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Research paper

The dorsal cochlear nucleus as a participant in the auditory, attentional and emotional components of tinnitus

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Abstract

The dorsal cochlear nucleus (DCN) has been modeled in numerous studies as a possible source of tinnitus-generating signals. This hypothesis was originally developed on the basis of evidence that the DCN becomes hyperactive following exposure to intense noise. Since these early observations, evidence that the DCN is an important contributor to tinnitus has grown considerably. In this paper, the available evidence to date will be summarized. In addition, the DCN hypothesis of tinnitus can now be expanded to include possible involvement in other, non-auditory components of tinnitus. It will be shown by way of literature review that the DCN has direct connections with non-auditory brainstem structures, such as the locus coeruleus, reticular formation and raphe nuclei, that are implicated in the control of attention and emotional responses. The hypothesis will be presented that attentional and emotional disorders, such as anxiety and depression, which are commonly associated with tinnitus, may result from an interplay between these non-auditory brainstem structures and the DCN. Implicit in this hypothesis is that attempts to develop effective anti-tinnitus therapies are likely to benefit from a greater understanding of how the levels of activity in the DCN are influenced by different states of activation of these non-auditory brainstem structures and vice versa.

Keywords: Tinnitus; Dorsal cochlear nucleus; Attention; Anxiety; Depression; Raphe nucleus; Locus coeruleus; Reticular formation

1. Introduction

Numerous studies have shown that tinnitus often has a central rather than a peripheral origin. The most direct evidence for this are clinical studies showing that tinnitus frequently persists following transection of the auditory nerve ipsilateral to the tinnitus. The percentage of patients not experiencing relief from tinnitus after eighth nerve section ranges across studies from 38% to 85% (House and Brackman, 1981; Dandy, 1941; Silverstein, 1976; Gardner, 1984). Tinnitus can also develop secondarily as a result of eighth nerve sections. Berliner et al. (1992) reported that approximately half of non-tinnitus patients who undergo surgical section of the auditory nerve for treatment of eighth nerve tumors develop tinnitus post-operatively. Moreover, tinnitus can develop as a result of vascular compression of the eighth nerve (Jannetta et al., 1986; Moller et al., 1993), and surgical nerve decompression in patients with this form of tinnitus can produce improvements in tinnitus (Moller et al., 1993). These findings emphasize the importance of the central auditory system as a source of tinnitus-generating signals.

But, where in the central auditory system does tinnitus begin? For much of the past decade, numerous investigations have explored the role of the dorsal cochlear nucleus (DCN) as a possible source of tinnitus-producing signals. Excessive exposure to intense sound was found to cause spontaneous activity in the DCN to increase dramatically (Kaltenbach and McCaslin, 1996; Kaltenbach et al., 1998; Zhang and Kaltenbach, 1998; Kaltenbach and Afman, 2000; Brozoski et al., 2002). This led to the hypothesis that DCN hyperactivity might be an important neural correlate

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of tinnitus. Subsequent studies showed that hyperactivity can be induced in the DCN by another tinnitus-inducing agent, cisplatin (Melamed et al., 2000; Kaltenbach et al., 2002). The studies with cisplatin have been especially helpful in revealing an important mechanism that triggers hyperactivity in the DCN. Cisplatin can selectively destroy cochlear outer hair cells (OHCs) without damaging inner hair cells. In animals with cisplatin-induced OHC lesions, a strong correlation was found between the level of hyperactivity in the DCN and the amount of OHC loss (Kaltenbach et al., 2002). However, subsequent studies have made it clear that hyperactivity in the DCN can also be triggered by other mechanisms. For example, hyperactivity can develop following exposures that are below the threshold of hair cell loss (Kaltenbach et al., 2005). Indeed, acoustic insults and other causes of inner ear injury have been shown to produce a wide range of changes in the cochlear nuclear complex. Chief among these are fiber degeneration (Morest and Bohne, 1983; Kim et al., 1997), axonal sprouting (Bilak et al., 1997; Kim et al., 2004), down-regulations of inhibitory neurotransmitter receptors (Caspary et al., 2005), and changes in neurotransmitter release and reuptake (Potashner et al., 1997, 2000; Milbrandt and Caspary, 1995; Suneja et al., 1998a,b). All of these changes affect the balance of excitatory and inhibitory inputs to DCN neurons, and are therefore likely to contribute to the development of hyperactivity.

Is tinnitus related to the observed changes in DCN activity? There are multiple lines of evidence supporting the view that changes in activity in the DCN are important in the pathogenesis of tinnitus. The purpose of Section 1.1 of this paper is to summarize this evidence. But, the connection of the DCN to tinnitus may be much broader. Tinnitus begins as an auditory disorder, but in its clinically significant form, has two other important components. The persistent auditory percept is often associated with *attentional* problems: the tinnitus becomes the focus of too much attention and sufferers often have difficulties concentrating (Jacobson et al., 1996; Cuny et al., 2004; Newman et al., 1997; Tyler and Baker, 1983; Sanchez and Stephens, 1997). The percept(s) of tinnitus can also have undesirable *emotional* components such as persistent annoyance, frustration, anger, anxiety, and depression. These attentional and emotional disturbances are the aspects of tinnitus that affect sleep patterns and ultimately have the most impact on quality of life. If changes in DCN activity and tinnitus are related, then it should be possible to find relationships between the DCN and other areas of the brain that are involved directly in the etiology of attentional and emotional disturbances. In this paper, such relationships are explored. It will be shown through an extensive review of the literature that areas of the brain subserving the early stages of attentional control and emotional arousal have direct connections with the DCN and can both influence and be affected by the levels of spontaneous activity in the DCN. Sections 1.2 and 1.3 will review the evidence demonstrating these connections and present the hypotheses that they may work in conjunction with the DCN to contribute to the attentional and affective components of tinnitus.

1.1. The DCN and the auditory component of tinnitus

Over the past decade, there has been a growing body of evidence that the DCN may be a site of generation of signals that contribute to the auditory percepts of tinnitus. This evidence comes from a combination of neurophysiological, clinical, and behavioral observations, and is summarized as follows:

(1) Electrical stimulation of the DCN results in changes in the loudness of tinnitus. This effect has been demonstrated by a study conducted in human patients who had received auditory brainstem implants following surgical removal of vestibular Schwannomas (Soussi and Otto, 1994). In each patient, a stimulus electrode (auditory brainstem implant) was placed on the surface of the DCN. The effects of electrical stimulation were examined in 10 subjects, 7 of whom used their implants daily and were tested after several weeks of electrode use. Three others did not use the implants daily, but were tested in the laboratory. Of the 7 that used their implants regularly, 6 reported reductions in the loudness of tinnitus, and 1 reported no change in tinnitus loudness. Of the three tested in the laboratory, 1 reported a reduction in tinnitus loudness during stimulation, 1 reported an increase in loudness, and 1 reported no effect. Thus, of the 10 subjects examined, 8 reported changes in the loudness of their tinnitus with DCN stimulation. There was no evidence that stimulation of the DCN resulted in residual inhibition of tinnitus in any of these patients. These results may indicate that the changes in tinnitus loudness caused by DCN stimulation probably are not the result of simultaneous masking, since simultaneous masking usually produces residual inhibition (Terry et al., 1983; Vernon and Schleuning, 1978; Henry and Meikle, 2000).

(2) Spontaneous neural activity in the DCN of hamsters becomes dramatically elevated after the animals are exposed to intense sound (Kaltenbach and McCaslin, 1996; Zhang and Kaltenbach, 1998). This condition of hyperactivity resembles activity that is elevated during sound stimulation and therefore seems a likely candidate for a tinnitus-producing signal. Sound-induced hyperactivity has now been observed in numerous other species including rats (Zhang and Kaltenbach, 1998), chinchillas (Brozoski et al., 2002), guinea pigs (Imig and Durham, 2005) and mice (Kaltenbach et al., 2001). Hyperactivity has been induced in the DCN following prolonged exposure to both moderate and intense sounds, has been observed at both the single and multiunit levels (Kaltenbach et al., 1998; Kaltenbach et al., 2000; Brozoski et al., 2002), and is not the result of increased activity in the auditory nerve (Zacharek et al., 2002; Liberman and Dodds, 1984). Exposure conditions effective in causing this hyperactivity range from 80 dB to more than 125 dB and can consist of pure tones or bands of noise (Brozoski et al., 2002; Kaltenbach et al., 2000). The

onset time appears to be variable, depending on the exposure conditions. Very high intensity exposure causes hyperactivity with a delayed onset (Kaltenbach et al., 2000), whereas more moderate level exposures induce hyperactivity with a rapid onset (Kaltenbach et al., 2005). The latter finding is in line with psychophysical studies demonstrating that tinnitus develops more or less immediately after moderate level tone or noise exposure (Atherley et al., 1968; Loeb and Smith, 1967; George and Kemp, 1989).

(3) Noise-induced hyperactivity displays a tonotopic profile similar to that of stimulus-driven activity. The activity is characterized by an increase in the amplitude of multiunit field potentials and an increase in the frequency of those potentials. Plots of activity vs. distance along the tonotopic axis yield activity profiles resembling those for high frequency, tonal stimulation. Both show peaks in the middle of the DCN that roll off toward normal spontaneous rates in the high and low frequency regions of the DCN. However, two important differences should be emphasized. First, the profile of activity induced by intense sound exposure rolls off gradually toward the high and low frequency directions whereas the peak evoked by tonal stimulation is sharp and narrow. This finding is in agreement with psychophysical evidence that tinnitus is usually matched to a band of noise rather than a tone (Penner, 1983; Norena et al., 2002). Second, unlike the peak of tone-evoked activity, the peak of hyperactivity induced by intense tone exposure occurs at a higher frequency locus than that representing the exposure tone frequency. This result is expected of a tinnitus-related signal, because the pitch of tinnitus after tone exposure is more commonly matched to frequencies higher than that of the exposure tone than to lower frequencies (Atherley et al., 1968; Loeb and Smith, 1967).

(4) Exposure conditions causing the DCN to become hyperactive also cause animals to develop tinnitus (Heffner and Harrington, 2002; Brozoski et al., 2002). This correlation has been observed in different laboratories using different behavioral methods for testing animals for tinnitus. In one of these studies, animals tested for tinnitus after intense sound exposure were later studied electrophysiologically, and the strength of the relationship between DCN hyperactivity and tinnitus was tested. The results of this analysis demonstrated a moderate and significant correlation between the strength of the behavioral evidence for tinnitus and the magnitude of activity in the DCN (Kaltenbach et al., 2004).

(5) Tinnitus can be modulated by manipulations of somatosensory structures which are known to cause changes in the level of activity in the DCN. In humans, clenching of the jaws or contracting certain muscles of the neck, can cause changes in tinnitus percepts, the most common being increases or decreases in its loudness (Levine, 1999; Levine et al., 2003; Lockwood et al., 1998). This phenomenon, referred to as 'somatic tinnitus' (Levine, 1999) would seem to require the operation of circuits that integrate auditory with somatosensory inputs. Anatomical studies show that the DCN receives direct input from both auditory and somatosensory systems (Weinberg and Rustioni, 1987; Itoh et al., 1987; Shore et al., 2000; Wright and Ryugo, 1996; Zhou and Shore, 2004). Moreover, spontaneous activity in the DCN can be modulated by stimulating peripheral nerves from the head and neck muscles, especially the 2nd cervical nerve, trigeminal nerve or ganglion, or by stimulating medullary somatosensory nuclei (Kanold and Young, 2001; Young et al., 1995; Shore, 2005, 2004). All of these structures provide either direct or indirect input to the DCN and are likely substrates for the observed changes in DCN activity and, perhaps also, the modulation of tinnitus percepts.

(6) Another possible form of tinnitus which may have neural underpinnings in the DCN is gaze-evoked tinnitus. This is a form of tinnitus that sometimes develops following surgical injury to the eighth nerve. The condition is characterized by the induction of a form of tinnitus that is induced when the angle of gaze is changed (Whittaker, 1983; House, 1982; Cacace et al., 1994). The onset of this condition can vary from 1 day to several months following eighth nerve injury (Coad et al., 2001). A possible role of the DCN in this form of tinnitus is raised by earlier studies showing that (a) the granule cells, which modulate the activity of DCN fusiform cells, receive input from Roller's nucleus, a structure that is involved in the control of eye gaze (McCrea et al., 1987), and (b) the direction of eye orientation during the paradoxical phase of sleep causes changes in the level of multiunit activity in the DCN (Mori et al., 1972).

(7) Tinnitus displays several forms of plasticity, and each form is paralleled by related forms of neural plasticity in the DCN. These parallels were reviewed in detail in a recent publication (Kaltenbach et al., 2005). Three examples will be summarized briefly here. (A) Tinnitus exhibits *temporal plasticity*, apparent as changes in its loudness and pitch over time (Tyler and Conrad-Armes, 1983; Penner, 1983). Such changes are quite common. For example, Meikle and Greist (1991) found that 80% of 519 patients questioned in the tinnitus clinic at the Oregon Health and Science University experienced either increases or fluctuations in the loudness of their tinnitus over time. This suggests that temporal changes may occur in the magnitude and tonotopic location of the tinnitus-producing signal. Experiments examining the profiles of activity in the DCN after intense sound exposure are consistent with this prediction. Both the level of hyperactivity in the DCN and the location along the tonotopic axis where hyperactivity reached its peak were found to shift over time (Kaltenbach et al., 2000). (B) Tinnitus often develops secondarily after injury to the cochlea or auditory nerve. A good example of this *injury-induced plasticity* is tinnitus resulting from microvascular compression of the eighth nerve. Patients with this condition develop tinnitus, and the tinnitus can disappear gradually following surgical decompression of the nerve (Moller, 1991; Moller et al., 1993). Damage to the cochlea or auditory nerve also induces hyperactivity in the DCN as well as a number of

anatomical and chemical changes that affect the balance of excitatory and inhibitory inputs to DCN neurons (Kaltenbach et al., 2002; Kim et al., 1997, 2004; Potashner et al., 1997, 2000; Milbrandt and Caspary, 1995; Suneja et al., 1998a,b). (C) Tinnitus usually displays the property of *activity-dependent plasticity*. For example, tinnitus is often transiently suppressed following offset of an acoustic stimulus, such as a noise masker, a phenomenon referred to as *residual inhibition* (Vernon and Schleuning, 1978; Terry et al., 1983; Goldstein et al., 2001). The duration of the suppression effect usually lasts for seconds to minutes, although durations of several weeks have occasionally been reported. A possible correlate of this form of plasticity is activity-dependent plasticity of DCN neurons. DCN neurons exhibit the property of short and long-term potentiation and long-term depression whereby the currents across the cell membrane can be transiently increased or decreased for extended periods. Short term depression lasts from less than a second to minutes, while long term depression lasts from days to weeks (Fujino and Oertel, 2003; Tzounopoulos et al., 2004).

1.2. The DCN and the attentional component of tinnitus

1.2.1. Attention-targeted and untargeted tinnitus percepts

Hearing, like other sensory modalities, consists of percepts that fall into a hierarchy of awareness levels. At the top of this hierarchy are percepts that are the focus of attention. At the bottom are percepts that lie in the periphery of attention. A person driving a car might be focused on the news broadcast coming from the radio, whereas the sound produced by the car's friction on the road are normally in the periphery of attention. Auditory percepts are thus organized by the brain along a continuous spectrum ranging from high priority, attention-targeted percepts and low priority attention-untargeted percepts.

Tinnitus is a good example of a percept that alternates between opposite ends of this continuum. Tinnitus is sometimes the focus of attention while at other times it exists in the periphery of attention (Jastreboff and Hazell, 2004). The tinnitus becomes severely troubling only on certain days or at certain times of day, such as when in the quiet, when stressed, when physically exhausted, when lying awake at night, or when other sounds interact with the tinnitus to produce an even more annoying 'hybrid' sound (Stouffer et al., 1991). Alternations between the targeted and untargeted states of tinnitus are thus common. Such alternations may arise from the following factors. (1) The severity of tinnitus may increase during periods of stress or anxiety. This may be because stress decreases one's tolerance of unwanted sound or may increase ones level of arousal, which could, in turn, increase the level of tinnitus-producing activity. (3) Tinnitus can become more noticeable in quiet environments when there are no other sounds that compete or mask the tinnitus. Both factors probably influence the level of priority tinnitus assumes in the hierarchy of attention. Many of the available treatment strategies for tinnitus are aimed at reducing the amount of attention the tinnitus percept receives. An example of a management strategy which embodies this approach is *tinnitus retraining therapy* (Jastreboff and Hazell, 2004).

1.2.2. Brainstem and cortical contributions to attentional functions

Questions of considerable interest are what the neural correlates are of these different states of tinnitus perception, and what regions of the brain underlie percepts in their targeted and untargeted states. This issue is important in the context of the present discussion because clinically significant tinnitus has been found to be associated with abnormalities in auditory attentional focus (hyper-attentiveness) (Jacobson et al., 1996; Newman et al., 1997) and with difficulties with attentional control (Cuny et al., 2004) or concentration (Tyler and Baker, 1983; Sanchez and Stephens, 1997). In addition, attentional problems associated with tinnitus are further implicated as factors that can worsen the emotional impact of tinnitus (Jacobson et al., 1996; Tyler and Baker, 1983).

Insight into these questions can be obtained from previous studies of the areas of the brain implicated in auditory attentional functions. Auditory cortical areas AI and AII probably have important roles in auditory attention. This is suggested by studies in humans (Sokolov et al., 2004) and cats (Lakatos et al., 2004) which have shown that enhancements of spontaneous gamma bursting activity (20–80 Hz) occur in the auditory cortex when attention is shifted from non-auditory to auditory stimuli. Focusing attention on auditory stimuli has also been found to result in increased levels of activation of the primary and secondary auditory cortices in humans using fMRI (Grady et al., 1997; Jancke et al., 1999) and whole-head neuromagnetometry (Fujiwara et al., 1998). But, auditory attention also has subcortical components. Children born with hydranencephaly, a condition that can result in a nearly complete failure of both cerebral hemispheres to develop, show severe attentional deficits but nonetheless retain a surprising degree of auditory attentional function. Hydranencephalics can display normal auditory evoked responses and can orient to sounds by shifts in head or eye position; some can even respond to music with emotional reactions (smiling) and mimic certain vocal sounds (Shewmon et al., 1999). Such cases demonstrate the adequacy of brainstem structures for the execution of simple auditory oriented behavior and simple emotional responses.

People who have experienced bilateral infarctions of the auditory regions of the temporal lobe and thalamus also attest to the importance of brainstem structures in the mediation of auditory attention. Patients with such lesions typically develop a condition known as cortical deafness. This condition is characterized by a loss of the ability to attend to and interpret the complex dimensions of auditory stimuli (Tanaka et al., 1991; Kazui et al., 1990; Taniwaki et al., 2000; Hood et al., 1994); however, the ability to discern simple features of sound, such as loudness and

acoustic texture, and the ability to feel and express certain basic emotional reactions to sound are often spared. Lower brainstem components of awareness and attention have also been demonstrated in animals. Cats retain the ability to learn to discriminate small changes in sound intensity or changes in sound arrival times at the two ears even after combined bilateral ablations of auditory cortex and inferior colliculi (Neff et al., 1975; Jane et al., 1965). Cats can also attend to auditory stimuli even after the trapezoid body has been transected or the auditory cortex has been ablated bilaterally; however this ability is lost if the dorsal part of the inferior colliculus has been ablated (Jane et al., 1965). Thus, attentional targeting required for detecting the presence of a sound, discriminating its simplest features (e.g., loudness and arrival times) and using them to orient to sounds and primitive emotional responses are, at least in part, functions of the lower auditory brainstem, whereas higher level attentional targeting required for sustained focusing of awareness and for extraction of complex associations are forebrain and probably, in large part, dependent on thalamo-cortical functions.

1.2.3. The DCN as a target or gate-keeper of attentional focusing mechanisms

There are anatomical, physiological and behavioral reasons to suggest that the DCN is an integral part of the brainstem circuits underlying auditory attentional targeting, particularly that aspect of targeting that manifests behaviorally as orientating to auditory stimuli. Connections between the DCN and at least three major structures implicated in attentional targeting have been identified. The auditory cortex, which participates in attentional focusing on auditory stimuli (Lakatos et al., 2004; Sokolov et al., 2004; Grady et al., 1997; Jancke et al., 1999; Fujiwara et al., 1998), sends corticofugal inputs to the granule cells, which, in turn, modulate activity of DCN fusiform cells (Waller et al., 1996; Manis, 1989; Jacomme et al., 2003). DCN fusiform cells receive inputs from noradrenergic neurons in the locus coeruleus (LC) (Thompson and Thompson, 2001; Thompson et al., 1995; Jones and Yang, 1985). There is substantial evidence that the LC plays a role in promoting selective attention and orientation to sensory stimuli (Aston-Jones et al., 1999; Aston-Jones and Bloom, 1981; Foote et al., 1980; Rajkowski et al., 1994). DCN neurons also receive input from and project to gigantocellular neurons in the caudal pontine reticular nucleus, which has been shown to play a role in acoustic startle (Koch et al., 1992; Lingenhohl and Friauf, 1994) and attention (Pragay et al., 1978; Kinomura et al., 1996). Stimulation of the LC causes changes in the level of activity in the DCN (Chikamori et al., 1980; Gonzalez-Lima and Scheich, 1984), and stimulation of the DCN produces EPSPs in gigantocellular neurons in the pontine reticular nucleus (Lingenhohl and Friauf, 1994). These results support the view that the DCN both informs and responds to structures directly involved in attention, arousal and startle.

Behavioral manifestations of the early stages of auditory attention focusing include alerting the animal to the presence of a sound followed by the directing of the head, eyes and pinnae toward the sound source. Auditory stimuli that are potentially more threatening can elicit the acoustic startle reflex. Evidence suggesting that the DCN may be involved in orientation of the head and/or pinnae to the direction of a sound source has been presented and discussed in several recent papers (Kanold and Young, 2001; Oertel and Young, 2004; Ryugo et al., 2003). The level of activity of fusiform cells is strongly affected by stretching the muscles of the pinnae (Kanold and Young, 2001). Stimulation of the cervical nerve roots, especially C2, which innervates muscles involved in the control of pinna and head orientation, causes changes in the level of fusiform cell discharge rates (Kanold and Young, 2001). This effect is probably mediated by the activation of the granule cell-cartwheel cell path via the cuneate nucleus (Davis et al., 1996). Transecting the dorsal acoustic stria, which carries the ascending axons of DCN fusiform and giant cells, causes deficits in orientation of the head and pinnae to sounds, particularly those varied in elevation (Sutherland et al., 1998a,b; May, 2000).

Previous work provides reason to suspect that the DCN might also be involved in the orientation of the eyes to sound sources. Granule cells of the cochlear nucleus, which modulate fusiform cell activity, receive input from Roller's nucleus, a structure which is involved in the control of eye movements (McCrea et al., 1987). Although no study has yet examined fusiform cell activity during eye movements in awake animals, a study in sleeping animals showed that changes in eye position during paradoxical sleep are synchronized to changes in multiunit activity in the DCN (Mori et al., 1972). Perhaps the DCN has a role in the control of eye gaze which is part of a broader attention-targeting program that orchestrates the orientation of head, pinnae and eyes to auditory stimuli of interest. A more direct role of the DCN in attentional targeting is suggested by an early study showing changes in the level of multiunit activity in the DCN of cats when their attention was shifted from auditory to non-auditory stimuli (Hernandez-Peon et al., 1956).

These findings, when considered together, converge on the hypothesis that the DCN is involved in the process of attentional targeting and/or 'gate-keeping'. Because the DCN is both a recipient and a source of projections to and from areas implicated in attentional control, its role in attentional processes may to inform and receive feedback from areas that direct attention. The DCN may thus be a structure that areas of the brain concerned with attention 'listen to' to determine whether the head, eyes, and ears are properly oriented to an auditory signal of interest. The attractiveness of this model is that it provides a basis for explaining why tinnitus often has a strong attentional component.

1.3. The DCN and the emotional components of tinnitus

Clinically significant tinnitus often has one or more strong emotional components. While most subjects tolerate their tinnitus quite well, when attended to, the sound can nonetheless be perceived as an unwelcome intrusion. In more severe cases, the tinnitus is perceived as an ongoing source of annoyance that can interfere with sleep and lifestyle. The most severe tinnitus is associated with more serious emotional disorders such as anxiety and/or depression (Dobie, 2003; Erlandsson, 2000; Tyler and Baker, 1983; Andersson, 2002). A few clinical studies have found a significant correlation between the severity of tinnitus and the severity of anxiety or depression (Folmer et al., 1999; Halford and Andersson, 1991; McKenna et al., 1991; Robinson et al., 2003). In a recent review of the literature, found that the reported incidence of mood or anxiety disorders in tinnitus patients has varied across studies from 15% to 70%; they concluded that anxiety and depression are more prevalent in patients with tinnitus than in the general population, that the concurrence of these disorders with tinnitus may increase the level of the auditory impairment, and that treatment directed toward depression and anxiety may lead to improvement in the quality of life.

The cause and effect relationship between tinnitus and these emotional disturbances is unclear. It has been suggested that psychological disorders are a cause of tinnitus (Holgers, 2003). Pre-existing anxiety or depression might produce stressors that exacerbate or worsen tinnitus. A more common view is that tinnitus may be a cause of anxiety or depression. Subjects may perceive the presence of a persistent, unwanted sound as potentially threatening or dangerous, which could secondarily trigger anxiety reactions. Difficulty steering attention away from the tinnitus percept might trigger anxiety responses. Given these considerations, it is evident that an understanding of tinnitus as a clinical problem will not be complete without an understanding of mechanisms underlying its emotional manifestations. This section examines some possible interactions between the DCN and other brainstem structures that might contribute to the emotional components of tinnitus.

1.3.1. Cortical and brainstem contributions to emotional responses

In much of the classical literature emotional states are viewed as the domain of the limbic system while the behavioral expressions of these states ('fight or flight' responses) are the domain of the autonomic nervous systems. The limbic system includes forebrain structures such as the hippocampus, amygdala, hypothalamus, fimbria, fornix, mammillary bodies, and cingulate cortex. Attempts to image regions of the brain that are active in patients with tinnitus have sometimes revealed areas of hyperactivity in some limbic regions of the brain (Shulman et al., 1995, 1996; Lockwood et al., 1998). However, the limbic response to tinnitus, like other emotional responses, may have important subcortical origins. Along these lines, the brainstem reticular core and nearby structures such as the LC and raphe nucleus, have been modeled as the subcortical drivers of limbic and autonomic responses. Certain emotional disorders, such as anxiety and depression are known to have important components at medullary, pontine and midbrain levels of the brainstem. Some brainstem structures mediating arousal and attentional targeting (LC, reticular formation, raphe nucleus) also play roles in the generation of anxiety and depression. A brainstem structure strongly implicated in anxiety reactions is the LC (Redmond and Huang, 1979; Pohl et al., 1987; Tanaka et al., 2000). Electrical stimulation of the LC or drugs that increase LC activity induce anxiety and fear in humans (Nashold et al., 1977; Holmberg and Gershon, 1961) and monkeys (Redmond et al., 1977), whereas drugs that reduce LC firing diminish anxiety (Tanaka et al., 2000).

Anxiety as a trigger of tinnitus. The projection of noradrenergic neurons from the LC to the DCN provides a potential anatomical link between tinnitus generating mechanisms and mechanisms underlying stress and anxiety (Kromer and Moore, 1980; Jones and Yang, 1985). Since some forms of anxiety arise, in part, from increases in the level of activity in the LC (Tanaka et al., 2000), and since fusiform cells are among the targets of LC efferent projections (Kromer and Moore, 1980), a condition of hyperactivity in the LC might be expected to result in a facilitatory effect on DCN fusiform cells. This could contribute to a condition of DCN hyperactivity that could lead to the induction of tinnitus; if the DCN is already generating tinnitus signals, then increases in LC activity could cause a worsening of tinnitus. This could account for why changes in stress or arousal sometimes produce changes in tinnitus percepts. Evidence supporting an excitatory effect of LC neurons on DCN neurons has been published previously (Ebert, 1996).

Tinnitus as a trigger of anxiety. A possible circuit mediating this cause and effect relationship may involve connections among the DCN, the reticular formation and the LC. The available evidence suggests that neurons in the DCN send projections to two subdivisions of the reticular formation, including the caudal pontine reticular nucleus, and the lateral paragigantocellular nucleus (Lingenhohl and Friauf, 1994; Kandler and Herbert, 1991; Bellintani-Guardia et al., 1996). Both of these structures also receive input from cochlear root neurons which participate in the acoustic startle reflex (Lopez et al., 1999; Sinex et al., 2001). The lateral paragigangtocellular nucleus is one of the main sources of input to the LC (Aston-Jones et al., 1986). This input exerts an excitatory effect on LC neurons (Aston-Jones et al., 1986; Ennis and Aston-Jones, 1988; Van Bockstaele et al., 1998; Guyenet and Young, 1987). If hyperactivity in the DCN is relayed to the lateral paragigantocellular nucleus, then paragigantocellular cells might become hyperactive, which could, in turn, cause increases in LC activation. This pathway could therefore provide a route by which hyperactivity in the DCN could contribute to anxiety responses to tinnitus.

Tinnitus and depression. As yet, no anatomical or physiological circuits have been invoked to explain the link between tinnitus and depression. Some models of mood disorders have implicated the raphe nuclei in the etiology of depression. These are mostly unpaired nuclei that lie along the midline and are distributed at different locations along the brainstem from the lower medulla to the rostral midbrain. A large proportion of neurons in this complex are serotonergic. Many, if not most, antidepressant drugs (e.g., the tricyclics and selective serotonin reuptake inhibitors (SSRIs)), are believed to work by increasing the level of serotonin in the brain. The dorsal raphe nucleus is a primary source of sertotonergic inputs to brain regions implicated in the pathology of depression (Imai et al., 1986; Ma et al., 1991; Vertes, 1991; Kazakov et al., 1993). The number of neurons in the raphe nuclei are reduced in patients with unipolar and bipolar mood disorders (Baumann and Bogerts, 2001). Some antidepressant drugs, when used to treat depression, also sometimes have an effect on tinnitus (Folmer and Shi, 2004; Folmer et al., 1999).

It is possible that the DCN may be involved in the dual effect of antidepressants on depression and tinnitus. Serotonergic neurons in the dorsal raphe nucleus project to all three subdivisions of the cochlear nucleus (Thompson and Thompson, 2001; Klepper and Herbert, 1991; Thompson et al., 1995; Thompson and Thompson, 2001). Serotonin administered iontophoretically to the CN produces both excitatory and inhibitory effects on spontaneous and sound-evoked discharge rates of CN neurons (Ebert and Ostwald, 1992). The DCN receives a disproportionately larger share of serotonergic inputs from the dorsal raphe nucleus than either the AVCN or PVCN (Klepper and Herbert, 1991; Thompson and Thompson, 2001). The majority of these projections are found in the molecular and fusiform cell layers of the DCN. However, the influence of dorsal raphe neurons on the DCN may be greater since additional serotonergic inputs are found in the granule cell region, which provides input to DCN fusiform cells. The common association between tinnitus and depression may thus reflect disturbances in serotonergic systems of the dorsal raphe nucleus. Interestingly, exposure to noise causes plastic up-regulations in serotonergic inputs to the DCN (Cransac et al., 1998), the degree of up-regulation increasing with the level of exposure up to at least 110 dB SPL. This finding raises the possibility that noise-induced effects on raphe inputs to DCN may contribute to the hyperactivity that develops in the DCN after noise exposure. How this relates to the presence of depression, which is usually thought to be associated with decreased serotonin, remains to be clarified.

2. Implications

From the preceding discussion, it is apparent that the DCN possesses numerous characteristics expected of a structure involved in the pathology of tinnitus. The hyperactivity that develops in the DCN following exposure to tinnitus inducing agents provides a cohesive model for understanding how tinnitus might emerge after injury to or overstimulation of peripheral auditory input. The integration of inputs from auditory and somatosensory systems that occurs in the DCN provides a basis for understanding somatic modulations of tinnitus, and its input from a nucleus that is involved in eye gaze and the fact that DCN activity changes when eyes move during paradoxical sleep suggest that circuits exist which, under conditions of injury and plasticity, could explain the modulation of tinnitus by changes in the angle of gaze. These findings all point to the DCN as being important for the generation and modulation of tinnitus. Of course, one cannot be sure that the DCN of humans is identical to that of laboratory animal species on which much of the data described above are based. Although the human DCN is well-developed and has most of the same cell types that have been observed in the cat and rat, the available evidence does suggest that the human DCN contains far fewer granule cells and a thinner molecular layer relative to that of cats and rats. On the other hand, this does not mean that the human DCN should be considered to be completely lacking circuitry similar to that of the DCN of other species. Rather, it seems more likely that descending pathways terminating on granule cells in laboratory species either have a relatively weaker influence in the human DCN or exert their effects on cell types in the human DCN other than granule cells. Physiological studies of the human DCN are needed to test these possibilities. The study demonstrating that electrical stimulation of the DCN results in a modulation of tinnitus loudness is perhaps as close as we have come to probing the physiology of the human DCN.

If knowledge gained from animal studies is to serve as any guide to the functional role of the DCN in humans, then we have reason to suspect that the DCN's role in tinnitus may be much broader than has been previously hypothesized. As discussed above, the DCN of animals has direct connections with structures implicated in the control of auditory alerting and attentional control. There is some basis for hypothesizing that an interplay between the DCN and the attentional control pathways, particularly the LC, could contribute to some of the attentional problems associated with tinnitus. The condition of hyper-attentiveness to the tinnitus percept or difficulties concentrating that commonly afflict tinnitus patients may have their origins in circuits involving these connections. The DCN of most animals studied thus far also receives inputs from structures implicated in the generation of mood and anxiety disorders. Findings from physiological and pharmacological studies provide a basis for understanding why tinnitus is often seen in association with anxiety or depression. Discussions of the DCN's involvement in the pathological symptoms of tinnitus can thus be expanded to include roles not only in the auditory component of tinnitus, but also the attentional and emotional components.

This point of view is not intended to imply that the DCN is the only structure contributing to these functions. Forebrain structures are probably also important contributors to the various components of tinnitus. Indeed, hyperactivity at any level in the auditory system could, in theory, lead to the generation of tinnitus percepts, as has been suggested previously (Evans and Borerwe, 1982; Jastreboff and Sasaki, 1986; Moller, 1984, 1995; Moller et al., 1992; Salvi and Ahroon, 1983; Salvi, 1976; Eggermont and Kenmochi, 1998; Eggermont and Sininger, 1995; Norena and Eggermont, 2003; Seki and Eggermont, 2003). Moreover, numerous other areas of the brain have polysensory or multimodal functions, and could contribute to somatic modulations of tinnitus. Brain areas other than those in the midbrain and medulla could contribute to the attentional and emotional sides of tinnitus. However, the fact that the DCN has so many of the key features needed to explain the generation, modulation and psychological associations of tinnitus makes the DCN model particularly compelling. Future studies will be necessary to determine the extent to which this combination of features in the DCN differs from other structures in the central auditory system. It will also be important to clarify the extent to which the DCN's circuitry in laboratory species on which this model of tinnitus has been based approximates the circuitry of the human DCN and its connections with other brain areas involved in attention and emotional responses to sound.

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