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Review

Tinnitus: Models and mechanisms

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ABSTRACT

Over the past decade, there has been a burgeoning of scientific interest in the neurobiological origins of tinnitus. During this period, numerous behavioral and physiological animal models have been developed which have yielded major clues concerning the likely neural correlates of acute and chronic forms of tinnitus and the processes leading to their induction. The data increasingly converge on the view that tinnitus is a systemic problem stemming from imbalances in the excitatory and inhibitory inputs to auditory neurons. Such changes occur at multiple levels of the auditory system and involve a combination of interacting phenomena that are triggered by loss of normal input from the inner ear. This loss sets in motion a number of plastic readjustments in the central auditory system and sometimes beyond the auditory system that culminate in the induction of aberrant states of activation that include hyperactivity, bursting discharges and increases in neural synchrony. This article will review was has been learned about the biological origins of these alterations, summarize where they occur and examine the cellular and molecular mechanisms that are most likely to underlie them.

1. Introduction

For many years, the search for tinnitus mechanisms was a highly speculative endeavor, with few clues concerning the underlying pathologies other than those derived from clinical and psychoacoustic observations. Some important new ground was broken in the late 1970s and early 1980s with studies examining stimulus driven and spontaneous activity in the auditory nerves and ventral cochlear nucleus of animals treated with inducers of tinnitus such as noise or ototoxic drugs (Liberman and Kiang, 1978; Liberman and Dodds, 1984; Evans and Borerwe, 1982; Evans et al., 1981; Dallos and Harris, 1978; Salvi and Ahroon, 1983; Lonsbury-Martin and Martin, 1981). However, these manipulations were found to have either little effect on or to weaken spontaneous activity in ways that seemed more related to hearing loss than tinnitus. Further complicating the picture were clinical reports showing that most tinnitus patients who undergo eighth nerve transections continue to experience their tinnitus, often in a worsened condition (Dandy, 1941; House and Brackman, 1981; Gardner, 1984). Experimental approaches were needed to reconcile these findings with the common notion that tinnitus is largely a problem of the auditory periphery.

A major turning point came in the latter half of the 1980s and early 1990s with the introduction of the first animal models of the acute form of tinnitus (Jastreboff and Sasaki, 1986, 1988; Jastreboff, 1990; Chen and Jastreboff, 1995). These models, which were developed in rodents treated with sodium salicylate, demonstrated experimentally that animals can experience tinnitus and that the observed 'phantom auditory percepts' are associated with alterations of neural activity in the central auditory system quite different from those related to hearing loss. The field received additional impetus in the late-1990s and early 2000s with the first animal models of chronic tinnitus (Chen et al., 1999; Kaltenbach and McCaslin, 1996; Kaltenbach et al., 2004; Zhang and Kaltenbach, 1998; Eggermont and Kenmochi, 1998; Seki and Eggermont, 2003; Brozoski et al., 2002; Heffner and Harrington, 2002). Such studies were based on experiments conducted in rats, hamsters and cats variously exposed to intense sound and examined weeks to months after exposure.

Since that time, there has been a steady crescendo of interest in using animal models to elucidate mechanisms of tinnitus. This reflects increased study at multiple levels, including the auditory periphery, the auditory CNS and non-auditory areas of the brain. Models have now been developed in several species for studying mechanisms of tinnitus in vivo and in vitro, and for studying acute and chronic forms of tinnitus. These studies have ushered in a new era of tinnitus investigation that has resulted in a number of important new concepts on the biological basis of tinnitus. Despite a late start, the formal study of tinnitus in animals is fast becoming

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comparable to the study of other related sensory disorders in animals, such as neuropathic pain and phantom limb, which have had much longer histories.

This article will begin with a brief summary of the types of models that have been developed. This will be followed by a review of what has been learned from these models, what some of the challenges that have been confronted by these studies, and what problems need to be addressed to move animal research closer to an effective treatment for tinnitus. This review will focus on the auditory component of tinnitus rather than the emotional and attentional aspects of tinnitus.

2. Types of animal models of tinnitus

Animal models of tinnitus published to date can be classified in two general categories. Behavioral models are concerned with the measure of tinnitus percepts in animals. These models allow examination of the psychophysical attributes of those percepts, how such percepts are induced, and ultimately, provide opportunities to test potential new approaches to tinnitus treatment. Physiological models are concerned with changes in the nervous system that underlie tinnitus. They seek to identify, localize and measure the signals at the neuronal level that lead to tinnitus percepts and explain the mechanisms by which such signals are triggered. The following section will describe some of the methodologies that have been employed in the establishment of each type of model and discuss some of their strengths and limitations.

2.1. Behavioral models

Most behavioral models to date have assessed the presence of tinnitus in animals based on measures of conditioned motor responses (Jastreboff et al., 1988; Bauer et al., 1999; Turner et al., 2006; Lobarinas et al., 2004; Guitton et al., 2003; Rüttiger et al., 2003; Zheng et al., 2006; Jia and Qin, 2006). Animals are trained to show different motor responses to sound and silence using positive or negative reinforcement techniques. The measured behaviors have varied across laboratories, but all have included responses that are readily learned by the animals such as bar presses, licking behavior, or climbing behavior. In each case, animals are trained to display one of these behaviors in response to sounds, usually of different types, and to avoid these behaviors or show a different behavior in response to silence. Over time, the animals become very proficient in performing correctly and are able to indicate by differences in their responses whether or not they are hearing sound. Once trained, they are then treated with a tinnitus-inducing agent, such as an ototoxic drug or noise. Following the treatment, the behavioral response of each trained and treated animal is retested in trials similar to those used during training, except without any reinforcement. The most common approach is to test the animal's response to silence, the assumption being that if an animal has tinnitus, it would be expected to show an increased probability of displaying a behavior in response to silence that is similar to the behavioral response to sound during training. Usually inferences regarding the induction of tinnitus in animals are also made by comparison with control animals that show the normal response to silence. In practice, such responses need to be repeated and averaged over many trials, and sometimes across many individuals, before a statistically meaningful change in behavior caused by the treatment becomes apparent.

Behavioral models based on conditioning have considerable value in that they provide a demonstration of tinnitus in animals and thus can be used to define certain psychophysical attributes of tinnitus in animals, such as pitch and loudness (Jastreboff and Sasaki, 1994; Brozoski et al., 2002; Bauer et al., 1999) as well as the time course of tinnitus (Bauer et al., 1999; Brozoski et al., 2002). They have also been used to test efficacies of new approaches to treating tinnitus (see below). Another important value is their use in confirming that physiological effects implicated in tinnitus are associated with tinnitus. They can potentially be useful for localizing tinnitus origins in the nervous system, especially if combined with neuroimaging techniques (Paul et al., 2009). A weakness of the behavioral models based on conditioning is that such models are very time consuming to develop, since each animal typically requires several weeks of training to reach an adequate level of correct responses before tinnitus induction can be performed. Moreover, many control procedures need to be carried out to rule out other explanations of the results, such as hearing loss, hyperacusis, changes in motivational state or memory changes that may be induced by the tinnitus-inducing treatment or manipulation.

A partial solution to these limitations has been offered by the recent development of a behavioral model based on acoustic startle reflex testing (Turner et al., 2006; Turner, 2007; Yang et al., 2007; Turner and Parrish, 2008; Sun et al., 2009; Wang et al., 2009; Ralli et al., 2010). This paradigm capitalizes on two important facts: 1) that acoustic startle can be evoked by noise and 2) that the magnitude of this startle can be suppressed by a gap of silence in the background sound that precedes the noise. In theory, if an animal has tinnitus, the sound of tinnitus will fill in the gap and reduce the degree to which the gap suppresses the acoustic startle. This method has the important advantages that it circumvents the need for training, greatly reducing the time required to test each animal, and animals can more easily be retested over time, potentially showing the time course over which tinnitus develops. The reflex test is not dependent on a learned behavior and therefore seems less likely to be susceptible to any changes in memory or motivational state that might be caused by noise. Another possible advantage of this method is that it may provide insight into the psychoacoustic attributes of tinnitus. For example, louder tinnitus will tend to fill in the gap more than quieter tinnitus, leading to a greater reduction of gap-induced suppression of the startle reflex. The startle reflex test can potentially illuminate the subcortical contribution to tinnitus since the acoustic startle reflex is largely a lower brainstem reflex, involving the cochlear nucleus, the nuclei of the lateral lemniscus and pontine reticular formation (Davis et al., 1982). Thus, any tinnitus that interferes with this reflex would seem likely to involve similarly low levels of the auditory system. The startle test, however, shares with other tests of tinnitus the need to control for other explanations of the results, such as hearing loss and hyperacusis. Further, as with other behavioral models, it is limited in what it can reveal about underlying mechanisms as it yields no information at the neuronal level. This information relies on the availability of physiological models of tinnitus.

2.2. Physiological models

Physiological models permit measures of neural activity changes that are viewed as likely to be related to or correlated with tinnitus. The measures are obtained electrophysiologically by directly recording neural activity changes in selected auditory centers of animals treated with tinnitus-inducing agents. More recently, activity changes have been measured using neuroimaging techniques, such as microPET and MEMRI (Lobarinas et al., 2008; Brozoski et al., 2007a). They can also be studied by mapping of metabolic activity using 2-deoxyglucose or by mapping expression of c-Fos (Imig and Durham, 2005; Wallhauser-Franke et al., 1996; 2003). Changes are usually tested by comparison of data obtained before and after treatment or by comparison of data from treated and control animals. Since tinnitus is the perception of sound in the absence of a corresponding external stimulus, the expectation is that tinnitus would be associated with changes of activity that normally

occur only when sound is present. The most likely candidates are changes in spontaneous neural activity that simulate sound-elicited activity. The advantages of the physiological models are that they can tell us what the characteristics of these changes are and where in the auditory system they occur. The main disadvantage is that they do not directly prove that animals are experiencing tinnitus. The existence of tinnitus percepts in animals must be inferred from the existence of a physiological change, provided the physiological change is indistinguishable from the change that occurs in normal animals during acoustic stimulation with sounds that resemble tinnitus. Such changes can be of short duration, representing the acute form of tinnitus, or long duration, representing the chronic form.

3. What we have learned from animal models of tinnitus

3.1. Behavioral models

There is general agreement among behavioral studies that manipulations which cause tinnitus in humans, also cause animals to experience tinnitus. This has been shown using different behavioral paradigms, different species (rat, chinchilla, hamster and mouse) and different inducers of tinnitus (salicylate, quinine and noise) (Jastreboff et al., 1994; Bauer et al., 1999; Lobarinas et al., 2004; Guitton et al., 2003; Ruttiger et al., 2003; Heffner and Harrington, 2002; Brozoski et al., 2002; Turner et al., 2006; Zheng et al., 2007; Song et al., 2009; Kizawa et al., 2010). Information on the psychophysical attributes of tinnitus from the various behavioral models suggests that the main characteristics of noise-induced tinnitus in animals are very dependent on the exposure conditions and are not always consistent with those of human subjects. Chinchillas exposed to a high frequency tone (4 kHz) at levels as low as 80 dB SPL for 1 h develop tinnitus, but the induced tinnitus has a slow onset of weeks or months, and the pitch of the tinnitus is lower than the exposure frequency (Brozoski et al., 2002; Bauer et al., 2008). However, when similar methods were used in the rat, the pitch of tinnitus demonstrated behaviorally was found to be higher than that of the exposure tone (Bauer and Brozoski, 2001; Brozoski and Bauer, 2005). The latter result is more similar to that in human subjects, in whom it has been found that exposure to a tone of 3 kHz tone at levels of 90–120 dB SPL for brief periods (1–5 min) results in a tinnitus of immediate onset, but the tinnitus is of short duration (minutes), and the pitch is most often appreciably higher than the frequency of the exposure tone (Loeb and Smith, 1967; Atherley et al., 1968; George and Kemp, 1989; Chermak and Dengerink, 1987). However, differences in tinnitus onset time may depend on the conditions of exposure, since in contrast to what was just described, people with a history of exposure to occupational noise often report that their tinnitus developed gradually over time. These contrasting findings suggest that, in addition to possible species differences, there are important within-species differences that are dependent on the conditions of exposure, which may determine different underlying pathologies. A few behavioral studies have attempted to characterize the percepts of tinnitus after salicylate treatment. Tinnitus induced in rats by treatment with salicylate has been found to show certain similarities with tinnitus induced in humans on high doses of aspirin. This includes high pitch, slow onset delayed by days following ingestion, and slow decay over days following cessation of treatment (Jastreboff and Sasaki, 1994; Guitton et al., 2003). Since lidocaine has been found to be effective in reducing tinnitus percepts in human subjects (McFadden, 1981), studies examining the effect of lidocaine on tinnitus percepts in animals would be of value, and could provide additional validation of the behavioral models of tinnitus.

Behavioral models have been useful for testing efficacy on tinnitus of potentially new therapeutic drugs. The effects of several neuroactive agents have been examined in animals, including, gabapentin (Bauer and Brozoski, 2001, 2006), various NMDA receptor blockers (Puel and Guitton, 2007; Lobarinas et al., 2006), vigabratin (Brozoski et al., 2007b) and ginkgo biloba (Jastreboff et al., 1997). Evidence suggests that each of these agents has some ability to reduce or weaken behavioral evidence of tinnitus in animals. For some of these agents, there are also clinical case reports consistent with the findings in animals. Clinical trials have been carried out with at least two of these agents: ginkgo biloba (Holstein, 2001; Rejali et al., 2004; Morgenstern and Biermann, 2002; Drew and Davies, 2001) and gabapentin (Bauer and Brozoski, 2006; Witsell et al., 2007; Bakhshaee et al., 2008). However, the results of these trials have varied considerably across studies with some yielding positive findings (Bauer and Brozoski, 2006; Morgenstern and Biermann, 2002; Holstein, 2001) and others showing a lack of efficacy (Drew and Davies, 2001; Witsell et al., 2007; Bakhshaee et al., 2008. Part of this discrepancy likely reflects lack of homogeneity of the patient population, whereas the animal studies are typically conducted in subjects which are more uniform with respect to age and causes of tinnitus.

3.2. Physiological models

The available physiological models have yielded important insights into the location and characteristics of defects underlying tinnitus. They have also provided valuable clues concerning the mechanisms by which such defects are induced and how the induction process is set in motion. The following sections will review what is known about each of these aspects of tinnitus based on studies in animals.

3.2.1. Location and characteristics of neural generators

There is good agreement across studies that certain manipulations which cause tinnitus in humans or animals, cause changes in spontaneous activity in the auditory system (Eggermont and Roberts, 2004). There is less agreement on which of these changes is critical to tinnitus generation. This reflects, in part, a lack of understanding of the nature of the neural code for simple sounds, such as tones and noise. The most commonly assumed change to be relevant to tinnitus is an increase in neuronal activity or discharge rate. Increases in spontaneous activity are of special interest in the context of tinnitus because increases in activity can be evoked by sound stimulation or by electrical stimulation of peripheral or central auditory pathways, all of which lead to sound percepts in human subjects (Clark, 2008; Colletti et al., 2009). Acute or immediate increases in spontaneous activity have been observed in the auditory nerve, the inferior colliculus and the secondary auditory cortex following salicylate treatment (Mulheran and Evans, 1999; Manabe et al., 1997; Jastreboff and Sasaki, 1986; Eggermont and Kenmochi, 1998) and in the primary auditory cortex following moderate sound exposure (Kimura and Eggermont, 1999). Acute increases in spontaneous activity are also observed in the secondary auditory cortex after quinine treatment (Eggermont and Kenmochi, 1998). Chronic increases in spontaneous activity occur in the dorsal cochlear nucleus (Kaltenbach and McCaslin, 1996; Zhang and Kaltenbach, 1998; Kaltenbach and Afman, 2000; Kaltenbach et al., 1998, 2002; Brozoski et al., 2002), the inferior colliculus (Mulders and Robertson, 2009; Dong et al., 2010b; Bauer et al., 2008) and primary auditory cortex following intense noise exposure (Seki and Eggermont, 2003; Komiya and Eggermont, 2000; Noreña and Eggermont, 2005), in the dorsal cochlear nucleus and inferior colliculus after cisplatin treatment (Melamed et al., 2000; Kaltenbach et al., 2002; Bauer et al., 2008) and in the inferior colliculus after mechanical lesions to the cochlea (Dong et al., 2009). All such increases have been measured using electrophysiological methods. However, increases in activation level of some

of these same brain areas have also been demonstrated in animals by metabolic mapping and neuroimaging methods and by measures of c-fos expression (Imig and Durham, 2005; Wallhauser-Franke et al., 2003; Mahlke and Wallhausser-Franke, 2004; Brozoski et al., 2007a; Lobarinas et al., 2008; Paul et al., 2009).

The available evidence points to a central origin of the induced hyperactivity. This view is supported by the finding that hyperactivity in the DCN survives acute ablation of the ipsilateral cochlea (Zacharek et al., 2002). Moreover, hyperactivity has been found to be inducible in the cochlear nucleus by lesioning cochlear outer hair cells (Kaltenbach et al., 2002) or in the inferior colliculus by lesioning cochlear inner hair cells (Bauer et al., 2008). In addition, studies in cats have found that noise exposure does not lead to chronic increases in spontaneous activity in the auditory nerve, even when hair cell lesions are induced (Liberman and Kiang, 1978; Liberman and Dodds, 1984). These results are consistent with the clinical finding that tinnitus often persists in human subjects even after the auditory nerve has been surgically sectioned (House and Brackman, 1981). A different result has been obtained by Mulders and Robertson (2009). They found that hyperactivity induced in the inferior colliculus was abolished by ablation of the contralateral cochlea. However, they interpreted this finding as indicating that the central hyperactivity was dependent on afferent activity, even if that activity is not itself elevated. If correct, it would suggest that manipulations that affect primary afferent activity may have the potential to reduce tinnitus. The results of animal studies demonstrating effects of agents that block cochlear NMDA receptors also have a tinnitolytic effect (Guitton et al., 2003; Puel, 2007b) are consistent with this view. However, this model needs to be reconciled with the fact that tinnitus often persists in human subjects following sectioning of the eighth nerve (House and Brackman, 1981).

Some investigators have found evidence for other types of changes in spontaneous activity that may be related to tinnitus, including increases in neural synchrony and increased bursting activity. Bursting activity and synchronous discharges are of interest owing to their more powerful potential to drive post-synaptic targets at higher levels of the auditory system (Roberts et al., 2008, 2010). Chronic increases in bursting activity have been observed in the auditory nerve, dorsal cochlear nucleus and inferior colliculus after noise exposure (Liberman and Kiang, 1978; Finlayson and Kaltenbach, 2009; Chen and Jastreboff, 1995; Kwon et al., 1999; Bauer et al., 2008). Bursting activity is also increased in the inferior colliculus afer salicylate treatment (Chen and Jastreboff, 1995; Kwon et al., 1999) and cisplatin treatment (Bauer et al., 2008). However, no enduring increases in bursting activity have been observed in the auditory cortex after noise exposure, or salicylate or quinine treatment (Norena and Eggermont, 2003; Ochi and Eggermont, 1996, 1997; Seki and Eggermont, 2003; Eggermont and Komiya, 2000).

Increased synchrony of discharges across the neural population is one way in which the brain might bind different features of a stimulus into a single percept. There is some evidence that inducers of tinnitus can increase the incidence of synchronous discharges across the neural population at various levels of the auditory system. Increased synchrony has been observed in the auditory nerve following salicylate treatment (Cazals et al., 1998; Martin et al., 1993), inferior colliculus after noise and cisplatin treatment (Bauer et al., 2008) and primary auditory cortex immediately following noise exposure or quinine treatment (Ochi and Eggermont, 1997; Norena and Eggermont, 2003, 2005). Increased synchrony at these levels might play a role in binding loudness and pitch features of tinnitus. It could also play a role in magnifying the perceptual weight of the tinnitus signal.

Perhaps the most surprising turn taken in tinnitus research has been the discovery of non-auditory sensory influences on tinnitus percepts. It has been observed clinically that tinnitus is often associated with pathologies or symptoms of the head and neck regions, such as temporomandibular joint and cervical spine disorders (Björne, 2007; Levine, 2004; Boniver, 2002; Wright and Bifano, 1997). It is also well known that tinnitus can be modulated by certain manipulations of the head and neck areas (Abel and Levine, 2004; Levine, 1999, 2004; Levine et al., 2003; Møller et al., 1991). Pushing the head against a resistance or clenching the jaws often results in a change in the loudness or pitch of tinnitus. This would suggest that neural activity in the auditory system may be influenced by input from the somatosensory or somatic motor systems. Convergence of auditory and somatosensory inputs occurs at several levels of the auditory system, so the somatic modulation of tinnitus could potentially involve any of numerous structures. However, an important feature of somatic tinnitus that has emerged recently is that when the tinnitus is unilateral, the somatosensory stimuli that are effective in modulating the tinnitus involve muscles and/or nerves on the side ipsilateral to the tinnitus (Levine, 2004). Also, it has been reported that when tinnitus is unilateral and is associated with head or neck disorders, those disorders are most frequently on the same side as the tinnitus (Levine, 2004). The most likely site of the auditory system where convergence of somatosensory inputs and auditory inputs is primarily ipsilateral is the dorsal cochlear nucleus (Levine, 2004). There is work demonstrating that activity in the dorsal cochlear nucleus can be modulated by electrical stimulation of certain cervical nerves, as well as trigeminal and cuneate nuclei in the brainstem (Kanold and Young, 2001; Shore, 2004; Shore et al., 2008; Shore and Zhou, 2006). These studies point to the DCN as a likely participant, if not a key mediator, of somatic modulations of tinnitus.

3.2.2. *Mechanisms underlying induction of tinnitus-related activity*

The discovery of tinnitus-related changes in neural activity has led naturally to the next tier of questions which concern the mechanisms by which such changes are induced. Animal models of tinnitus have provided the means to address these questions.

Studies in these models have given rise to several concepts of how increases in spontaneous activity are induced by noise exposure. The most commonly invoked hypothesis is that exposure causes shifts in the balance of excitatory and inhibitory inputs to tinnitus-generating neurons or neuronal populations. Such shifts are thought to involve both degenerative changes as well as plastic readjustments in the brain which are triggered by loss of normal anatomical or functional input from the ear. This hypothesis has numerous lines of support. Animals exposed to intense noise show several types of changes that would decrease inhibition and/or increase excitation. For example, degeneration occurs in the cochlear nucleus and other auditory centers following noise exposure (Morest et al., 1997, 1998; Morest and Bohne, 1983), and the number of inhibitory synapses, and certain subunits of the glycine receptor or glycinergic immunolabeling have been found to be decreased in the cochlear nucleus, superior olivary complex and inferior colliculus of cochlear lesioned, noise exposed or ear plugged animals (Buras et al., 2006; Dong et al., 2009, 2010a; Kim et al., 1997; Muly et al., 2002; Wang et al., 2009; Whiting et al., 2009). Decreases in GABA receptor subunit expression, GABA release or glutamate decarboxylase, which catalyzes the synthesis of GABA have been found to occur in the cochlear nucleus and inferior colliculus after noise exposure (Bledsoe et al., 1995; Abbott et al., 1999; Dong et al., 2010a,b; Mossop et al., 2000) and aging (Caspary et al., 1995, 1999, 2008; Milbrandt et al., 1997). Decreases in GABA receptors have been shown to occur in the same tonotopic areas where hyperactivity emerges following cochlear lesioning (Dong et al., 2010b). There is also evidence for noise-induced upregulation of excitation. Glutamate or aspartate release are increased in dorsal and ventral cochlear nuclei while uptake is decreased after

noise exposure (Muly et al., 2004). Similar changes occur in these nuclei following ossicular removal or cochlear ablation (Suneja et al., 1998; Potashner et al., 1997, 2000). Vesicular glutamate transporter 2 (VGlut2), a marker for excitatory input from somatosensory nuclei, is upregulated in the granule cell domain of the cochlear nucleus following deafening, whereas VGlut1, a marker for primary afferent input, is decreased (Zeng et al., 2009). Another study showed evidence for redistribution of AMPA type glutamate receptors following cochlear ablation (Rubio, 2006). We do not yet have a full picture of the precise synaptologies or identities of the affected neurons, but recent studies of the cochlear nucleus have revealed that loss of normal input from the cochlea can trigger immediate and delayed changes in the distribution and subunit composition of AMPA receptors at the auditory nerve-fusiform cell, the auditory nerve-bushy cell synapse as well as at the parallel fiber-fusiform cell and parallel fiber-cartwheel cell synapses (Rubio, 2006; Whiting et al., 2009). Interestingly, when changes in the distribution and densities of AMPA receptors were induced by monaural ear plugging, they were found to be reversible when the ear plug was removed, suggesting that the changes may represent homeostatic responses to reduced input from the auditory periphery. Such changes might be expected to shift the excitatory/inhibitory pendulum toward the side of excitation of the ascending auditory pathway.

Shifts in the balance of excitatory and inhibitory inputs to neurons could also result from plastic alterations in the sensitivity to or expression of certain neuromodulators. Following noise exposure, there is an upregulation of cholinergic input in the dorsal cochlear nucleus as evidenced by an increase in choline acetyl transferase (the enzyme of acetylcholine metabolism) (Jin et al., 2006) and an increase in sensitivity to the acetylcholine receptor agonist, carbachol (Chang et al., 2002; Kaltenbach and Zhang, 2007). Expression of serotonergic receptors are increased in cochlear nucleus following noise exposure (Cransac et al., 1998). These types of changes suggest that loss of normal input from the auditory periphery triggers homeostatic plasticity centrally that is potentially compensatory for loss of normal input from the auditory periphery (Schaette and Kempter, 2006, 2008). Such compensatory adjustments likely involve descending pathways, such as the cholinergic olivocochlear projection or serotonergic projection from the dorsal and median raphe nucleus (Godfrey et al., 1997). Interestingly, a recent study indicates that stimulation of the olivocochlear bundle can attenuate noise-induced hyperactivity in the inferior colliculus (Mulders et al., 2010).

Another change that could lead to shifts in the balance of excitation and inhibition is activity-dependent plasticity, the best examples being long term potentiation and long term depression. Both types of plasticity have been observed in auditory centers of the brain following repetitive stimulation with current pulses that cause coincident activation of pre- and post-synaptic membranes (Tzounopoulos et al., 2007; Zhang and Wu, 2000; Seki et al., 1999). Tzounopoulos and colleagues (2007; 2008) have found evidence that stimuli that cause LTP in fusiform cells of the dorsal cochlear nucleus neurons also cause LTD of their inputting inhibitory cartwheel cells. Tzounopoulos (2008) hypothesized that a similar effect might be induced by intense sound exposure and that this mechanism might underlie tinnitus-related hyperactivity of fusiform cells, leading to tinnitus.

Independent of neurotransmission changes, increased activity of auditory neurons could result from changes in the intrinsic membrane properties of neurons or changes in downstream intracellular signaling cascades, or even alterations in neuroglia. The latter possibilities have received the least amount of attention, but a few studies suggest that manipulations that impair input from the cochlea to the brainstem can alter expression of ion channels in brainstem nuclei (Cui et al., 2007; Holt et al., 2006; see also Francis and Manis, 2000; Dong et al., 2010a; von Hehn et al., 2004).

3.2.3. Triggers of mechanisms underlying induction of tinnitus related activity

It is important to distinguish between triggers of mechanisms that lead to induction of hyperactivity and the actual mechanisms themselves. This must be stressed because although the auditory periphery is almost certainly the level at which the induction process is triggered, it is not necessarily where the changes underlying the tinnitus-related activity are induced. As mentioned above, the signals and mechanisms that have received the most attention in theories of tinnitus have been identified mainly at the central level of the auditory system.

There is evidence that tinnitus-related changes in the brain are triggered by injury to hair cells and/or spiral ganglion cells. Increases in spontaneous activity in the dorsal cochlear nucleus have been found to be correlated with the amount of outer hair cell loss following treatment of hamsters with cisplatin (Kaltenbach et al., 2002). Recently, tinnitus as well as tinnitus-related changes in the inferior colliculus were found to be associated with spiral ganglion cell loss induced by various means (Bauer et al., 2008). This suggests that damage to inner hair cells may also be an important tinnitus trigger. How hair cell loss would set in motion the mechanisms leading to central hyperactivity, bursting activity and increased synchrony has not yet been clarified. Overstimulation of the ear caused by noise exposure can result in anatomical deafferentation of the auditory brainstem through loss of hair cells and their primary afferents. Such changes are associated with degeneration of the axonal terminals synapsing on central target neurons and transneuronal degeneration of second or higher order neurons (Kim et al., 1997; Morest et al., 1998). Loss of this normal input has been found to stimulate sprouting of axonal collaterals from neighboring neurons in the dorsal and ventral cochlear nuclei (Benson et al., 1997). A second trigger might be excitotoxic injury caused by cochlear overstimulation. Evidence for excitotoxic injury to primary afferents has been well documented, although it tends to be temporary with moderate levels of sound exposure (Puel et al., 1998; Pujol and Puel, 1999). It is possible that the excitotoxic damage following more intense stimulation might be more severe, longer lasting and affect neurons centrally. If the affected neurons are mostly inhibitory, this would lead to a disinhibition of their post-synaptic targets. If so, this could result in permament loss of axonal inputs to central neurons.

4. Challenges to existing animal models

4.1. The problem of correlating physiological and behavioral evidence for tinnitus

Ultimately, the case that changes in physiology are linked to tinnitus rests on the ability to show a relationship between the observed activity changes and the percept of tinnitus based on behavioral measures. As just reviewed, there is good evidence that exposure conditions that cause putative tinnitus-producing changes in spontaneous activity (hyperactivity, increased neural synchrony, increased bursting activity) also cause animals to experience tinnitus. This concurrence is a strong suggestion that the two measured phenomena are related. However, neither approach proves a cause and effect relationship between tinnitus and the observed changes in spontaneous activity. Nor does limiting a demonstration of an electrophysiological change to animals with behavioral evidence of tinnitus demonstrate a link, since this indicates only that the two phenomena can occur together; it dose not show that they co-vary. One would ideally like

to see a strong relationship between physiological or other functional change and behavioral measures based on a formal correlational analysis. An attempt to use correlational analysis for this purpose has, in fact, shown a significant relationship between hyperactivity and tinnitus induced by noise exposure (Kaltenbach et al., 2004). However, the strength of the relationship, measured in terms of the correlation coefficient, was found to be only moderate. A fundamental problem that is difficult to overcome in attempting to test physiological/behavioral relationships using correlational analysis is that behavioral measures represent a much broader sphere of brain activity than do physiological measures. Measures of spontaneous activity are usually unidimensional, being obtained unilaterally from only a single level (auditory nerve, nucleus or cortical area) of the auditory system. In contrast, behavioral measures of tinnitus are multidimensional based on a binaural percept that arises from activation of multiple levels of the auditory system. It is not clear that behavioral tests are sufficiently sensitive to detect all cases of tinnitus, especially cases in which the tinnitus sensation level is very low. Moreover, in studies that involve training of motor responses to sound, the behavioral measure is a product not only of the activation of auditory centers producing the tinnitus but also of motor areas of the brain producing the behavioral response. Furthermore, both the percepts of tinnitus and the motor responses are sensitive to numerous external factors such as the motivational state of the animal, the state of arousal, attention and the skill of the animal in hearing and listening to its tinnitus. These factors involve several pathways outside the auditory system which are not likely to be represented in local recordings of neural activity in an auditory center. The recently developed acoustic startle test of tinnitus (see section 2.1) begins to circumvent this problem by focusing on a behavior that is perhaps more hard wired and reflects a more limited number of brain areas. One might therefore expect that measures of tinnitus based on the startle reflex may show a stronger correlation with changes in activity in the lower auditory system.

5. Summary and the future of animal research on tinnitus

The last decade has seen a major transformation in the way we think about the biological basis of tinnitus. The traditional view that chronic tinnitus was exclusively an auditory disorder originating in the ear has been largely supplanted. The contemporary view is that although tinnitus may be triggered by injury to the ear, the neural generators are most readily found centrally and while the neural generators may be primarily auditory, non-auditory centers often participate. Studies of noise-induced tinnitus have given rise to the general theory that tinnitus begins with injury to the inner ear hair cell populations, which decreases auditory nerve activity, and this change leads to plastic adjustments in the central auditory system that culminate in alterations of spontaneous activity. The contemporary theory also holds that plasticity is the main centerpiece of these adjustments, whereby reduced auditory nerve input triggers a shift in the balance of excitation and inhibition centrally. This shift leads to the emergence of a tripartite complex of changes that includes hyperactivity, increased bursting activity and increased synchrony. Such changes reflect a loss of inhibitory drive to neurons, particularly of glycinergic and GABAergic systems, but increases in excitation via upregulations of glutamatergic and cholinergic systems may also be involved. Such changes are found at multiple levels of the auditory pathway and even in some non-auditory centers, including somatosensory and limbic regions. Tinnitus may thus be a system-wide problem in which auditory and non-auditory systems play important roles. This view is consistent with the three-faced nature of tinnitus which includes auditory, attentional and emotional components.

Several years ago, the American Tinnitus Association published a ‘Roadmap to a cure’ describing the steps that need to be taken to achieve an effective treatment for tinnitus. The roadmap consists of 12 different steps in four categories. Approximately half of the steps in this roadmap require studies in animal models. These involve defining the centers of the nervous system where the tinnitus-producing signals arise, elucidating the mechanisms by which tinnitus signals are induced, and identifying the specific neuronal populations and their defects giving rise to tinnitus signals. As the foregoing discussion and summary convey, much momentum has been gained in recent years in carrying out some of these steps in animal models. However, much work lies ahead. Although we now have much information about what types of changes contribute to tinnitus and where in the nervous system they occur, there is need for a more complete picture of the details of these changes and for a transition to the translational level.

Completing the picture will require a more thorough characterization and mapping of tinnitus-related defects than we currently have. While we are beginning to define which neuronal populations show these abnormalities at the lowest levels of the system, research is needed to identify abnormal cell populations at all levels of the auditory system and to define their defects at the subcellular and molecular levels. There is also need to define the roles each brain level and each type of changes within those levels plays in tinnitus, and especially, to determine how hyperactivity, increased bursting activity and neural synchrony contribute to the auditory, attentional and emotional components of tinnitus. Theories of how these changes in spontaneous activity lead to tinnitus will require additional knowledge of how neurons encode simple sound stimuli and how the nervous system assembles the basic building block of that code into an actual auditory percept. A more complete picture will also require an understanding of how each level of the involved systems influences the others. Defining the relative importance of top-down vs. bottom-up processing and determining the potential modulatory effects of input pathways at each level where the tinnitus-related changes occur are of fundamental importance. This information will, in turn, lead to better translational approaches to tinnitus treatment that are more plasticity-based, designed to restore the normal balance of excitation and inhibition in the auditory signaling pathways. As the details of the picture become more complete, it will become increasingly important to improve modes of treatment delivery so that the abnormal cell populations can be targeted without compromising functions that are essential for normal hearing. Behavioral and physiological models will be essential to our ability to achieve these goals.

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