Available online at www.sciencedirect.com
SCIENCE DIRECT
Hearing Research 216–217 (2006) 224–234
Hearing Research
www.elsevier.com/locate/heares

Research paper

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

James A. Kaltenbach *

Department of Otolaryngology, Wayne State University School of Medicine, 5E-UHC, Detroit, MI 48201, United States

Received 4 December 2005; received in revised form 24 December 2005; accepted 2 January 2006
Available online 15 February 2006

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

* Tel.: +1 313 577 1257; fax: +1 313 577 0085.
E-mail address: jkalten@med.wayne.edu.

0378-5955/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2006.01.002

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