low spontaneous rate auditory nerve fibers, which are the neurons responsible for coding moderate-to-high sound levels.[31] Another possible mechanism includes the loss of the Schwann cells closest to the synapse, impairing the early part of the transmission of the neural signal from the cochlea to the brain.[57] In either case, this incomplete reconnection or damage to the synapse or reduced transmission of neural information to the brain may result in tinnitus, even in patients with a normal audiogram.

PARAMETERS

In the United States, guidelines have been designed to determine a safe daily exposure to noise to minimize the risks for hearing loss over a lifetime. Exposure is estimated on a daily exposure basis, averaged using a time-weighted method (TWA) detailed on the Websites of the cognizant agency. It is measured on a dBA scale. This "A-weighting" is a frequency-dependent curve that is applied to the physical sound pressure levels (SPL) measured to mimic the effects of human hearing, for instance the fact that our hearing is poor above 70 Hz and is nonexistent above 20 kHz. The US Department of Labor's Occupational Safety and Health Administration (OSHA) guidelines set legal limits on noise exposure in the workplace. OSHA's "Permissible Exposure Limit" is 90 dBA for all workers based on a worker's TWA over an 8-hour day, whereas the Center for Disease Control and Prevention's National Institute for Occupational Safety and Health "Recommended Exposure Limit" for occupational noise exposure is 85 dBA, as an 8-hour TWA. Exposures at or greater than this level are considered hazardous to hearing.

However, no such guidelines exist to predict lifetime noise exposures that might lead to tinnitus. A few experiments were conducted in humans, exposing small groups of volunteers to what is now considered traumatic sounds. Exposure to a 1/3 octave, 110 dB SPL for 5 minutes noise band, induced tinnitus in 75% of (previously) normal-hearing subjects.[58,59] Impulse noise from assault rifles,[60,61] from airbag deployment,[62] or associated with sudden sensorineural hearing loss were also shown to be strongly associated with tinnitus.[63]

Although the noise exposure is generally well controlled in animal studies (although this is not necessarily the case in the animal facilities where animals are often assumed to be recovering in quiet, a likely confounding factor in many studies[64]), the parameters used to induce behavioral evidence of tinnitus through acoustic trauma are quite variable. Typically, a high-level noise stimulus is applied for 1 to 2 hours, under anesthesia or not, either to one or both ears. Focusing on the rat, a typical stimulation paradigm consists of an octave-band noise with a peak intensity of 116 dB SPL centered at 16 kHz for 1 hour.[65] However, sound level (80 dB SPL –130 dB SPL), duration (2 min–7 hours), frequency (2 kHz –22 kHz), and frequency range (pure tones to broadband noise) vary significantly between studies. Given the large variability, no clear rule of thumb emerges as to which *combination* of parameters consistently leads to tinnitus, and in the case of blast-wave–induced tinnitus, parameters might be even harder to quantify. Despite uncertainty on the exact parameters, these studies indicate that the reliable emergence of noise-

induced tinnitus will depend on a yet-to-be-determined function of intensity, spectrum, duration, and statistics of the traumatic stimulus.

Additional "modulators" of this function will include sex or gender and stressor factors.[36,43]

If the characteristics of the noise exposure (intensity, spectrum, duration) can be used to predict the pattern of the resulting audiologic threshold shifts, then it should be possible to predict the patients' tinnitus percept ("What does your tinnitus sound like?") that would correspond to the shifted audiogram. In several early human experiments previously mentioned, some rules were consistently observed, such as the fact that when subjected to pure tone trauma, the participants' tinnitus was half an octave greater than the frequency of trauma.[66] Unfortunately, more general rules regarding the relationship between hearing deficits as measured by an audiogram and the tinnitus percept, even for stable losses associated with PTS, are ambiguous and rarely linear. This is no doubt due in part to the fact that high-frequency (human) audiometric data are usually very sparse above 4 kHz. If subjects have a perception of pitch to their tinnitus, about three-quarters of these subjects report it as being greater than 8 kHz, limiting the actual scope of many studies that never measured the audiogram densely enough, if at all, around the tinnitus frequency. The consistent finding is that tinnitus pitch, if it is perceived, generally falls within the area of hearing loss, with the strongest predictor of tinnitus pitch being the degree of hearing loss or location along the frequency axis of deepest hearing loss.[67,68] However, it should be noted that other researchers have found a "lack of reliability," with the pitch match to a pure tone being quite variable on repeated measures, often spanning a range of 2 to 3 octaves.[69]

CENTRAL ISSUES ASSOCIATED WITH HEARING LOSS

It is likely that an acute trauma to the cochlea leads to hearing loss, decreasing the neural input to the CNS. For instance, it is known that even normal hearing volunteers who wore silicone earplugs for 7 days to simulate a temporary hearing loss developed tinnitus in that short timescale, although the tinnitus resolved after removing the earplug.[70] It is thought that a sudden reduction in part of the cochlear output may be compensated for by a change in the neural gain of neurons along the auditory pathway, resulting in increased spontaneous neural activity. Thus, localized cochlear injury/trauma manifested as synaptopathy, hair cell loss/dysfunction, or a significant change of endocochlear potential results in a location- or frequency-specific decrease in the activity of part of the auditory nerve. Upregulation of activity in the central auditory pathway is a compensatory effort to counteract the lack of signals in that particular frequency region. This, possibly coupled with other factors such as increased synchrony across neighboring auditory nerve fibers, may underlie the initial induction of tinnitus. This gain increase leads to the perception of a continuous sound and may also underlie the hyperacusis often associated with chronic noise-induced tinnitus.[71,72]

It might be helpful to think of the frequently used analogy between the pathophysiology of tinnitus and that of pain and phantom limb perception.[73] It has been noted that[74] (1) pain and tinnitus can arise from a great variety of lesions; (2) there is no one specific mechanism for pain perception; (3) pain is a subjective phenomenon that is difficult to quantify; and (4) treatment of pain symptoms is difficult and often ineffective. The analogy between chronic pain and tinnitus is particularly apt with respect to their acute peripheral generation and their chronic central persistence once the acute injury has resolved or at least stabilized. Chronic pain is often a consequence of peripheral injury, in which the initial injury does not typically account for the

sustained nature of the pain. Similarly, although tinnitus is often associated with peripheral cochlear dysfunction, that dysfunction may not account for the sustained and distressing tinnitus perception. The consequent large variation between individual experiences of pain makes the development of effective therapy difficult.

Although, in this article, for lack of space, the authors have not touched on the importance of the interactions between the somatosensory system and tinnitus, they briefly mention that in an important segment of the tinnitus population, nonauditory networks also involved in chronic pain (perception, salience, distress) are implicated.[75] These networks might be involved in the maintenance of the perception of tinnitus even once the initial tinnitus triggering event has resolved.[76] Phantom pain and phantom sound perception might share the same basic underlying mechanisms, wherein the maladaptive cortical activity in the auditory cortex becomes a conscious percept by the larger brain networks located in the frontal and parietal areas of cortex, such as "self-awareness" and "salience network." The latter network intersects with the central autonomic control system and affects the limbic–auditory and somatosensory interactions, which are indispensable for consciously maintaining the phantom perception. This perception may become associated with distress, simultaneously activating distress networks located in anterior cingulate cortex, anterior insula, and amygdala.[75,76]

SUMMARY

There are many types of hearing loss; the broad categories being conductive hearing loss, sensorineural hearing loss (itself divided into temporary, hidden, and permanent), and hearing loss of central origin. All indications are that tinnitus, when not caused directly by a CNS issue (eg, stroke), is always associated with one or more forms of hearing loss. On the one hand, this strong comorbidity indicates that, although medical treatment of tinnitus might exist, it is unlikely there will a cure for tinnitus independently of a cure for hearing loss. On the other hand, it points to tinnitus potentially being an early symptom of an underlying auditory injury before measurable audiometric changes.

Be that as it may, the relationship between the characteristics of the hearing loss (for instance the shape of the audiogram) and the tinnitus percept (its pitch if any and its perceived spectrum and localization) does not follow any clear rules. Also, although tinnitus is intimately linked with peripheral cochlear dysfunction, cochlear damage does not account for the sustained and sometimes distressing nature of tinnitus perception, and in particular it does not account for the reaction of the patient to the tinnitus.

A lot of progress has been made in understanding the events that lead to hearing loss and its associated tinnitus from noise exposure, whether sudden and traumatic or resulting from a lifelong exposure to noise, but much more has yet to be observed, learned, and understood before we can hope to have a cure for hearing loss in all its forms and the associated tinnitus.

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