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Review

Tinnitus in men, mice (as well as other rodents), and machines

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ABSTRACT

The phantom auditory sensation of tinnitus is now studied in humans, animals, and computer models, and our understanding of how tinnitus is triggered and which neural mechanisms give rise to the phantom sensation in the brain has increased considerably. In most cases, tinnitus is associated with hearing loss, and even tinnitus patients with normal hearing thresholds might have cochlear damage that is not detected through conventional audiometry, as has been recently shown through auditory brainstem response measurements. Animals show behavioural signs of tinnitus after induction of hearing loss, indicating a causal relation. Moreover, surgical reduction of hearing loss in otosclerosis can reduce or even abolish tinnitus. However, hearing loss does not always lead to tinnitus. Psychophysical measurements have indicated that certain types of cochlear damage might be more closely linked to tinnitus than others. Recent animal studies have used behavioural testing to distinguish between animals with and without tinnitus after noise exposure. Comparisons between these groups of animals have helped identify neural correlates of tinnitus as well as factors that could represent a predisposition for tinnitus. Human neuroimaging studies have also begun to separate the neural signature of tinnitus from other consequences of hearing loss. The functional mechanisms that could underlie tinnitus development tinnitus have been analysed in computational modelling studies, which indicate that tinnitus could be a side-effect of the brain's attempt to compensate for hearing loss. Even though causal treatments for tinnitus are currently not available, hearing aids can provide considerable benefit when used in conjunction with counselling, tinnitus retraining therapy or cognitive behavioural therapy. Finally, animal studies demonstrate that the development of chronic noise-induced tinnitus might be prevented through timely interventions after noise exposure.

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Tinnitus, the perception of a phantom sound in the absence of a corresponding acoustic stimulus, is one of the most frequent sensory disorders. It is estimated that 5–10% of the population perceive chronic tinnitus and that about 1% of the population suffer from severe tinnitus that substantially reduces their quality of life (Hoffman and Reed, 2004; Henry et al., 2005). In some cases, the tinnitus is objective, and the sound can be traced back to a physical generator within the body, like for example a blood vessel anomaly close to the ear that gives rise to a pulsating whooshing sound. The sound can then also be heard (objectified) by an external observer. However, in more than 90% of the cases, no physical sound source can be found and the percept is purely subjective. As "subjective tinnitus" is by far the most common case, the term "tinnitus" is usually just used as a short form for this condition. In this review, we will focus on subjective tinnitus and simply refer it as tinnitus. To understand how the phantom sound of tinnitus is generated has remained a challenging research topic. Research on tinnitus has intensified considerably in the past decade, and tinnitus has become a topic of neuroscience research since it is now known that tinnitus is generated in the brain and not in the ear (Eggermont and Roberts, 2004; Roberts et al., 2010). Research has consequently focussed on studying how tinnitus might emerge through plasticity and aberrant processing of information in the auditory brain.

1. Hearing loss and tinnitus

A major strand of research has been to investigate the relation between tinnitus and hearing loss. Tinnitus is associated with hearing loss in most patients (Axelsson and Ringdahl, 1989; Nicolas-Puel et al., 2002), and the prevalence of tinnitus rises with increasing hearing loss (Chung et al., 1984). Moreover, 75–90% of patients with otosclerosis experience tinnitus (Ayache et al., 2003; Sobrinho et al., 2004), as do 80% of patients with idiopathic

Abbreviations: ABR, auditory brainstem response; AN, auditory nerve; DCN, dorsal cochlear nucleus

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sudden sensorineural hearing loss (Nosrati-Zarenoe et al., 2007). Further indication for a relation between hearing loss and tinnitus comes from tinnitus pitch measurements, as tinnitus patients with sensorineural hearing loss usually match the pitch of their tinnitus sensation to frequencies where their hearing is impaired (Henry et al., 1999; Norena et al., 2002; König et al., 2006; Sereda et al., 2011) or to the audiogram edge (Moore and Vinay, 2010). Moreover, animal studies have demonstrated that the induction of hearing loss, for example through noise exposure, leads to behavioural signs of tinnitus (Brozoski et al., 2002; Heffner and Harrington, 2002; Kaltenbach et al., 2004; Turner et al., 2006; Engineer et al., 2011; Ahlf et al., 2012; Dehmel et al., 2012; Ruttiger et al., 2013), thus suggesting a causal relation between hearing loss and tinnitus.

However, about 10% of the tinnitus patients present with clinically normal hearing thresholds, i.e. with audiometric thresholds less than 20 dB HL for frequencies up to 8 kHz (Barnea et al., 1990; Sanchez et al., 2005), which has been interpreted as evidence that hearing loss might not be required for tinnitus to occur. This view has recently been contested by studies that examined the auditory brainstem response (ABR) of normal-hearing subjects with tinnitus and compared them to control groups matched for age, sex, and hearing thresholds (Schaette and McAlpine, 2011; Gu et al., 2012). It was found that the amplitudes of wave I of the ABR were significantly smaller in the tinnitus groups for high sound intensities [about 25% smaller at 90 and 100 dB SPL (Schaette and McAlpine, 2011), see also Fig. 1c; 40% smaller at 80 dB HL (Gu et al., 2012)], indicating that the auditory nerve (AN) was producing a signal of smaller magnitude. Studies in mice and guinea pigs have recently shown that deafferentation AN fibres can cause a reduction of the amplitudes of ABR wave I even when hearing thresholds are normal (Kujawa and Liberman, 2009; Furman et al., 2013), and that deafferentation seems to be selective for fibres with low spontaneous rates and high response thresholds (Furman et al., 2013), thus sparing the low-threshold fibres that detect soft sounds and guarantee low hearing thresholds (see also Fig. 1a). Deafferentation of AN fibres could therefore also be present in normal-hearing subjects with tinnitus. In contrast to the reduction of the peripheral signal, the amplitudes of the centrally generated wave V were of normal size (Schaette and McAlpine, 2011, see also Fig. 1c) or even enhanced (Gu et al., 2012) in the tinnitus subjects, suggesting an increase in neuronal response gain at the level of the brainstem. A similar enhancement of the amplitude ratio between ABR wave V and wave I has also already been reported in an earlier study (Kehrle et al., 2008), but this study did not report the absolute amplitudes of the individual waves. A putative explanation for the enhancement in neuronal response gain in tinnitus subjects could be homeostatic compensation for decreased input from the AN (Schaette and McAlpine, 2011). Studies employing psychophysical tests have also found indications for deafferentation in tinnitus subjects with normal hearing thresholds, as evidenced through increased tone-detection thresholds in high-intensity background noise (Weisz et al., 2006) in the TEN-test (Moore et al., 2000) or through increased intensity discrimination thresholds in the tinnitus frequency range (Epp et al., 2012). These results suggest that tinnitus might always be associated with cochlear damage, even when hearing thresholds are within the normal range.

2. Indications for a causal relation between hearing loss and tinnitus

A central question on the relation between hearing loss and tinnitus has been whether the development of tinnitus is triggered by the actual process of damage to structures of the ear, or whether the subsequent reduction in input to the central auditory system through the hearing loss might be the driving factor. It has long been known that auditory deprivation can induce phantom sounds when subjects spend time in complete silence in a sound-proof booth (Heller and Bergman, 1953; Del Bo et al., 2008). Recently, it has been reported that continuous use of an earplug can also lead to the perception of phantom sounds (Schaette et al., 2012). Eleven out of 18 normal-hearing participants, who wore a silicone earplug continuously in one ear for seven days, reported hearing phantom sounds at the end of the earplug period. Tinnitus spectrum measurements showed that the phantom sounds were perceived predominantly as high-pitched, corresponding to the frequency range most affected by the earplug. In all cases, the auditory phantom slowly disappeared when the earplug was removed, indicating a causal relation between reduction of input to the auditory system and the occurrence of phantom sounds. Since only a conductive hearing loss was induced through the earplug, without damage to structures of the inner ear, these results suggest that tinnitus might be triggered through loss of auditory input. Reduction of auditory nerve activity is in fact the common denominator of different kinds of cochlear damage associated with tinnitus, even when there is no shift of the hearing thresholds (Fig. 2).

Further support for a causal relation between loss of auditory input and tinnitus comes from studies demonstrating that tinnitus can be reduced by treating hearing loss. While it is currently not possible to cure noise-induced or age-related hearing loss, conductive hearing loss can often be substantially decreased through surgery. In patients with otosclerosis, stapedectomy and stapedotomy have shown remarkable results for tinnitus. It has been reported that in more than half of the patients, tinnitus was completely abolished after surgery, and the majority of the remaining patients experienced improvement (Gersdorff et al., 2000; Ayache et al., 2003; Sobrinho et al., 2004). A more recent study has reported slightly lower success rates, though, with

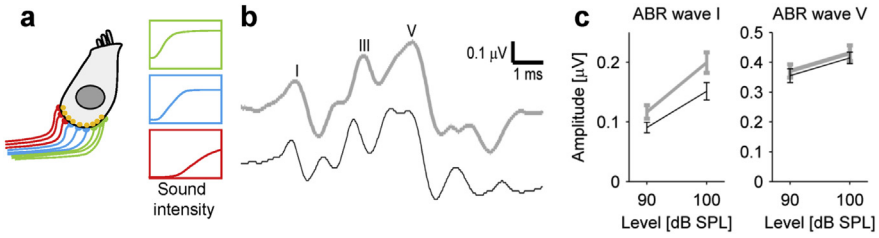

Fig. 1. Auditory brainstem response measurements indicate AN fibre deafferentation in tinnitus subjects with normal audiograms. a) Schematic depiction of an inner hair cell of the cochlea, of the AN fibres contacting it, and the rate-vs.-intensity functions of the different types of AN fibres (green – low threshold fibres; blue – medium threshold fibres; red – high threshold fibres). b) Example ABR waveform of a tinnitus (black line) and a control subject (grey line) with normal hearing thresholds for 50 µs clicks at 100 dB SPL. The roman numerals label waves I, III, and V of the ABR. c) Mean amplitudes of peripherally-generated ABR wave I were significantly lower in the tinnitus (black) than in the matched control group (grey, $p = 0.009$, 2-way ANOVA). In contrast, amplitudes of centrally-generated wave V did not differ significantly.
Figure modified from Schaette and McAlpine (2011).