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Underlying Mechanisms of Tinnitus: Review and Clinical Implications

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Abstract

Background—The study of tinnitus mechanisms has increased tenfold in the last decade. The common denominator for all of these studies is the goal of elucidating the underlying neural mechanisms of tinnitus with the ultimate purpose of finding a cure. While these basic science findings may not be immediately applicable to the clinician who works directly with patients to assist them in managing their reactions to tinnitus, a clear understanding of these findings is needed to develop the most effective procedures for alleviating tinnitus.

Purpose—The goal of this review is to provide audiologists and other health-care professionals with a basic understanding of the neurophysiological changes in the auditory system likely to be responsible for tinnitus.

Results—It is increasingly clear that tinnitus is a pathology involving neuroplastic changes in central auditory structures that take place when the brain is deprived of its normal input by pathology in the cochlea. Cochlear pathology is not always expressed in the audiogram but may be detected by more sensitive measures. Neural changes can occur at the level of synapses between inner hair cells and the auditory nerve and within multiple levels of the central auditory pathway. Long-term maintenance of tinnitus is likely a function of a complex network of structures involving central auditory and nonauditory systems.

Conclusions—Patients often have expectations that a treatment exists to cure their tinnitus. They should be made aware that research is increasing to discover such a cure and that their reactions to tinnitus can be mitigated through the use of evidence-based behavioral interventions.

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Keywords

Auditory cortex; cochlear nucleus; hyperacusis; tinnitus; tonotopy; spontaneous activity

Many articles, chapters, and books have been written to describe what is known or theorized about underlying mechanisms of tinnitus. Research has been conducted around the world in the attempt to understand what takes place at the molecular, cellular, or neural network level that would explain the symptoms defining tinnitus. Such research has increased exponentially over the past decade, and currently many biomedical researchers conduct work devoted solely to this effort. Audiologists typically are not aware of ongoing research, recent discoveries and advances, and the importance of the research. The primary purpose of this article is to review some of the putative tinnitus mechanisms in a manner comprehensible to audiologists and other clinicians who provide tinnitus-specific services. The ultimate goal of the basic research reviewed herein is to identify the biologic mechanisms that give rise to tinnitus so that scientifically rational therapies can be developed to completely suppress tinnitus. Understanding these mechanisms may also lead to a cure for hyperacusis, since tinnitus and hyperacusis may result from a common mechanism (Nelson and Chen, 2004; Noreña, 2011). Support for this view comes from clinical studies showing that sound therapy and counseling reduce symptoms of not only tinnitus but also hyperacusis (Jastreboff and Jastreboff, 2006).

What is currently known about neural correlates of tinnitus has mostly been discovered through animal studies, psychoacoustic measures of tinnitus in humans, imaging studies, and speculation based on knowledge of auditory pathology. Tinnitus studies may be informed by studies on chronic pain that involve many of the compensatory central nervous system changes in response to the loss of peripheral input similar to that seen in tinnitus.

BACKGROUND

Objective and Subjective Tinnitus

Most broadly, there are two types of tinnitus—objective tinnitus and subjective tinnitus. Objective tinnitus refers to the perception of acoustic vibratory activity that is generated mechanically within the body. Objective tinnitus can have its origin in vascular, muscular, skeletal, or respiratory structures (Henry et al, 2005). These “body sounds” (somatosounds) have an internal acoustic source (Hazell, 1995; Dobie, 2004). The most common somatosound is pulsatile tinnitus that fluctuates in synchrony with the heartbeat (Sismanis, 2003; Lockwood et al, 2004). Somatosounds can also be nonpulsatile, such as the spontaneous contraction of middle ear muscles or the Eustachian tube. Information about diagnosing and identifying objective tinnitus is available elsewhere (Perry and Gantz, 2000; Schwaber, 2003; Levine, 2004; Wackym and Friedland, 2004).

By far the majority of patients have subjective tinnitus that is not associated with an identifiable sound source. Tinnitus of this type is assumed to be caused by or associated with damage to the auditory system (Dobie, 2001; Roberts, 2011), that is, “sensorineural” tinnitus or tinnitus with a neurophysiologic origin. The histopathologies or cellular changes that

presumably give rise to subjective tinnitus can exist anywhere between the cochlea and auditory cortex, although the majority of cases are triggered by or associated with cochlear damage (Espir et al, 1997; Hazell, 1998; Rodriguez-Casero et al, 2005). Tinnitus is sometimes only heard when in quiet environments; however, in some cases, tinnitus is perceived constantly and can become very bothersome, interfering with concentration, sleep, and daily activities. Some individuals experience tinnitus that can even be heard in fairly intense background noise (Tyler et al, 2008). Further references to tinnitus in this article pertain to tinnitus of the subjective type, which is by far the most common type of tinnitus (Møller, 2011a).

Perception versus Reactions

Tinnitus is often characterized in terms of its loudness, pitch, spectral qualities, location within the ear or head, and temporal features. The perceptual features of tinnitus are assessed with psychoacoustic measures, verbal descriptions, or subjective rating scales. An individual's *reactions* to tinnitus refer to its impact on daily life, such as emotional distress, depression, concentration difficulties, reduced sense of control, sleep disturbance, and other factors that may involve nonauditory regions of the nervous system (e.g., hippocampus or amygdala) (Henry et al, 2005). *The present article focuses on mechanisms that underlie tinnitus perception and as such are likely to involve the classical auditory pathway and its interaction with other brain systems. An individual's reactions to tinnitus, on the other hand, are a consequence of tinnitus perception interacting with these additional circuits/systems.* We will return to this important distinction later, when we discuss nonauditory systems/circuits that are active in tinnitus and their role in the perception of tinnitus. Although it is presently not possible to eliminate the tinnitus percept (i.e., to "cure" tinnitus), an individual's reactions to tinnitus are clearly modifiable.

Noise and Other Causes of Tinnitus

Events associated with the onset of tinnitus, for example, impulse noise exposure, are often considered "causes" of tinnitus. Significant insults to the auditory periphery lead to a subsequent loss of normal input to the auditory brain and numerous neurophysiologic and neurochemical changes (described below); however, which of the biologic and/or structural changes is responsible for tinnitus is still not fully known, even when the causal event is unequivocal. We therefore use the term *cause* in the context of events leading to the onset of tinnitus. Similarly, tinnitus *etiology* refers to events associated with tinnitus onset—not to the underlying mechanism. The terms *cause* and *etiology* can thus be used interchangeably.

Any disorder of the brain, especially to the auditory system, can cause tinnitus (Coles, 1995; Dobie, 2001). Hearing loss in particular increases the likelihood of experiencing chronic tinnitus (Coles, 2000). Among young adults, the most common cause of tinnitus is noise exposure (Axelsson and Barrenas, 1992; Penner and Bilger, 1995). Among the elderly, age-related hearing loss (presbycusis) is the most common cause of tinnitus (Nicolas-Puel et al, 2002), although the impact of early cochlear insults could sum with aging to accentuate tinnitus (Roberts et al, 2010). Other tinnitus etiologies include cardiovascular and cerebrovascular disease, medications, head/neck trauma and injury, and hyper- and hypothyroidism (Hoffman and Reed, 2004). Often, the etiology of tinnitus is considered

idiopathic, as 40% of patients report “no known events” associated with their tinnitus onset (Meikle and Griest, 1989). Importantly, if a person with tinnitus has hearing thresholds “within normal limits” (i.e., within 25 dB HL), there may still be evidence of auditory damage, such as cochlear dead regions (Weisz et al, 2006; Roberts, 2011) or elevation of hearing thresholds in the tinnitus frequency range (see below; Roberts et al, 2008). Importantly, many individuals who claim to have tinnitus with “normal hearing” in the conventional audiometric range (125 to 8000 Hz) often have elevated thresholds at frequencies above 8000 Hz. One quarter (8/32) of the tinnitus cases studied by Roberts et al (2006) had thresholds 25 dB or better in both ears up to 8 kHz but varying degrees of impairment at higher frequencies.

Although specific events associated with the onset of tinnitus may vary, the great majority of patients with tinnitus have some degree of hearing loss indexed by the audiogram (Axelsson and Ringdahl, 1989; Davis and Refaie, 2000; Henry and Wilson, 2001). This suggests that tinnitus, associated with different specific etiologies, impacts a final common path, irrespective of the degree or pattern of impairment in peripheral or central auditory pathways. When individuals with tinnitus are asked to rate sound frequencies between 5 and 12 kHz for similarity or “likeness” to their tinnitus, the resulting likeness ratings scores mirror the pattern of hearing loss (Noreña et al, 2002; Roberts et al, 2008). This finding suggests that tinnitus is generated by aberrant neural activity taking place in frequency regions deafferented by hearing loss (Roberts et al, 2010). However, paradoxically some young patients with normal hearing thresholds experience tinnitus while some older individuals with significant hearing loss do not experience tinnitus (Kentish et al, 2000; Mrena et al, 2002; Weisz et al, 2006; Savastano et al, 2009). Nonetheless, when these two groups are compared with their appropriate controls (i.e., young individuals without tinnitus and older patients with tinnitus), in both cases hearing thresholds above 2 kHz were ~10 dB greater in the groups with tinnitus, suggesting a relationship to audiometric function (Roberts et al, 2008). Moreover, normal audiometric function per se is unlikely to detect inner hair cell loss or auditory nerve damage (Weisz et al, 2006).

COCHLEAR DAMAGE AND IMPAIRMENTS OF HEARING

Mechanisms of cochlear damage leading to hearing loss have been described elsewhere, both with respect to noise damage (Liberman and Beil, 1979; Salvi et al, 1979) and drug-induced ototoxicity (Huang and Schacht, 1989; Yorgason et al, 2006). Reversible hearing loss is manifested by a temporary threshold shift (TTS), that is, increased hearing thresholds that recover within days after exposure to hazardous noise or after discontinuing an ototoxic drug. Repeated exposure to hazardous noise will eventually result in permanent threshold shift (PTS) (Dobie, 2001).

TTS can result from a number of different cochlear pathologies (Henderson et al, 2011). The structural changes associated with TTS are either repairable or they result in permanent pathology that is undetectable by conventional audiometric testing. Brainstem evoked-response studies reveal altered wave I/V amplitude ratios in individuals with tinnitus and normal audiograms (Schaette and McAlpine, 2011). Also, a single exposure to impulse noise or some drugs can result in immediate and permanent hearing loss. Both TTS and PTS can

result in either temporary or permanent tinnitus. Paradoxically, some cases of tinnitus precede the appearance of hearing loss while in other cases, tinnitus appears many years after a PTS. The “trigger” for tinnitus onset in such cases is often associated with aging and/or emotional stress (Hazell, 1995; Roberts et al, 2010).

Recent studies have shown how cochlear damage can lead to unexpected functional changes in the central auditory system that may be related to hyperacusis and tinnitus. Schaette and McAlpine (2011) and Gu et al (2012) found that Wave I of the auditory brainstem response (ABR) evoked by noise bursts of 90 and 100 dB SPL were reduced in tinnitus patients with hearing thresholds at 20 dB HL or better at 8 kHz compared to controls. This indicated reduced output from the cochlea in the tinnitus patients compared to controls despite their normal audiometric function. Paradoxically, ABR Wave V evoked by the same sounds was either normal (Schaette and McAlpine, 2011) or augmented (Gu et al, 2012) in the tinnitus patients compared to controls. These results imply that following cochlear damage neural gain increased in central auditory pathways, somewhere between the generators of Wave I (the cochlear nucleus) and Wave V (the inferior colliculus) and possibly in higher centers as well. Evidence for increased gain in central auditory structures may account for reduced loudness tolerance reported in human tinnitus patients (see Syka, 2002, for a review). Hébert et al (2013) found that tinnitus sufferers chosen to have audiometric thresholds 15 dB or better up to 8 kHz perceived sounds to be louder than did threshold matched controls, for sounds presented above but not below 60 dB SPL, revealing heightened sensitivity to sound in the tinnitus group. Animal studies have also reported hidden cochlear damage reflected as a reduced Wave I of the ABR but not the audiogram (Kujawa and Liberman, 2009), and increased neural gain in central auditory structures (Salvi et al, 1990; Qiu et al, 2000; Heinz and Young, 2004; Engineer et al, 2011) after noise exposure.

NEURAL CHANGES IN TINNITUS

While human tinnitus is relatively easy to characterize perceptually or psychoacoustically, the neural signals in the human auditory system that give rise to tinnitus are practically inaccessible to invasive intracranial or intracerebral scientific exploration (Brix, 1995). Therefore, other functional measures have been used to assess tinnitus in humans that are less invasive such as imaging (see Adjamian et al, 2009; Lanting et al, 2009; Melcher, 2012, for excellent reviews) and magnetoencephalography (Weisz, Moratti, et al, 2005; Baizer et al, 2012). Auditory evoked potential (AEP) measures, also noninvasive, have demonstrated various patterns of neural activity recorded in tinnitus individuals (e.g., prolonged latencies, enhanced and/or reduced amplitudes), but replication of these results is lacking. Results from these measures suggest abnormal neural activity associated with tinnitus but do not offer insight into the neural mechanism(s) giving rise to the perception (ABR [Maurizi et al, 1985; Lemaire and Beutter, 1995; Rosenhall and Axelsson, 1995; Gerken et al, 2001; Kehrle et al, 2008; Schaette and McAlpine, 2011; Gu et al, 2012]; midlatency AEPs [Gerken et al, 2001; Theodoroff et al, 2011]; long latency AEPs [Attias et al, 1993; Jacobson et al, 1996; Noreña et al, 1999; Kadner et al, 2002]; and magnetic field responses [Hoke et al, 1989; Jacobson et al, 1991; Colding-Jørgensen et al, 1992; Diesch et al, 2004; Weisz, Wienbruch, et al, 2005]).

In animals, the reverse is true—the neural changes associated with tinnitus can be directly studied, while a description of its perceptual features (loudness, pitch, location) is difficult to obtain except by time-consuming behavioral methods. Nonetheless, animal studies have enabled the direct investigation of neural changes associated with tinnitus. There are also many studies of the neural changes associated with hearing loss induced by different methods in animals, which are putative correlates of tinnitus.

Animal Models of Tinnitus

The first animal behavioral model for assessing tinnitus was developed in 1988 (Jastreboff et al, 1988). Numerous animal models have since been developed to conduct biomedical research in tinnitus (Bauer et al, 1999; Heffner and Harrington, 2002; Guitton et al, 2003; Rüttiger et al, 2003; Heffner, 2011; Salvi, Lobarinas, et al, 2011). Most of the behavioral methods to assess tinnitus have utilized rats, hamsters, chinchillas, and mice (Salvi, Lobarinas, et al, 2011). A variety of methods have been used. To illustrate, a period of silence in background noise may be paired with foot shock in animals trained to press a lever for food. In the presence of silence, which signals an impending foot shock, lever-pressing will be suppressed. If the animals are then exposed to a tinnitus-inducing agent (high doses of sodium salicylate or quinine or intense sound), then animals with tinnitus may respond to the quiet condition *as if sound is present*. While behavioral paradigms are important for investigating tinnitus mechanisms, a limitation is that they require prior behavioral conditioning (Brozoski et al, 2007; Tzounopoulos, 2008).

In 2006, a new, more efficient method of testing for tinnitus in animals was introduced (Turner et al, 2006). This new method, which obviates behavioral conditioning, is based on the acoustic startle reflex elicited by a short duration, high-intensity sound. The animal is placed on a platform that detects muscle activity associated with the startle reflex (Turner et al, 2006; Salvi, Lobarinas, et al, 2011). The normally robust startle reflex can be suppressed by embedding a silent gap in a continuous low-level background noise just prior to presenting the startle stimulus. If after a tinnitus-inducing procedure the silent gap in the background noise fails to suppress the startle reflex, then the animal is assumed to have tinnitus under the assumption that the tinnitus percept fills in the silent gap. If a narrow band noise is used as the background signal in the gap startle paradigm, then the pitch of the tinnitus can be assessed by varying the center frequency of the background noise. While promising, there are reasons for caution when interpreting the results of this and other animal models of tinnitus (Eggermont, 2013). For example, it is possible that compromised auditory processing can impair detection of the silent gap. Also, hearing loss, hyperacusis, and disinhibition of the startle response itself may affect the results (see Dehmel, Eisinger, et al, 2012, for discussion of these issues). Further work is underway to elucidate this model (Fournier and Hebert, 2013; Lobarinas et al, 2013; Longenecker and Galazyuk, 2012).

Development of animal models for tinnitus is creating the framework to conduct research leading to a better understanding of tinnitus mechanisms as well as determining the effects of potential tinnitus-suppressing treatments (Guitton et al, 2003; Lobarinas et al, 2006; Guitton and Dudai, 2007; Brozoski et al, 2007, 2010; Salvi, Lobarinas, et al, 2011). Already, numerous drugs have been tested for tinnitus suppression using animal models, including

calcium channel antagonists, gamma aminobutyric acid (GABA) agonists, n-methyl d-aspartate (NMDA) antagonists, benzodiazepines, and potassium channel modulators. While some results are promising, much more research is needed to determine if these different drugs are viable for suppressing or eradicating tinnitus in humans.

Peripheral or Central Origin of Tinnitus

Early theories of tinnitus mechanisms assumed the generator for tinnitus resides in the inner ear (Møller, 2011b). *Peripheral* generation of tinnitus was posited because: (a) patients often perceive tinnitus within their ears (Jastreboff, 1990); and (b) a strong association exists between tinnitus and hearing loss caused by cochlear damage (Kiang et al, 1970). It seemed only logical to assume that the tinnitus generator was located at the site of known pathology, especially when both occurred on the same side of the head (Hazell, 1995). However, the finding that bilateral auditory nerve sectioning did not always eliminate tinnitus (Fisch, 1970; House and Brackmann, 1981; Pulec, 1984) suggested that tinnitus could be generated centrally (Douek, 1987; Feldmann, 1995). This finding supported early theories of *central* tinnitus generation. For example, it was theorized that tinnitus that could be “masked” by sound originated in the cochlea, whereas unmaskable tinnitus had a central origin (Shulman et al, 1985). Tonndorf (1987) suggested that numerous mechanisms could be responsible for tinnitus, including mechanisms involving central generators. Over time, the prevailing view shifted to a belief that tinnitus, even when triggered by cochlear damage, has its origin in the central auditory system (CAS) (Jastreboff, 1990; Penner and Bilger, 1995; Lockwood et al, 1998).

Current Understanding

Nearly all forms of cochlear damage decrease the neural output from the cochlea that is sent to the CAS. This decreased output is readily detected as a reduction in the amplitude of the acoustic nerve compound action potential (CAP) (Popelár et al, 1987; Schmiedt et al, 1996; Qiu et al, 2000; Lobarinas et al, 2006). Cochlear destruction and noise damage initially cause a reduction in spontaneous discharge rates in the cochlear nucleus (the CN) (Koerber et al, 1966; Salvi et al, 1978). However, beginning approximately seven days following cochlear damage, neurons in the dorsal part of the cochlear nucleus (DCN) respond by increasing (up-regulating) both spontaneous and sound-evoked neural activity (Zhang and Kaltenbach, 1998; Kaltenbach, 2000; Brozoski et al, 2002; Vogler et al, 2011). This increase in activity occurs over much of CN, but it tends to be centered near regions tuned to the cochlear damage. Moreover, increases in spontaneous rate in the DCN were correlated with behavioral evidence of tinnitus (Brozoski et al, 2002; Kaltenbach et al, 2004). This up-regulation in spontaneous activity is thought to be caused by an alteration in the normal balance between excitatory and inhibitory nerve transmission brought about by loss of inhibition (disinhibition), which leads to an increased firing rate (Milbrandt et al, 2000; Wang et al, 2009). These changes occur because of plastic central nervous system (CNS) changes based on experience and/or loss of CAS input due to damage (Brozoski et al, 2002; Møller, 2011b). In essence, pathology in the cochlea and reduced auditory nerve activity can result in increased and/or bursting neural activity in response to plastic compensatory changes within central auditory structures that attempt to restore homeostasis (Møller, 2003; Noreña 2011; Richardson et al, 2012).

Dorsal Cochlear Nucleus

The auditory nerve enters the brainstem (just below the juncture between the medulla and pons) to synapse in the CN. The DCN receives input from the descending branch of the auditory nerve, the first synapse in the CAS. Changes in DCN as a result of damage to the periphery have been extensively studied in a number of tinnitus models, beginning with the finding that exposure to intense noise caused a marked increase in DCN spontaneous activity (Kaltenbach et al, 1998). DCN hyperactivity could also be induced by the cancer chemotherapeutic cisplatin, which selectively destroys outer hair cells (OHCs) (Melamed et al, 2000; Kaltenbach et al, 2002). Additional studies showing a variety of causes of DCN hyperactivity have been reviewed by Kaltenbach (2006).

DCN studies have focused on fusiform (also called pyramidal) cells because they are the projection neurons to the inferior colliculus and are thought to possess qualities of plasticity associated with aging and noise exposure (Brozoski et al, 2002; Caspary et al, 2005; Baizer et al, 2012). Indeed, fusiform cells in the DCN have been shown in a number of studies to become hyperactive in animals displaying behavioral evidence of tinnitus.

At least two lines of evidence have emerged from extensive study of the DCN. First, studies have shown that DCN hyperactivity caused by peripheral damage correlates with behavioral evidence of tinnitus. A caveat to this known correlation is that the DCN may be necessary for tinnitus initiation but may not be necessary for maintenance in chronic tinnitus (Brozoski et al, 2002).

Second, somatosensory inputs to the DCN can modulate the DCN hyperactivity (Dehmel, Koehler, et al, 2012). These inputs may explain why the acoustic properties of tinnitus (its loudness, pitch, or timbre) can often be modulated by movements of, or pressure on, the head, neck, and jaw (Pinchoff et al, 1998; Levine, 2004; Simmons et al, 2008). Somatic modulation of tinnitus has been reported to occur in up to two-thirds of patients with tinnitus when systematically studied (Sanchez et al, 2002; Levine et al, 2003; Shore et al, 2007). These observations reflect the neural connections known to exist between somatosensory centers and the CAS. With regard to the DCN, somatosensory fibers connect to the apical dendrites of the fusiform cells, which affect the output of the DCN to more central levels of the CAS. Details of the neural connections between the DCN and somatosensory systems have been described (Shore et al, 2007). Strikingly, inputs from somatosensory pathways to the DCN are up-regulated over a time interval of approximately 2 wk after deafening, revealing a form of neural plasticity that may compensate for diminished auditory input to the DCN and enhance the somatic modulation of tinnitus (Zeng et al, 2009). Considerable evidence supports the role of the DCN as mediating somatic modulation of tinnitus (Shore et al, 2007; Dehmel et al, 2008), but other regions of the CAS that receive somatic inputs (e.g., trigeminal inputs) from the shoulders, neck, and head are likely to be involved (Lockwood et al, 1998; Simmons et al, 2008). In addition to the DCN, the tinnitus percept as well as activity at different levels in the auditory pathway can be modulated in other ways such as with a cochlear implant that stimulates the auditory nerve (Ito and Sakakihara 1994; Di Nardo et al, 2009), transcranial magnetic and electrical stimulation of auditory and nonauditory cortex (De Ridder, Vanneste, et al, 2011; Zhang et al, 2011), eye movements

(Whittaker, 1982; Lockwood et al, 2001), and sound stimulation (Henry et al, 2006; Jastreboff, 2007).

Ventral Cochlear Nucleus

Vogler et al (2011) observed increased activity in the ventral cochlear nucleus (VCN) following cochlear damage. One possibility is that the same circuit that provides inhibition to the projection neurons of the DCN, and appears down-regulated in tinnitus, projects to the VCN (Wickesberg and Oertel, 1990). This suggests that the same inhibitory cells whose function may be down-regulated by partial peripheral deafferentation in DCN models of tinnitus (Brozoski et al, 2002), project less inhibition to the anteroventral cochlear nucleus (AVCN), which could account for increased AVCN activity. Regardless of its source, hyperactivity in specific cell types in the VCN following noise trauma may contribute to hyperactivity expressed in higher levels of the auditory projection pathway including the inferior colliculus (Robertson et al, 2013).

Several observations point to neuroplastic changes occurring in the VCN after deafening or noise exposure, which may play a role in tinnitus. Gu et al (2012) suggested that augmentation of ABR wave V in relation to wave I in human tinnitus sufferers may reflect a neuroplastic compensatory increase in activity in a pathway originating in spherical bushy cells in the VCN following reduced output from the cochlea. Up-regulation of somatosensory inputs to the DCN after cochlear ablation (also described above) is expressed as well in the VCN (Zeng et al, 2012). Kraus et al (2011) found a strong increase in a growth-associated protein (GAP-43) in the medial central VCN of rats after acoustic trauma. GAP-43 is a well-established marker for axonal outgrowth and synaptic sprouting known to occur in this region following cochlear ablation or noise trauma in this species. However, in the latter study up-regulation of GAP-43 was significantly greater in rats that did not give behavioral evidence of tinnitus. This suggests that the neuronal changes mediated by GAP-43 may have reduced tinnitus.

Inferior Colliculus

Partial peripheral deafferentation/decreased acoustic nerve input to the cochlear nucleus leads to increased fusiform/DCN output to the inferior colliculus (IC), which sends activity to higher levels of the CAS. More specifically, both DCN and AVCN project either directly or indirectly to the contralateral IC. It was hypothesized that this increased discharge rates/input to the IC would impact activity of cells in the IC (Jastreboff and Sasaki, 1986). As predicted in both human and animal studies, IC neurons showed increased spontaneous neural activity following noise exposure, suggesting that this might be a neural correlate of tinnitus (Robertson and Mulders, 2012). Animal studies involving noise exposure have shown hyperactivity in IC neurons with tuning close to the exposure frequency (Ma et al, 2006; Mulders and Robertson, 2009; Mulders et al, 2010; Longenecker and Galazyuk, 2011; Manzoor et al, 2012). In addition, Bauer et al (2008) showed that, in animals with behavioral evidence of tinnitus from three different insults, the increase in spontaneous firing rates in the IC was delayed for a number of days following the exposure. This suggests that hyperactivity of IC neurons may be associated with chronic tinnitus but not acute tinnitus, which begins immediately following a noise exposure (Atherley et al, 1968; Stolzberg et al,

2012). The increase in spontaneous activity may be related to reduced IC inhibitory neurotransmission in tinnitus and noise exposure models (Milbrandt et al, 2000; Dong et al, 2010; Roberts et al, 2010; Wang et al, 2011). In summary, although studies to date clearly show increased neural activity in tinnitus models, presumably due in part to the down regulation of inhibitory neurotransmitter function, the role and extent of the IC in the perception of tinnitus is not presently known (Robertson and Mulders, 2012).

Medial Geniculate Body

Few studies have examined the impact of tinnitus and sound exposure in auditory thalamus, that is, the medial geniculate body (MGB). The MGB is the thalamic station in the CAS; thus, it must at least serve as a conduit for the tinnitus signal. The connections of the MGB with the ascending and descending CAS and with nonauditory structures strongly suggest that it is a key structure in tinnitus pathology (Rauschecker et al, 2010; Leaver et al, 2011; Malouff et al, 2011). Individuals most impacted by their tinnitus have a significant emotional component to their tinnitus (tinnitus sufferers). The MGB projections to the amygdala are important for auditory fear conditioning, making this pathway a possible key connection between the tinnitus percept and the emotion component (Quirk et al, 1995; McKernan and Shinnick-Gallagher, 1997; Rogan et al, 1997; Rauschecker et al, 2010; Weinberger, 2011), and recent studies have revealed hyperactivity in the amygdala following a salicylate treatment that reliably induces tinnitus (Chen et al, 2012). Well-characterized inhibitory MGB inputs from the thalamic reticular nucleus and the inferior colliculus may be impacted by tinnitus (see Richardson et al, 2012). The inputs from the thalamic reticular nucleus are involved in the regulation of attention and gating signals in the thalamus (Guillery et al, 1998; Cotillon-Williams et al, 2008; see Richardson et al, 2012, for review). The importance of the thalamus as a structure gating sensory signals to the cortex and its connections to the limbic/emotional structures of the brain, make it an important structure for future study.

Auditory Cortex

Numerous animal studies have shown that cochlear damage caused by high or moderate level noise exposure and ototoxic drugs leads to an increase in the amplitude of cortical evoked potentials and in some cases a reorganization of tonotopic maps in primary auditory cortex (Robertson and Irvine, 1989; Salvi et al, 1990; Rajan and Irvine, 1998; Qiu et al, 2000; Syka, 2002; Noreña et al, 2003; Yang et al, 2007; Roberts, 2011; Yang et al, 2011). The reorganization involves the cortical region of hearing loss being retuned to respond to frequencies close to the edge of normal-hearing frequencies. This finding led to the theory that the “over-representation of edge frequencies” contributes to the generation of tinnitus corresponding to the edge frequencies (Rauschecker, 1999; Yang et al, 2011). Map reorganization, which has been documented in human tinnitus sufferers (Wienbruch et al, 2006), suggests that after hearing loss preexisting inputs on lateral connections to neurons in the hearing loss region have a stronger influence on these neurons than do surviving inputs from thalamocortical pathways.

Map reorganization in animal models of hearing loss is associated with changes in the response properties of auditory neurons in the hearing loss region that may be important in the generation of tinnitus. These changes include a shift in the balance of excitation and

inhibition in auditory cortical networks (Scholl et al, 2008), increased spontaneous activity of neurons in central auditory structures including the auditory cortex (Eggermont and Kenmochi, 1998; Noreña et al, 2003), increased burst firing in some of these structures including the auditory cortex (Noreña et al, 2003) and the DCN (Finlayson and Kaltenbach, 2009), changes in the gain of auditory cortical neurons (Engineer et al, 2011), and increased synchronous activity among cortical neurons affected by hearing loss (Noreña and Eggermont, 2003; Seki and Eggermont, 2003). Age-related changes in brain function affecting intracortical inhibition may play a contributing factor (Llano et al, 2012). Although the specific contribution of these various neural changes to tinnitus percepts is not fully understood, enhanced neural synchrony (phase locked firing) among auditory cortical neurons is a likely proximal correlate of tinnitus, because more than most neural correlates it is largely confined to the hearing loss frequencies (Noreña and Eggermont, 2003) where in human subjects tinnitus percepts also localize (Noreña et al, 2002; Roberts et al, 2008).

Nonauditory Structures

Research in animal models has identified several changes in the activity of auditory neurons that may contribute to the generation of tinnitus. Using c-fos immunolabeling to identify regions of increased activity, Wallhäuser-Franke (1997) found increased labeling in brain regions associated with stress such as locus coeruleus, periaqueductal gray, and lateral parabrachial nucleus in animals with salicylate-induced tinnitus. More recently, Chen et al (2012) found enhanced sound-evoked activity and retuning of neurons in the amygdala following salicylate-induced tinnitus. While many of these changes reflect reduced input to central auditory structures from damaged ears, the output of the affected neurons remains intact and distributes back down auditory pathways as well as to other regions of the brain concerned with nonauditory functions.

The most common procedures used to image the neural correlates of tinnitus in humans are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Lanting et al, 2009; Middleton and Tzounopoulos, 2012). Most generally, these procedures enable the observation of changes in regional cerebral blood flow, or in glucose or oxygen metabolism in the blood, within the CNS. These changes are indirectly related to the magnitude of neural activity. It is important to note, however, that the changes observed by imaging techniques may not directly correlate with spontaneous spike rates measured in animals. The most important information obtained from these techniques is the location, the extent, and the magnitude of neural activity. Because of the limited temporal resolution of fMRI and PET these techniques can primarily identify which brain regions have an abnormal amount of neural activity in tinnitus subjects (Lanting et al, 2009).

Numerous imaging studies for tinnitus have been conducted and have been reviewed in detail (Weissman and Hirsch, 2000; Lanting et al, 2009; Langguth and DeRidder, 2011; Melcher, 2012; Middleton and Tzounopoulos, 2012). One of the first imaging studies was conducted by Lockwood et al (1998). Subjects with unilateral tinnitus were selected because they were able to modulate the loudness of their tinnitus by performing voluntary oral facial movements. Using PET, changes in cerebral blood flow were observed in the hippocampus, part of the limbic system, and auditory cortex contralateral to the tinnitus in response to the

voluntary changes in loudness. This and other studies provide general evidence for changes in structure and function at various sites in the CAS that are associated with tinnitus (Adjamian et al, 2009).

While these studies strongly implicate the CAS and the limbic system as being critically involved in the processing of tinnitus, other findings have implicated brain regions known to be involved in attention, memory, and cognitive processing. Prominent among these regions are the middle and superior frontal gyri (Mirz et al, 2000; Mirz et al, 1999), the cingulate gyrus (Mirz et al, 1999; Plewnia et al, 2007), the precuneus (Mirz et al, 1999), and the parietal cortices (Mirz et al, 1999). Notably, these same brain regions were identified by Dehaene and Changeux (2011) as components of a “global neuronal workspace” that is engaged by normal hearing subjects when they are required to consciously process task stimuli and make discriminated behavioral responses to achieve task goals. On the basis of this evidence, De Ridder, Elgoyhen, et al (2011) proposed that engagement of brain structures in the global workspace is essential for the conscious experience of a tinnitus sound.

In addition to these findings from fMRI and PET research, there are several reports of resting-state oscillatory brain changes recorded by electroencephalography (EEG) and its magnetic counterpart magnetoencephalography (MEG) in tinnitus patients. Compared to controls, tinnitus patients showed decreased oscillatory activity in the alpha band (10–14 Hz) (Weisz, Moratti, et al, 2005) and increased slow-wave delta activity (1.5–4 Hz) (Weisz, Moratti, et al, 2005; Adjamian et al, 2012). Increased gamma activity (40 Hz) has also been reported and in two studies this effect tracked the laterality of the tinnitus percept (Weisz et al, 2007; van der Loo et al, 2009), although, unlike changes in slow wave activity, reports of changes in gamma have not been consistent (Adjamian et al, 2012). Slow wave oscillations have been attributed to hyperpolarization of thalamic nuclei consequent on deafferentation, which may disinhibit thalamocortical oscillations in the 40 Hz range giving rise or contributing to synchronous activity underlying the tinnitus percept (Llinás et al, 2005). Increased functional connectivity among the frontoparietal, temporal, and cingulate cortices has also been reported in tinnitus patients compared to controls with greater involvement of frontal and parietal regions in longer term compared to acute cases of tinnitus (Schlee et al, 2008; Schlee, Mueller, et al, 2009). These results underscore that distributed brain network activity is present in tinnitus.

NEURAL MODELS OF TINNITUS

The presence of so many neural changes in tinnitus raises the question of which changes are crucial and how they generate the sensation of tinnitus and its accompanying features including hyperacusis and distress behavior so often seen in tinnitus patients. Here we give a brief account of current neural models of tinnitus based on the results reviewed above and some of their strengths and weaknesses.

DCN Hyperactivity Model

There are several caveats related to the role of DCN in the establishment and maintenance of tinnitus, two of which are briefly discussed here. (1) Brozoski and Bauer (2005), using

animals with behavioral evidence of tinnitus, reasoned that lesioning the DCN would alleviate well-established (several months), chronic tinnitus. Unilateral DCN lesions seemed to exacerbate the tinnitus, and bilateral DCN lesions did not abolish the behavioral evidence of chronic tinnitus. There are two interpretations of these results. First, spontaneous hyperactivity in the DCN is not related to tinnitus; it is just an epiphenomenon. Second, DCN hyperactivity may be needed to initialize/stabilize/signal hyperactivity at more central sites within the auditory pathway. Removing or inactivating the DCN does not alter/eliminate hyperactivity at more central loci once it has been established. (2) Animal noise-induced tinnitus studies suggest that tinnitus may begin immediately after the sound exposure whereas spontaneous hyperactivity is not elevated until around 7 days postexposure; that is, the onset of tinnitus begins sooner than the onset of DCN spontaneous activity. Moreover, neurophysiological measurements from the cochlear nucleus obtained immediately after the noise exposure show a decrease in spontaneous activity in regions of hearing loss (Salvi et al, 1978); these results conflict with the spontaneous hyperactivity model of tinnitus. These issues relate to the differences between mechanisms subserving acute versus chronic tinnitus and reflect our lack of understanding of the mechanisms but especially those subserving acute tinnitus. It is likely that acute tinnitus reflects altered peripheral activity reflected in TTS and central compensatory mechanisms that are as yet poorly understood.

Tonotopic Reorganization Model of Tinnitus

Expansion of the tonotopic map at the edge of the hearing loss has been proposed as a mechanism for tinnitus (Rauschecker, 1999). Presumably, because of the map expansion more neurons represent sounds at the audiometric edge, and the increased activity would generate the tinnitus percept. However, while some studies have localized the tinnitus pitch at the edge of steep hearing loss, other results cited above have found that tinnitus frequencies do not localize to the audiometric edge but instead occur in the region of maximum hearing loss (Pan et al, 2009; Sereda et al, 2011). Likewise, the edge-frequency expansion model would have difficulty accounting for tinnitus that has broadband pitch characteristics. Moreover, the time course of map expansion may take place over days or weeks (Rajan et al, 1993; Willott et al, 1993) whereas tinnitus begins almost immediately after noise exposure (Atherley et al, 1968) or sudden hearing loss (Michiba et al, 2013). The underlying mechanisms comparing acute and chronic tinnitus may in fact be different and require further study. Finally, tonotopic reorganization can be induced by long-term, low-level acoustic stimulation or by pairing sounds with electrical stimulation of the nucleus basalis (Weinberger, 2003; Pienkowski and Eggermont, 2009). If tonotopic expansion/reorganization is the mechanism for tinnitus, then animals exposed to these conditions should experience tinnitus. A key test of the tonotopic edge model of tinnitus may be to perform behavioral tests on these animals.

Central Gain

The idea that tinnitus is the result of an increase in gain (or sensitivity) within the CAS was first proposed by Jastreboff (1990). Schaette and Kempter (2006) and more recently Noreña (2011) advanced this concept by suggesting that a “homeostatic plasticity mechanism” stabilizes the mean firing rates of CAS neurons around a set point value. Computational

studies by Schaette and Kempter (2006), Chrostowski et al (2011), and Noreña (2011) confirm that such a mechanism could explain the increased spontaneous activity that occurs (e.g., in the DCN) in response to sensory deprivation. With this neural homeostasis model, a damaged cochlea would result in reduced output from the auditory nerve, which would, in turn, trigger the amplification of "neural noise," which would be perceived as tinnitus. Up-regulation of somatosensory inputs to the DCN over a period of 2 wk following deafening (Zeng et al, 2009) may be an example of this type of compensation, which could occur at multiple levels of the auditory projection pathway. Although its underlying mechanisms are not fully known (Pozo and Goda, 2010), homeostatic plasticity is a well-established phenomenon that may contribute to changes in central gain in tinnitus associated with detected or hidden cochlear damage. Other mechanisms that could alter central gain include loss of inhibition in central auditory pathways consequent on hearing injury (Eggermont and Roberts, 2004; Richardson et al, 2012), changes in inhibition associated with aging (Caspary et al, 2005) that may occur independently of hearing decline, or forms of tinnitus associated with moderate doses of salicylate that have little effect on peripheral hearing function (Stolzberg et al, 2012).

Models invoking changes in central gain are viable models for tinnitus. There are, however, other findings to consider. One is that while tinnitus can occur immediately after noise exposure and is accompanied by increased neural synchrony in the gamma band (Ortmann et al, 2011), changes in spontaneous firing rates of auditory neurons typically take longer to develop in subcortical (Kaltenbach et al, 2004) and cortical (Noreña and Eggermont 2003) auditory regions. Computational factors also suggest that phase locked (synchronous) output from a network of neurons is more likely to depolarize a postsynaptic target than is temporally incoherent input to the same neurons (Stevens and Zador, 1998; Singer, 1999; Niebur et al, 2002). These considerations have led some researchers to propose that while increases in central gain may be sufficient for abnormal loudness tolerance (hyperacusis), synchronous neural activity may be needed for tinnitus.

Neural Synchrony

Models of tinnitus related to neural synchrony have their origins in the work of Llinás et al (1999) on the effects of deafferentation on brain rhythms, and in physiological studies of the effects of noise trauma on auditory cortical activity by Eggermont and colleagues (Noreña and Eggermont, 2003; Seki and Eggermont, 2003). An influential result from the latter studies was that while the spontaneous firing rates of auditory cortical neurons was increased inside and outside of the frequencies that were affected by hearing loss (although more so inside than outside), changes in phase-locked synchronous activity were confined to the hearing loss region where tinnitus percepts also localize (Eggermont and Roberts, 2004). Some of the most compelling data for oscillatory changes in tinnitus come from Weisz et al (2007) and van der Loo et al (2009), who observed changes in gamma band activity for tinnitus subjects compared to controls, although Adjamian et al (2012) did not find this result. On the other hand, increased low-frequency oscillations in tinnitus have been replicated across laboratories (Weisz, Moratti, et al, 2005; Adjamian et al, 2012), a result that was forecast by Llinás et al (1999).

As mentioned above, phase locked activity among auditory neurons is more likely to depolarize synaptic targets and propagate to other brain regions than is temporally incoherent input from the same neurons. The neural synchrony hypothesis draws further strength from the observation that neural oscillations in the gamma band are correlated with the conscious perception of objects in humans and primates (Tallon-Baudry and Bertrand, 1999).

Network Models of Tinnitus

Network models of tinnitus have been motivated by two main lines of inquiry. The first line comes from the human functional imaging studies described above, which revealed augmented activity in tinnitus patients in several brain regions beyond classical auditory pathways. In particular, several of the affected regions (regions of the frontal and parietal lobes, cingulate cortex) are believed to be important in attention, memory, and executive functions such as encoding and recalling sensory information from memory and relating it to task objectives. These are functions attributed to the global workspace described by Dehaene and Changeux (2011). The second line of inquiry comes from studies showing that elevated metabolic activity in these regions is correlated in normal hearing subjects with conscious awareness (for a review, see De Ridder, Elgoyhen, et al, 2011). Because tinnitus is a conscious percept, the same neural system may be involved if not in the generation of tinnitus at least in its perception.

Network models are appealing because they allow that one’s awareness of tinnitus can be temporally suppressed by engagement in resource-demanding cognitive tasks. Research evidence supports this phenomenon (Knobel and Sanchez 2008), which is commonly reported by tinnitus patients, and the explanation given is that access to the global workspace has been denied by the demands of the task. Increased functional connectivity among the frontoparietal, temporal, and cingulate cortices has also been reported in tinnitus patients compared to controls with greater involvement of frontal and parietal regions in longer term compared to acute cases of tinnitus (Schlee et al, 2008; Schlee, Hartmann, et al, 2009). One novel variation of a network model has suggested that an area of reduced gray matter found in the ventromedial prefrontal cortices of tinnitus patients is important in the perception of tinnitus (Muhlaü et al, 2006). Based on this result, Rauschecker et al (2010) proposed that chronic tinnitus is caused by failure of the ventromedial prefrontal cortices (a nonauditory structure) to suppress aberrant activity in the auditory system.

Which Model Will Prevail?

Each of the models summarized above is based on research findings and hence each captures some aspect of tinnitus. It may be evident that in several respects the models are not mutually exclusive. For example, increased spontaneous neural activity consequent on changes in gain in central auditory structures could increase the likelihood that aberrant synchronous network activity may be forged in auditory regions affected by hearing loss. And such activity may be important in gaining access to nonauditory regions that are important for conscious perception. While many important gaps exist in our current knowledge, an unmistakable sense of progress prevails as the field moves toward a more complete understanding of the neural basis of tinnitus.

CONCLUSIONS AND IMPLICATIONS

The common denominator for all of the studies reviewed here is that each attempts to elucidate underlying neural mechanisms of tinnitus with the ultimate purpose of finding a cure. The neural mechanism(s) of tinnitus must be understood because procedures intended to cure tinnitus must appropriately interact with the mechanism (Roberts, 2011). Achieving this goal may not be immediately relevant to the clinician who works directly with patients to assist them in learning to manage their reactions to tinnitus. In this section, we discuss some of the reasons why tinnitus mechanisms research has relevance to clinical practice.

1. Patient expectations can substantially affect outcomes of intervention. Many patients have expectations that a treatment exists to eliminate ("cure") their tinnitus. The present review reveals the explosion of research to discover such a cure. Patients should be aware of these efforts and be presented with a compelling explanation of how reactions to tinnitus can be mitigated through the use of behavioral interventions.

2. Although cochlear damage is a triggering factor, in most cases the sensation of chronic tinnitus is not generated by persisting irritative processes occurring in the ear but by changes that take place in the brain following loss of input from the ear to central auditory structures. Consequently, tinnitus should be considered a disorder of the brain with management conducted accordingly.

3. Tinnitus is not likely generated by a single neural source but is rather a network phenomenon involving several brain structures, neural transmitters, and receptor types in a cascade of changes initiated in most cases by hearing impairment (Eggermont, 2012; Robertson and Mulders, 2012). As such, it is unlikely that a single curative treatment can be found, short of reversing or compensating for hearing loss. Many patients who receive a hearing aid or cochlear implant for hearing loss report that their tinnitus has also improved (Quaranta et al, 2008; Chang and Zeng, 2012; McNeill et al, 2012). One implication for drug treatments is that drugs that have multiple effects on synaptic processes (therapeutic "shotguns") may prove to be more effective at disrupting network behavior and reducing tinnitus than pharmaceuticals that have more specific action profiles.

4. Neural plasticity plays an important role in the brain changes that underlie tinnitus. This opens the possibility that therapies based on neuroplastic principles may benefit tinnitus sufferers. An important demonstration comes from Noreña and Chery-Croze (2007) who showed that passive exposure to a low-level, complex background sound covering the hearing loss region for a few hours a day for 15 wk rescaled abnormal loudness tolerance by as much as 15 dB in hyperacusis patients. Homeostatic plasticity was proposed to underlie this beneficial change in central gain. Bidirectional rescaling of loudness growth by 2 wk of low-level in-the-ear sound exposure (decreased loudness percept) or occlusion (increased

loudness percept) has also been demonstrated in normal hearing subjects (Formby et al, 2003). The field is ready for a larger scale assessment of this approach to treating hyperacusis using appropriate controls and standardized measurements. At present, the effects of this procedure on tinnitus are not known.

5. Relevant to the latter point, there is a growing literature assessing sound therapies for tinnitus (e.g., Jastreboff and Hazell, 2004; Henry et al, 2008; Hobson et al, 2010; McNeill et al, 2012). Some studies that applied background sound to the hearing loss (tinnitus frequency) region have reported positive effects (Davis et al, 2008) and others negative ones (Vanneste et al, 2013), while sound therapies using notched music or off-frequency listening (these sounds distributing lateral inhibition into the tinnitus region) have reported benefits for tinnitus patients (Herraiz et al, 2010; Okamoto et al, 2010). Relevant variables in this literature may include whether the therapeutic sounds are processed in attention or are presented passively as low-level, immersing background signals (Pienkowski and Eggermont, 2009; Roberts et al, 2012), and whether the exposure frequencies cover the tinnitus (hearing loss) region or spare this region (Roberts, 2011). Although at this time no approach can make a convincing claim for an advantage over others, a consistent finding has been that while it may not be possible to eliminate the tinnitus sound, many patients (often a majority) report an improvement in questionnaire scores assessing their reactions to tinnitus (El Refaie et al, 2004). Cognitive-behavioral therapy (CBT) is a psychological counseling technique that has been shown to benefit patients with tinnitus (Martinez-Devesa et al, 2010; Hesser et al, 2011).

6. Progress has been made toward standardizing tools and environments for measuring tinnitus and referring the results to baseline data (Meikle et al, 2012). There is reason to think that these measurements themselves have therapeutic value. In one recent study (Lehner et al, 2012), tinnitus handicap scores improved significantly between two baseline measurements that were taken before treatment had begun. Most of the treatment effect occurred between these two measurements.

7. Many innovative treatments are being tested, and this should be encouraged. Repetitive transcranial magnetic stimulation (rTMS) is one, although its benefits currently remain elusive (Folmer et al, 2006; Peng et al, 2012). Other innovative treatments will undoubtedly appear in the area of acoustic therapy as discoveries are made with respect to the long-term effects of sound on the tinnitus percept.

8. Both our understanding of tinnitus and its prevention would be greatly assisted by developing improved measures of cochlear damage and collecting baseline data on these measures. A compelling case can be made that we should assess the effects on these measures not only of

recreational sound but also of background sounds commonly encountered in the workplace and other human environments.

9. Evidence is growing that many if not most cases of tinnitus involve deafferentation of central auditory structures subsequent to changes in the cochlea due to aging, noise exposure, otologic injury, or other causes. Understanding mechanisms of tinnitus will be assisted by identifying the sites of tinnitus generation in central auditory structures. Additional questions pertain to understanding (a) the relationships between underlying tinnitus mechanisms and different sensitivities to tinnitus, including distress behavior; (b) why different susceptibilities to reacting to tinnitus exist among those experiencing tinnitus (Salvi, Bauer, et al, 2011); (c) genetic and biologic markers of tinnitus; and (d) why there are different susceptibilities to incurring tinnitus, particularly among older individuals where hearing loss is often present.

In summary, it is now clear that tinnitus is a pathology involving synaptic plasticity (Guitton, 2012). The origin of tinnitus can occur either at the level of the synapses between inner hair cells and the auditory nerve, within the auditory nerve itself, or from CAS structures. Long-term maintenance of tinnitus is likely a function of a complex network of structures in the CAS and nonauditory systems. While much has been learned, much remains to be learned. The ultimate goal of tinnitus mechanisms research is to develop a cure. This goal is particularly challenging because different forms of tinnitus may relate to specific pathophysiologies. We know that anything that can cause hearing loss can also cause tinnitus, including noise exposure, ototoxicity, traumatic brain injury, and so on. No single origin of tinnitus has yet been identified; thus, it is unknown if each cause of tinnitus results in different forms of tinnitus generation, each of which may require a different therapeutic cure. However, it is also known that, in all cases of tinnitus, the tinnitus neural signal is transmitted through the auditory pathways with conscious perception involving complex processing between sub-cortical structures, the auditory cortex, and higher pathways (Lockwood et al, 1998; Leaver et al, 2011). There is thus hope that a single cure can be found that would target a common mechanism.

Abbreviations

ABR	auditory brainstem response
AEP	auditory evoked potential
AVCN	anteroventral cochlear nucleus
CAS	central auditory system
CN	cochlear nucleus
CNS	central nervous system
DCN	dorsal cochlear nucleus

fMRI	functional magnetic resonance imaging
GAP	growth associated protein
IC	inferior colliculus
MGB	medial geniculate body
PET	positron emission tomography
PTS	permanent threshold shift
TTS	temporary threshold shift
VCN	ventral cochlear nucleus

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