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Review

The cochleo-vestibular secretory senescence

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The vestibular and cochlear senescence is a complex degenerative disease and one of the most prevalent chronic conditions of elderly, affecting tens of millions of people worldwide. In this review, we will try to summarize the most important sites and involved mechanism trying to figure out strategies to prevent its clinical consequences.

Key words: vestibular and cochlear ageing, EP, presbyvestibulopathy, BPPV, vHIT, VEMPs

THE COCHLEAR SECRETORY SENESCENCE

Age related hearing loss is the most known manifestation of cochlear aging. It affects about two-thirds of people over seventy years of age [1], resulting in social isolation and decreased quality of life [2]. It is a complex degenerative disease and one of the most prevalent chronic conditions of the elderly, affecting tens of millions of people worldwide. Authors all over the world focus their attention on cochlear aging mechanism, trying to figure out strategies to prevent its clinical consequences, acting on one or more of the key points involved on it.

In this review, we will try to summarize the most important sites and involved mechanism in cochlear aging. Potential sites of pathology include the inner and outer hair cells (IHCs and OHCs), the stria vascularis, and afferent spiral ganglion neurons [3]. In mammals, the tissue involved in the generation of the endolymphatic potential (EP) resides in the lateral wall [4,5]. The stria vascularis, a specialized multi-layered and highly vascularized non sensory epithelial thickening of the lateral wall, contains the secreting marginal cells as well as the intermediate and basal cells, which build up the gradient for K^+ and the highly positive EP. The stria vascularis provides the high EP and potassium concentration of the endolymph [K^+_e] in the scala media. Both a high EP (~+80 mV) and a high [K^+_e] (~180 mM) are necessary for proper cochlear amplification and signal transduction. The marginal cells are primarily responsible for the [K^+_e], and since the intrastriatal space already maintains a high positive potential it is hypothesized that the EP is generated by intermediate and basal cells. Potassium ions are constantly re-circulated back to the spiral ligament and stria vascularis after they pass through the hair cells, and then back into the endolymphatic space where the cycle begins again; this cycle serves to sustain the endocochlear EP as the energy source for the conduction current and the cochlear amplifier. Actually, the major pathway for recycling and secretion

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of cochlear endolymph involves a flow of K^+ from perilymph to fibrocytes in the spiral ligament and then to basal cells, intermediate cells, and marginal cells, the last of which release K^+ into the scala media. Each of these steps is precisely orchestrated by a series of gap junctions, channels, pumps, and transporters, many of which have been molecularly identified.

Based on current measurements [6], some of the K^+ seems to simply diffuse extracellularly through the perilymph toward the spiral ligament. A possible intracellular pathway would start with the K^+ uptake by supporting cells. K^+ released by OHCs is taken up by Deiters cells and then passed via gap junctions to a series of different cell types: first to epithelial cells, from there to outer sulcus cells, and finally to fibrocytes of the spiral ligament.

In the lateral wall of the gerbil cochlea the most common finding with increasing age is a decrease in the area or volume of the stria vascularis, starting from the most apical and basal turn and extending to the middle turn.

The loss of the conduction current and the endocochlear potential has the greatest effect on high-frequency hearing, because of the reduced amplification, which explains the very common increase in hearing thresholds above 1-2 kHz seen in aged human audiograms.

Also, we found several changes involving (with the same topography) its capillaries with decrease in capillary diameter and a thickening of their basement membrane. It results in strial atrophy.

These histopathologies in the stria vascularis are linked to changes in the endolymph of the scala media. Indeed, aged gerbils typically have a decreased EP [7,8], which correlates with strial atrophy [9] and with degeneration of the microvasculature in the stria vascularis.

Human temporal bone studies have shown similar pathologies of the stria vascularis. Strial atrophy, measured as a reduction of strial volume, has been frequently observed in cochleae of aged humans. Since the stria vascularis is responsible for generating and maintaining the EP and because the age-related pathologies in the gerbil correlate with a pronounced EP reduction, it is highly likely that humans with strial presbyacusis also have a decreased EP. However, EP reduction has never been shown experimentally in aged humans [10].

One more site involved in cochlear aging is the IHC-auditory nerve fiber synapse, also called the ribbon synapse. Here, acoustic information is transformed into a neural spiking signal that is carried to the central auditory system. The presynaptic part, i.e. the IHC active zone, consists of a ribbon at which numerous vesicles, filled with the excitatory neurotransmitter glutamate, are anchored [11]. The postsynaptic density comprises mostly α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type receptors that bind the released glutamate [12]. The complex molecular makeup of the pre- and post-synaptic structures gives rise to the unique abilities of type I auditory neurons to accurately encode rapid temporal acoustic fluctuations. In the mammalian cochlea, each auditory afferent makes only one synaptic connection with an IHC, whereas each IHC is innervated by multiple afferents. Around 10-25 auditory nerve fibers connect to one IHC in the normal-hearing gerbil ear, depending on its location along the cochlea. In aged gerbils, a mild loss in the number of ribbons per IHC of about 20%, which is most pronounced at the apex, was reported [13]. Correspondingly, in an earlier study in which nerve fibers were counted in the osseous spiral lamina (OSL), it was shown that the number of nerve fibers per IHC decreased in aged gerbils [14]. An age-related decrease in ribbon synapses per IHC is also apparent in rats and mice.

Excitotoxicity may be an important mechanism involved in the loss of ribbon synapses with age. Triggered by a variety of factors, excessive glutamate in the synaptic cleft induces prolonged depolarization and results in large ion influxes and subsequent water influx into the afferent post-synaptic fiber. This leads to swelling and retraction of the afferent terminal [12]. These retracted terminals can either regenerate and form a new synapse with the IHC or remain permanently separated, eventually leading to spiral ganglion neuron (SGN) loss. Recent studies have begun to quantify synapse loss in human temporal bones. The number of ribbons per IHC decreased with increasing age, with only 2-7 ribbons/IHC remaining in the oldest individual, depending on the cochlear location [15]. Based on the loss of synapses, peripheral axons, and SGNs shown in human temporal bone and animal studies, some Authors suggest that age-related ribbon synapse loss is an early stage of neural presbyacusis as defined by Schuknecht and Gacek [3] as a primary loss of SGNs of at least 50% in the absence of any apparent pathology in the IHCs and OHCs.

It is prospectively very important to understand mechanisms of auditory senescence. In the last two decades, the association between cognitive impairment and age-related hearing loss (ARHL) has received great attention [16]. ARHL has recently been defined as the modifiable risk factor with the greatest impact on the development of dementia [17]. The cochlear changes responsible for peripheral ARHL have a causal role in reducing grey matter volume in the auditory cortex [18]. In particular, Lin et al. [19] showed that ARHL is associated with shrinking of the total brain volume and, specifically, of the right temporal lobe volume. Actually, age related hearing loss results as a substantial marker for frailty in older age, another age-related clinical condition that

identify older persons at elevated risk for numerous adverse health outcomes such as falls, institutionalization, hospitalization, disability, and death [16].

THE AGEING OF VESTIBULAR SYSTEM: ANATOMICAL-CLINICAL CORRELATIONS

Balance problems prevalence increases with age. It has been estimated that about 20% of elderly subjects experience with balance disorders or dizziness every year, including unsteadiness (68.0%), difficulty in walking on irregular surfaces (54.8%), vertigo (30.1%), and faintness (29.6%) [20]. These data are generally attributed to the progressive deterioration of the proprioceptive, visual and vestibular functions, although it is clinically difficult to establish which functional deterioration has the greatest impact on a single subject [20]. A lot of recent studies demonstrate physiological changes occurring with aging in sensorial systems as well as in the vestibular one, so that, in analogy with the terms "presbyopia" and "presbycusis", a pathological condition known as "presbyvestibulopathy" has been recognized. This latter is defined as a chronic vestibular syndrome characterized by unsteadiness, gait disturbance, and/or recurrent falls in the presence of mild bilateral vestibular deficits caused by the vestibular organs deterioration [21].
Benign Paroxysmal Positional Vertigo (BPPV) is the most common vestibular disorder in adults, it causes 17-42% of all diagnosed vertigo and its prevalence increases abruptly with patients age, especially in the over 60 years old population [22]. According to a retrospective study, almost 40% of patients over 70 years old were diagnosed with BPPV [23], on the other hand, another epidemiologic study stated a 2.4% lifetime BPPV prevalence with a cumulative incidence reaching 10% by the age of 80 [24].
The most commonly accepted theory about BPPV pathophysiology claims that particles of calcium carbonate-calcite (otoconia), detached from the macula of the utricle, move inside one or more semicircular canals and make the cupula gravity sensitive [25].
The higher incidence of BPPV in the elderly probably reflects either labyrinth aging or functional and structural changes of the vestibular organs, playing a crucial role in causing higher prevalence of such a disease in advanced age.

Structural and functional changes in semicircular canals

Anatomical studies have reported significant age-related changes in vestibular epithelium, concerning the hair cells. Two types of vestibular hair cells are known: type I and I cells.
These two cell types differing in morphology, function, and resistance to senescence: type I hair cells, more responsive to high frequencies, and type II low-frequency responsive hair cells; type I have higher age-related degradation compared to type II [26].
Despite age-related reduction of hair cells has been described in all the vestibular sensory epithelium, histopathological studies suggest that type I hair cells degenerate mainly in semicircular canals compared to otolithic organs, conversely type II hair cells have the same age-related rate of decline in all vestibular organs [27,28]. Furthermore, also vestibular ganglion cells and vestibular nucleus cells populations decrease in number over time [21].
The semicircular canals are endolymph-filled rotational sensors that transduce head rotational acceleration into a neural signal roughly proportional to head acceleration. Due to the inertia of the endolymph fluid, head rotation causes a relative fluid flow, which bends the cupula and deflects the hair cells. The activation of semicircular canals is responsible for the angular vestibulo-ocular reflex (a-VOR) which stabilizes images on the retinas during head rotations. The VOR gain quantifies the VOR functionality, it is defined as the modified eye angle divided by the modified head angle in course of head rotation.
Hair cells decrease in the semicircular canals and consequent VOR functional deterioration can be detected by vestibular tests, such as reduced response to caloric test and VOR gain reduction either in rotatory chair tests or in video-Head Impulse Test (vHIT) [21].
vHIT is probably the test most used to measuring semicircular canals function at their physiological working frequency. Recent studies investigated the VOR in large population-based samples of older adults, detecting age-related reduction in angular VOR gain [29,30]. Age-related decline in VOR processing due to velocity storage mechanisms disfunction has been also hypothesized [31].

Structural and functional changes in otolithic organs

The utricular and saccular macula provides neural feedback about head linear accelerations on the horizontal and vertical plane, respectively. These sensorial receptors consist of a small area of hair cells, polarized according to their position around the striola, whose ciliary bundles project into the overlying otoconial membrane. This latter is a complex, acellular structure that comprises 3 layers: the otoconial layer, the gel layer, and the column filament layer.
In the otolithic organs, the age-related degenerative processes are not limited to cellular damage but also affect the number and composition of the otoconia.
The otoconia of humans are not "embedded" in the

otolithic membrane, but rather make up a separate crystalline layer on the top of the otolithic membrane. The otoconia have an averaging size of about 10 microns with hexagonal symmetry and are composed of calcium carbonate or calcite ($CaCO_3$) micro-crystals combined with protein matrix called otoconial proteins or otoconins. The most represented is Otoconin-90 (Oc90): it plays not only a structural role, but it is essential for $CaCO_3$ crystallization, binding calcium from the surrounding calcium-poor endolymph [32].

Calcification of the otoconia protein matrix requires an ordered sequence of events. Once otoconia are formed, their outer component containing calcium presents a slow turnover rate. It is not clear if also the inner part of otoconia (namely the matrix) can be replaced in humans but it has long been supposed that, once detached by otoconial membrane, the damaged ones can be dissolved and reabsorbed by the "dark cells" of the labyrinth (melanocytes which have been found adjacent to the utricle and the crista) [33].

Otoconial degeneration increases above the age of 50 or 60 [34]. Igarashi et al. [35] found a decrease in otoconial volume of 41% in the utricle and 70% in the saccule comparing infants to older adults (58-87 years). A recent study on vital specimens detected the degeneration of human utricular otoconia using energy dispersive X-ray microanalysis (EDX) and powder X-ray diffraction (XRD). The outcome of this research demonstrated the degeneration processes in the human utricle take place gradually: minor changes (low-grade degeneration) reveal mild structural alterations such as fissures and surface roughening of the less dense belly area with a modest reduction of material. Major changes (high-grade degeneration) are characterized by profound morphological alterations (fractures and disintegration) showing a successive loss of otoconia material [36].

Other indirect evidence of aging-related demineralization of otoconia emerged from a study conducted on 79 subjects between 22 and 95 years of age, reporting increased blood levels of the otoconia matrix protein otolin-1 in individuals older than 65 years old [37].

Vestibular evoked myogenic potentials (VEMPs) are short-latency electromyographic activities evoked by air-conducted loud sound (tone burst or click), bone-conducted vibration, or galvanic stimuli in order to evaluate the macular function. There are two types of VEMP testing: c-VEMP and o-VEMP. In c-VEMPs, the selected stimulus evokes a response within the ipsilateral sternocleidomastoid muscles that represents the inhibition of the ipsilateral vestibulo-collic reflex, reflecting predominantly the saccular and inferior vestibular nerve functions. Similarly, o-VEMP evokes a response that is largest when recorded from the inferior oblique muscle and represents the activation of the contralateral vestibulo-ocular reflex, reflecting the utricular and superior vestibular nerve functions.

The analysis of VEMPs in elderly subjects reflects the aging-related decline of macular function. Considering c-VEMPS, the amplitude and the response rate decline, whereas the threshold increases, after 60 years of age. Despite the differences among sex and stimulation protocol, the decreased amplitude of c-VEMPs is a common finding in elderly subjects to be considered by some Authors as a sensitive indicator of vestibular senescence [38,39].

Also, o-VEMPs showed age-related amplitude decrease and latency increase, the response rate seems to be more stable and it decreases after 80 years, this latency modification is less evident in women compared to men20 (Tab. I).

Future perspectives: can vitamin D prevent macular senescence?

The otoconial composition and the maintenance of their integrity seem to be closely connected with the systemic calcium metabolism that could be accompanied by a dysregulation of the ionic components in the microenvironment surrounding the otoconia [40].

A common cause of disordered calcium metabolism is vitamin D deficiency, which can change the structure of the otoconia, inducing them to easily detach from the statoconial membrane. This hypothesis is supported by an observational study by Vibert et al, according to which 75% of women who suffer from BPPV also show signs of osteopenia or osteoporosis [41]. The underlying causes suggested by the Authors might be otoconial degeneration or decreased estrogen levels, leading to a reduced capacity to resolve otolithic debris [42].

The sum of the abovementioned age-related degeneration affecting the otoconia and the higher incidence of metabolic calcium disorders seem to be closely related to both the increased incidence and the higher

Table I. effect of aging on vestibular examination techniques.

Effect aging on clinical vestibular evaluation techniques		
Technique	**Parameter**	**Effect**
cVEMPS	Amplitude	Decrease
	Threshords	Increase
	Latencies	Inconclusive
	Response rate	Inconclusive
oVEMPS	Amplitude	Decrease
	Thresholds	Increase
	Latencies	Increase
	Response rate	Inconclusive
Caloric stimulation	Slow-phase velocity	Inconclusive
vHIT	VOR gain	Reduction

recurrence rates of benign paroxysmal positional vertigo (BPPV) in elderly [43]. Considering this evidence, vitamin D supplementation has been proposed as a promising prophylactic therapy for recurrent attacks of BPPV in patients with insufficient or deficient serum Vitamin D levels.

CONCLUSIONS

The comprehension of both peripheral and central mechanisms of hearing and vestibular senescence could predict, control and prevent the frailty condition, a multidimensional syndrome characterized by a nonspecific state of vulnerability, reduced multisystem physiological reserve, and decreased resistance to stressors. This complex condition is strictly connected to social isolation and loneliness, caused by communication impairments in older subjects with ARHI that can induce cognitive decline.

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