Hearing Research 334 (2016) 20–29

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Review

Tinnitus: Maladaptive auditory–somatosensory plasticity

Calvin Wu, Roxana A. Stefanescu, David T. Martel, Susan E. Shore*

Department of Otolaryngology, Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Article history:
Received 5 March 2015
Received in revised form
25 May 2015
Accepted 2 June 2015
Available online 12 June 2015

Keywords:
Tinnitus
Somatosensory
Somatic tinnitus
Hyperactivity
Dorsal cochlear nucleus

ABSTRACT

Tinnitus, the phantom perception of sound, is physiologically characterized by an increase in spontaneous neural activity in the central auditory system. However, as tinnitus is often associated with hearing impairment, it is unclear how a decrease of afferent drive can result in central hyperactivity. In this review, we first assess methods for tinnitus induction and objective measures of the tinnitus percept in animal models. From animal studies, we discuss evidence that tinnitus originates in the cochlear nucleus (CN), and hypothesize mechanisms whereby hyperactivity may develop in the CN after peripheral auditory nerve damage. We elaborate how this process is likely mediated by plasticity of auditory–somatosensory integration in the CN: the circuitry in normal circumstances maintains a balance of auditory and somatosensory activities, and loss of auditory inputs alters the balance of auditory somatosensory integration in a stimulus timing dependent manner, which propels the circuit towards hyperactivity. Understanding the mechanisms underlying tinnitus generation is essential for its prevention and treatment.

This article is part of a Special Issue entitled <Tinnitus>.

Contents

1. Introduction 21
2. Animal model 21
 2.1. Gap detection paradigm and procedure for assessing tinnitus 21
  2.1.1. Limitations 21
3. Hyperactivity and tinnitus 22
 3.1. Relationship to behavioral results 22
 3.2. Hyperactivity in IC and its dependence on DCN 23
4. Multisensory mechanisms in CN and their contribution to tinnitus-related hyperactivity 24
 4.1. Convergence of auditory and somatosensory inputs in CN and IC 24
 4.2. Differential synaptic markers for auditory and somatosensory terminals in CN 24
 4.3. Redistribution of VGLUT expression after hearing loss: evidence for cross-modal compensation 24
 4.4. Synaptic plasticity of the DCN circuitry 24
 4.5. Somatosensory inputs induce persistent changes in CN activity 25
 4.6. Auditory–somatosensory stimulus timing-dependent plasticity in fusiform cells 26
 4.7. Alteration of stimulus-timing dependent plasticity underlies fusiform cell hyperactivity 26
 4.8. Molecular mechanisms of tinnitus-related changes in DCN plasticity 27

Abbreviations: ABR, Auditory brainstem response; CN, Cochlear nucleus; DCN, Dorsal cochlear nucleus; VCN, Ventral cochlear nucleus; DCoN, Dorsal column nuclei; GCD, Granule cell domain; IC, Inferior colliculus; LTP/LTD, Long-term potentiation/depression; RLF, Rate-level functions; Sp5, Spinal trigeminal nucleus; TG, Trigeminal ganglion; VGLUT, Vesicular glutamate transporters

* Corresponding author. Tel.: +1 734 647 2116; fax: +1 734 764 0014.
E-mail address: Sushore@umich.edu (S.E. Shore).

http://dx.doi.org/10.1016/j.heares.2015.06.005
0378-5955/

5. Concluding remarks 27
Acknowledgments 27
References 27

1. Introduction

Tinnitus, the phantom perception of sound, affects 50 million adults in the U.S, with 12 million experiencing disruption of daily lives and suffering severe psychological stress (Rizzardo et al., 1998). Associative risks for tinnitus include intense noise exposure (Nicolas-Puel et al., 2006), ototoxic insults (Seligmann et al., 1996), head and neck injuries (Folmer and Griest, 2003), and age-related hearing impairment (Sataloff et al., 1987). Peripheral trauma causes partial deafferentation of the auditory nerve fibers (ANF), which reduces afferent drive to its central target, the cochlear nucleus (CN). However, in experimental animal models (Section 2), noise-trauma paradoxically induces elevated spontaneous activity in ventral (VCN) and dorsal cochlear nuclei (DCN) (Bledsoe et al., 2009; Brozoski et al., 2002; Dehmel et al., 2012; Koehler and Shore, 2013a; Vogler et al., 2011; Zhang and Kaltenbach, 1998).

A large body of evidence supports DCN as the site of tinnitus induction, where diminished auditory nerve input initiates hyperactivity, which then spreads to higher areas (Brozoski and Bauer, 2005; Brozoski et al., 2012; Dehmel et al., 2012; Kaltenbach et al., 2005; Schaette and Kempter, 2006; Zacharek et al., 2002). How does a "loss-of-input" from the cochlea cause tinnitus? In this review, we show that the DCN is primed for such an induction process. The principle output neurons, fusiform cells, express a high degree of synaptic plasticity (Section 4.4), which largely involves integration of multisensory information (Sections 4.5 and 4.6). Somatosensory inputs provide a reservoir of excitatory drive that can be tapped during homeostatic changes (Section 4.3). It is therefore not surprising that more than two thirds of tinnitus patients are able to modulate tinnitus perception by somatic maneuvers (Levine et al., 2003; Shore et al., 2007): an epitome of maladaptive auditory–somatosensory plasticity.

2. Animal model

Tinnitus can be induced through several methods. Noise overexposure is the major cause of tinnitus in humans and serves as a plausible method for generating an animal model (Eggermont and Roberts, 2004). Early studies of noise-induced tinnitus in humans revealed several consistent relationships between the characteristics of the noise exposure spectrum and the resulting tinnitus pitch and quality (Heffner and Heffner, 2012; Loeb and Smith, 1967). Tinnitus tends to present at frequencies up to 1.5 octaves higher than the exposure frequency (Konig et al., 2006; Roberts et al., 2008; Schaette and Kempter, 2009). Subjects in these studies tended to report tinnitus having a tone-like quality, similar to the exposure sound. Extended frequency audiograms on patients with tinnitus and hearing loss show a correlation between the frequency of the falling edge or a maximum threshold shift and the tinnitus frequency (Moore et al., 2010; Schecklmann et al., 2012). These results suggest that noise exposure that damages hearing, even temporarily (Kujawa and Liberman, 2009; Schaette and McAlpine, 2011), can induce tinnitus, and that the noise damaging spectra correlate with the tinnitus spectra. However, noise damage does not always result in tinnitus (Lockwood et al., 2002; Roberts et al., 2010). Similarly, manipulation of the facial or neck muscles can induce or alter tinnitus in individuals without a clinically measurable threshold shift (Levine et al., 2007).

2.1. Gap detection paradigm and procedure for assessing tinnitus

To make claims about the neural mechanisms of tinnitus, animals must be determined to have tinnitus, preferably with an estimate of their tinnitus spectra. The first behavioral model of tinnitus relied on operant conditioning techniques that trained animals to discriminate between sound and no-sound (Jastreboff et al., 1988). Following salicylate administration, which is known to induce tinnitus in humans, animals with a decreased ability to detect a no-sound condition were classified with tinnitus. This technique, along with salicylate administration, have served as a "gold standard" for tinnitus assessment. As pioneering as this test was, it has several limitations. Training animals is a time-intensive process, and the behavioral outcomes of animals are dependent on additional factors such as learning and memory, which may contaminate the results. To overcome these limitations, the gap detection paradigm was developed (Turner et al., 2006). This method does not require training, and can be applied without timing constraints. The paradigm was derived from procedures used in schizophrenia, and has been cross validated against several operant conditioning techniques (Turner et al., 2006; Yang et al., 2007).

Gap detection is based upon two behavioral responses (Fig. 1). First, animals startle in response to an intense, rapid onset sound. Second, when a gap in the narrow-band background noise is inserted shortly prior to the startle pulse, the amplitude of the startle response is reduced, as the salience of the gap "warns" of the impending startle pulse. To quantify this behavior for comparisons within and across animals over time, the gap startle amplitude is normalized by the no gap startle amplitude, to produce a normalized startle response. Similarly, a noise pre-pulse can be used as a replacement for the gap to produce similar results. The pre-pulse is presented at a lower sound level than the startle pulse, warning the animal of the impending startle pulse. Pre-pulse inhibition has been used to ascertain whether the animal has hearing or temporal processing impairments. These stimuli are presented across the animals hearing range to establish a baseline profile of the animal's ability to process sounds. However, when a gap is introduced to animals with tinnitus that presents in the same frequency and intensity as the narrow-band background noise, they will startle as if there was no gap present. This frequency-specificity allows for a particular animal to be classified with tinnitus as well as estimates the perceived pitch of the tinnitus, as long as the PPI has been shown to be normal. Deficits in PPI could indicate a hearing loss at that frequency and thus, those animals would be excluded from the study (see below).

2.1.1. Limitations

The gap detection paradigm is an increasingly popular technique within the tinnitus research community. However, there are several perceived limitations to the technique (Campolo et al., 2013; Hickox and Liberman, 2014; Lobarinas et al., 2013). Noise exposure carries the potential confounding factor of permanent damage to the auditory pathway (Liberman and Dodds, 1984). This