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Research paper

Age-related structural and functional changes in the cochlear nucleus

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Abstract

Presbycusis – age-related hearing loss – is a key communication disorder and chronic medical condition of our aged population. The cochlear nucleus is the major site of projections from the auditory portion of the inner ear. Relative to other levels of the peripheral and central auditory systems, relatively few studies have been conducted examining age-related changes in the cochlear nucleus. The neurophysiological investigations suggest declines in glycine-mediated inhibition, reflected in increased firing rates in cochlear nucleus neurons from old animals relative to young adults. Biochemical investigations of glycine inhibition in the cochlear nucleus are consistent with the functional aging declines of this inhibitory neurotransmitter system that affect complex sound processing. Anatomical reductions in neurons of the cochlear nucleus and their output pathways can occur due to aging changes in the brain, as well as due to age-dependent plasticity of the cochlear nucleus in response to the age-related loss of inputs from the cochlea, particularly from the basal, high-frequency regions. Novel preventative and curative biomedical interventions in the future aimed at alleviating the hearing loss that comes with age, will likely emanate from increasing our knowledge and understanding of its neural and molecular bases. To the extent that this sensory deficit resides in the central auditory system, including the cochlear nucleus, future neural therapies will be able to improve hearing in the elderly.

Keywords: Presbycusis; Glycine; Auditory brainstem; Central auditory system; Aging

1. Introduction

Presbycusis – age-related hearing loss – is a major communication disorder and chronic medical condition of our aged population. Preventative and curative biomedical interventions will only come from increasing our understanding of the neural and molecular bases of this sensory deficit. The cochlear nucleus receives the outputs of the auditory portion of the inner ear, and sets up parallel processing pathways in the brainstem critical for sound analysis and perception. This key location for sound processing is a strong motivation for examining how its structure and function change with age.

Our presentation is organized such that age-related changes in the physiological responses of cochlear nucleus neurons will be highlighted first, followed by structural and chemical changes that occur with age. The goal is to gain insights into the neural bases of functional aging changes in the mammalian cochlear nucleus.

2. Neural processing aging changes in the cochlear nucleus

Anatomical and neurochemical studies of the cochlear nucleus outnumber the neurophysiological reports examining age-related alteration in neural encoding of sound. It is likely that there are two major explanations for this: (1) the difficulty in the surgical exposure necessary for access to the cochlear nucleus; and (2) the oftentimes deleterious effects of general anesthesia in old animals. The results described in the neurochemical and anatomical studies

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clearly suggest an age-related disruption of the interplay between excitation and inhibition in the cochlear nucleus complex and these discoveries support the emerging hypothesis that the neural representation of sounds is altered in the aged central auditory nervous system.

2.1. Peripheral hearing loss accentuates age-related physiological changes

Following his pioneering studies in the inferior colliculus, Willott and colleagues were the first to investigate neural encoding of basic sound properties in the cochlear nucleus of old CBA/J mice. The CBA mice have a slow, progressive loss of hearing sensitivity with age, displaying reasonably good hearing even in old age. Willott et al. (1991) measured simple receptive fields from the ventral (VCN) and dorsal (DCN) cochlear nucleus in mice of different ages and reported on alterations in minimum thresholds, best-frequencies and the frequency range of the response area. In CBA mice, they found no significant age-related modifications in minimum thresholds and response areas in old animals relative to young adults. The distribution of best frequencies, both in the VCN and DCN, was also comparable for young adult and old CBA mice. However, the width of the single neuron response areas at 80 dB SPL were compared, and were found to have decreased between 20% and 25% in both VCN and DCN units in old CBA mice.

C57BL/6J mice have a rapid, high-frequency hearing loss, which reaches severe levels by about one year of age, due to the presence of the *ahl* gene. This allele (Cdh23 gene) produces changes in an otocadherin transmembrane adhesion protein. These changes induce a disruption of hair cell stereocilia, resulting in a rapid peripheral sensorineural hearing loss (Noben-Trauth et al., 2003; Zheng et al., 2005). In comparison to the CBA strain, significant increases in the proportion and number of units with thresholds greater than 60 dB were found in middle-aged (about 1 year of age) C57 mice, which have moderate-to-severe high frequency hearing loss. The sensitivity changes in the C57 VCN were more drastic than in the DCN or inferior colliculus. Furthermore, whereas the low frequency portions of tuning curves in inferior colliculus neurons in high frequency tonotopic regions typically become 'sensitized' in middle-aged C57 mice (i.e., lower thresholds than young mice), this did not occur for VCN neurons. In contrast to VCN neurons, tuning curves for DCN neurons studied were statistically indistinguishable from those of the inferior colliculus. Perhaps, the stability in the DCN is a reflection of the divergent inputs which sculpt the receptive fields of DCN principle neurons. Measurements of single-unit response areas in C57 mice corroborated the tuning curve results. This was the first neurophysiological investigation which addressed the possibility that the effects of age might be different depending on the auditory brainstem nucleus under study, specifically, when comparing cochlear nucleus to the inferior colliculus.

Wang and Manis (2005) performed a recent investigation of age-related changes in AVCN end-bulb synaptic transmission in DBA mice. This mouse strain has an even more rapid age-related cochlear hearing loss than the C57 strain, due to an increased number of hearing loss alleles relative to the C57s. Using patch-clamp recordings in mouse cochlear nucleus slice preparations, they found that auditory-nerve fiber/bushy cell synaptic transmission decayed with age, in that the spontaneous miniature excitatory postsynaptic currents (mEPSC) were significantly reduced in frequency by about 60% (Fig. 1), in speed by about 115% (time constant changes given in Fig. 2), and in size by about 70%, in high-frequency regions of the DBA AVCN in mice 45 days of age relative to those at 22 days. In line with this effect, synaptic release probability declined by 30% in the older DBAs, along with the evoked

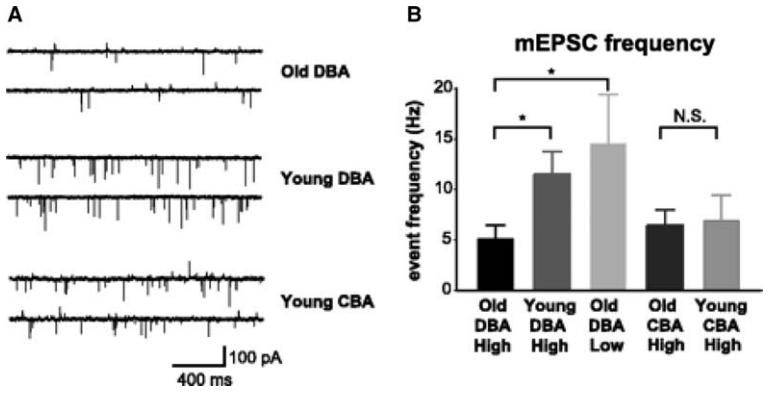

Fig. 1. Spontaneous miniature excitatory postsynaptic current (mEPSC) event frequency declined in hearing-impaired old DBA mice. (A): representative *mEPSC traces* from high-frequency bushy cells. Cells were held near their resting membrane potential at −60 mV. No glycine receptor antagonist was included in the bathing solution. (B): spontaneous mEPSC event frequency from different age and frequency groups. mEPSC event frequencies from high-frequency regions were lower in old DBA mice than those in young DBA mice, whereas the event frequency for normal hearing low-frequency old DBA mice was similar to that of young DBA mice. mEPSC event frequency was not significantly different between old and young CBA high-frequency bushy cells. With permission, figure and legend from Wang and Manis (2005), Fig. 2.