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BRAIN RESEARCH

Review

Understanding tinnitus: The dorsal cochlear nucleus, organization and plasticity

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ABSTRACT

Tinnitus, the perception of a phantom sound, is a common consequence of damage to the auditory periphery. A major goal of tinnitus research is to find the loci of the neural changes that underlie the disorder. Crucial to this endeavor has been the development of an animal behavioral model of tinnitus, so that neural changes can be correlated with behavioral evidence of tinnitus. Three major lines of evidence implicate the dorsal cochlear nucleus (DCN) in tinnitus. First, elevated spontaneous activity in the DCN is correlated with peripheral damage and tinnitus. Second, there are somatosensory inputs to the DCN that can modulate spontaneous activity and might mediate the somatic–auditory interactions seen in tinnitus patients. Third, we have found a subpopulation of DCN neurons in the adult rat that express doublecortin, a plasticity-related protein. The expression of this protein may reflect a role of these neurons in the neural reorganization causing tinnitus. However, there is a problem in extending the findings in the rodent DCN to humans. Classic studies state that the structure of the primate DCN is quite different from that of rodents, with primates lacking granule cells, the recipients of somatosensory input. To address the possibility of major species differences in DCN organization, we compared Nissl-stained sections of the DCN in five different species. In contrast to earlier reports, our data suggest that the organization of the primate DCN is not dramatically different from that of the rodents, and validate the use of animal data in the study of tinnitus.

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Contents

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1. Introduction

Tinnitus, the perception of a phantom sound, is a common correlate of damage to the auditory periphery, either to receptor cells or to neurons of the spiral ganglion. Damage can result from aging (Nicolas-Puel et al., 2002) or exposure to noise, the cancer drugs carboplatin and cisplatin (Ding et al., 1999; Godfrey et al., 2005; Hofstetter et al., 1997; Husain et al., 2001; Klis et al., 2002; Stengs et al., 1998), styrene (Chen et al., 2008) or other agents. Systemic administration of the drug salicylate can induce temporary tinnitus (Stolzberg et al., 2011; Sun et al., 2009; Wei et al., 2010; Yang et al., 2007). Tinnitus is thought to result from plastic reorganization in the central processing of auditory information triggered by these manipulations (reviews in Kaltenbach, 2011; Roberts et al., 2010; Wang et al., 2011). Many studies have sought to discover the loci and mechanisms of this reorganization, and to tease out which changes are simply correlates of peripheral damage and which are the critical determinants of tinnitus.

Discovery of the neural correlates of tinnitus must contend with a major obstacle in that tinnitus as a perception is most readily assessed in humans, but the investigation of neural mechanisms in humans is limited to imaging studies and relatively gross electrophysiological measures (review and references in Adjamian et al., 2009; Schaette and McAlpine, 2011). On the other hand, in animals it is relatively easy to assess the electrophysiological or neuroanatomical changes that follow peripheral auditory damage, but it is much more difficult to see how these changes relate to the perception of tinnitus. Several behavioral animal models of tinnitus have been devised to allow a more direct correlation of tinnitus and neural changes.

2. What is the neural basis of tinnitus?

Investigations of the neural correlates of tinnitus in animals have looked for electrophysiological, anatomical or neurochemical alterations subsequent to peripheral damage. Multiple sites along the auditory pathways have been implicated in tinnitus including the dorsal (DCN) and ventral (VCN) cochlear nuclei (Brozoski et al., 2002; Dehmel et al., 2012; Kaltenbach and Afman, 2000; Kaltenbach et al., 2000; Kaltenbach et al., 2002; Kraus et al., 2009; Middleton et al., 2011; Rachel et al., 2002; Wang et al., 2009; Wei et al., 2010; Zacharek et al., 2002), the inferior colliculus (Abbott et al., 1999; Bancroft et al., 1991; Basta and Ernest, 2004; Bauer et al., 2008; Burkard et al., 1997; Chen and Jastreboff, 1995; Dong et al., 2010; Jastreboff and Sasaki, 1986; Kazee et al., 1995; McFadden et al., 1998; Milbrandt et al., 2000; Salvi et al., 1990; Wang et al., 1996; Wang et al., 2002; Wang et al., 2008) and the auditory cortex (Liu et al., 2003; Lu et al., 2011; Mühlnickel et al., 1998; Ortmann et al., 2011; Stolzberg et al., 2011; Yang et al., 2007). More recently, neural changes correlated with hearing loss and tinnitus have been recognized in structures outside the classical auditory pathways, most notably the hippocampus and limbic system (Kraus et al., 2010; Leaver et al., 2011; Muhlau et al., 2006; Rauschecker et al., 2010). In this review, we will focus on the DCN as a possible site of tinnitus generation, since data from many studies suggest that the DCN undergoes neuroplastic reorganization following cochlear damage and that these changes correlate with behavioral evidence of tinnitus (Brozoski and Bauer, 2005; Brozoski et al., 2002; Dehmel et al., 2012; Jastreboff and Sasaki, 1994; Jastreboff et al., 1988; Kaltenbach, 2006a; Lobarinas et al., 2004; Turner et al., 2006; Yang et al., 2007). We will briefly summarize the anatomical organization of the DCN and then review the evidence for its role in tinnitus. We will then ask how applicable the results of these studies in rodents are to humans.

3. The DCN: laminar and cellular organization

The classic studies of DCN laminar and cellular organization were done in the cat (Brawer et al., 1974; Lorente de No, 1933; Osen, 1969). In that animal, the DCN is a distinctly laminar structure; the layers are easily recognized in Nissl sections. Laminar structure of the DCN is also seen in other animals used in auditory research. However, there are differences among authors regarding how many layers are recognized (3–5 in different studies, e.g. 4 layers in Hackney et al., 1990; Willard and Ryugo, 1983, mouse and guinea pig) and whether