

PATHOPHYSIOLOGY OF TINNITUS

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The hypothesis is presented that certain forms of tinnitus are related to abnormal phase-locking of discharges in groups of auditory nerve fibers. Recent developments in auditory neurophysiology have shown that neural coding of the temporal pattern of sounds plays an important role in the analysis of complex sounds. In addition, it has been demonstrated that when some other cranial nerves are damaged, artificial synapses can occur between individual nerve fibers such that ephaptic transmission between nerve fibers is facilitated. Such "crosstalk" between auditory nerve fibers is assumed to result in phase-locking of the spontaneous activity of groups of neurons which in the absence of external sounds creates a neural pattern that resembles that evoked by sounds.

Tinnitus is a symptom, not a disease. Because it may be caused by any of a number of different disorders in the ear or in the auditory nervous system, to try to describe the pathophysiology of tinnitus in all its manifestations may seem fruitless. However, certain restricted forms of subjective tinnitus may be explained on the basis of current knowledge about the function of the ear and the auditory nervous system. This paper critically examines the knowledge that exists about the generation of tinnitus and points toward the possibility that dysfunction of the auditory nerve and ascending auditory pathway may be the cause of subjective tinnitus; specifically, the ways in which complex sounds are coded in the auditory nervous system have a bearing on the production of tinnitus.

Tinnitus is often associated with disorders of the cochlea, and it is a commonly held belief that tinnitus is the result of an increase in the (spontaneous) firing rate of primary auditory nerve fibers caused by hyperactivity of hair cells in the cochlea. However, this hypothesis has not yet been verified. In fact, it is interesting that in auditory nervous systems exposed to noise and to aminoglycosides, a decrease is noted in the spontaneous activity, rather than the increase expected if the above theory were correct.¹⁻³ This seems to indicate that tinnitus is not necessarily caused by an increase in the rate of discharge of cochlear nerve fibers. In fact, on the basis of these results it was suggested that tinnitus is caused by reduced activity in the cochlear nerve.¹

Another hypothesis holds that tinnitus caused by noise exposure or other mechanical insult to the cochlea results from deafferentation hyperexcitability, but there has been no experimental confirmation of this hypothesis. Thus, no generally accepted explanation of the mechanism that leads to tinnitus has been presented. There is no doubt that many cases of tinnitus can be linked to insults that are known to affect the cochlea, and it is therefore plausible that tinnitus in such patients is the result

of one of several aspects of the induced cochlear dysfunction. In general, however, the auditory nerve and the central auditory nervous system have been little studied as possible sites of lesions that may cause tinnitus.

The finding that local anesthetics,⁴ particularly lidocaine, can relieve tinnitus^{5,6} supports the hypothesis that neural hyperactivity may cause tinnitus. It is known that increased sodium conductance increases the sensitivity of axons and in many cases makes axons into mechanoreceptors of high sensitivity. Lidocaine is a sodium channel-blocker⁷ that functions somewhat differently from other sodium channel-blockers.⁸ Lidocaine can only block sodium channels from the axoplasm side (inside) of the axon. The drug is carried inside the axon through sodium channels while it is in its electrically neutral state. When inside it is protonated, and in its charged state it cannot pass the sodium channels; instead it blocks them, thereby decreasing sodium conduction.⁷⁻¹⁰ The result is that lidocaine as a sodium blocker operates most efficiently in neurons with high discharge rates. Whether the action of lidocaine in reducing tinnitus occurs in the auditory nerve, the central auditory nervous system, or the cochlea itself (or any two, or all three) is not known. The fact that certain studies appear to indicate that lidocaine has a specific affinity for melanin granules in the inner ear has been interpreted as indicating that the site of lidocaine action is in the cochlea.¹¹ It is known that lidocaine has an anticonvulsive effect,¹² and there is thus the possibility that lidocaine acts on the ganglion by reducing its excitability, thereby preventing the reverberant activity which is caused by hyperactivity of a nerve. There is evidence that the anti-convulsants such as carbamazepine (Tegretol) or phenytoin sodium (Dilantin) also block sodium channels,¹³ although their function is not known in detail and other actions have been suggested. These drugs have been used with some success in the treatment of tinnitus.¹⁴⁻¹⁶

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No valid animal model has yet been developed in which to study tinnitus. Recently, Evans et al¹⁷ proposed the use of sodium salicylate in developing a model utilizing electrophysiological measures. Although it is well known that sodium salicylate in high dosages gives rise to tinnitus in humans,¹⁸ it is not at all certain that such is the case in animals, and it is doubtful that tinnitus induced by salicylate is caused by the same mechanism as is tinnitus caused by other insults.

In seeking other possible explanations of the mechanism for tinnitus it may be beneficial to consider how sounds are coded in the auditory nervous system and, particularly, how the ear signals to the CNS that a sound is present. We will direct our attention to the temporal coding of discharges instead of to the mean discharge rate, as has been done previously, to look for clues to the generation of tinnitus.

The most basic information that the ear can provide to the CNS is whether or not a sound exceeds the threshold of hearing. On the basis of what is known from studies of the discharges in single fibers in the auditory nerve and cells in the various nuclei of the ascending auditory pathway, it may seem as if the CNS makes use of the absolute value of the discharge rate in determining whether or not a sound exceeds the threshold. Since auditory nerve fibers are known to have a spontaneous activity that varies from fiber to fiber,¹⁹ it would seem as if the CNS must establish different discharge rate threshold values for different fibers in order to avoid constantly receiving spontaneously generated information that is indistinguishable from environmental sounds. It may then be suggested that there are threshold devices located somewhere in the ascending auditory pathway that make it possible to distinguish sound-driven activity from spontaneous activity. However, if weak sounds are to be detected, the spontaneous activity must remain within narrow limits in order to make it possible to distinguish the small increase that is caused by a weak sound.

In view of these difficulties inherent in using the (average) discharge rate in threshold detection and loudness determination, it may be reasonable to search for other properties of the discharge pattern which could convey information about such physical properties of sound as (threshold) intensity. Several properties of neural activity other than discharge rate are related to sound stimulation. One such property is the temporal pattern of the discharges,²⁰⁻²² and another is the temporal relationship between the discharge patterns of different fibers in a group of fibers. The relationship between the temporal pattern of the discharges of single nerve fibers or cells and that of sound is known as phase-locking, and it has been associated with the perception of pitch.²³

The results of recent studies²⁴ have shown that monaural phase-locking of the discharges of single auditory nerve fibers of low-frequency sounds may be detected by neurons in the medial superior olivary nucleus by measuring the delays between phase-locked activities which originate at different locations along the basilar membrane. The degree of phase-locking of the activity of single auditory nerve fibers depends on the intensity of a sound and its frequency in relation to the characteristic frequency of the individual fibers. It may therefore be suggested that phase-locking of neural discharges may also play a role in threshold detection and may convey information about the loudness of a sound to the central auditory nervous system. It is worth noting that phase-locking can be detected at lower sound intensities than can responses which produce a measurable increase in discharge rate. Thus, phase-locking may not only be important for frequency discrimination but it may also play a role in detection of the presence of a sound.

In the absence of sound it is generally assumed that the time pattern of the discharges in each auditory nerve fiber is random and that there is no correlation between the time patterns of the discharges of different nerve fibers. A low-frequency sound above threshold will cause discharges in individual nerve fibers to phase-lock to the time pattern of the sound. Sounds above threshold activate many fibers, which means that the relationship between the activity among fibers will be controlled by the time pattern of the sound, and discharges of many fibers will have an orderly temporal relationship to each other.^{25,26} In the range of auditory frequencies (above threshold) where neural discharges are phase-locked to the waveform of the sound, for all sounds — whether periodic or nonperiodic, transient or continuous — there is thus a certain degree of correlation between the time patterns of the discharges of different nerve fibers.²⁵

Spontaneous activity in single auditory nerve fibers in the absence of sound stimulation, on the other hand, may be assumed to be uncorrelated. Detection of the temporal correlation between the discharge patterns of different nerve fibers would therefore make it possible to detect sounds near threshold without having to rely on precise knowledge about the absolute value of the spontaneous firing rate. Detection of correlation between the discharge patterns of many neurons is not dependent on the absolute value of the spontaneous activity which, in fact, can vary over wide ranges without affecting such a detector. This hypothesis in a way challenges the widely held beliefs about specific nerve energies first proposed by Muller,²⁷ but it may also be regarded as adding another dimension to his hypothesis about specific nerve energies. The importance of the temporal pattern of auditory nerve discharges has also been emphasized in other neural systems. Thus, Emmers²⁸ has presented evi-

dence to indicate that pain may be coded through spike intervals.

The above hypothesis regarding the establishment of an auditory threshold on phase-locked activity allows us to explain tinnitus that is not necessarily related to hearing loss. The hypothesis regarding such tinnitus is based on the assumption that damage can occur to the electrical insulation (myelin) between auditory nerve fibers or sensory hair cells. It is generally assumed that various types of damage to nerves can give rise to artificial synapses between individual nerve cells that facilitate ephaptic transmission between nerve fibers^{29,30} or hair cells. It is also known that cross-compression of the root entry zone of at least two cranial nerves, the trigeminal nerve³¹⁻³⁵ and the facial nerve,^{34,36,37} can result in a clinically manifested dysfunction such as hemifacial spasm or trigeminal neuralgia, respectively. This cross-compression is most often caused by arterial loops, but can be caused by veins or tumors. It has been suggested that the mechanism by which an artery, for example, can cause cranial nerve disorder involves the application of pulsatile pressure by the artery to the root entry zone of the nerve; this pressure damages scattered areas of the myelin sheaths of the nerve fibers, which in turn may allow artificial synapses to arise between nerve fibers, thereby establishing ephaptic transmission ("crosstalk") between different nerve fibers.^{30,31,33-40} Such ephaptic transmission is likely to result in abnormal impulse generation with prolonged high frequency after discharges seen after injury.⁴¹ It is also likely that the temporal patterns of the spontaneous activities in different nerve fibers become correlated (phase-locked) with each other. Both of these types of abnormal firing of nerve fibers may be causing the dysfunction that is manifested by hyperactivity in the nerve and reverberant activity in the associated nucleus.

Damage similar to that caused by vascular or mass lesion compression of the cranial nerves may be caused in the auditory system by an acoustic neuroma growing into the auditory nerve, by compression of the nerve by blood vessels, or in the cochlea by pressure due to hydrops or by exposure to high-intensity sound (noise trauma). Disorders caused by such pathologies are often accompanied by tinnitus; indeed, tinnitus is often the earliest manifested clinical symptom of an acoustic neuroma.

The results of studies involving large numbers of human subjects have shown that trigeminal neuralgia and hemifacial spasm may be cured successfully by decompression of the offending vessel.^{32,33,35,37} In a few cases tinnitus has been relieved by a similar decompression of blood vessels pressing on the eighth nerve, and it has been shown that such decompression relieves both tinnitus and vertigo in people with Meniere's disease.^{42,43} Similar mechanisms have also been put forth to explain the

etiologies of some dysfunctions of the glossopharyngeal and vagus nerves.³⁴

Experiences in treating trigeminal neuralgia and hemifacial spasm by microvascular decompression of the nerve have shown us that the nerves themselves are relatively insensitive to pulsatile pressure from arterial loops, but that the root entry zones of the nerves are quite sensitive to these pressures. The fifth and seventh cranial nerves are covered by central myelin for only a few millimeters beyond the points where they exit the brainstem,^{44,45} while the auditory nerve is covered by central myelin for a much larger distance from the brainstem. For this reason we might expect that the auditory nerve would more frequently be affected by cross-compression than would the other cranial nerves. The Obersteiner-Redlich zone in the acoustic nerve is located at or inside the internal auditory meatus about 6 mm from the porus acusticus.⁴⁵ This leaves 15 to 20 mm of the nerve to be covered by central myelin and thus vulnerable to the symptoms of ephaptic transmission (tinnitus).

It may not seem reasonable at first to explain such seemingly different manifestations of disease as pain due to trigeminal nerve dysfunction, muscle spasm resulting from facial nerve malfunction, and tinnitus due to cochlear nerve dysfunction as occurring by the same mechanism, namely crosstalk between nerve fibers in different cranial nerves. However, if we assume that the time pattern of neural discharges in groups of neurons is important for the normal functioning of the nerve, it becomes plausible that the loss of the integrity of individual nerve fibers can cause such unnatural sensations as pain, muscle spasm, and tinnitus, which are symptoms of hyperactivity and caricatures of the normal functions of the nerves. In addition, there are several clinically manifested similarities between hemifacial spasm, trigeminal neuralgia, and tinnitus that are important to consider when seeking an explanation for tinnitus. For instance, tinnitus can in some cases be controlled by anticonvulsive drugs. The most studied, and also the most effective, of these drugs is lidocaine,^{5,6} but carbamazepine and phenytoin sodium¹⁶ both antiepileptic drugs, as well as other local anesthetics,^{4,46} have also been shown to have such an effect, although not as pronounced and not occurring as often. All three drugs are generally assumed to act by blocking sodium channels of the nerve membrane, thus stabilizing membrane potentials and decreasing the chance of eliciting reverberant activity in the associated nucleus.

The well-known fact that, of two people with the same audiometric threshold shift as a result of noise-induced hearing loss, one may and one may not have tinnitus, can be explained in that some types of noise cause mechanical damage to the sensory epithelium that is associated with a breakdown of the

electrical insulation between hair cells without necessarily damaging them. It is also a general clinical experience that exposure to impulsive noise is more often associated with tinnitus than is long-term exposure to continuous noise. To our knowledge, however, no systematic study has been published regarding the relative incidence of tinnitus associated with different types of noise-induced hearing loss. The fact that the frequency of the tinnitus in many cases of noise-induced hearing loss bears a close relationship to the high-frequency cutoff of the audiogram has been taken as an indication that loss of normal suppression may be a cause of tinnitus in these cases.⁴⁷

Studies of cochlear echoes have indicated that there are active processes in the cochlea, and that certain types of cochlear damage can give rise to an instability in these active processes such that sustained self-oscillation of the basilar membrane results. The validity of this mechanism is supported by the fact that cochlear echoes can be measured as sounds in the ear canal.⁴⁸ It is likely that impulse noise causes structural damage to the sensory epithelium, which in turn may reduce the electrical resistance between hair cells. The hypothesis that a mechanical insult to neural structures in the peripheral auditory system can cause tinnitus is supported by the finding that patients with cochlear hydrops usually have tinnitus and, moreover, that their tinnitus in the beginning of the disease occurs only at the time of the vestibular attacks.⁴⁹ Later in the course of the disease, tinnitus is a constant phenomenon; according to the hypothesis, this would be the result of permanent damage to the peripheral auditory system.

It has been shown that applying an electrical current to the human cochlea can eliminate tinnitus.⁵⁰ In addition, the results of animal experiments have shown that passing a DC current through the cochlea can cause either an increase or a decrease in the firing of single auditory nerve fibers, depending upon which direction the current flows through the organ of Corti. It seems difficult to explain how this can affect the function of the auditory nerve. However, the current applied to the human subjects passed between a unipolar electrode placed on the round window and a reference on the earlobe, and may in fact have passed through the internal auditory meatus as well.⁵¹ Such a current could change or eliminate the crosstalk between nerve fibers and thereby affect the synchronizing of the activity in individual nerve fibers. The results of animal experiments have shown that direct current passed through the basilar membrane can cause an increase or a decrease in the discharge rate of single auditory nerve fibers, depending upon the direction of the current.⁵² It is also conceivable that tinnitus might disappear when the artificial current passed through the cochlea reduces the spontaneous firing rate of single auditory nerve fibers to an intensity

below that which is necessary for synchronized activity to be generated by crosstalk between nerve fibers.

The temporal pattern of discharges in single auditory nerve fibers that can be evoked by sound stimulation is proscribed somewhat by the nature of the mechanical disturbance on the basilar membrane, which in turn is a characteristic of the stimulus and of the specific arrangement of the sensory epithelium along the basilar membrane. Crosstalk between auditory nerve fibers, however, is not so proscribed, which may explain the general finding that most patients with tinnitus find it difficult to match their tinnitus to sounds presented to them. Most important may be the finding that masked audiograms in patients with tinnitus do not bear any relationship to those obtained in psychoacoustic masking experiments when the ear is stimulated with sounds.⁵³ Also, the fact that contralateral masking in many cases is more efficient than is ipsilateral masking points to the nervous system as the site where tinnitus is generated.⁵³

Procedures performed to relieve intractable tinnitus include sectioning of the auditory nerve. The results of such procedures seem to indicate that more peripheral sectioning has less chance of success than sectioning close to the brainstem. This may be explained by the fact that the auditory nerve is a relatively long nerve (25 mm)⁴⁵ and that a considerable portion of it is covered by central myelin. The Obersteiner-Redlich zone, where the transition between peripheral myelin and central oligodendrital myelin occurs, is located inside the porus acusticus. Also the fact that a large portion of the auditory nerve has central myelin makes it more likely that this nerve will be affected by cross-compression from blood vessels than will other cranial nerves which have less extensive central myelin.

Phase-locking of the discharges of auditory nerve fibers has not been shown experimentally to occur above 6,000 Hz. This seemingly contradicts the hypothesis presented in the present study that tinnitus is caused by crosstalk between fibers in the auditory nerve (abnormal phase-locking) because the subjective experience of tinnitus often is that of a sound with a higher frequency than 6 kHz. However, studies on auditory adaptation⁵⁴ indicate that the inability of the auditory nerve to phase-lock to high-frequency sounds may not be the result of a limitation in the nerve itself but of a limitation in the hair cells or in their synaptic connection to the nerve fibers. Thus, even tinnitus that is perceived as a high-frequency sound might be generated by abnormalities in the temporal firing patterns of auditory nerve fibers.

In summary, it seems that hemifacial spasm, trigeminal neuralgia, and some forms of tinnitus may be divergent responses to a common cranial nerve abnormality: alteration in the temporal pat-

tern of discharges as the result of pulsatile vascular compression of the cranial nerve. The alteration in the temporal pattern of discharges in each nerve then gives rise to reverberant activity in the involved nerve and associated nucleus. The symptoms of these three disorders can be suppressed by anticonvulsant drugs or relieved permanently by removing the cause of the altered impulse activity in the cranial nerve (microvascular compression). In

this report attention is drawn to other explanations of tinnitus than the prevailing assumption that the cochlea is the locus of the disturbance and, particularly, that tinnitus is the result of an increased firing rate of auditory nerve fibers. These new ideas about the etiology of tinnitus should lead to new research that will ultimately uncover new and more effective ways of treating this disorder.

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