Chapter 31
The Neuroscientist

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Keypoints

1. This chapter reviews the current state of knowledge of tinnitus from the neuroscientist's perspective.
2. Tinnitus is viewed as a disorder involving changes in the rate and timing of spontaneous discharges at multiple levels of the auditory system.
3. Its mechanisms vary, depending on etiology, but most commonly the disorder stems from increases in the excitability of neurons in the central auditory system.
4. Most of the available data suggest that this increase is synaptic in origin, caused by shifts in the balance of excitatory and inhibitory inputs to neurons.
5. However, other mechanisms, such as shifts in the expression of ion channels that determine the resting membrane potential of neurons, may also play a contributing role.
6. Since these changes occur at multiple levels of the auditory system, it is likely that new therapies that will prove most effective will be those that take a system-wide approach rather than those that target specific generator sites.

Keywords Tinnitus • Dorsal cochlear nucleus • Plasticity • Excitotoxicity • Neurodegeneration • Inferior colliculus • Auditory cortex

Abbreviations

DCN	Dorsal cochlear nucleus
GABA	Gamma amino butyric acid
IC	Inferior colliculus
LTD	Long-term depression
LTP	Long-term potentiation
NMDA	*N*-Methyl-D-aspartate
rTMS	Repetitive TMS
TMS	Transcranial magnetic stimulation

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Introduction

Over the past 20 years, a great deal has been learned about tinnitus mechanisms from neuroimaging studies in humans and neurophysiological studies in animals. We now have substantial literature examining where and how activity in the auditory system is altered by tinnitus-inducing agents. Coupled with the growing number of behavioral studies demonstrating that animals develop tinnitus after exposure to various tinnitus-inducing agents, the available evidence provides us with compelling reasons to suspect that some of the reported changes in activity underlie the percepts of tinnitus. This chapter reviews the current state of knowledge of tinnitus from a neuroscientist's perspective.

Is Tinnitus Primarily a Peripheral or Central Problem?

The term "ringing of the ears" implies that tinnitus is largely a problem of the ear. However, we now have a considerable body of evidence that the major changes underlying tinnitus can occur peripherally or centrally. House and Brackman [1] found that tinnitus persisted in 62% of patients in whom input to the brain from the auditory nerve was surgically abolished. In many of

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these patients, the post-surgical tinnitus was worse than the pre-surgery tinnitus. Other studies have reported that tinnitus develops secondarily following surgical removal of eighth-nerve tumors (vestibular Schwannoma) [1–3], a procedure that can lead to major impairment of the auditory nerve. These findings point to the central auditory system as an important source of tinnitus, although there is little doubt that tinnitus in most cases begins with trauma in the auditory periphery. Thus, although agents such as noise or aminoglycoside, which cause hearing loss, often also cause tinnitus (see Chaps. 37, 42), they either have a weak long-term effect on spontaneous activity in the auditory nerve or cause this peripheral activity to decrease [4–6].

At the same time, it is important to acknowledge that in 38% of House and Brackman's patients, tinnitus was abolished by eighth-nerve section. Although spontaneous activity is reduced following noise or aminoglycoside treatment, other alterations have been found in the auditory nerve, such as increase spontaneous bursting activity (see next section), which could potentially be tinnitus producing. Moreover, some studies suggest that sodium salicylate can cause increases in spontaneous activity and changes in the timing of spontaneous spikes in the auditory nerve that could generate tinnitus percepts [7–11]. Thus, it seems likely that some forms of tinnitus may originate peripherally, although, as discussed in the following section, most contemporary studies of tinnitus have focused on the central auditory system for the reasons given above.

Neurophysiological Correlates of Tinnitus

The most commonly reported effects of tinnitus-inducing agents on neurons in the auditory system are increases in spontaneous activity, bursting activity, and synchronous discharges. Chronic increases in spontaneous activity can be induced in the dorsal cochlear nucleus (DCN) [12–18], inferior colliculus (IC) [15, 19–26], and auditory cortex [27–31] using exposure or treatment conditions that have been shown in a variety of other studies to induce tinnitus in animals [17, 21, 32–39]. Increased spontaneous activity occurs in the IC and auditory cortex after salicylate treatment [40–45]. There is evidence for increased spontaneous activity in the DCN following treatment with cisplatin [44] (see Chap. 16) and in the auditory cortex following treatment with quinine [46]. Both salicylate and quinine have also been shown to cause tinnitus in animals at doses known from other studies to cause increased spontaneous activity in the auditory system [47–49]. That the increase in activity is likely to be perceptually sound evoking is supported by the following:

1. The hyperactivity displays similar spatial and temporal distribution patterns as increases in activity evoked by tonal stimulation.
2. It is well established from electrophysiological studies that increases in activity are observed throughout the central auditory system during sound stimulation, so there can be little doubt that sound percepts are linked to increases in discharge rates.
3. Cochlear and central auditory prosthetics are based on the notion that auditory percepts can be evoked by stimuli designed to increase discharge rates of auditory neurons.
4. Increased activation has been observed in the IC and auditory cortex of individuals with tinnitus [50–59].
5. Stimulation of the somatosensory system via the trigeminal nucleus or cervical nerves modulates both spontaneous activity in central auditory centers [60–63] and tinnitus [64–67]. Taken together, these findings give strong support to the view that tinnitus is linked to changes in discharge rates in the central auditory system.

However, just increased discharge rates, per se, may not be the whole story. Noise exposure, and salicylate cause increases in a specific type of activity called bursting discharges in the auditory system. Chronic increases in bursting activity have been observed in the auditory nerve following noise exposure [6], in the DCN following noise exposure [14], and in the IC following salicylate and noise exposure [23, 41]. No increased bursting has been found in the auditory cortex following noise exposure, salicylate, or quinine [23, 46, 68, 69]. Increases in bursting activity, even if limited to the auditory brainstem, may be an important correlate of tinnitus. Bursts of spikes carry an important feature that is likely to signal the presence of sound, namely, periodicities, and brief clusters of spikes with nearly identical interspike intervals. Of these, periodicities in firing are critical to the ability of neurons to encode the frequency of sounds [70, 71]. If bursting is increased, then periodicities in a restricted frequency range would probably also be

increased, and this could lead to perception of a tinnitus-like sound in a correspondingly restricted pitch range.

In addition to increased discharge rates and increased bursting activity, there is evidence for an increase in synchrony of discharges among neurons in the IC following noise exposure [23] and in the auditory cortex following noise or quinine administration [27, 30, 69]. Increased synchrony of auditory nerve fibers following salicylate treatment is suggested by increases in the amplitude of 200 and 900 Hz peaks in the frequency spectrum of ongoing ensemble activity [9–11]. This means that instead of impulses being more or less randomly related across the neural population, the impulses become increasingly coincident. This is sometimes referred to as temporal coherence (see Chaps. 12 and 13). Neurons showing increased synchrony occur in frequency bands of the hearing loss that are also the areas in which tonotopic map reorganization occurs. Increased synchrony has been hypothesized to be a neural correlate of tinnitus [72, 73] (see Chaps. 12 and 13). Pitch percepts corresponding to frequency regions with increased synchrony might be enhanced, leading to the often pitch-like percepts of tinnitus.

In summary, central auditory nuclei and cortical areas develop some of the types of changes following cochlear trauma that are also evoked by acoustic stimulation. Issues that will be addressed next are what the underlying triggers of changes in spontaneous activity might be as well as what mechanisms underlie their induction.

The Triggers of Tinnitus-Related Activity

The Role of Deafferentation

Tinnitus is often viewed as a deafferentation disorder triggered by loss of normal input from the auditory periphery. Evidence for a deafferentation mechanism of tinnitus comes from a wide range of clinical and experimental observations. Tinnitus is most commonly associated with hearing loss. Between 80 and 90% of tinnitus patients have an associated hearing loss [74] (see Chap. 5). Tinnitus can be induced by surgical damage to [75, 76] as well as compression or tumors of the eighth nerve [2, 3, 77, 78] (see Chap. 39). Tinnitus is also sometimes seen in association with conductive hearing loss [79–81] (see Chap. 83). All these conditions involve impairment of peripheral auditory functions, so there is good reason from human observations alone to suspect that loss of peripheral function and peripheral input are key triggers of tinnitus. Animal models have also yielded evidence consistent with a deafferentation-induced mechanism of tinnitus. Tinnitus percepts in animals and tinnitus-related changes in activity in the IC have been found to be associated with loss of spiral ganglion cells [23]. The induction of tinnitus-related hyperactivity in the dorsal cochlear nucleus has been found to be correlated with loss of outer hair cells [45]. This is consistent with reports that tinnitus is often found to be associated with defects in outer hair cell function, as reflected by alterations of transient-evoked or distortion product otoacoustic emissions (see review of [82]). It has been hypothesized that loss of outer hair cells may induce hyperactivity in the dorsal cochlear nucleus by causing loss of peripheral input to the granule cell system [45]. This hypothesis builds on the facts that the granule cell domain in the cochlear nucleus receives input from type II spiral ganglion neurons, which originate from outer hair cells [83–85], and there is some evidence that granule cells are among the recipients of type II input [86]. Moreover, activation of granule cells influences the level of activity of the principal cells of the DCN, the likely generators of tinnitus signals [13, 41, 60, 87].

Deafferentation can also involve loss of input to auditory structures from non-auditory areas. This possibility is raised by the fact that many subjects with tinnitus possess disorders of other systems. For example, many cases of somatic tinnitus (such as that experienced by people who can change the loudness or pitch of their tinnitus by manipulations of head and neck musculature) occur in people with somatic pathologies of the head and neck, including craniofacial anomalies, temporomandibular joint disorders, or inflammatory conditions of the neck muscles [64, 65, 88]. Furthermore, Levine [65] found that in his patients with somatic tinnitus, when the tinnitus was monaural, it was usually on the same side as the somatic disorder. Lastly, an increasing number of articles suggest that tinnitus can be induced or exacerbated by emotional conditions such as stress and anxiety [89–91]. There are several levels of the auditory pathway where auditory centers receive input from non-auditory areas. The best described example, in terms of circuitry, is the dorsal cochlear nucleus, whose output is modulated

by the cochlear granule cell system. This system receives input not only from auditory sources but also from cuneate and trigeminal nuclei and ganglion of the somatosensory system [61, 92–94] (see Chap. 9) and a variety of other pathways [87]. Since activation of the granule cell system is known to affect the level of spontaneous activity [13, 60, 95], conditions in which inputs from these areas are impaired or damaged could affect output of the dorsal cochlear nucleus via their effects on the granule cell system.

The Role of Plasticity

There are two general mechanisms by which deafferentation might induce tinnitus-related activity in the central auditory system by activating neural plasticity (see also Chaps. 12 and 13). The most frequently hypothesized mechanism is a shift in the balance of excitatory and inhibitory synaptic inputs to central target neurons toward the side of excitation. Such a shift could involve direct loss of inhibitory inputs (disinhibition) and/or an increase in excitatory inputs.

Several lines of evidence indicate that both a loss of inhibition and an increase in excitation occur centrally after loss of auditory nerve input and that such changes involve plasticity. First, loss of primary afferent input leads to loss of inhibitory influence in brainstem auditory nuclei, as signaled by reductions in glycinergic and GABAergic neurotransmission [96–104]; these reductions change over time, suggestive of a temporal or possibly homeostatic plasticity mechanism [105]. Second, there are suggestions of up-regulations of excitatory synapses – for example, cochlear ablation, noise exposure, and conductive hearing loss trigger up-regulations of cholinergic and glutamatergic systems in the central auditory systems [106–113]. Some of these adjustments vary over time. Third, degeneration of second-order neurons in the brain following noise exposure [114] is followed by regrowth of excitatory and inhibitory terminals, but a more complete return of excitatory than inhibitory synapses, indicating a reorganization of synaptic connections that favors excitation [115].

A second mechanism that could lead to tinnitus-related activity is an increase in excitability of neurons caused by alterations in their intrinsic membrane properties. Such alterations might involve up- or down-regulations of specific ion-conductance channels. Studies pointing to changes in the intrinsic membrane properties of cochlear nucleus neurons following cochlear deafferentation have been published. Cochlear ablation was found to cause increases in membrane resistances of neurons in the ventral cochlear nucleus (Francis and Manis, 2000). Hearing impairment has also been found to be associated with decreases in the expression of the two-pore domain potassium channels and reductions of Kv3.1 channels in central auditory neurons [116, 117]. Changes in spike waveform have been observed in the dorsal cochlear nucleus after noise exposure [14]. The relationship between these changes and alterations in spontaneous activity has not yet been determined.

Non-deafferentation Triggers of Tinnitus Induction

Deafferentation is not the only triggering mechanism by which tinnitus-related activity could be induced. Some inducers of tinnitus may act through non-deafferentation mechanisms, such as excitotoxicity or activity-dependent plasticity.

Excitotoxicity

Excess release of excitotoxic neurotransmitters in the brain caused by acoustic overstimulation could lead to degeneration of second-order neurons, many of which may be inhibitory. Glutamate is the most common excitatory and most powerfully excitotoxic neurotransmitter in the nervous system. It is also the excitatory transmitter of hair cells, auditory nerve fibers, granule cells of the cochlear nucleus, and the main projection neurons that make up the ascending auditory pathway. Normally, toxicity of this transmitter is prevented by its reuptake following its release by the presynaptic membranes. However, under certain conditions, such as when there is excessive sound stimulation, glutamate is released in excess, and this excess can sometimes overwhelm the reuptake mechanism. This leads to its accumulation in the synaptic cleft. Excess glutamate binds to *N*-methyl-D-aspartate (NMDA) receptors, which stimulates excess calcium influx into postsynaptic neurons via the calcium channels of NMDA receptors; the excess calcium stimulates intracellular enzymes that are damaging to cells and can culminate in apoptosis.

A case for excitotoxicity acting through excess glutamate release in the auditory system is suggested by the following: Overstimulation would be expected to cause excess release of glutamate from excitatory terminals in and beyond the cochlear nucleus. An increase in glutamate release and a decrease in glutamate uptake have been found to occur in the cochlear nucleus and persist for at least 5 days following acoustic overstimulation [110]. This would be expected to result in an accumulation of glutamate in the synaptic cleft and thereby trigger excitotoxic injury. Evidence consistent with this hypothesis is the finding that degeneration occurs in broad areas of the cochlear nucleus well beyond zones of peripheral deafferentation [114, 118]. These findings have been interpreted as possibly resulting from excitotoxic injury in the central auditory system [110, 118]. The loss of second-order neurons by this mechanism would be expected to shift the balance of excitation and inhibition in the central auditory system in ways that could be tinnitus inducing.

Activity-Dependent Plasticity

One of the most commonly described mechanisms by which synaptic excitability of neurons is chronically shifted is long-term potentiation (LTP). This is a long-lasting enhancement in synaptic transmission between two neurons that results from stimulating them synchronously. LTP results in a sensitization of neurons to their inputs, which is manifest as an augmentation in the response of the postsynaptic neuron to its excitatory inputs. Another manifestation of LTP is an increase in spontaneous activity [119]. If LTP occurs in the auditory system, it seems likely that the affected neurons would become hypersensitive and spontaneously hyperactive. A related, but opposing process is long-term depression (LTD), which is manifest as a reduction in the response of neurons to their inputs. These activity-dependent phenomena were originally discovered in the hippocampus and have been implicated as neural mechanisms of long-term memory. They are now known to be ubiquitous throughout the brain.

The question at hand is whether inducers of tinnitus can cause LTP in auditory neurons. There is evidence that LTP can be induced in various auditory centers by synchronous stimulation of pre- and postsynaptic neurons. LTP has been demonstrated by this method in the dorsal cochlear nucleus [120–122], inferior colliculus [123, 124], and auditory cortex [125, 126]. Thus far, it is not known whether tinnitus inducers can cause LTP in these same brain areas. However, it has been hypothesized that noise might increase the probability of synchronous firing of pre- and postsynaptic firing and thereby cause induction of LTP [127]. This possibility seems plausible since acoustic stimuli increase the frequency of firing and the occurrence of coincident spikes in the auditory system [29]. Induction of tinnitus by LTP and excitotoxicity offers an explanation of why tinnitus often occurs without any accompanying hearing loss.

Why Tinnitus Does Not Always Accompany Hearing Loss

If tinnitus is the result of increases in neuronal activity (increased discharge rate and bursting) and/or increased synchrony triggered by loss or overstimulation of afferent input to the auditory centers of the brain from the ear, and also possibly involving non-auditory inputs to these centers, then why do many people with hearing loss have no tinnitus? [128, 129] The simplest explanation is that the direction of the shift in the balance of excitation and inhibition following cochlear injury may depend on the pattern of cochlear injury. Tinnitus induction would be expected to occur when there is more degeneration centrally of inhibitory than excitatory neurons, causing disinhibition and an increase in excitation. However, it is conceivable that certain patterns of peripheral injury may not be sufficient to shift the balance of excitation and inhibition or could even favor a shift toward the side of greater inhibition. Support for this concept is demonstrated by the finding that tinnitus-related hyperactivity is initially absent following induction of noise-induced threshold shift but emerges slowly over several days following the noise exposure, only after a transient decline of activity [16]. Moreover, it has been shown that when cochlear injury induced by cisplatin is restricted to outer hair cells, there is a strong relationship between the degree of centrally recorded hyperactivity and the amount of outer hair cell loss, but when the outer hair cell loss is accompanied by mild damage to the inner hair cells, particularly disarray of their stereocilia, activity is not elevated centrally. However, when the inner hair cell injury becomes

more severe or outer hair cell loss is accompanied by inner hair cell loss, hyperactivity is clearly apparent [45]. This suggests that the effect of peripheral injury on central auditory activity depends on the balance and type of injury to the two hair cell populations and their connecting primary afferents.

Implications for Tinnitus Treatment

The state of knowledge on tinnitus mechanisms has provided a much-needed theoretical framework for conceiving and testing new therapeutic treatments for tinnitus over the past decade. Among the various modalities that have received the most attention are drug therapy, electrical stimulation, and transcranial magnetic stimulation. Efforts also continue to improve treatment through sound therapy and psychological counseling.

Drugs that are attracting interest as potential tinnitolytic agents are those that decrease neural activity. Initial studies with gabapentin were suggestive of a tinnitolytic effect in animals and some human subjects [130]. However, more recent clinical trials showed that when the effects are compared with placebo across a sample of patients, no significant difference was observed [131, 132]. Thus, if gabapentin has a tinnitolytic effect, it may be that only a small proportion of patients who have been treated with gabapentin experience benefit. Agents that activate the inhibitory receptors for $GABA_A$ and $GABA_B$ receptors (e.g., benzodiazepine and baclofen, respectively) have been found to have a suppressive effect on tinnitus-related activity in animals [133, 134]; studies with these agents in clinical trials have yielded mixed results. While baclofen was not found to have a significant effect on tinnitus [135], there are indications that administration of benzodiazepines, benefits many patients suffering from tinnitus [136] (see review of Gananca et al. [137]) (see also Chap. 30). In some patients, the benefit may be achieved primarily by reducing the severity of the emotional reaction to tinnitus, but there is usually a subgroup that also experiences a decrease in the loudness of tinnitus.

There has been growing interest in targeting NMDA receptors, which are implicated in plasticity for tinnitus treatment. The data thus far are preliminary, but there are indications that NMDA receptor antagonists (acamprosate, caroverine, ifenprodil) have tinnitolytic effects in animals [36, 138–140]. Preliminary results suggest that the NMDA receptor antagonist, neramexane, may reduce tinnitus-related activity in the DCN of animals [141]. A recent clinical trial with neramexane yielded results suggestive of a significant tinnitolytic effect in human subjects [142]. The drug is now being tested in a phase III clinical trial: http://clinicaltrials.gov/ct2/show/ (NCT00405886) (see also Chaps. 22 and 30).

Electrical stimulation studies have been conducted in areas of the brain that have been implicated as sites of tinnitus generation. The benefits have been most remarkable for patients stimulated at the cochlear level, either transtympanically or intracochlear using a cochlear implant [143, 144] (see also Chap. 77). Stimulation of the dorsal cochlear nucleus using the auditory brainstem implant has been found to be effective in suppressing tinnitus [145], and there are some recent indications that stimulation of the auditory cortex can suppress tinnitus [146–148].

Another approach that has generated considerable interest is repetitive transcranial magnetic stimulation (rTMS). This procedure is used primarily to stimulate the auditory cortex or nearby areas (see Chap. 88). A recent review of the literature [149] concluded that rTMS is a promising approach for the treatment of patients with certain forms of tinnitus. At present, the results of both stimulation modalities vary significantly across studies and within studies across individuals. This variability may stem from differences in stimulus parameters, differences in what parameters are optimal for each patient, and differences in the precise location of the stimulating electrode(s) or magnetic field relative to the primary generator sites giving rise to the tinnitus-producing signals. The fact that tinnitus has many forms (see Chap. 2) also contributes to the variability in the results of treatments. However, the findings provide a proof of concept that stimulation of auditory areas can, under optimal conditions, bring considerable relief to a significant number of tinnitus patients.

Summary and Conclusions

The foregoing review of tinnitus summarizes the areas of the nervous system that display activity changes believed to underlie the percepts of tinnitus. The available

evidence indicates that tinnitus is associated with more than one type of change in the auditory system. At the brainstem level, increases in bursting and non-bursting spontaneous activity are clearly demonstrable after noise exposure and salicylate treatment, while at the cortical level, increases in non-bursting spontaneous activity and neural synchrony are more apparent. The literature review also indicates that tinnitus of different etiologies likely involves different structures and possibly different mechanisms. This is best demonstrated by clinical studies showing that sectioning the eighth nerve sometimes alleviates tinnitus, but more commonly tinnitus persists and is often worsened following this procedure. This suggests that there may not be a single final common path for tinnitus and supports that there are many forms of tinnitus (see Chap. 2). Another important concept is that tinnitus of central origin emerges as a consequence of activation of neural plasticity, which alters the excitability of neurons, primarily by shifting the balance of their excitatory and inhibitory inputs, but also possibly by shifting the balance of ion channels that control the resting membrane potential.

Our current state of knowledge provides a useful framework for developing new therapeutic approaches to tinnitus treatment. The multi-tiered distribution of tinnitus-related changes suggests that the most effective treatments for tinnitus will be those that take a system-wide approach rather than those that target specific structures. Therapies that quiet resting activity throughout the auditory system without lowering the activity of other brain pathways and without compromising sensitivity to sound will bring the type of benefits desired by most patients with tinnitus. A demonstration that such effects can be achieved on a short timescale is already indicated by the brief periods of tinnitus suppression provided by residual inhibition, somatic modulation of tinnitus, and, in some cases, by lidocaine. The goal now is to exploit these mechanisms further to increase the duration of the suppression to bring a longer lasting period and possibly chronic state of relief from tinnitus. With the foundation presently in place, we have good reason to expect that this knowledge will lead to major improvements in the treatment of tinnitus.

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