Neurophysiologic Mechanisms of Tinnitus

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Abstract
Research over the past decade has provided new insights into the neural mechanisms likely to produce the false percepts of sound associated with tinnitus. These insights have emerged mainly as a result of electrophysiologic studies, examining changes in brain activity, and behavioral studies, examining changes in perception, in animals that have been treated with well-known tinnitus inducers such as salicylates, quinine, and intense sound. The available evidence, based on electrophysiologic studies, suggests that tinnitus is associated with disturbances in spontaneous neural activity in the auditory system. These abnormalities include increases in spontaneous activity (hyperactivity), changes in the timing of neural discharges (i.e., the temporal firing properties of neurons), and an increase in bursting activity of neurons. Parallel studies using behavioral testing methods have demonstrated that agents, which produce these neural changes, also cause tinnitus in animals. This article reviews the literature concerned with both behavioral evidence for tinnitus in animal models and the associated changes that occur at peripheral and central levels of the auditory system.

Key Words: Animal models, behavioral models, hyperactivity, intense sound, neurophysiology, noise, salicylates, spontaneous activity, tinnitus, tinnitus perception

Abbreviations: AI = primary auditory cortex, AIi = secondary auditory cortex, AFF = anterior auditory field, CF = characteristic frequency, CO2 = carbon dioxide, DCN = dorsal cochlear nucleus, EEG = electroencephalogram, FMRI = functional magnetic resonance imaging, IC = inferior colliculus, OAEs = otoacoustic emissions, PET = positron emission tomography, SA = spontaneous activity, SOAEs = spontaneous otoacoustic emissions

Interest in understanding the physiologic basis of tinnitus has grown exponentially over the past decade. This growth reflects the increasing awareness of the prevalence of this disorder in industrial societies where tinnitus ranks among the major causes of absenteeism from the workplace and among the chief reasons for patient visits to the otolaryngology clinic. Despite its importance, the ability to treat tinnitus successfully in the vast majority of cases is severely limited, due in part to a lack of understanding of the underlying pathologies. However, recent studies in neurophysiology have dramatically expanded knowledge about these pathologies and the likely mechanisms that generate the tinnitus signal. It is reasonable to expect that a continuation of research on this issue will open up new avenues for the treatment of tinnitus in the foreseeable future.

The purpose of this article is to provide a summary of what has been learned from neurophysiologic studies about the mechanisms underlying tinnitus. The main insights have come from studies in animal models designed to identify and localize specific functional alterations in the auditory system that are caused by tinnitus-inducing agents, including salicylates, quinine, and noise. Studies of this type have demonstrated that each agent causes the auditory system of animals to behave as though it is responding to a sound. Moreover, complementary studies, employing behavioral testing methods, have demonstrated that animals do develop tinnitus after being exposed to these agents. In the present article, a brief summary of these behavioral studies is presented and is followed by a review of the relevant neurophysiologic literature.

BEHAVIORAL MODELS OF TINNITUS

Behavioral models of tinnitus have been established for three tinnitus-inducing agents including sodium salicylate (aspirin), quinine, and intense sound. These agents have
been used for studying both acute (tinnitus of rapid onset, which lasts only a few minutes or hours) and chronic tinnitus (which lasts for at least several days).

**Behavioral Studies with Salicylate and Quinine**

In humans, tinnitus induced by salicylate or quinine develops within a few hours to days after commencement of treatment and is perceived as a high pitch (between 7 and 9 kHz) tone or narrow band of noise (McCabe and Dey, 1965; Mongan et al, 1973; McFadden et al, 1984; Day et al, 1989; Karlsson and Flock, 1990). It usually disappears gradually over a period of hours to days after cessation of treatment. Tinnitus induced by high doses of these agents is often associated with hearing loss, although generally the induced tinnitus has an earlier onset than the hearing loss (Mongan et al, 1973).

Several studies demonstrate that animals develop tinnitus after exposure to high doses (350 mg/kg) of salicylate. The relevant experiments have been carried out in rats using a Pavlovian conditioned-suppression paradigm, and the reader is referred to papers by Jastreboff et al (1988a, b) for details on the behavioral methods used to test animals for tinnitus. The results of these experiments indicate that the tinnitus induced in rats by salicylate is similar in psychophysical attributes and time course to that induced in humans. Measurable tinnitus percepts develop within 1 to 2 days after salicylate injection, become more severe with dose and duration of treatment (Jastreboff and Brennan, 1994; Bauer et al, 1998), and are characterized by a high pitch (Jastreboff et al, 1988a, b). A more recent study by Jastreboff et al (1991) demonstrated that tinnitus can also be induced in rats by quinine. This tinnitus showed a similar time course and dose dependence to that induced by salicylate and was found to be reversible with the calcium channel blocker, nimodipine.

**Behavioral Studies with Intense Sound**

Intense noise exposure is the most commonly cited cause of tinnitus (Meikle and Taylor-Walsh, 1984; Axelsson and Barrenas, 1992; Coles, 1995; Penner and Bilger, 1995; Vernon, 1995). Noise-induced tinnitus is usually characterized as having a high pitch, being matched to frequencies between 1.5 and 8 kHz (Man and Naggan, 1981; Cahani et al, 1983; Axelsson and Sandh, 1985). People with chronic noise-induced tinnitus also commonly have a permanent hearing loss.

It is important to distinguish between acute and chronic tinnitus in the context of noise exposure because some intense sounds, especially moderate-level explosive sounds, may cause an immediate, but short-lived, tinnitus. This acute form lasts a few seconds to a few days, although depending on the subject's exposure history, may develop into chronic tinnitus. Indeed, most clinical cases of noise-induced tinnitus are chronic in nature, lasting months to years. People with chronic noise-induced tinnitus usually do not remember the time of tinnitus onset but instead perceive their tinnitus as having a slow onset, progressing gradually over a period of weeks to years (Axelsson and Barrenas, 1992).

As yet, no behavioral studies have formally reported that animals develop tinnitus after noise exposure. However, behavioral models for acute and chronic forms of noise-induced tinnitus have been developed in several laboratories, and the results have already been presented in preliminary form (Jastreboff et al, 1997; Bauer et al, 1999; Heffner and Kaltenbach, 1999). Here we describe experiments conducted by Heffner and Kaltenbach (1999) that tested animals for chronic tinnitus after exposure to an intense tone. The procedure used is described as follows. Before sound exposure, hamsters were trained for several weeks to discriminate between the presence and absence of a conditioning sound. The ability of the animals to discriminate was signaled by differences in licking behavior. Thus, when the conditioning sound was presented, the animals were trained to maintain contact with a water spout, and when the sound was absent, they were trained to break contact with the spout. After training, the animals were divided into two groups, one of which was exposed to a high-level (125 dB SPL), continuous tone (10 kHz) for 4 hours; the other group was not. Five days after exposures, animals in both groups were tested for tinnitus. The procedure for this test was similar to that used during training except that no conditioning sound was presented. When this test was performed, normal, unexposed animals tended to break contact with the spout as they did during training when no sound was presented. In contrast, the animals that had been exposed to an intense tone 5 days earlier tended to maintain contact with the spout as though they were hearing a conditioning sound, even though no sound was presented. In other words, they were
behavior as though they had tinnitus. Preliminary experiments have been carried out in rats and have yielded similar results. Experiments are now in progress to determine the loudness and pitch of the induced tinnitus. This model will facilitate neurophysiologic experiments seeking to identify the relevant changes in the auditory system that underlie chronic tinnitus, as described in the next section.

NEUROPHYSIOLOGIC MODELS OF TINNITUS

Although tinnitus is commonly referred to as ringing of the ears, clinical studies of patients with tinnitus who have undergone transection of their auditory nerves indicate that the underlying pathology may be peripheral or central in origin. Generally, between 30 and 80 percent of tinnitus patients who undergo these resections continue to experience their tinnitus, and many such patients experience it in a worsened condition (Dandy, 1941; House and Brackman, 1981; Moller et al, 1993; Wazen et al, 1997). Additionally, although tinnitus is primarily an auditory disorder, the clinical condition usually includes secondary symptoms that are nonauditory in nature. Evidence for the involvement of nonauditory structures in the symptomatology of tinnitus has been presented previously (Shulman et al, 1995; Jacobson, 1996; Lockwood et al, 1998). This review focuses on the auditory system components of tinnitus and is organized according to the type of dysfunction, beginning with defects at the level of the inner ear and auditory nerve and proceeding centrally.

Peripheral Mechanisms of Tinnitus

Inner Hair Cell Dysfunction

The inner hair cells have been the focus of several models of tinnitus because of the role they play in afferent neurotransmission. One model invokes alterations in hair cell physiology as the triggering mechanism of tinnitus induction. The model begins with disturbances in cochlear function due to mechanical trauma or changes in vascular supply. The consequence of these disturbances is a change in the biophysical properties of the hair cells leading to increases in ion conductance (leaky membranes), which triggers an increase in spontaneous neurotransmitter release from the basal pole of the hair cell (Zenner and Ernst, 1995). The excess transmitter release results in overactivation of the connecting auditory nerve fibers.

Evidence consistent with this model has been obtained in experiments with chemical agents that interfere with chemical neurotransmission of the hair cell. Glutamate is the presumed hair cell neurotransmitter (Drescher and Drescher, 1992), and its release increases the level of activity of auditory nerve fibers (Ehrenberger and Felix, 1995). The binding of glutamate to the postsynaptic membrane of auditory nerve fibers can be blocked with caravorine (Ehrenberger and Felix, 1992) or glutamic acid diethyl ester (Ehrenberger and Felix, 1991). Both of these agents were also reported to have a protective effect against ototoxicity and some forms of tinnitus in humans (Ehrenberger and Brix, 1983; Denk et al, 1997). This protective effect might be achieved by inhibiting glutamate's excitatory effect on the auditory nerve (Ehrenberger and Felix, 1995). This view is supported by evidence that memantine, another antagonist of glutamate, had the effect of reducing spontaneous activity of auditory nerve fibers when injected into the cochlea of guinea pigs (Oestreicher et al, 1998). The ability of memantine to suppress tinnitus has not yet been reported.

Outer Hair Cell Dysfunction

Outer hair cells are thought to increase the sensitivity of the inner ear by amplifying sounds through an energy-dependent active process (Davis, 1983). Outer hair cells are electromotile cells capable of contracting and producing vibrations that influence the mechanical properties of the organ of Corti. Such vibrations manifest as very low-level sounds that are emitted by the cochlea in the form of otoacoustic emissions (OAEs). These emissions can be measured with very sensitive microphones placed in the ear canal and have been widely studied in humans with and without tinnitus (see reviews of Norton et al, 1990; Penner, 1990; Plinkert et al, 1990; Ceramic et al, 1995). On average, 28 percent of men and 56 percent of women show measurable OAEs that occur in the absence of acoustic stimulation. These are called spontaneous otoacoustic emissions (SOAEs). However, the reported incidence of tinnitus that can be explained by SOAEs is generally rare, comprising less than 10 percent of the tinnitus-bearing population. Evidence that the tinnitus of these cases is linked to SOAEs has been reviewed previously (Norton et al, 1990; Penner, 1990;
includes the following: (1) the pitch of the tinnitus correlates with the frequency of a spectral component of the SOAEs, (2) suppression of emissions by aspirin makes tinnitus inaudible, (3) masking of the tinnitus abolishes SOAEs, and (4) iso-masking contours for masking tinnitus display similar frequency tuning properties as SOAEs.

The mechanism by which SOAEs give rise to tinnitus is not yet clear, although a study relevant to this issue was reported by Powers et al (1995). They induced robust SOAEs in two chinchillas using intense sound exposure and found that the induced SOAEs were associated with increases in spontaneous activity of auditory nerve fibers. The affected fibers had abnormally high response thresholds and were tuned to frequencies close to the frequency of the SOAE, demonstrating that they originated from cochlear regions with enhanced mechanical vibrations. Histologic analysis, however, revealed no significant inner hair cell loss in the corresponding region of the cochlea. In one animal, the induced SOAE was reversed by salicylate, a manipulation that also resulted in reversing the increase in spontaneous activity. The authors interpreted these findings as indicating that increases in spontaneous activity were probably linked to the SOAEs and probably occurred as a result of enhanced inner hair cell activation. Perhaps the rarity of SOAE-linked tinnitus in humans is related to the much lower magnitude of SOAEs that are normally observed in the human ear.

Central Mechanisms of Tinnitus

Increases in Spontaneous Activity (Hyperactivity)

It is expected that since sound is normally signaled in the auditory system by an increase in neural firing rate, the sounds of tinnitus might be generated by pathologic increases in background or spontaneous activity. This hypothesis has been tested in numerous animal models using electrophysiologic techniques and in humans using brain imaging techniques. This section reviews published work relevant to this issue.

Experiments with Sodium Salicylate. The first studies to implicate altered spontaneous activity as an underlying correlate of tinnitus were those of Evans and his colleagues (Evans et al, 1981; Evans and Borerwe, 1982). They reported an increase in spontaneous discharge rates within a subpopulation of auditory nerve fibers in cats treated with high doses of sodium salicylate ($\geq 400$ mg/kg). The units affected were characterized by high predrug spontaneous rates and were tuned to high frequencies. The authors hypothesized that the high-frequency selectivity of the affected neurons might account for the high pitch of tinnitus induced by salicylate.
Efforts to reproduce these findings in subsequent studies have produced varying results, although it now appears that some of these variations are attributable to differences in the dosage of salicylate used. No significant effects of low to moderate doses (≤ 200 mg/kg) of salicylate were found on mean VIIIth nerve spontaneous rates in guinea pigs (Mulheran, 1990; Kumagai, 1992) or cats (Stypulkowski, 1990), but increasing the dose to 400 mg/kg caused increases in spontaneous rates in the guinea pig (Kumagai, 1992). Slight increases in spontaneous rates were also found in the pigeon after intracochlear perfusion of high doses of salicylate (Shehata-Dieler et al., 1994). The interpretation of the increased activity induced by these high doses of salicylate has been questioned by Chen and Jastreboff (1995), who have cited the fact that salicylate may cause a number of toxic effects when administered at doses of 400 mg/kg and higher. Such effects in their experience included profound changes in body temperature, respiration, and EKG. However, a recent study by Mulheran and Evans (1999) shows that increases in spontaneous activity following salicylate treatment occur in the auditory nerve of guinea pigs, even when body temperature, blood pressure, and respiratory end tidal CO₂ remain constant.

An increasing number of studies indicate that salicylate has a potent effect on the central auditory system, even at doses that do not cause a more general toxicity. A central effect was first described by Kauer et al. (1982), who showed that very high doses of this drug caused an increase in metabolism in auditory brainstem nuclei of guinea pigs. More recent studies, focusing on the inferior colliculus (IC), have revealed a potent effect of more moderate doses (200 mg/kg) of salicylate (Chen and Jastreboff, 1995; Manabe et al., 1997; Wallhauser-Franke, 1997). Within 2 to 3 hours after salicylate injection, mean spontaneous discharge rates for single units increased between two- and threefold above their predrug levels (Chen and Jastreboff, 1995; Manabe et al., 1997). The greatest increases were found among units tuned to high frequencies (Chen and Jastreboff, 1995).

Several aspects of this increased activity suggest that it represents an important neural correlate of tinnitus: (1) The doses of salicylate used to induce the increased discharge rate (200 mg/kg) were within the dose range that was previously shown to cause tinnitus in rats (i.e., 150–300 mg/kg) without toxic side effects (Jastreboff et al., 1988a, b). (2) The increased activity was found mainly among units tuned to frequencies between 10 and 16 kHz (Chen and Jastreboff, 1995). This range is consistent with evidence suggesting that salicylate-induced tinnitus in both rats and humans is high in pitch (McCabe and Dey, 1965; Jastreboff et al., 1988a, b). (3) The increased activity was reversible using a calcium supplement (Chen and Jastreboff, 1995) or lidocaine (Manabe et al., 1997), factors that are known for their ability to attenuate tinnitus for short periods (Gejrot, 1963; Melding et al., 1978; Jastreboff and Brennan, 1992).

The conscious awareness of annoying sound, which people experience after salicylate ingestion, implies that the induced tinnitus must involve structures at cortical levels of the auditory system. Indeed, results of recent studies by Eggermont and his colleagues are consistent with this expectation (Ochi and Eggermont, 1996; Eggermont and Kenmochi, 1998). They compared the influences of salicylate on each of three different auditory cortical areas including primary (AI) and secondary (All) cortices and the anterior auditory field (AAF). The conclusions drawn from these studies were that salicylate causes a decrease of mean spontaneous rates in AI and AAF but an increase in rates in All. The increased rates in All occurred among units tuned to high frequencies (between 10 and 16 kHz), in agreement with the results from IC (Chen and Jastreboff, 1995). This similarity suggests that the increased activity seen in cortical area All may originate from subcortical auditory centers such as the IC or even lower level nuclei. Alternatively, the changes seen in AII after salicylate may be a cortical expression of a more general effect of this drug on the extralemniscal pathway. These possibilities are discussed in detail by Eggermont and Sininger (1995).

**Experiments with Quinine.** The case that increased spontaneous activity is an important correlate of tinnitus has gained further strength from evidence that changes in activity can also be induced by the tinnitus-inducing agent, quinine. Although quinine and salicylate have different modes of action (Smith et al., 1985; Puel et al., 1990), the tinnitus induced by both drugs is similar in being described as high in pitch and in being matched to a narrow band noise or tone. The effects of quinine on spontaneous discharge rate have so far been studied at the levels of the auditory nerve and auditory cortex. In the auditory nerve, quinine affected the
distribution of fibers with low and high spontaneous discharge rates. A significant increase in the percentage of fibers with low spontaneous rates was observed after quinine treatment (Mulheran, 1990). Quinine has also been found to cause an increase in the duration of action potentials of spiral ganglion cells in vitro (Lin et al., 1998). Although the relationship of this latter effect to tinnitus is unknown, prolonged action potentials could increase the probability of spatial or temporal summation, thereby leading to enhanced activity in postsynaptic neurons (Lin et al., 1998). This would be expected to cause hyperactivity in brainstem auditory nuclei. Although this hypothesis remains untested, changes in spontaneous activity have been observed in the auditory cortex after quinine treatment (Kenmochi and Eggermont, 1997; Ochi and Eggermont, 1997; Eggermont and Kenmochi, 1998). These effects have been examined in the cat, and in most respects resembled those induced by salicylate. That is, quinine caused increases in mean spontaneous rates in area AII but decreases in rates in AI and AAF.

**Experiments with Intense Sound.** Despite the fact that noise exposure is the most common cause of tinnitus, animal models of its underlying mechanisms have been slow to emerge in the literature. Early attempts to develop a model of chronic noise-induced tinnitus using electrophysiologic methods yielded disappointing results. Studies carried out at the auditory nerve level indicated that noise exposure either caused no significant change in activity over the short term (Van Heusden and Smoorenburg, 1983) or caused activity to decrease over the long term (Liberman and Kiang, 1978; Liberman and Dodds, 1984). When increases in activity were found, they were either very marginal in degree (Salvi and Ahroon, 1983) or involved a small fraction of nerve fibers whose activity recovered within a few minutes after the exposure (Alder, 1978; Lonsbury-Martin and Martin, 1981). This led some investigators to speculate that tinnitus was not the result of increased spontaneous activity per se but rather a neural “edge effect” produced by contrasting levels of activity between cochlear regions having normal and low activity (Liberman and Kiang, 1978).

It is now apparent that noise-induced tinnitus has important central components. Hyperactivity induced by intense sound exposure has been demonstrated in the dorsal cochlear nucleus (DCN) of hamsters and rats (Kaltenbach and McCaslin, 1996; Kaltenbach et al., 1996; Kaltenbach et al., 1998; Zhang and Kaltenbach, 1998). This hyperactivity was found throughout much of the DCN when animals were examined 1 month following exposure to an intense (125–130 dB SPL) tone (10 kHz) for 4 hours. The magnitude of the increased activity generally ranged between three- and tenfold above control levels, reaching a peak in the region of the DCN corresponding to the frequency of the exposure tone. An important aspect of this hyperactivity is that its magnitude depended on how long after exposure the animals were studied. No evidence of hyperactivity was observed 2 days after exposure, but a strong indication of hyperactivity was found in animals observed at 5 days after exposure. The degree of hyperactivity continued to increase very gradually over the next few months.

The relationship of DCN hyperactivity to tinnitus is also being studied by carrying out electrophysiologic recordings in animals tested previously for tinnitus (Heffner and Kaltenbach, 1999). Preliminary studies have demonstrated a correlation between the level of activity in the DCN and the strength of evidence for tinnitus (Kaltenbach and Heffner, 1999). The highest level of DCN activity was found in animals showing the strongest evidence for tinnitus, whereas lower levels of activity were found in animals with weaker evidence for tinnitus. The lowest activity was found in unexposed animals showing no evidence of tinnitus. This relationship suggests that the level of activity may provide not only a measure indicating whether tinnitus is present but may also serve as an index of its severity.

Since noise-induced tinnitus is a conscious percept, it probably involves higher brain centers as well as the DCN. Data described by Salvi (1976) are consistent with the view. His studies in chinchillas showed that noise exposure caused increases in spontaneous activity in the inferior colliculus. A similar finding was obtained by Gerken et al. (1984) based on studies comparing ongoing EEG activity in cats before and after noise exposure. One interpretation of the increased activity seen in the IC is that it represents a relay of hyperactivity that develops in the DCN.

**Human Studies.** Some patients can modulate the loudness of their tinnitus by certain somatosensory or motor behaviors. The tinnitus can be turned on or amplified at will by such manipulations as changing the direction of eye...
gaze (Cacace et al, 1996), clenching the jaws (Lockwood et al, 1998), or applying pressure to certain areas of the upper limbs (Levine, 1999). When subjects with unilateral tinnitus responsive to such manipulations have been studied with modern brain imaging techniques, some remarkable findings have been obtained. Brains imaged by positron emission tomography (PET) showed increased metabolic activity in the auditory cortex when subjects turn on their tinnitus (Lockwood et al, 1998). Similarly, brains imaged by functional magnetic resonance imaging (fMRI) showed evidence of increased blood flow to the contralateral auditory cortex when tinnitus was switched on (Levine, 1999). The origin of this increased activity is unclear; however, there are indications that subcortical auditory centers are involved since fMRI images also showed evidence of increased blood flow in the inferior colliculus (Sigalovsky et al, 1998). Levine (1999) has hypothesized that the origin of the increased activity may be the DCN, a structure that receives both auditory and somatosensory inputs and whose main outputs project to the contralateral inferior colliculus.

Changes in Temporal Discharge Patterns

Increased Bursting. For many years, it has been known that exposure to some tinnitus-inducing agents alters the temporal properties of auditory neurons. One type of property affected is the time between successive neural impulses. Normally, impulses are generated by most auditory neurons in an irregular or quasiregular fashion in the absence of stimulation. However, during stimulation, impulses can become highly regular such that the intervals between successive impulses are uniform. These uniformities produce periodicities in the neural discharge pattern. Periodicities normally result from a synchronization of impulses to the cycles of the stimulus waveform, a property known as phase locking, and are thought to play an important role in coding of low-frequency (< 5 kHz) sounds in the auditory system (Evans, 1978). Periodicities resembling those produced by phase locking can also be induced in the auditory system by treating animals with either salicylate or noise or by inducing endolymphatic hydrops (Harrison and Prijs, 1984), a condition commonly associated with Meniere's disease (McFadden, 1982). Such periodicities are manifest as an increase in the incidence of bursting activity in which two or more impulses occur in rapid succession (a few milliseconds apart) at regular intervals. Bursting behavior after salicylate or noise exposure has been observed in both the auditory nerve (Liberman and Kiang, 1978; Evans et al, 1981; Harrison and Prijs, 1984) and IC (Chen and Jastreboff, 1995). It is possible that the regular discharge pattern that comprises this bursting activity is interpreted by the brain in a manner similar to the regular discharges that characterize phase locking, and thereby leads to tinnitus (Moller, 1984).

How bursting leads to a conscious percept of tinnitus, however, remains problematic, since no change in the incidence of bursting activity has been found in the primary or secondary auditory cortex after treatment with salicylate (Ochi and Eggermont, 1996, 1997) or quinine (Ochi and Eggermont, 1997). An additional problem is that patients with tinnitus induced by salicylate or quinine generally match the pitch of their tinnitus to frequencies between 7 and 9 kHz (McCabe and Dey, 1965). This frequency range is well above the presumed 5-kHz limit of phase locking by the auditory system (Evans, 1978).

Coincident Firing. Another theory of tinnitus generation is based on the notion that sounds are encoded in the auditory system by an increase in the coincidence of neural discharges (Moller, 1984; Eggermont and Sinerger, 1995). According to this view, in the absence of stimulation, different neurons fire independently or asynchronously, but in the presence of a stimulus, the discharges among different neurons become synchronized. By analogy, tinnitus would be generated by any pathologic condition that increases the degree of synchrony of discharges among two or more neurons. Since synchronous firing is a normal property of neurons, tinnitus generation would have to involve an increase in the degree of synchronization either within the same auditory structure or among neurons in different auditory structures.

Support for this theory has been developed by Eggermont and his colleagues based on investigations conducted in the cat auditory cortex (Eggermont and Sinerger, 1995; Ochi and Eggermont, 1996, 1997). They measured the degree of synchrony among neurons using cross-correlation analysis, a method that quantifies the number of times two simultaneously recorded neurons fire coincidentally over some arbitrary time frame. Strongly correlated activity between two neurons is indicated in cross-correlation histograms as a central peak, the peak becoming higher and narrower the stronger the correlation (i.e., the greater the degree of synchronous firing). Using this approach, they
found no increase in the number of neuron pairs showing coincident firing following either salicylate or quinine treatment; however, both drugs caused a narrowing of the central peak in the cross-correlograms, suggesting that the degree of synchronization in their activities was increased (Ochi and Eggermont, 1996, 1997).

A question these findings raise is whether the synchronous firing seen at the cortical level originates in the cortex or reflects changes relayed from subcortical nuclei. Direct studies of neural synchrony after treatment with tinnitus-inducing agents have yet to be reported for peripheral and brainstem levels of the auditory system. However, the possibility of such changes at peripheral levels has been suggested by studies based on spectral averaging of electrical activity recorded from the auditory nerve (Dolan et al., 1990; Schreiner et al., 1990; Zheng et al., 1996; Cazals and Huang, 1996). It is thought that changes in the amplitudes of the spectral peaks from this activity result from changes in the degree of neural synchronization (Cazals and Huang, 1996; Cazals et al., 1998). The reasoning here is that if neural firing becomes more synchronized, this synchrony should manifest as an increase in the amplitude of spectral components corresponding to the firing rate at which synchronization occurs. Using this method in cats, Martin et al. (1993) found that increases in the average spectrum of spontaneous auditory nerve activity, recorded with a gross electrode placed either at the round window or on the auditory nerve itself, could be induced acutely in cats and humans by treatment with salicylate. After one high dose of salicylate in cats, an emergence of a 200-Hz peak and a decrease in the 1.7-kHz peak was seen (Shreiner and Snyder, 1987; Martin et al., 1993). These alterations could be reversed by treatment with lidocaine (Lenarz and Schreiner, 1990; Schreiner et al., 1990) and resembled the alterations in patients suffering from tinnitus (Martin, 1995).

More recently, Cazals et al. (1998) used spectral averaging of cochleoneural activity to compare the acute and chronic effects of salicylate on auditory nerve spontaneous activity. Changes in average spectra were most apparent at 200 Hz and 1 kHz, in agreement with the findings of Martin et al. (1993) and Schreiner and Snyder (1987). However, the direction and magnitude of the change were strongly dependent on the duration of salicylate exposure. Short-term exposures (a few hours) caused a decrease in spectral amplitude, whereas long-term exposure (a few days to a few weeks) caused an increase. The spectral amplitude at 1 kHz increased to a maximal value after 3 weeks of salicylate exposure. Several aspects of these changes in spectra were cited in support of the idea that they are related to tinnitus. First, the changes in spectra occurred without an accompanying change in response threshold (measured using the compound action potential), a finding that parallels the clinical picture of salicylate-induced tinnitus, which often occurs in humans without a hearing loss. Second, the change in spectrum could be reversed by treatment with the antitinnitus agent lidocaine. Third, similar patterns of change in average spectrum were seen when normal, nonsalicylate-treated animals were stimulated with sound, suggesting that salicylate produces changes in the auditory nerve that mimic the effects of acoustic stimulation. Fourth, the time course of development of the change in spectrum was similar to that of salicylate-induced tinnitus in humans (McCabe and Dey, 1966; Mongan et al., 1973; Day et al., 1989) and rats (Jastreboff et al., 1988a, b). These considerations suggest that the spectral averaging method may provide a useful and objective measure of tinnitus or at least of a neural phenomenon that is closely associated with tinnitus.

Changes in Tonotopic Maps

Another theory that has attracted interest in recent years is the idea that tinnitus is related to changes in tonotopic organization in central auditory structures (Meikle, 1995). Tonotopic organization refers to the orderly arrangement of cells within an auditory nucleus or cortical area according to their frequency selectivities. Neuronal frequency selectivity means that a neuron is capable of responding only to a limited range of frequencies and responds most sensitively to single frequency, called the characteristic frequency (CF). In general, auditory structures of the brain are arranged spatially so that neurons with high CFs are located at one end of the structure, those with low CFs are located at the opposite end, and intermediate CFs are located in between. This tonotopic order reflects the frequency organization established in the cochlear partition.

In the normal tonotopic map of the auditory cortex, each frequency within the audiometric range is represented by a narrow strip of cells. However, when input to one of these strips is damaged or weakened, the adjacent strips expand and take over the function of the damaged strip. This reorganizes the tonotopic map so that there is a wider than normal area
dedicated to the analysis of frequencies represented along the edge of the damaged strip. It has been shown that the tonotopic map does, in fact, reorganize in some structures of the central auditory system following cochlear damage. Such reorganizations have been demonstrated in the auditory cortex and inferior colliculus of cats and guinea pigs (Robertson and Irvine, 1989; Harrison et al, 1991; Rajan et al, 1992, 1993; Irvine and Rajan, 1997). The pattern of reorganization seen in the auditory cortex after cochlear injury is analogous to the reorganization of somatosensory cortex after loss of limb function. Patients who have undergone limb amputation commonly experience phantom pain in the amputated limb, a symptom that in some respects is a somatosensory counterpart of tinnitus. Clinical studies using magnetic source imaging indicate that map areas in patients with tinnitus are reorganized (Muhlnickel et al, 1998). The changes were described as a shift of cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic location. This change resembles the reorganization pattern observed in animals after partial injury to the cochlea.

An issue that remains unclear is how map reorganizations lead to percepts in the absence of stimulation. It is possible that the expanded map area contains neurons that are hyperactive due to changes in the balance of excitatory and inhibitory inputs or to an increase in sensitivity to inputs from other synaptic sources. Future studies combining recordings of tonotopic maps with recordings of activity in the absence of stimulation are needed to test this hypothesis.

**SUMMARY AND FUTURE RESEARCH NEEDS**

The establishment of well-defined animal models has facilitated rapid progress in understanding the neural basis of tinnitus. Studies in neurophysiology have determined that exposure to tinnitus-inducing agents such as salicylates, quinine, or intense sound causes abnormal activity throughout the auditory system. Evidence has been presented that these agents act peripherally to alter the normal function of the cochlea or auditory nerve, triggering changes at central levels of the auditory pathway. These changes include increases in spontaneous activity, alterations in temporal firing patterns (increases in bursting activity and synchronous discharges among different neurons), and changes in frequency representation. Evidence has also been presented that at least some of these changes, such as increases in spontaneous activity after intense sound exposure, follow a different time course of development from threshold shift, suggesting that tinnitus-generating mechanisms are not necessarily the result of hearing loss. The above-cited neurophysiologic findings have been complemented by behavioral studies demonstrating that the same agents that cause abnormal activity also induce tinnitus in animals. Some of the neurophysiologic changes associated with tinnitus have also been verified in humans using brain imaging techniques (PET and fMRI).

Despite these insights, the understanding of tinnitus mechanisms is still in its early stages of development. A number of fundamental issues need to be addressed to smooth out and complete the picture of how and where tinnitus is generated. Chief among these is how to reconcile the various theories of tinnitus-producing mechanisms with each other. That is, which of the several types of changes that have been implicated (hyperactivity, changes in temporal properties, and altered frequency representation) is (are) most critical in determining whether tinnitus is present. This is the problem of separating the causes from the epiphenomena. A second issue is where the critical changes originate. Are they induced at all levels of the auditory pathway or are they induced at one level, then relayed to other levels? What elements within the neuronal circuit are the generators of these disturbances? Third, what are the mechanisms by which the observed changes are induced? Although the relevant changes in neural function have been at least partially identified, it remains unclear how these changes are triggered. There is a need to identify, for example, why intense sound or salicylates cause neurons in the central auditory system to become hyperactive when there is no corresponding change in the auditory nerve. Fourth, are the changes in neural activity that produce tinnitus accompanied by changes in chemistry and gene expression? This issue is important because the development of effective drug therapies depends on an understanding of the chemical substrates producing the changes in activity. Finally, do the mechanisms of tinnitus that have been identified with salicylates, quinine, and noise also underlie other forms of tinnitus such as those induced by ear infection, head trauma, and other ototoxicities? Clearly, although the past decade
has seen a major expansion in our understanding of tinnitus and its underlying neural mechanisms, the stage is now set for even more dramatic advances in the near future.

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REFERENCES


Neurophysiologic Mechanisms of Tinnitus/Kaltenbach


