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Review

Molecular aging of the mammalian vestibular system

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ABSTRACT

Dizziness and imbalance frequently affect the elderly and contribute to falls and frailty. In many geriatric patients, clinical testing uncovers a dysfunction of the vestibular system, but no specific etiology can be identified. Neuropathological studies have demonstrated age-related degeneration of peripheral and central vestibular neurons, but the molecular mechanisms are poorly understood. In contrast, recent studies into age-related hearing loss strongly implicate mitochondrial dysfunction, oxidative stress and apoptotic cell death of cochlear hair cells. While some data suggest that analogous biological pathomechanisms may underlie vestibular dysfunction, actual proof is missing. In this review, we summarize the available data on the molecular causes of vestibular dysfunction.

Contents

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1. Introduction

Disequilibrium of aging (presbyastasis) causes significant morbidity and limits the quality of life in the elderly (Sturnieks et al., 2008; Zhang et al., 2011). Stance and gait is maintained by an intriguingly complex neuronal network that can be disrupted by stroke, inflammation, trauma, toxicity and neurodegenerative processes. Thus, etiology varies greatly and individuals presenting with vertigo, gait disorders or falls require comprehensive neurological testing (Strupp and Brandt, 2008). The precise clinical description of gait patterns is a distinct clinical skill of experienced neurologists and commonly follows a classification system categorizing disturbances into higher-, intermediate-, and lower-level disturbances, as proposed by Nutt et al. (1993). Such description is decisive in determining the necessary and expedient diagnostic procedures. Despite its long tradition, the field is continuously evolving and a wealth of excellent review articles are available for the interested reader (Jahn et al., 2010; Strupp and Brandt, 2008; Strupp et al., 2011a).

Movement is planned and initiated in the pre-motor, supplementary motor and primary motor cortex. Accordingly, cortical and subcortical frontal lobe dysfunction is considered an important factor in age-related disequilibrium (Baezner and Hennerici, 2005). Inhibitory and stimulatory feedback loops involve the basal ganglia, the cerebellum, brainstem nuclei and the thalamus (Groenewegen, 2003; Jueptner and Weiller, 1998; Lanciego et al., 2012). Sensory signals from the peripheral vestibular system are processed through the vestibular brainstem nuclei and project to the cerebellum, the reticular formation, the spinal cord and the thalamus (Angelaki and Cullen, 2008). These vestibular signals contribute to automatic reflexes and motor coordination, whereas projections to the hippocampus and the vestibular cortex facilitate spatial perception and orientation (Brandt et al., 2014).

The function of the vestibular system declines with age, but considering the impact on quality of life, surprisingly little is known about the pathomechanisms and risk factors underlying the neurodegenerative processes involved (Agrawal et al., 2013; Agrawal et al., 2009; Matheson et al., 1999; Park et al., 2001a). In contrast, a great many clinical and molecular studies are available on the pathogenesis of age-related cochlear dysfunction (presbycusis). Although this knowledge may be relevant, it cannot simply be transferred. This review focuses on the relevance and the mechanisms of age-related degeneration of the primary afferent vestibular system, including data coming from human post-mortem tissue as well as animal studies.

2. Histopathological changes in the aging vestibular system

The peripheral vestibular system consists of five vestibular endorgans. The three semicircular canals are responsible for angular accelerations; the two otolith organs – saccule and utricle – sense linear accelerations. Mechanosensory hair cells are located in the cristae ampullaris of the semicircular organs and in the macula of the otolith organs. Morphologically, type I and II hair cells can be differentiated (Wersall, 1956). These neurons are equipped with stereocilia that are anchored in the cuticular plate at the top of the cell and transmit electrochemical signals produced by mechanical excursion of the cilia to the vestibular ganglion neurons (Roberts et al., 1988). The central processes of the bilateral vestibular ganglions form the two vestibular nerves, which unite with the cochlear nerve to enter the brainstem as the vestibulocochlear nerve on either side. In the brainstem, the vestibular nerve fibers terminate in one or more of the vestibular nuclei or project to other regions of the brain i.e., the cerebellum (Tascioglu, 2005).

2.1. Roadblocks to human neuropathological studies

As we will outline below, age-related degeneration has been verified histologically in all parts of the vestibular system. Unfortunately, most studies are limited to single or few vestibular structures at a time. To our knowledge, there are currently no systematic neuropathological studies that include analysis of all peripheral and central vestibular structures in the same individual. Major obstacles in vestibular research include the post-mortem sample acquisition of clinically well characterized individuals, as well as the parallel neuropathological characterization of peripheral and central vestibular tissue. Furthermore, inner ear structures are safely 'buried' in the hardest bone of the human body and vestibular and cochlear structures lie in different anatomical planes. Thus, optimal orientation for serial sectioning of one structure restrains analysis of the other, which is of particular relevance for unbiased stereology (Tang et al., 2002). Quantification of the neuroepithelium has also been limited because of the difficulty in distinguishing hair cells from supporting cells and type I from type II hair cells. Certainly, protocols for the dissection of human temporal bone are available, but the nature of the lengthy decalcification process may cause 'shrinkage' and distortion of structures. Furthermore, the nature of these protocols largely interferes with reliable DNA, RNA or protein analysis of inner ear structures. Initiatives, such as the *Human Temporal Bone Consortium** (http://otopathologynetwork.org/) strive to overcome some of these problems. Despite the obvious question of translational relevance, murine studies provide valuable clues to the molecular mechanisms underlying age-related neurodegenerative processes.

2.2. Otoconial degeneration

The maculae of the otolithic organs are covered by a dense gelatinous layer consisting of filaments linking the attached otoconia (Lins et al., 2000; Lundberg et al., 2006; Thalmann et al., 2001). Age-related decrease in the number of otoconia and linking filaments has been demonstrated particularly in the saccule (Igarashi et al., 1993; Ross et al., 1976). Dislodged filaments and degenerated otoconia may accumulate in the circular canal endolymph and cause '*benigne paroxysmal positional vertigo (BPPV)*', which is common in the elderly population (Brandt and Steddin, 1993; Brandt et al., 1994; Jang et al., 2006). One possible cause for otoconial degeneration may be dysregulation of the ionic components in the microenvironment surrounding the otoconia, such as calcium metabolism (Jeong et al., 2009; Lundberg et al., 2006). There is a strong correlation between BPPV and osteopenia or osteoporosis in older women (Vibert et al., 2003), as 75% of women with BPPV also had osteopenia or osteoporosis. The authors discussed two possible causes: otoconial degeneration or decreased capacity to resolve otolithic debris due to estrogen deficiency.