Dorsal Cochlear Nucleus Hyperactivity and Tinnitus: Are They Related?

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**Purpose:** Eight lines of evidence implicating the dorsal cochlear nucleus (DCN) as a tinnitus contributing site are reviewed. We now expand the presentation of this model, elaborate on its essential details, and provide answers to commonly asked questions regarding its validity.

**Conclusions:** Over the past decade, numerous studies have converged to support the hypothesis that the DCN may be an important brain center in the generation and modulation of tinnitus. Although other auditory centers have been similarly implicated (Eggermont & Roberts, 2004; Gerken, Saunders, & Paul, 1984; Lockwood et al., 1998; Melcher, Sigalovsky, Guinan, & Levine, 2000), the DCN deserves special emphasis because, as a primary acoustic nucleus, it occupies a potentially pivotal position in the hierarchy of functional processes leading to the emergence of tinnitus percepts. Moreover, because a great deal is known about the underlying cellular categories and the details of synaptic circuitry within the DCN, this brain center offers a potentially powerful model for probing mechanisms underlying tinnitus.

**Key Words:** tinnitus, dorsal cochlear nucleus, hyperactivity, plasticity, noise exposure

Over the past decade, numerous studies have converged to support the hypothesis that the dorsal cochlear nucleus (DCN) may be an important brain center in the generation and modulation of tinnitus. Although other auditory centers have been similarly implicated (Eggermont & Roberts, 2004; Gerken, Saunders, & Paul, 1984; Lockwood et al., 1998; Melcher, Sigalovsky, Guinan, & Levine, 2000), the DCN deserves special emphasis because, as a primary acoustic nucleus, it occupies a potentially pivotal position in the hierarchy of functional processes leading to the emergence of tinnitus percepts. Moreover, because a great deal is known about the underlying cellular categories and the details of synaptic circuitry within the DCN, this brain center offers a potentially powerful model for probing mechanisms underlying tinnitus. Here, eight lines of evidence implicating the DCN as a tinnitus contributing site are reviewed. Some of the information presented has been published previously in a more condensed form (Kaltenbach, 2006, 2007). We now expand the presentation of this model, elaborate on its essential details, and provide answers to commonly asked questions bearing on its validity.

**Electrical Stimulation Studies**

The earliest report suggesting that the DCN may be an important region involved in tinnitus was published by Soussi and Otto in 1994. They examined 10 neurofibromatosis-2 patients who had received an auditory brainstem implant (ABI) on the surface of the DCN following bilateral acoustic neuroma surgery. Normally, the ABI is intended to restore hearing, but in this study, the ABI was used to investigate the potential of brain stimulation as a means of suppressing tinnitus. All patients selected for the study had chronic tinnitus, although some had developed it secondarily after the surgical procedure. Each patient received the implant unilaterally, and the effects of stimulation were examined in two groups. In one group (n = 7), the effects of stimulation were tested daily with the patient controlling the stimulus. In the other (n = 3), the effects of stimulation were tested in the laboratory.

Results obtained from the 10 patients are summarized in Table 1. Six of the 7 patients who used their ABIs daily reported improvements in the loudness of their tinnitus. In the one patient from this group who did not experience improvement, the implant was on the side contralateral to the tinnitus. One of the patients tested in the laboratory reported a complete suppression of his tinnitus, while one other reported a worsening of tinnitus during stimulation. Mostly, stimulation affected the loudness of tinnitus, but changes in pitch and/or the number of tinnitus sounds were sometimes also reported. When changes in the loudness of tinnitus were reported, the loudness change lasted only as long as the
studies have demonstrated that stimulation on tinnitus (data from Soussi & Otto, 1994).

Table 1. Summary of effects of dorsal cochlear nucleus stimulation on tinnitus.

<table>
<thead>
<tr>
<th>Patient</th>
<th>ABI side</th>
<th>Side of tinnitus</th>
<th>Daily use</th>
<th>Effects of ABI stimulation on tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L</td>
<td>L</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>2</td>
<td>L</td>
<td>L</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>R</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>Both</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>5</td>
<td>L</td>
<td>Not lateralized</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>Not lateralized</td>
<td>Y</td>
<td>Decrease</td>
</tr>
<tr>
<td>7</td>
<td>L</td>
<td>R</td>
<td>Y</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>L</td>
<td>None</td>
<td>Decrease</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>R</td>
<td>None</td>
<td>Increase</td>
</tr>
<tr>
<td>10</td>
<td>L</td>
<td>L</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Note. ABI = auditory brainstem implant; L = left; R = right; Y = yes; N = no.

The results of this study show that a stimulus designed to change the level of activity in the DCN results in a change in tinnitus percepts. While they tell little about the mechanism by which stimulation produces these changes, they nonetheless do suggest that the DCN is part of a circuit that influences tinnitus loudness and pitch. They further indicate that the changes in loudness can be bidirectional, toward either improvement or worsening of tinnitus. This could indicate that, depending on the location of electrodes, the stimuli may affect different pathways and/or neuronal populations within the DCN whose activations evoke opposing effects. An additional study of the positive effects of ABI stimulation on tinnitus has recently been reported (Behr et al., 2007).

**Effects of Intense Sound Exposure on Neural Activity**

The notion of a relationship between tinnitus and the DCN was given a more formal platform when it was realized that tinnitus-inducing agents cause neurons in the DCN to become hyperactive. The original observations were made in hamsters following their exposure to intense sound (Kaltenbach & Afman, 2000; Kaltenbach et al., 1998; Kaltenbach & McCaslin, 1996). Similar noise-induced increases in activity were found to occur in several other species, including rat (J. S. Zhang & Kaltenbach, 1998), mouse (Kaltenbach, Heffner, Zhang, Mathog, & Zacharek, 2001), chinchilla (Brozoski, Bauer, & Caspary, 2002), and guinea pig (Imig & Durham, 2005; Shore, Koehler, Oldakowski, Hughes, & Syed, 2008). The induced hyperactivity was evident as an increase in spontaneous activity (i.e., activity in the absence of sound). The experiments in our laboratory were typically conducted as follows: Animals, such as hamsters or rats, were anesthetized and exposed for 4 hr to an intense (125–130 dB SPL) tone (10 kHz). After the exposure, the animals emerged from anesthesia and were allowed a postexposure recovery period of approximately 1 month. At the end of the recovery period, multiunit activity was recorded electrophysiologically on the surface of the DCN using low-impedance micropipettes.

Spontaneous activity levels in exposed and control animals are shown in Figure 1. The activity in the exposed animals was considerably higher in amplitude and displayed more frequent high-amplitude potentials than that of control animals. For example, relatively few high-voltage potentials (50 mV or larger; see scale bar in bottom left panel of Figure 1) were observed in the control animal, but such potentials were frequent in the exposed animals (bottom right panel). A similar state of hyperactivity in the DCN was observed in animals approximately 1 month after they were treated with the ototoxic drug cisplatin, which is a well-known inducer of chronic tinnitus (Kaltenbach et al., 2002; Melamed, Kaltenbach, Church, Burgio, & Afman, 2000).

It should be noted that noise exposure does not generally cause similar long-term increases in the auditory nerve (Liberman & Dodds, 1984; Liberman & Kiang, 1978; Salvi & Ahroon, 1983). At this level, activity is either minimally changed or decreased following cochlear damage. Moreover, the hyperactivity induced in the DCN by intense sound exposure is not abolished by cochlear ablation (Zacharek, Kaltenbach, Mathog, & Zhang, 2002). These findings suggest that hyperactivity in the DCN is not just a reflection of chronic hyperactivity in the periphery. This does not mean that the induction of hyperactivity in the DCN is independent of the cochlea. Intense sound exposure causes damage to cochlear hair cells that is often accompanied by loss of auditory nerve fibers. The prevailing view is that cochlear injury sets in motion plastic changes that lead to the hyperactive state of DCN neurons.

The significance of noise- and cisplatin-induced hyperactivity in the DCN is threefold: It suggests that tinnitus is triggered by peripheral injury, may result from changes at a very early stage of processing in the central auditory pathway, and can endure for extended periods. The studies in the rodent models have established that hyperactivity persists for periods of at least 6 months (Kaltenbach et al., 2002). Noise-induced hyperactivity of the DCN therefore provides a model for the study of chronic tinnitus mechanisms.

**Noise-Induced Hyperactivity Resembles Activity in the Sound-Activated State**

An additional feature of DCN hyperactivity, which underscores its potential as a tinnitus-generating signal, is its resemblance to the activity increases that result from normal sound stimulation. This resemblance was made apparent in studies that examined the distribution and levels of hyperactivity along the frequency axis (Kaltenbach & Afman, 2000). The DCN is organized tonotopically, reflecting the frequency representation of the cochlea. High frequencies activate the basal end of the cochlea, and low frequencies activate the apical end (Kaltenbach & Lazor, 1991). Similarly, in the DCN, high-frequency stimuli activate neurons in the medial part of the nucleus, whereas low frequencies activate neurons laterally (see Figure 2). A systematic gradient is thus produced along the medial-lateral axis, which spans the audible frequency range. When an electrode is used to measure spontaneous activity at different sites along this axis, the results can...
be used to plot an activity profile, showing rate of spontaneous activity versus distance along the tonotopic gradient. Activity profiles for two groups of animals are compared in Figure 2. The group represented by the squares consisted of control animals, which had been anesthetized for 4 hr in a silent environment 1 month earlier. The dashed curve represents animals that had been exposed to intense sound (10 kHz, 125–130 dB SPL, 4 hr) 1 month earlier. The activity profile in the control group is relatively low, generally not exceeding spontaneous activity levels of 30 events/s (events/s refers to the average number of times high-amplitude (>100 mV) potentials occurred each second). In contrast, the profile from the exposed animals shows much higher levels over most of the DCN, increasing toward a peak of 80 events/s in the middle range of the tonotopic gradient. This peak of hyperactivity in the exposed animals takes on particular significance when it is compared with the profile of activity obtained from control animals during presentation of a high-pitch sound to the ear. In the latter case, a sound similar in frequency (10 kHz) to that which was used to induce hyperactivity was presented, except that the sound level was low enough (20 dB SL) to activate neurons without causing damage to the ear. This type of stimulus caused activity to increase in the middle range of the tonotopic axis, as shown by the solid circles in Figure 2. It is apparent that this high-frequency tonal stimulus evoked an activity profile similar to that observed in the animals that had been exposed to intense sound a month earlier (dashed curve). Both show a trend toward high activity that peaks in the middle of the DCN. Thus, the tonotopic pattern of ongoing hyperactivity induced by previous exposure to intense, high-frequency sound is fundamentally similar to that in unexposed animals during low-level, high-frequency sound stimulation. This similarity leads to the expectation that hyperactivity in exposed animals would produce tinnitus percepts, and those percepts would be high in pitch.

**Parallels Between DCN Hyperactivity and Psychoacoustic Attributes of Tinnitus**

The parallels between DCN hyperactivity and psychoacoustic attributes of tinnitus are listed in the Appendix. One important parallel is in the spectral characteristics of hyperactivity and tinnitus. In Figure 2, it can be seen that the peak of the tone-elicited activity profile (solid circles) in the middle range of the curve is sharp, with shoulders rolling off rapidly in the medial (high-frequency) and lateral (low-frequency) regions of the tonotopic gradient. In contrast, the peak of the profile of hyperactivity in animals exposed a month earlier to the intense, high-frequency tone (dashed curve in Figure 2) is much broader, with shoulders that roll off from the peak more gradually toward the high- and low-frequency directions. This broader spread of activity suggests that exposed animals might experience a sound percept that is more like a narrow band of noise than a pure tone. Although this prediction has not yet been tested in animals,
the frequency spectrum of noise-induced tinnitus in human subjects tested psychoacoustically has been found to be more like that of a narrow band of noise than that of a pure tone (Norena, Micheyl, Chery-Croze, & Collet, 2002).

Another parallel is apparent in a comparison between the tonotopic locus of peak hyperactivity and the pitch of tinnitus relative to the frequency of the exposure tone. It can be seen in Figure 2 that the profile of hyperactivity in animals exposed to an intense 10-kHz tone reaches a peak at the 12–13-kHz locus of the DCN (dashed curve) rather than at the location responding best to a 10-kHz tone (solid circles). Peak activity in exposed animals is thus offset toward the high-frequency direction, relative to the frequency of the exposure tone. Similarly, when the tinnitus induced by intense tone exposure was tested psychoacoustically in human subjects, it was found to have a pitch that was most commonly matched to frequencies that were shifted upward relative to the exposure frequency (Atherley, Hempstock, & Noble, 1968; Loeb & Smith, 1967). The amount of this shift varied, depending on the frequency of the exposure, but averaged approximately 1 octave.

Noise-Induced Hyperactivity in the DCN and Behavioral Evidence of Tinnitus

A relationship between DCN hyperactivity and tinnitus is further supported by evidence suggesting that the exposure conditions that cause hyperactivity in the DCN also cause animals to develop tinnitus-like percepts (Brozoski et al., 2002; Heffner & Harrington, 2002). Behavioral testing is the usual tool for determining whether animals develop tinnitus after exposure to a tinnitus-inducing agent. In the study by Heffner and Harrington, hamsters were presented with tones of different frequencies and intensities. They were trained to respond to sounds by licking from a water spout and to respond to silence by avoiding contact with the spout. After approximately 3 weeks of training, the animals became quite skilled in responding appropriately, performing correctly on 80%–85% of the test trials. After reaching this level of performance, they were exposed to an intense tone, similar to that which was previously shown to cause hyperactivity in the DCN. After the intense tone exposure, the animals were retested by observing their behavior during silence (no sounds presented). The prediction was that if the animals developed tinnitus, they would respond to the silent test trials as though they were hearing a sound; that is, they would lick from the water spout more frequently in response to silence than animals that were not previously exposed to the tinnitus-inducing sound. The percentage of correct responses to silence would thus be decreased relative to those of unexposed control animals.

The results of the study were consistent with this prediction. On each of the 5 days when the animals were tested after being exposed to an intense tinnitus-inducing sound, the exposed animals performed correctly in their response to silence less frequently than control animals; the exposed animals tended to lick from the spout more frequently than controls when silence was presented. Heffner and Harrington interpreted this result as indicating that the exposed animals increased their contact with the water spout because they were hearing the sounds of tinnitus. The alternate explanation of their behavior is that it might have been due to hearing loss. However, one would expect that animals with hearing loss would have heard less sound as a result of hearing loss, and therefore would have tended to lick from the water spout less than control animals when tested with the condition of silence. This would have produced higher performance scores in the exposed animal group, the opposite of what was actually observed. Thus, hearing loss alone seems an unlikely explanation of the observed behavioral results.

The relationship between DCN hyperactivity and tinnitus was tested more directly in a follow-up study in which electrophysiological recordings were conducted in the same animals that had previously been tested behaviorally for tinnitus. The results of this experiment are presented in Figure 3. The top row of graphs shows the distributions of behavioral scores expressed as a percentage of trials in which the animals responded correctly to silence by avoiding contact with the water spout. Lower scores are interpreted as evidence of tinnitus and higher scores as the absence of tinnitus. Note that the exposed animals generally had lower scores than controls, suggesting that they had tinnitus. When the levels of DCN activity of these two groups are compared, significant differences are found.

The analysis of the data is broken down into three comparisons. The first (bottom left) compares activity in exposed and control animals. This comparison reveals a significantly
higher level of activity in exposed animals than controls, consistent with other studies. The second (top and bottom middle) compares activity in animals with stronger evidence of tinnitus with that in animals with weaker evidence of tinnitus. This comparison shows a wider separation in levels of activity than the comparison between exposed and controls. The third (bottom right) compares activity levels in animals with the strongest evidence for tinnitus with those with the weakest evidence for tinnitus. This comparison yields the widest separation between groups among the three comparisons. To be noted is that the increasing separation between activity levels in the three comparisons as the behavioral evidence for tinnitus becomes stronger is due to both an increase in the level of hyperactivity in animals with tinnitus as well as a decrease in the level of activity in animals without tinnitus. When tested statistically, the levels of peak activity and behavioral performance score yielded a correlation coefficient, \( r \), of .44 (\( p < .01 \)), supporting the interpretation that tinnitus correlates with DCN hyperactivity.

**Somatic Modulation of Tinnitus and DCN Spontaneous Activity**

The modulation of tinnitus and DCN spontaneous activity by manipulations of the somatosensory system has been well known for many years, although only recently has a possible link between these two phenomena been realized. Various dimensions of tinnitus percepts, especially loudness and pitch, can be modulated by cutaneous stimulation or by forces that cause contractions of head and neck musculature (Abel & Levine, 2004; Levine, 1999, 2004; Levine, Abel, & Cheng, 2003; Møller, Møller, & Yokota, 1992). For example, clenching the jaws or resisting pressure applied to the side of the head or neck often causes increases or decreases in the loudness of tinnitus. In some cases, a person who does not normally experience tinnitus can turn tinnitus on by these maneuvers. A middle ear muscle contraction mechanism of this modulation seems unlikely because even profoundly deaf patients with no functional inner ears can modulate their tinnitus in this manner. The observation that the ability to modulate tinnitus by these manipulations can be abolished by muscle fatigue argues in favor of the interpretation that the effect is mediated by proprioceptive somatosensory input, which would not be active in a noncontracting muscle (Levine, 2004). This interpretation is consistent with the observation of Kanold and Young (2001) that DCN principal cell activity can be modulated by proprioceptive input.

It seems likely that these somatic modulations of tinnitus involve structures in the auditory brainstem that integrate
inputs from auditory and somatosensory systems. There are several brain areas where responses to sound can be modulated by somatosensory stimuli, but the DCN figures prominently in discussions about somatically modulated tinnitus because it receives inputs from somatosensory nuclei that are predominantly ipsilateral. This is significant because, when tinnitus is unilateral, the manipulations that are most effective in modulating the tinnitus involve muscles on the same side as the tinnitus (Levine, 2004). Additionally, when unilateral tinnitus is accompanied by craniofacial pathologies, such as temporomandibular joint syndrome, those pathologies were usually found to be on the same side as the tinnitus (Levine, 2004). Levine reported that the somatosensory manipulations that are most effective in modulating tinnitus involve muscles innervated by the second and third cervical nerves (C2 and C3). The cutaneous modulation of tinnitus probably involves skin receptors that are innervated by the sensory branches of the trigeminal nerve (N.V). The cervical and trigeminal nerves converge centrally on the ipsilateral medullary somatosensory nuclei (spinal trigeminal and cuneate nuclei). These somatosensory nuclei project to the ipsilateral DCN, where they converge on the granule cell domain (Itoh et al., 1987; Shore, 2004, 2005; Shore, Vass, Wys, & Altschuler, 2000; Weinberg & Rustioni, 1987; Wright & Ryugo, 1996; Zhou & Shore, 2004). Electrical or chemical activation of granule cells, either by stimulating the axons of granule cells (parallel fibers) or by stimulating C2, N.V, or medullary somatosensory nuclei, produces changes in the discharge rates of DCN fusiform cells (Kanold & Young, 2001; Shore, 2005; Shore et al., 2008). These are the major output neurons from the DCN and project to neurons in the inferior colliculi (see Figure 4). Changes in their activity would therefore likely affect auditory perception at a higher level of processing.

Thus, the DCN possesses the appropriate circuit connections and has the relevant electrophysiological properties to explain somatic modulations of tinnitus in general, and unilateral somatic tinnitus modulation in particular.

**DCN Plasticity Correlates With Several Forms of Tinnitus Plasticity**

Numerous studies have shown that damage to the ear causes plastic changes in the central auditory system that produce alterations in the excitability of neurons. The emergence of hyperactivity in the DCN after cochlear damage is a byproduct of this injury-induced plasticity (see Figure 5A). There is evidence that the damage in the cochlea that triggers

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**Figure 4.** Circuitry of the DCN involved in the control of spontaneous activity. Neuron types that normally lack spontaneous activity are not shown. The core of the circuit is the fusiform cell, which occurs in the middle layer (fcl) and provides the major output from the DCN to the contralateral inferior colliculus. Hyperactivity is thought to arise from fusiform cells due to plastic changes in the balance of their normal excitatory and inhibitory inputs. Changes in the level of hyperactivity can also be induced by stimulation of pathways from the somatosensory system. These provide input to granule cells, which excite fusiform cells and cartwheel cells; cartwheel cells then inhibit fusiform cells. This cross-modality integration may underlie somatic modulations of tinnitus. ml = molecular layer; dl = deep layer. (Modified after Kaltenbach et al., 2002.)

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hyperactivity begins with loss of outer hair cells (OHCs), in line with the theory advanced earlier by Tonndorf (1987) and again by Jastreboff (1990). Hyperactivity develops after either intense noise or cisplatin, both of which are known for their stronger destructive effects on OHCs. In studies with cisplatin, correlations between the levels of hyperactivity in the DCN and the amount of OHC loss have been found (Kaltenbach et al., 2002; Melamed et al., 2000; Rachel, Kaltenbach, & Janisse, 2002). Once induced, however, the hyperactivity no longer depends on peripheral inputs, for cochlear ablation does not abolish it (Zacharek et al., 2002). These findings suggest that OHC loss triggers plastic changes in DCN circuitry that result in a chronic state of increased excitability. Such changes involve loss of inhibitory and increases in excitatory neurotransmission (see review of Kaltenbach, 2007). Once these changes are induced, they become chronic, no longer influenced by removal of input from the cochlea.

Tinnitus shows a similar tendency to develop after cochlear injury (injury-induced plasticity; see Figure 5A), and there is some evidence to suggest that OHC damage is a common accompaniment. Several studies have found that human subjects with tinnitus exhibit abnormal otoacoustic emissions (Lonsbury-Martin & Martin, 2004), which are reflective of an alteration in the functional status of OHCs. Once established, however, tinnitus may become independent of auditory nerve input. This is evidenced by the clinical finding that patients continue to experience their tinnitus after the auditory nerves have been bilaterally severed. In a comprehensive study of 414 tinnitus patients, House and Brackman (1981) found that 55% continued to experience tinnitus after eighth nerve section. Although the percentages vary across studies, there is general agreement that tinnitus is often not abolished by eighth nerve section, even when it is bilateral, underscoring the importance of central auditory plasticity as an underlying basis. Thus, like DCN hyperactivity, although tinnitus may be triggered by cochlear injury, once established it becomes a chronic condition that is commonly not abolished by removal of cochlear input to the cochlear nucleus.

Another parallel between DCN hyperactivity and tinnitus is their tendencies to change over time (i.e., their temporal plasticities). In a study of activity profiles (similar to those presented in Figures 2 and 3) at different postexposure recovery times, it was found that both the amplitude and tonotopic locus of peak hyperactivity changed over time (see Figure 5C). Between 1 week and 4 weeks, the profile changed from broad to narrow and increased in peak amplitude. At 1 month after exposure, peak activity was found at the 11–13-kHz locus of the DCN, whereas at 6 months, the peak occurred at the 17-kHz locus (Kaltenbach, Zhang, & Afman, 2000). Similarly, the amplitude of the peak at 1 month was lower than that at 6 months. These changes predict that any tinnitus caused by hyperactivity would vary over time in its spectral content, pitch, and loudness. Although we were unable to find studies examining the psychoacoustic feature of tinnitus at these long postexposure recovery times, a few investigations have shown that the psychoacoustic attributes of tinnitus, such as pitch and loudness, vary over short periods of time (Burns, 1984; Meikle, 1987; Penner, 1983, 1995; Penner & Bilger, 1992; Tyler & Conrad-Arms, 1983, 1984). Such changes may reflect the temporal shifts in the tonotopic locus and amplitude of hyperactivity discussed above.

The DCN and Gaze-Evoked Tinnitus?

Gaze-evoked tinnitus sometimes develops after surgical injury or resection of the eighth nerve. It is characterized by the ability to switch between tinnitus-on versus tinnitus-off states or loud versus quiet tinnitus by changing the angle of gaze (Cacace, Lovely, McFarland, Parnes, & Winter, 1994; Cacace, Lovely, Winter, Parnes, & McFarland, 1994; Wall, Rosenberg, & Richardson, 1987). For example, tinnitus may become apparent only when the eyes are shifted horizontally from straight ahead to the lateral direction. This phenomenon sometimes appears secondarily after injury to the auditory nerve. It can develop slowly over a period of days to months following surgery. Since all auditory nerve fibers project no further centrally than the cochlear nucleus (Lorente de No, 1981; Moster, Kim, & Bohne, 1997; Osen, 1970), these features suggest that the resulting deafferentation of the cochlear nucleus represents the initial trigger of plastic changes at central levels of the pathway. The DCN is among the first nuclei in which plasticity is triggered by eighth nerve deafferentation. Loss of peripheral input causes chronic alterations in the balance of excitation and inhibition in the DCN and ventral cochlear nuclei (reviewed by Kaltenbach, 2007). Is there a connection between this plasticity and gaze-evoked tinnitus?
The DCN possesses both the physiological properties and circuit connections (see Figure 6) to suggest that its function may be linked to changes in eye position. This was shown by Mori, Mitani, Fujita, and Winters (1972), who recorded multiunit activity in the DCN while animals moved their eyes during sleep. Rapid bursts of multiunit activity in the DCN were found to be synchronized to the contractions of eye muscles during the rapid eye movement (REM) phase of sleep (see Figure 6). The neuronal pathways mediating this modulation of activity have not yet been clarified. However, it is possible that it may involve the influence of Roller’s nucleus, a structure in the vestibular portion of the brainstem. This nucleus has been implicated in the coordination of eye movements during head displacements (McCrea, Strassman, & Highstein, 1987). Roller’s nucleus projects to the granule cell domain of the cochlear nucleus (Ryugo, Haenggeli, & Doucet, 2003).

The granule cells of the cochlear nucleus occupy regions near its surface and share a layer of the DCN with the fusiform cells (Godfrey et al., 1997; Osen, Mugnaini, Dahl, & Christiansen, 1984). These regions receive cholinergic innervation from descending pathways (Godfrey, Park-Hellendall, Dunn, & Ross, 1987; Osen et al., 1984). Intense tone exposure appears to increase the cholinergic influence on granular regions of the hamster cochlear nucleus (Jin, Godfrey, Wang, & Kaltenbach, 2006) and to increase the bursting spontaneous activity in slices of the hamster DCN (Chang, Chen, Kaltenbach, Zhang, & Godfrey, 2002). This bursting spontaneous activity has been associated with cartwheel cells (Manis, Spirou, Wright, Paydar, & Ryugo, 1994; S. Zhang & Oertel, 1993), which receive excitatory glutamatergic input from granule cells, as do fusiform cells (Godfrey et al., 1997; Petralia, Rubio, Wang, & Wenthold, 2000; Waller, Godfrey, & Chen, 1996). Acetylcholine agonists can strongly activate bursting neurons (cartwheel cells) of the DCN, and this influence appears to be exerted indirectly via activation of granule cells (K. Chen, Waller, Godfrey, & Godfrey, 1999). Intense tone exposure has been found to lead to increased responsiveness of cartwheel cells to acetylcholine agonists, an effect that is presumably mediated via increased responsiveness of granule cells (Chang et al., 2002). Thus, there is evidence that intense tone exposure may lead to increased activity of granule cells, mediated at least partly through changes in cholinergic descending pathways. Increased activity of granule cells would lead, in turn, to increased excitatory input from their axons onto cartwheel and fusiform cells. This might lead to short-term decreases in fusiform cell spontaneous activity, because of the powerful inhibitory influence of the cartwheel cell input onto the fusiform cells. However, there might be a long-term change in excitability of fusiform cells in response to this chronic increase of inhibitory input, as reported in a previous study (Nelson, Krispel, Sekirnjak, & du Lac, 2003), and this might eventually lead to increased fusiform cell spontaneous activity. This would be opposite to an effect observed in the medial vestibular nucleus after removal of inhibitory input from cerebellar Purkinje cells (Bäurle, Helmchen, & Grüsser-Cornehls, 1997; Sun, Godfrey, Chen, Sprunger, & Rubin, 2007). In that case, removal of the inhibitory input led to decreased spontaneous activity of neurons instead of the expected increase. It was proposed that this might have resulted from compensatory changes in other neurons when the Purkinje cell influence was reduced or from decreased intrinsic excitability of the neurons when their inhibitory input was decreased. Such alterations could lead...
to changes in the balance of excitation and inhibition of DCN fusiform cells, which might make them more sensitive to inputs from Roller’s nucleus and cause increases in the activity of fusiform cells, when the angle of gaze is changed. This pattern is also consistent with the observation that gaze-evoked tinnitus is often observed as a secondary aftereffect of surgically induced damage to the eighth nerve (Cacace, 2003).

**Responses to Comments and Questions Regarding the DCN Model of Tinnitus**

**Comment 1:** The fact that ABI stimulation affects tinnitus does not mean anything for a source in the DCN; it will only refute a more peripheral source such as the cochlea or auditory nerve. Stimulation with a cochlear implant does much the same as, or better than, an ABI to alleviate tinnitus and yet does not mean anything for a source in the DCN; it will only influence the loudness and pitch of tinnitus. The fact that stimulation with a cochlear implant can have a similar or better effect indicates that the auditory nerve is also part of this circuit.

**Response:** We are not suggesting that the ABI evidence indicates that tinnitus originates in the DCN. Rather, the ABI evidence indicates that the DCN is part of a circuit that influences the loudness and pitch of tinnitus. The fact that stimulation with a cochlear implant can have a similar or better effect indicates that the auditory nerve is also part of this circuit.

**Comment 2:** It has been pointed out in a previous publication by this group that the increase in spontaneous firing rate in the DCN occurs 2–5 days after intense sound exposure. This poses two questions. First, how can this be reconciled with the immediate onset of tinnitus that occurs following sound exposure that has been reported in the psychoacoustic literature (Atherley et al., 1968; Loeb & Smith, 1967)? Second, does the delayed onset suggest that the changes in the DCN are secondary to those in cortex where changes occur within a few hours after exposure?

**Response:** Although the onset times of tinnitus in humans exposed to intense sound have never been formally studied, the available literature suggests that there may be significant variability in the onset times following noise exposure. For example, the studies by Atherley et al. (1968), Chermak and Dengerink (1987), and George and Kemp (1989), which were based on moderate sound exposure (90–110 dB SPL for 1–5 min), reported tinnitus with immediate onset. In contrast, the studies of Alberti (1987) and Axelson and Barrenas (1992), which were based on examination of patients working in noisy environments, reported onsets ranging from immediate to years following exposure to intense noise. Similarly, we found that the onset of hyperactivity after sound exposure was also variable. When animals were exposed to very intense sound for 4 hr, the hyperactivity was not observed until between 2 and 5 days after exposure, whereas when animals were exposed to a more moderate level of sound (10-kHz tone, 80 dB SPL, 4 hr), the hyperactivity was already apparent by 1 hr following the end of the exposure, the time required to expose the DCN surgically (Kaltenbach, Zhang, & Finlayson, 2005). This indicates that the onset of hyperactivity, as with the onset of tinnitus, depends on the exposure conditions, and by implication, the type of damage induced in the inner ear.

**Comment 3:** It seems unlikely that increases in spontaneous activity could cause tinnitus. Spontaneous activity increases do not constitute an auditory signal for tonal percepts, such as tinnitus.

**Response:** If spontaneous activity increased uniformly across the tonotopic array, then there would effectively be no peak of activity that would stand out above the general background. This might not necessarily result in the perception of tinnitus, at least not with a distinct pitch. However, we do not see evidence of a uniform increase in activity across the entire DCN. Instead, activity is increased very non-uniformly, as shown in Figure 2. The activity increases toward a peak level in one part of the DCN and approaches normal background levels of activity in adjacent regions. The peak constitutes a signal against a background of lower activity in the same way that the traveling wave reaches a peak in one part of the cochlea, rolling off toward baseline in the basal and apical parts of the cochlea.

**Comment 4:** It is difficult to conceive of a persistent signal caused by increased spontaneous activity causing ongoing tinnitus because the auditory system would be expected to adapt to the signal over time, so that even if the increased activity persists, the percept would not.

**Response:** There is evidence that the auditory system adapts to sounds that are maintained in the acoustic environment. However, this adaptation is usually experienced as a decrease in loudness over time, rather than a complete disappearance of the sound. Loudness adaptation functions (sound loudness vs. time) vary with stimulus level and frequency. Chronic tinnitus induced by noise exposure is most commonly matched to frequencies between 1 and 8 kHz (Axelsson & Barrenas, 1992); the loudness adaptation curves for frequencies between 2 and 12 kHz provide some insight into how a tinnitus-like sound changes in loudness over time. The most systematic study of loudness adaptation functions in human subjects was reported by Hellman, Miśkiewicz, and Scharf (1997), who quantified changes in loudness percepts for tones presented at different frequencies and intensities. They found that, for tones in the 2–12-kHz frequency range, human participants experienced relatively little loudness adaptation when the tone was presented at a level of 40 dB SL (i.e., level in dB above hearing threshold). That is, the loudness declines by no more than 30% after 6 min of stimulation, at which point further increases in duration of the stimulus had little effect on loudness. At 20 dB SL, loudness decayed by about 55%–70% of its original level after 6 min. At either 5 or 10 dB SL, loudness decayed by up to 70%–85% of the loudness experienced at tone onset. The point here is that, regardless of its sensation level, the loudness of tones between 2 and 12 kHz diminishes over time, but it does not become inaudible. On the other hand, Hellman et al. found that the loudness of a 16-kHz tone diminished by nearly 100% when presented at 5 dB SL. Thus, depending on pitch and loudness, sounds may or may not become inaudible over time.

What pitch and sensation level would the sound percept have for the hyperactivity that we have found in the DCN after intense sound exposure? The peak of the hyperactivity profile occurs at about the 12–13-kHz locus of the DCN, and the level of peak activity is between 80 and 100 events/s.
This level of activity was also observed when a tone of approximately 20 dB SL (20 dB above neural response threshold) was presented to the ear. As indicated above, at 20 dB SL, loudness for frequencies between 2 and 12 kHz decays by up to 70%. Thus, we would expect that the loudness of the sound percept produced by this level of hyperactivity in the DCN might decay by an equivalent amount, but it would not become inaudible. This expectation is consistent with studies reporting that chronic noise-induced tinnitus is typically low in loudness, averaging approximately 5 dB SL (Axelsson & Barrenas, 1992).

Comment 5: The plot of activity in control animals also shows a peak. If the hypothesis is correct that the peak of activity is what leads to a tinnitus percept, then this would predict that normal animals should experience tinnitus also, contrary to what is actually reported.

Response: While it is true that the activity profile from control animals shows a peak, this peak is much lower than that in exposed animals. We would expect that such a low peak in the activity profile might produce a sound percept that is insufficiently loud to be detected in most acoustic environments, which are characterized by significant levels of ambient noise. Furthermore, because control animals are likely to have experienced this low-level peak of spontaneous activity during development and throughout life, the central auditory system, which probably has much greater plasticity during development, would very likely habituate to it, relegating the percept into the background of attention.

Comment 6: It seems unlikely that the DCN would contribute significantly to tinnitus in view of recent evidence that DCN ablation in animals does not eliminate tinnitus (Brozoski & Bauer, 2005).

Response: If we assume that this finding is correct, then there are still at least two possible explanations of the results that would not invalidate the DCN model of tinnitus. (a) The DCN is only one of several auditory structures where hyperactivity develops independently after cochlear injury. Tinnitus percepts are generated by hyperactivity in any of these structures. Removal of any one structure, with the possible exception of the auditory cortex, would therefore not be expected to eliminate tinnitus, since other sites of hyperactivity survive. (b) The DCN is required for the induction of hyperactivity at higher levels of the auditory system but not for their maintenance. This model assumes that the DCN is not a feed-forward system but rather serves as a trigger site for the induction of hyperactivity elsewhere. Thus, removal of the DCN after tinnitus is induced would not be expected to abolish tinnitus any more than removal of the cochlea or sectioning the auditory nerve necessarily abolishes tinnitus, once it has become established. However, removal of the DCN previous to tinnitus induction (e.g., before intense sound exposure) would prevent the induction of hyperactivity elsewhere and would therefore prevent the induction of tinnitus.

Comment 7: Why is there so much focus on the relationship between tinnitus and the DCN when there is so much more to the auditory system than the DCN?

Response: The DCN is viewed as only one of a hierarchy of structures involved in tinnitus. The emphasis on the DCN is based on the prominence of the changes that have been described, and which show relevance and statistically measurable relationships with tinnitus. Also, the DCN, by virtue of its position as a primary acoustic nucleus and its unique circuitry that includes a convergence of inputs from other sensory systems, may be pivotal in triggering or inducing tinnitus-related changes in higher auditory centers. For example, hyperactivity in the DCN might trigger plastic alterations in the inferior colliculus, which may be related to tinnitus.

Comment 8: Is it possible that DCN hyperactivity reflects hearing loss rather than tinnitus?

Response: It is generally believed that the neural correlate of hearing loss in primary ascending auditory neurons is a decrease of activity, not an increase. This has been demonstrated in numerous studies at the eighth nerve level and in central auditory structures using measures of electrophysiological and metabolic activity. Noise exposure, deafferentation, and ototoxic insult all cause decreased stimulus-driven, spontaneous and/or metabolic activity in primary afferents and central nuclei, at least in the classical lemniscal pathway, which includes the ventral cochlear nucleus, superior olivary complex, and central nucleus of the inferior colliculus. Our basic understanding is that hearing loss is associated with this loss of activity in the lemniscal part of the auditory system, not by a gain (i.e., an increase) in activity. The notion that an increase in the spontaneous activity of DCN fusiform cells (i.e., hyperactivity) reflects hearing loss seems to ignore a fundamental relationship between firing rates and sound perception. Generally, when firing rates are increased in these ascending projection neurons, the brain interprets this as sound. This occurs when sound percepts are evoked by electrical stimulation of the auditory nerve, cochlear nucleus, and inferior colliculus. An increase in the level of activity in the auditory system as an underlying basis of tinnitus is also indicated by numerous imaging studies in human subjects with tinnitus. There is some evidence that hyperactivity in the DCN may be related to tinnitus in the absence of hearing loss. Brozoski et al. (2002) recorded activity in the DCN of chinchillas that tested positive for tinnitus 5 months after exposure to a moderate level tone (80 dB SPL). In their study, hearing loss was demonstrated in the chinchillas examined shortly after the exposure, but by 5 months after exposure, the thresholds had recovered to normal levels, indicating an absence of hearing loss. The recordings conducted at about the same time indicated that spontaneous activity was significantly higher in the animals with tinnitus than in the control group.

Although hyperactivity does seem to have a relationship with tinnitus, we cannot rule out the possibility that hyperactivity may in some way contribute to hearing loss as well.

Comment 9: Could hearing loss play a role in the induction of hyperactivity?

Response: Hearing loss may be a trigger of hyperactivity and tinnitus. Approximately 80%–90% of people with tinnitus have hearing loss (for review, see Axelsson & Barrenas, 1992). Similarly, most of the animals that have been exposed to intense sound and later found to develop hyperactivity in the DCN also have shifted response thresholds (Kaltenbach et al., 1998; J. Zhang, Heffner, Koay, & Kaltenbach, 2004).
Moreover, the topographic pattern of hyperactivity correlates with the topographic pattern of neural response threshold shift (Kaltenbach & McCaslin, 1996). However, the onset time for the hyperactivity, at least following the most intense exposure conditions, was delayed relative to the onset of threshold shift. This delay suggests that hyperactivity develops secondarily as a result of either the hearing loss itself or the pathologies that lead to hearing loss.

Comment 10. What do you view as likely mechanisms by which noise exposure causes tinnitus-related hyperactivity in the DCN?

Response: One can hypothesize several mechanisms, one of which is described above in the “The DCN and Gaze-Evoked Tinnitus” section. For purposes of this discussion, we will assume that the hyperactivity originates from fusiform cells, one of the two principal cell types in the DCN, as suggested by recent studies (Brozoski et al., 2002; Finlayson & Kaltenbach, 2008; Shore et al., 2008). Loss of OHCs might cause a reduction of spontaneous activity of type II primary afferents, which would reduce input to granule cells or other interneurons in the cochlear nucleus. If granule cells are among the cell types that lose these inputs, granule cell spontaneous activity could be reduced, which would reduce input to DCN cartwheel cells and the apical dendrites of fusiform cells. Since there is evidence that the granule cell input to cartwheel cells dominates over that to the fusiform cells (Waller et al., 1996), loss of granule cell activity might be expected to have a net disinhibitory effect on fusiform cells, raising their levels of activity (Kaltenbach et al., 2002). This mechanism could explain the more rapid onset of tinnitus following exposure to moderate levels of sound (see response to Comment 2).

Overstimulation of OHCs might also cause excessive stimulation of the type II primary afferents, leading to excessive levels of activation of granule cells. This could lead to excessive release of glutamate at the granule cell-cartwheel cell synapse, resulting in excitotoxic injury of cartwheel cells. Again, the result could be a disinhibition of fusiform cells, leading to hyperactivity. Alternatively, the overactivation of granule cells could induce activity-dependent plasticity, such as long-term potentiation of fusiform cells or long-term depression of cartwheel cells, as recently suggested by Tzounopoulos (2008). Either of these mechanisms could cause a shift toward higher levels of spontaneous activity in the fusiform cell population.

If the damage involves loss of inner hair cells, then an additional layer of change would occur. Loss of inner hair cells is usually associated with degeneration of type I primary afferents and loss of axon terminals on cochlear nucleus neurons. Loss of primary afferents often triggers transneuronal degeneration of cochlear nucleus neurons (Morest et al., 1997). If inhibitory interneurons are among the cell types that undergo transneuronal degeneration, the vacant synaptic spaces on deafferented DCN neurons might be taken over by the sprouting of new excitatory synapses. The net effect of these changes would be disinhibition of fusiform cells. Evidence for loss of inhibitory neurotransmission and increases in excitatory neurotransmission in the DCN following loss of primary afferents has been reported previously (Asako, Holt, Griffith, Buras, & Altschuler, 2005; Jin & Godfrey, 2006; Potashner, Suneja, & Benson, 2000; Suneja, Potashner, & Benson, 1998).

Another mechanism might be mediated by loss of stimulus-driven activity, without necessarily involving loss of primary afferents. This idea is invoked in the homeostatic plasticity model described by Schaepte and Kempter (2006, 2008). Reduction of normal primary afferent drive caused by cochlear hair cell damage might trigger compensatory adjustments in the level of activity of one or more neuronal populations within the DCN. This could be mediated by changes in receptor expression or in the intrinsic membrane properties of neurons. The model also allows for changes in sensitivity to descending inputs, such as those arising from branches of the olivocochlear bundle.

Comment 11. There are a number of factors that could lead to increases in multiunit activity, such as you show in the traces of Figure 2. For example, increased multiunit activity could reflect increases in single unit discharge rate, increases in spike amplitude, spike bursts, or neural synchrony. Some of these types of changes have been observed in the auditory system of animals treated with other tinnitus-inducing agents, such as salicylate or quinine (G.-D. Chen & Jastreboff, 1999; Eggermont & Roberts, 2004). Can you say at this point which of these accounts for the increase in activity following noise exposure?

Response. We have conducted a single unit study to address this question. Our results suggest that the increase in multiunit activity is partly a reflection of increased single unit discharge rate, but most of the increase in discharge rate is due to an increase in the incidence of spike bursts. Both of these changes probably increase the temporal overlap of spikes from different neurons (increased neural synchrony), leading to the large increases in multiunit activity that we observe. These results are the subject of a manuscript that has been submitted for publication (Finlayson & Kaltenbach, 2008).

References

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Received November 17, 2007
Accepted September 16, 2008
DOI: 10.1044/1059-0889(2008/08-0004)

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Appendix
Parallels Between DCN Hyperactivity and Psychoacoustic Features of Tinnitus

<table>
<thead>
<tr>
<th>DCN hyperactivity</th>
<th>Tinnitus</th>
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<tbody>
<tr>
<td>Hyperactivity has a tonotopic profile similar to that of a high-frequency band of noise.</td>
<td>The spectrum of tinnitus resembles that of a high-frequency band of noise (Norena et al., 2002).</td>
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<tr>
<td>Peak hyperactivity occurs at a frequency locus that is higher than that of the exposure tone (Kaltenbach &amp; Afman, 2000).</td>
<td>The pitch of tone-induced tinnitus is matched to a frequency that is higher than that of the exposure tone (Atherley et al., 1968; Loeb &amp; Smith, 1967).</td>
</tr>
<tr>
<td>The tonotopic profile of hyperactivity corresponds to the tonotopic profile of neural response threshold shift (Kaltenbach &amp; McGaslin, 1996).</td>
<td>The spectrum of tinnitus corresponds to the spectrum of the associated hearing loss (Norena et al., 2002).</td>
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