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 SENECE

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 marginal cells are primarily responsible for the K+ 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 recycled 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...
of cochlear endolymph involves a flow of $K^+$ from peri-
lymph 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 peri-
lymph toward the spiral ligament. A possible intracellu-
lar pathway would start with the $K^+$ uptake by support-
ing 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 com-
mon 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 endococh-
lear potential has the greatest effect on high-frequency
hearing, because of the reduced amplification, which
explains the very common increase in hearing thresh-
holds 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 di-
ameter 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. In-
deed, aged gerbils typically have a decreased EP $^7,8$,
which correlates with strial atrophy $^9$ and with degen-
eration of the microvasculature in the stria vascularis.

Human temporal bone studies have shown similar pa-
thologies of the stria vascularis. Strial atrophy, meas-
ured 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 audi-
tory 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 most-
lly $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic
acid (AMPA)-type receptors that bind the released glu-
tamate $^{12}$. 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 synap-
tic connection with an IHC, whereas each IHC is in-
nervated 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 osse-
sous 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 syn-
apse 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 mecha-
isms 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 oto lithic 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 otoconial 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 (CaCO₃) micro-crystals combined with protein matrix called otocional proteins or otoconins. The most represented is Otocoin-90 (Oc90): it plays not only a structural role, but it is essential for CaCO₃ crystallization, binding calcium from the surrounding calcium-poor endolymph. 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).

Otoconial degeneration increases above the age of 50 or 60. Igarashi et al. found a decrease in otoconial volume of 41% in the utricle and 70% in the sacculum 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. 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.

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-colic 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.

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 men (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. 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. The underlying causes suggested by the Authors might be otoconial degeneration or decreased estrogen levels, leading to a reduced capacity to resolve otolithic debris.

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 incidence of BPPV and other forms of vertigo in the elderly population.

### Table I. Effect of aging on vestibular examination techniques.

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<thead>
<tr>
<th>Technique</th>
<th>Parameter</th>
<th>Effect</th>
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<tbody>
<tr>
<td>cVEMPS</td>
<td>Amplitude</td>
<td>Decrease</td>
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<tr>
<td></td>
<td>Thresholds</td>
<td>Increase</td>
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<td></td>
<td>Latencies</td>
<td>Inconclusive</td>
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<td></td>
<td>Response rate</td>
<td>Inconclusive</td>
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<tr>
<td>oVEMPS</td>
<td>Amplitude</td>
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<td>Thresholds</td>
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<td>Latencies</td>
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<td></td>
<td>Response rate</td>
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<td>Caloric stimulation</td>
<td>Slow-phase velocity</td>
<td>Inconclusive</td>
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<td>vHIT</td>
<td>VOR velocity</td>
<td>Reduction</td>
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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.

References

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