Insights on the origins of tinnitus: An overview of recent research

By James A. Kaltenbach

Tinnitus is classically defined as the perception of sound that has no external source. It plagues as many as 50 million Americans, about 3 million of them so severely that it affects their ability to live a normal life. For many years, progress toward effective treatments for tinnitus was hindered by an almost complete lack of understanding of its underlying mechanisms. Tinnitus was assumed to be primarily a disorder of the ear. Over the past decade, however, research on brain mechanisms of tinnitus has progressed rapidly, and insights have emerged into the possible neurological origins of tinnitus.

This research increasingly suggests that tinnitus is most commonly a disorder originating in the brain, although it can undoubtedly be triggered by injury to the ear. These insights are having a major impact on how we think about tinnitus and how strategies are being developed to alleviate it. This paper seeks to provide an overview of these insights.

THE THREE FACES OF TINNITUS

While tinnitus is often assumed to be primarily an *auditory* problem, it actually has three major components. The first is the *acoustic* component, which is the unwanted sound. The perception is most commonly experienced as a continuous, high-pitched ringing.

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This form occurs in people who have sustained injury to the ear as a result of excessive sound exposure or over-treatment with certain ototoxic drugs.[1,2] Patients with Meniere's disease usually experience more of a low-pitched roaring tinnitus.[2] It is not uncommon for patients to report perceiving other types of tinnitus, to experience more than one sound, or to experience changes in the pitch and loudness over time.

The second dimension of tinnitus is the *attentional* component. This refers to the degree to which the afflicted person listens to or focuses on the tinnitus. Patients often become so preoccupied with the tinnitus sound(s) that they find it difficult to concentrate on anything else. Many have trouble reading or falling asleep due to their preoccupation with tinnitus.[3]

The third aspect of tinnitus is the *emotional* component, which is defined as the affective reaction to the tinnitus. This component usually determines the severity of a person's response to tinnitus. There is a hierarchy of reactions ranging from frustration or annoyance in milder cases to anxiety or depression in more severe cases. In the most severe cases, the emotional reaction to tinnitus is highly disruptive to a person's way of life and can prevent participation in normal daily activities such as work and recreation.

The three components of tinnitus interact with and influence one another. Heightened attention to tinnitus can lead to a magnification of the emotional reaction. For example, loss of sleep caused by paying too much attention to tinnitus can evolve into more serious emotional conditions, such as mood disorders or anxiety. Conversely, when tinnitus evokes a strong emotional reaction, the patient will often pay more attention to it. Some evidence has been published suggesting that tinnitus may be worse during periods of stress.

THE ACOUSTIC COMPONENT AND THE THEORY OF TINNITUS INDUCTION

Tinnitus is thought to be caused by plastic changes in the auditory system that alter the normal balance of excitatory and inhibitory inputs to its neurons, the functional units of the nervous system.[4,5]

When hearing loss occurs, such as after a loud or explosive noise, there is usually damage to the auditory receptors, called hair cells, in the cochlear portion of the inner ear. The damage to the hair cells leads to a loss of normal function in the auditory nerve or even loss of auditory nerve fibers, leading to hearing loss. The loss of normal auditory nerve anatomy or function leads to loss of normal input to neurons throughout the auditory system of the brain. This loss of input then causes a shift in the normal balance of excitation and inhibition toward the side of excitation. The end result is an alteration of neuronal activity, leading to tinnitus. Most commonly, there is increased activity in the auditory system, but other changes occur as well.

CENTRAL PLASTICITY AS A CAUSE

Tinnitus-related activity has been identified in several regions of the brain (see Figure 1). The first level where

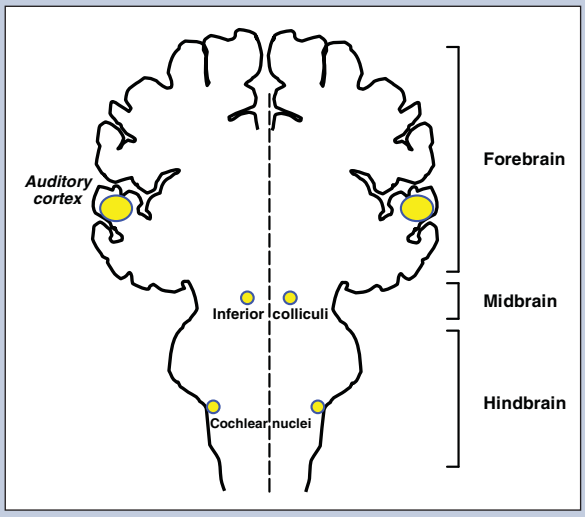

Figure 1. *Principal sites in the central auditory system where tinnitus-related changes (plasticity) have been observed.*

it is most obvious is the dorsal cochlear nucleus (DCN).[6,7] This structure lies in the hindbrain, where it receives direct input from the auditory nerve.

Loss of normal auditory nerve anatomy or function, as after noise exposure or cochlear destruction, triggers a number of physiological changes. The most prominent is an increase in spontaneous neural activity. Spontaneous activity refers to the firing of neurons at rest in the absence of sound stimulation. When the DCN loses its normal input from the auditory nerve, its neurons fire at abnormally high rates. This increase in activity is similar to the elevations of firing that occur when neurons are stimulated by sound.

One theory is that the brain interprets the increased spontaneous activity as sound, and this interpretation leads to the percepts of tinnitus. The increased activity does not occur equally in all parts of the DCN, and tends to be greatest in the part that normally responds to high frequencies. This is probably because the manipulations that cause tinnitus, such as intense noise, tend to be most damaging to the high-frequency part of the cochlea. This leads to more loss of hearing in the high-frequency range, which affects the high-frequency region of the DCN. This could underlie the high pitch of tinnitus, particularly when it's caused by noise or ototoxic drugs.

Tinnitus-related changes are also found in at least two other areas of the auditory system, including the inferior colliculus[8,9] and the auditory cortex (Figure 1).[10] The inferior colliculus is a pair of auditory centers in the midbrain. They receive much of their input from the DCN. Agents that cause tinnitus, such as noise or salicylate, have been found to cause increases in spontaneous activity of inferior colliculus and auditory cortex neurons.

In the auditory cortex, two other types of changes have also been found (Figure 2). One is an increase in synchronous firing. Normally, when neurons fire, their impulses occur more or less randomly and independently. However, after noise exposure or salicylate treatment, the impulses tend to occur at the same time, as though they are firing simultaneously. Some investigators have suggested that the increase in synchronous firing could augment the perception of tinnitus.

The other type of change that has been observed in the auditory cortex, and to a more limited degree in the inferior colliculus, is a change in frequency representation. In most auditory areas of the brain, sound frequencies are represented more or less equally, with no single frequency dominating. However, after noise exposure the frequency map becomes distorted such that there is a loss of sensitivity to sound frequencies in the range of the hearing loss.

The neurons whose input has been lost do not stop responding to sound. Instead, they become sensitive to sounds at frequencies at the edge of the hearing loss. This results in loss of frequency representation over the range of the hearing loss and an expansion of representation of frequencies bordering on the hearing loss. This change is referred to as a reorganization of the frequency map, and some investigators have suggested it could be another factor contributing to tinnitus.

NEURAL BASIS OF PLASTICITY

How a loss of hearing or of normal cochlear function causes the changes in neural pathways thought to underlie tinnitus is not very well understood, but some clues are beginning to emerge.

The most commonly reported change in the auditory system is a shift in the balance of excitatory and inhibitory synapses. Synapses are the connections between neurons. Some of these synapses are excitatory, which means they cause activity to increase. Others are inhibitory in that they reduce the level of the neurons' activity.

Excitation is required for transmitting messages about stimuli from one level of the brain to the next and for enhancing signals of special importance. Inhibition is needed to turn off responses to certain stimuli so that the brain is not overwhelmed with all the auditory information that it receives at one time.

There is now considerable evidence that hearing loss is accompanied by a general decrease in the amount of inhibition in the auditory system. For example, there are reductions in the release of inhibitory neurotransmitters, such as glycine and gamma-aminobutyric acid (GABA).[11-13] There is also evidence for

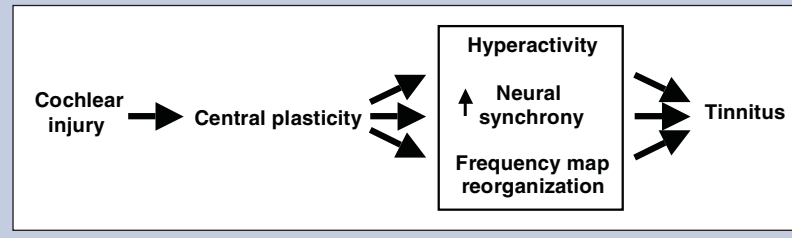

Figure 2. *Contemporary view of changes in the brain that are thought to contribute to the emergence of tinnitus percepts.*

an increase in the number of excitatory synapses. Two excitatory neurotransmitters that are increased in some auditory centers after damage to the inner ear are glutamate and acetylcholine.[14-17]

Both types of changes are likely to contribute to the imbalance of inputs to auditory neurons that result in increased levels of spontaneous activity. The loss of inhibition could also account for the difficulty many tinnitus sufferers have in filtering out their tinnitus and concentrating on more important stimuli.

The increase in acetylcholine is especially interesting, as its function is largely modulatory throughout the brain. This means that it acts to control the level of central gain. Some investigators have long suggested that the increase in spontaneous activity seen throughout the auditory system might be due to an increase in the gain of the auditory system.[18,19] The brain has circuits that amplify incoming signals. One of the neurotransmitters released by these circuits is acetylcholine. When auditory signals become weakened, as during hearing loss, these acetylcholine-releasing circuits may kick in to boost the gain.

We can recall the experience of losing a radio station as we drive away from a city to appreciate this amplification concept. If we are trying to hear the end of a news report as the radio signal fades away, our initial response may be to turn up the volume to make the fading sound more audible. In the process, the background sound, which may manifest as static noise, may also be amplified. The auditory system may respond to hearing loss in much the same way, turning up the level of activity on certain neurons to compensate for the lost input. This is what is meant by an increase in central gain. Indeed, evidence consistent with plasticity of a central gain control mechanism has recently been reported.[20]

REVERSING PLASTICITY

It has been conjectured that since cochlear insult and/or hearing loss causes plastic alterations leading to increased activity, it might be possible to reverse this plasticity by restoring sound stimulation to the areas of the brain that have lost their normal input. The theory is that by focusing the energy of sound stimulation in the frequency range of the hearing loss, a form of neural plasticity is induced in the auditory system, which results in a reduction of tinnitus-related activity caused by the hearing loss.

Norena and Eggermont recently published two studies that directly tested this concept. In these studies, cats were exposed to an intense noise at a high enough level to cause hearing loss.[21,22] The researchers found that after the loud noise exposure, the animals developed all three types of changes in the auditory cortex that had been described previously, including increases in spontaneous activity, increased synchrony, and frequency map reorganization.

They then took a similar animal group that had been exposed to the same sound conditions that induced the tinnitus-related changes, but then presented noise in a frequency range that would stimulate the auditory cortex over the frequency range of the hearing loss. They found that these animals showed a dramatic reduction in all three abnormalities in the auditory cortex: spontaneous activity and the degree of neural synchrony were reduced, and the map of frequency was remodeled so that different frequencies were represented more equally. These findings suggest that if tinnitus is related to increases in activity or neural synchrony or to reorganized frequency maps in the auditory cortex, then tinnitus might be expected to improve as a result of acoustic therapies that stimulate the auditory cortex in the frequency range of the hearing loss.

THE ATTENTIONAL COMPONENT

Tinnitus is like other sensory percepts in that it can fall anywhere in the hierarchy of one's consciousness. In people whose tinnitus is barely an annoyance, the sound is relegated to the background of their attention, occupying a low level of consciousness. But in people with debilitating tinnitus, the unwanted sound is higher up in the hierarchy, such that it becomes the focus of attention.

What accounts for the different positions tinnitus occupies in the attentional hierarchy? The answer is not well understood, but it could be related to the degree to which tinnitus involves the higher levels of the auditory system.

In general, it is believed that higher levels of the auditory system perform more cognitive functions in sensory processing. People who have sustained stroke of the auditory cortices experience a condition known as *cortical deafness*. They can hear sounds, but they are unable to decipher their meaning or associate them with other stimuli. The absence of cortical function means that, although tinnitus may be present, it does not rise high enough in the framework of awareness to become a significant problem.

One possible reason that people with some remaining function at the level of the auditory cortex suffer more severely from tinnitus is that its sound has an unusually piercing quality or some other quality that is interpreted by other regions of the cortex (the limbic cortex) as a disturbance. This interpretation may lead to a negative emotional association with the sound. The cortex may respond to this association by focusing its attentional control pathways onto the tinnitus signal. One area of the brain that may be important in this regard is the amygdala.

Lower auditory structures, involving the DCN, inferior colliculi, and their connections with non-auditory areas of the brainstem, probably also play a role in attention. The evidence comes from several reported observations. First, cats can discriminate sounds of different intensities and sound arrival times at the two ears, even after their auditory cortices have been completely removed.[23] The ability to make these discriminations would seem to require some degree of attention.

Second, activity in the DCN changes when an animal shifts its attention between auditory and non-auditory stimuli. This suggests that the DCN plays a role in attentional control. The DCN and inferior colliculi have connections with non-auditory areas of the brain that play a role in attentional focusing. This helps reinforce the notion that these auditory areas are in some way involved in the process of attentional control.

Third, individuals with a rare condition known as hydranencephaly, characterized by an almost complete lack of cerebral hemispheres but an intact brainstem, are not only able to show interest in certain sounds, they can also show

primitive emotional responses to them. In one recent study, a patient with this condition was reported to be able to look in the direction of a sound source and attempt to mimic people speaking. And, when pleasant music was played, the patient showed signs of being pleased. These considerations lead to the suggestion that these low-level auditory centers might serve as attentional gatekeepers, enabling the brain to track and focus on specific details in the sensory world and focus on sounds that are important or threatening while ignoring those that are irrelevant.

In contrast, the auditory cortex and other cortical areas may act in concert with the gatekeepers to analyze these details and extract their complex meanings. Accordingly, we can expect that disturbances in these lower auditory areas could not only give rise to tinnitus, but might also affect how much the attentional system focuses on the tinnitus signal.

THE EMOTIONAL COMPONENT

Emotional responses to tinnitus have often been assumed to be solely the domain of the limbic system. This system occupies a relatively high position in the forebrain. But the emotional system is known to have sublimbic components that involve regions of the lower brainstem as well as the autonomic nervous system.

For example, centers in the lower brainstem called the reticular activating system and the locus coeruleus are thought to mediate emotional responses to stimuli. These structures are activated when stimuli are judged to be an immediate danger or threat. Some studies suggest that anxiety disorders are associated with changes in the level of activation of neurons in the locus coeruleus.

Nearby are the nuclei of Raphe, a chain of nerve cell clusters that are distributed along the length of the brainstem near its midline. These nuclei are the major source of the neurotransmitter serotonin. Imbalances of serotonin are considered to be key elements leading to depression. There are direct connections between these centers and auditory nuclei in the lower half of the brainstem.

There is evidence that excessive levels of noise exposure cause changes in the amount of serotonin released in the DCN.[24] Such changes could conceivably play a role in shaping the emotional responses to tinnitus. The limbic system may operate at a higher level shaping the emotional reaction to sound after the incoming sound has been compared with sounds stored in memory. The involvement of the limbic system in tinnitus has been shown by imaging studies in both animals and humans. Whether this limbic activity is driven by sublimbic sources or is independent of this input has yet to be determined.

SUMMARY

Much progress is being made toward understanding potential tinnitus-producing changes in the brain, where they occur, and what the underlying mechanisms are at the chemical level. It is clear that the brain is plastic and highly sensitive to alterations of its normal circuitry. We now have workable models that may explain some aspects of tinnitus, and these models are already influencing the development of treatment strategies.

While we cannot yet say when a "cure" for tinnitus will emerge, we have more reason for optimism now than ever to believe that effective treatments may soon be within reach.

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