Handbook of Clinical Neurology, Vol. 129 (3rd series)
The Human Auditory System
G.G. Celesia and G. Hickok, Editors

Chapter 20

Aging of the auditory system

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GENERAL ASPECTS OF AGING

From a biologic point of view, an individual life cycle begins with the fusion of two chromosome sets, continues with proliferation and differentiation, and ends with the loss of cell and organ function, leading to death. Hence, life can be considered a genetic program depending on innumerable factors and interacting with just as many promoting, as well as potentially destroying, influences. This process of development is controlled meticulously by mechanisms responding to the need of the cell and the organ.

These mechanisms oscillate between proliferation and degeneration in order to maintain a dynamic equilibrium in the continuous cycle of metabolism.

The ability of proliferation requires the capability to deplete the ancient state of function and to create a new condition that permits mutation in another state. Hence, in this mutation process, various actions, such as inhibition and stimulation, agonists and antagonists, degeneration and proliferation, are all present at the same time throughout the body and interact in a multitude of feedback mechanisms.

In a more general aspect the growth of any species is a controlled development of different organs and structures that on the one hand depend on one another and on the other hand permit the species to interact with other species.

In large, complex, multicellular organisms, each part of the body has its specific function, leading to a balanced and interconnected system able to survive in the prevailing circumstances and to respond to both internal and external factors.

As proliferation is a genetically controlled process that depends in a certain way on the senescence of the antecedent cellular state, aging is in a comparable way a genetic process that affects cells, organs, or the whole organism itself. The rare syndrome of progeria that describes the premature senescence emphasizes the genetic impact in the process of aging (Coppedè, 2013).

Illnesses and pathologies develop due to disturbed regulation or overwhelmed adaptation mechanisms. Pathologic decline of specific organs may entail deleterious knock-on effects on other organs. For example, diabetes mellitus, whilst being a primarily exocrine pancreatic problem, leads to a multitude of distant effects, including accelerated arteriosclerosis and polyneuropathy.

To what extent aging itself is "pathologic" is debatable. Certain age-related changes are normally regarded as physiologic, for example the growth spurt of puberty, the involution of the thymus, or even the menopause. Such changes may be viewed as positive for the body and have protecting reasons, e.g., for the hosting female organism and for the potentially new embryo as well.

The specific aging mechanisms of the inner ear include genetic and environmental/systemic factors. leading to a progressive hearing loss of significant individually variation (Walters and Zuo, 2013). Beyond the cochlea itself, changes in the auditory pathway and brain also significantly affect our sense of hearing.

In this chapter, general and epidemiologic aspects as well as histologic changes based on Schuknecht's classification are discussed. Furthermore, some molecular biologic considerations, e.g., oxidative stress, endocochlear potential, the role of mitochondria and supporting elements such as fibrocytes and their effect on presbycusis, are discussed with the aim of giving further insights to the age-related cellular metabolism that may explain histologic changes and the clinical characteristics of age-related hearing loss (ARHL). Furthermore, some aspects of age-related changes in the central nervous system are also considered. Finally, management of the consequences of ARHL is discussed.

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DEFINITION AND TERMINOLOGY

Presbyacusis is a term that literally translates to "hearing in the older age." It includes all factors and structural changes leading to hearing loss in elderly people. Nowadays the term "age-related hearing loss," abbreviated ARHL, is used preferably. The disorder is characterized by high-frequency-dominated hearing loss, reduced speech understanding (particularly in noisy environments), slowed central processing of acoustic information, and impaired localization of sound sources. These difficulties have a direct impact on lifestyle and social activities by impairing communication (Gates and Mills, 2005).

Additional terms may complement the description of the clinical presentation of ARHL. The term "sensory hearing loss" refers to an elevated hearing threshold level as measured in pure-tone audiometry demanding a higher acoustic level to excite the organ of Corti, while "sensorineural hearing loss" includes the signal transduction of sensory cells, their synapses, and the cochlear nerve. ARHL seems to belong mainly to this latter category. The term "perceptual" derives from the Latin verb *percipere*, signifying to understand or to hold something, and includes perceiving or catching on to the meaning of spoken words or other acoustic messages; this term may include a disturbed central auditory process in conjunction with age-related changes of the sensory and neural parts of the auditory system. Finally, the term "central" restricts the origin of the hearing disorder to the central nervous system, including the auditory cortex.

Patients with presbycusis typically describe two types of difficulty: on the one hand they complain, "I do not hear well" or "My hearing has become worse," whereas on the other hand, "I can hear, but I can't understand in a noisy environment." The observation of these two different aspects implies that it is not only the peripheral cochlear part with decreased hearing threshold that plays an important role in the aging process of the auditory pathway, but that other elements in neurophysiologic signal transduction – including the central neural framework – are involved, leading to hearing difficulties, especially in noisy situations (Otto and McCandless, 1982). Consequently, auditory perception presupposes both a well-functioning peripheral part and a well-interconnected central framework of modulating and sensory areas.

The age-related decline in function of the peripheral hearing organ is related to an individual's genetics background and the cumulative damage of noise, middle-ear inflammation, medication, exposure to toxins including nicotine, and cardiovascular and rheumatologic factors. Indeed, innumerable factors influence the severity and onset of ARHL, and there is no generally accepted single etiologic factor. Even a multifactorial analysis is extremely complex and likely an oversimplification, though some of the factors thought to be most significant are discussed below in more detail.

Aging also affects central nervous function in general by slowing down processing speed and making task-related inhibition less effective. Poorer speech understanding in ARHL often has both peripheral and central components and it is often difficult to assess which is the most significant contributor (Otto and McCandless, 1982; Gates and Popelka, 1992). Moreover, patients with disease-related impairment of the central nervous system typically exhibit deficits in other cognitive functions affecting daily life more severely than patients with an isolated hearing loss.

EPIDEMIOLOGY

It is difficult to assess the prevalence and epidemiology of ARHL because of manifold influences and different factors contributing to hearing loss and due to a variety of sociocultural, behavioral, and psychologic aspects. Furthermore, difficulties arise because of a lack of standardization and different selection criteria that have their impact on hearing function. The lack of consistent definitions prevents the compiling of accurate data on hearing loss.

Epidemiologic data are easy to measure for certain types of information, for example mortality, or well-defined and measurable states, such as whether a pathohistologic diagnosis of cancer exists. In contrast, ARHL is on a continuous scale without a clear border between normal and impaired function. Furthermore, such objective measures do not necessarily correlate with subjective complaints and perceived handicaps. For example, a professional musician will notice hearing impairment more strongly than someone who does not rely on hearing for a profession.

Any definition of ARHL is unavoidably subjected to arbitrary limits due to the vast variety of factors, and this gives rise to methodologic problems. An evident and primary difficulty in comparing reported prevalence data is the different measures and cut-offs for hearing impairment. There is also a difficulty in defining chronologic "age" itself related to the prevalence of ARHL. While several international systems of hearing loss classification exist, they do not include age in their definitions. Even if a chronologic age may have limited biologically relevance, definitions are necessary to obtain clear epidemiologic data. International classification systems such as those of the European Union or the World Health Organization (WHO) differ considerably. Standard age limits may be even more difficult to define than limits of

Table 20.1

Standardized hearing loss categories

Categorization	WHO classification
Normal	dBHL < 26
Mild	26 ≤ dBHL < 40
Moderate	41 ≤ dBHL < 60*
Severe	61 ≤ dBHL < 80
Profound	80 < dBHL

*According to the World Health Organization (WHO), hearing impairment of the better ear >41 dB has been defined as disabling.

hearing loss. For example, ISO-7029 is a statistical distribution of hearing threshold as a function of age from the International Organization for Standardization (ISO); this standard is based on a linear model for ages 18–70 years (ISO, 2000), but does not include older ages with their non-linear increase in hearing loss. A single and widely accepted universal classification of ARHL is needed to collect epidemiologic data and to compare prevalence in different countries. Because no system has clear advantages over the other, the WHO classification system is recommended to be used for future data collection (Table 20.1).

In addition to problems associated with a lack of standardized methods for defining ARHL, a recent systematic review of epidemiologic data on the prevalence of ARHL in Europe revealed significant information gaps, for example, heterogeneity of selection criteria and differences in cut-offs for grades of hearing impairment (Roth et al., 2011). Neither geographic distributions nor developments over time could be extracted to a reasonable degree. Nevertheless, the studies reflect the well-known patterns of a non-linear increase of hearing loss, with age affecting men more than women. If the data are crudely averaged and interpolated, roughly 30% of men and 20% of women in Europe have a hearing loss of 30 dB HL or more at age 70 years, and 55% of men and 45% of women at age 80 years. The geographic distribution of European studies showed a relative paucity of studies in the middle, southern, and eastern parts of Europe; this may reflect differences in public health systems which attach more or less importance to ARHL in different regions (Table 20.2).

Differences in the language spoken in different regions may also impact epidemiologic data for ARHL. For example, vowels have a distinct perceptual advantage over consonants in determining speech intelligibility (Kewley-Port et al., 2007; Fogerty and Kewley-Port, 2009), which could affect the prevalence of self-reported hearing impairment across different languages (Roth et al., 2011).

In the United States, the overall prevalence of ARHL, defined as hearing loss of more than 25 dB HL in speech frequency, was reported to be 39% for men and 17% for women at the age range of 60–69 years, and 63% for men and 48% for women at the age range of 70–79 years (Agrawal et al., 2008). Another estimate reported a prevalence of 23% of American people aged between 65 and 75 years and 40% of people over 75 years of age, illustrating the vastly different results obtained in different studies (Seidman et al., 2002). Considerations about the difference between men and women are discussed in the section below. Another interesting aspect of the American data is that Afro-Americans seem to be considerably less affected by ARHL than white people (Agrawal et al., 2008; Lin et al., 2011).

Table 20.2

Prevalence of age-related hearing loss in Europe*

Reference	Country	Prevalence with nearest cut-offs for HL and age
Bergmann and Rosenhall, 2001	Sweden	> 19% (70 years at 30–39 dB)
Borchgrevink et al., 2005	Norway	> 14.2% (60–64 years at 35 dB)
Davis, 1989	UK	> 7.4% (61–70 years at 45 dB)
Davis, 1995	UK	> 24.5% (61–70 years at 30 dB)
Hietanen et al., 2005	Denmark, Sweden, Finland	>16.5% (75 years at 40–69 dB)
Hietanen et al., 2004	Finland	>28.3% (80 years at 40–69 dB)
Johansson and Arlinger, 2003	Sweden	> 8.8% (60–70 years at 35 dB)
Moller, 1981	Sweden	9% (70 years at 35 dB)
Quaranta et al., 1996	Italy	6.7% (61–70 years at 45 dB)
Rahko et al., 1985	Finland	10.3% (65 years at 30 dB)
Rosenhall and Karlsson Espmark, 2003	Sweden	24% (70 years at 30–39 dB)
Wilson et al., 1993	UK	54.3% (≥65 years at 35 dB)

*This table lists the minimum prevalence in men and women for minimum better-ear hearing loss (HL) of 30 dB and lower age interval border of 60 years.

These epidemiologic data confirm that ARHL is a major health concern in the aging population. They also demonstrate the need for standardized collection of epidemiologic data on hearing loss.

Epidemiology and etiology are intimately related in that population-based endogenous factors will be exposed to geographically varying exogenous factors. Given the variable epidemiologic data and the complex interaction of etiologic factors and their influence on ARHL, it is not surprising that meaningful connections between epidemiology and etiologic factors are difficult to be established.

The most relevant factors in the etiology of ARHL seem to be heredity (that may contribute up to 50%), noise exposure, history of chronic middle-ear inflammation, and cardiovascular factors, including diabetes, smoking, and hypertension. Additional relevant factors are hormones (including gender-related differences), exposure to ototoxic medication or chemicals and comorbidities, such as rheumatologic disease (Murdin et al., 2008; George and Pradhan, 2009). All these factors may cause oxidative stress as a common end molecular pathway. Such stress leads to alteration of cochlear homeostasis and to changes of the different anatomic structures accelerating the aging process.

HISTOPATHOLOGIC CHANGES AND SCHUKNECHT'S CLASSIFICATION

Different components of the cochlea have specific functions in inner-ear homeostasis and are prone to age-related changes; for example, the spiral ligament with its cellular and fibrous part as well as the important role of fibroblasts on the basilar membrane or the stria vascularis, considered as the "cochlear battery," with its impact on the electrolyte homeostasis in the endolymphatic liquid. The inner and outer hair cells with their stereocilia covered by the tectorial membrane are also vulnerable to aging.

Beyond the organ of Corti, the poorly understood neural framework of afferent and efferent fibers, the spiral ganglion, and the cochlear nucleus of the brainstem exhibit age-related changes (Frisina and Walton, 2006; Makary et al., 2011). Furthermore, there is evidence that age-related pathologies of the central nervous system have a negative impact on the peripheral cochlear organ (Otto and McCandless, 1982; Eckert et al., 2012).

The classification of Schuknecht is based on the age-related changes of the cochlea. In correlation with rather crude audiometric data archived in his laboratory, Schuknecht described in various temporal bone studies degeneration or age-related changes of the organ of Corti, ganglion cell, stria vascularis and basilar membrane. This led to a classification of ARHL in sensory, neural, strial or metabolic and cochlear-conductive categories. Two more categories, indeterminate and mixed, were also added. The latter was reported to be responsible for up to 25% of cases. This classification is called the Schuknecht's typology of ARHL and has been revised recently by Merchant and Nadol (Nadol, 2010) as follows.

Sensory presbycusis

Histopathologically, this diagnosis rests on the finding of hair cell loss at the beginning of the basal end of the cochlea. Schuknecht connected this kind of histopathologic finding to audiograms showing typically an abrupt high-tone hearing loss (Fig. 20.1) (Schuknecht and Gacek, 1993). The earliest notable degenerative changes in hair cells affected the sterocilia, followed by slightly distorted and flattened organ of Corti, and subsequently loss of hair cells and supporting cells. Both cell types accumulate lipofuscin in the apical cytoplasm. This accumulation correlates with the presence of lysosomes, indicating exhausted enzyme activity.

Neural presbycusis

When the loss of cochlear neurons was more than 50%, the term neural presbycusis was used. The progressive loss of neurons was observed throughout the cochlea (Fig. 20.2). There is a debate about the causes of spiral ganglion cell loss and whether it is primary or secondary. Loss of inner hair cells, supporting elements, and injury to dendritic fibers are proposed factors for secondary degeneration, but primary degeneration has been identified in different entities, e.g., sudden deafness, Friedreich's ataxia, Ménière's disease, or Usher's syndrome, and age-related primary degeneration has been reported in both humans and animals.

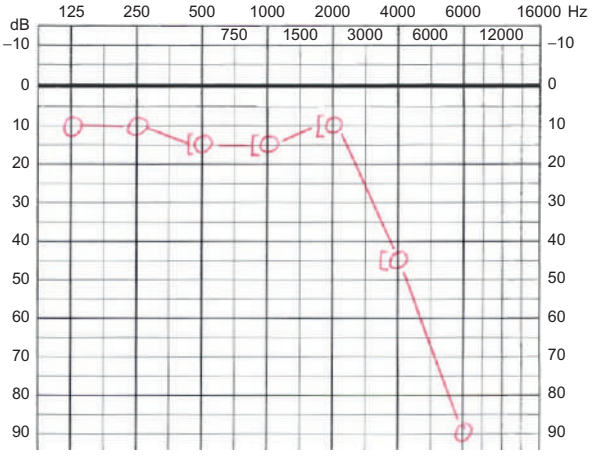

Fig. 20.1. Sensory presbycusis.

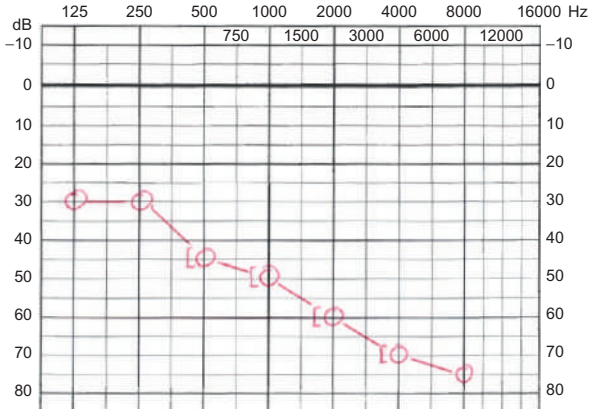

Fig. 20.2. Neural presbycusis.

The characteristic clinical finding is a progressive loss of word discrimination, termed phonemic regression. Elderly people with rapidly progressive neural presbycusis exhibit signs of general central neurodegeneration, including motor weakness, coordination problems, irritability, loss of memory, and intellectual deterioration.

Strial presbycusis

Strial presbycusis is defined as a loss of 30% or more of the strial tissue. When strial loss exceeded this percentage, threshold levels deteriorated in the tone audiogram. The stria vascularis is considered to have an important functional role in inner-ear homeostasis, particularly in the generation and maintenance of the endocochlear potential. Strial atrophy was noted to have a familial correlation, and hence may have a genetic predisposition. The main audiometric characteristic is a flat or slightly descending threshold level (Fig. 20.3). Usually patients do not complain of discomfort with loud sounds. The histologic changes are predominantly in the apical and basal turn of the cochlea (Figs 20.4 and 20.5).

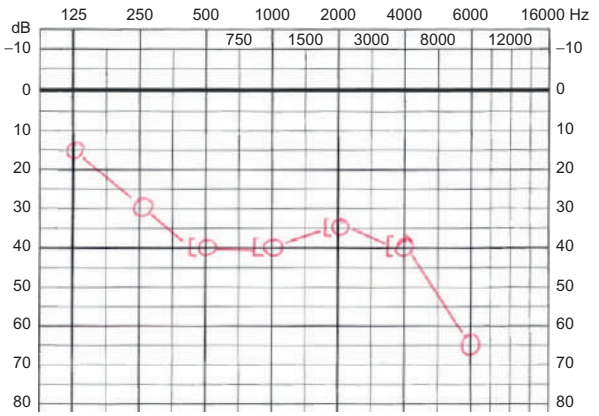

Fig. 20.3. Strial presbycusis.

Atrophy of the spiral ligament

Schuknecht observed a degeneration of the spiral ligament as a function of age, beginning in childhood. The atrophy was most severe in the apical region of the cochlea. Degeneration of the enzyme-producing spiral ligament seems to play an important role in the development of presbycusis in animal studies. Degeneration of fibrocytes preceded the loss of hair cells and neurons. In humans as well, the earliest alteration is the loss of fibrocytes; these changes were more frequent in ears exhibiting descending audiometric patterns. Figures 20.6–20.9 show differences between a young and an aged gerbil in the spiral ligament.

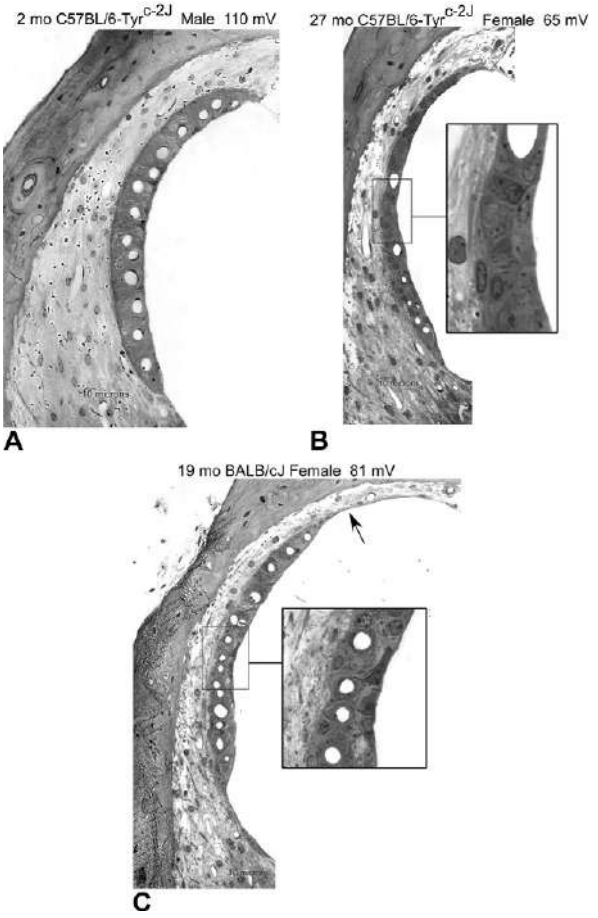

Fig. 20.4. Strial atrophy and spiral ligament pathologies. Examples of lateral wall in the lower cochlear base of young B6 albino (**A**), old B6 albino (**B**), and old BALB/c (**C**). Age, gender, and basal turn endocochlear potential are indicated). Aging was associated with strial thinning and marginal cell loss in both strains. Severity of capillary loss and ligament thinning in (**B**) are atypical for this strain. BALB (**C**) features greater loss of marginal cells along the luminal surface. Marginal cells in (**C**) inset show dense staining and retraction of processes. Arrow in (**C**) denotes somewhat unusual strial atrophy. (Reproduced from Ohlemiller, 2009.)

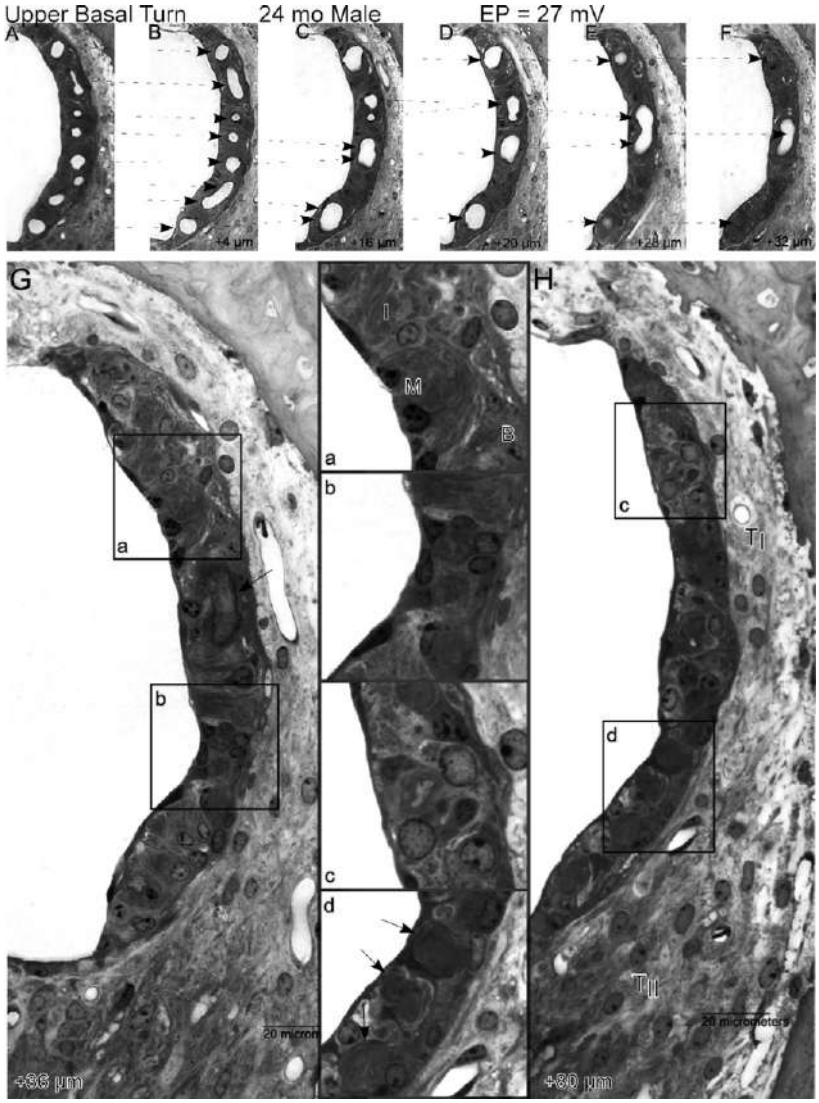

Fig. 20.5. Strial microvascular pathologies in 24-month-old male gerbil. Sequential sections (**A–H**) proceeding apically from the upper base of a 24-month-old male gerbil, showing progressive merging of strial capillaries, leaving the stria completely avascular over a span of 80 µm. Dashed arrows in **A–F** show how capillaries progressively merge, ultimately forming a blind loop. The first completely avascular segment (**G**) features well-organized regions (inset a), as well as regions with increased numbers of poorly differentiated cells (inset b). The arrow in **G** shows the wall of the last capillary loop. By 80 µm (**H**), the stria is still present but thin, and shows hyperplasia of undefined cell types over most of its length (inset c). Traces of degenerated capillaries can still be seen (inset d, arrows). The ligament at this location appears normal. TI, type I fibrocytes; TII, type II fibrocytes; B, basal cells; I, intermediate cells; M, marginal cells; EP, endocochlear potential. (Reproduced from Ohlemiller et al., 2008.)

Indeterminant presbycusis

When no significant age-related change of any structure was present, the term "indeterminant presbycusis" was used. Twenty-five percent of all clinical cases of human presbycusis do not exhibit cochlear changes by light microscopy. However, degeneration of the dendritic arborization in the spiral ganglion cells and alteration of the tip links on hair cells have been described in electron microscopy. Changes of altered enzymatic pathways at molecular levels on the lateral cochlear wall have been put forward as a possible pathophysiologic explanation. These pathways seem to exhibit an important role in inner-ear homeostasis and maintenance of cellular function. Other hypotheses are age-related changes affecting more central parts of the hearing pathway, e.g., the cochlear nuclei.

Mixed presbycusis

When significant age-related changes are observed in more than one structure, they are classified as mixed

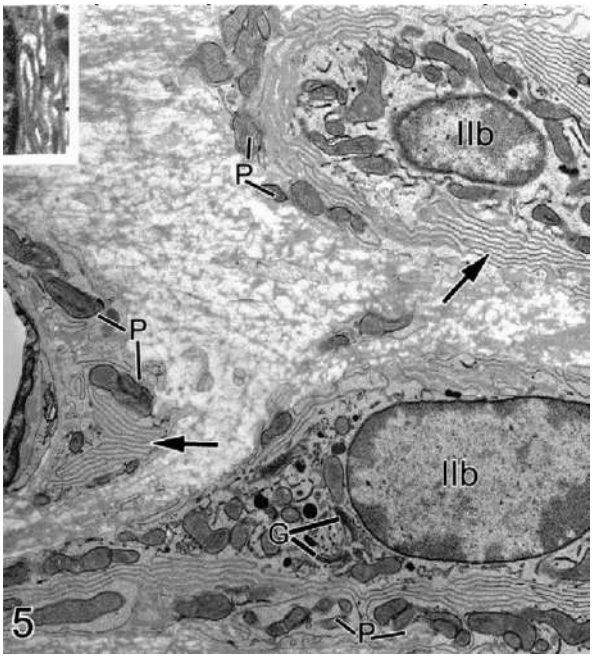

Fig. 20.6. Spiral ligament of a young gerbil. In the spiral ligament of a young control, elongated type IIb fibrocytes display elaborately pleated foldings that greatly amplify the cell surface (arrows and inset). The fibrocytes enclose numerous large mitochondria bordering the nucleus and infiltrating primary processes (P), together with prominent Golgi zones (G). Magnification × 6000. Basal region. (Reproduced from Spicer and Schulte, 2002.)

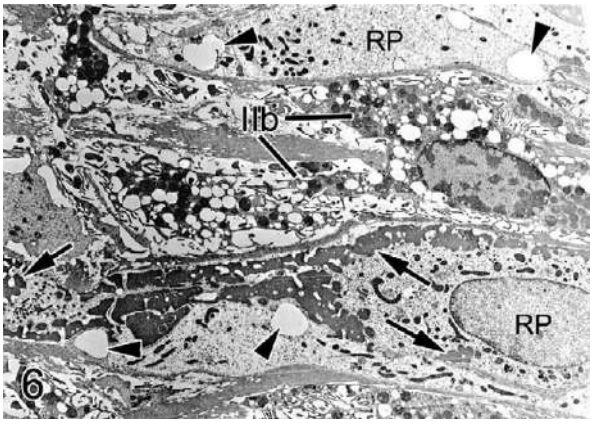

Fig. 20.7. Spiral ligament pathologies of an aged gerbil. Type IIb fibrocytes from aged gerbil 1 exhibit shrunken cell bodies heavily infiltrated with variable-sized clear vacuoles. Empty-looking spaces separate the cells and their plasmalemmal projections. A thick layer of dense substance lines the periphery (arrows) of a root process (RP) paralleling a vacuolated fibrocyte. Neighboring root processes enclosing a few vacuole-like spaces (arrowheads) lack the marginal dense deposits. Magnification × 2800. Basal region. (Reproduced from Spicer and Schulte, 2002.)

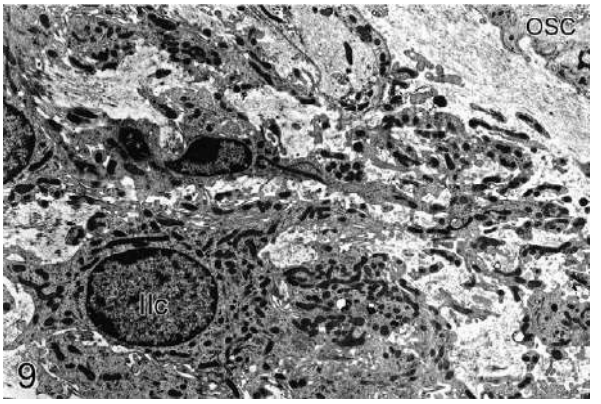

Fig. 20.8. Spiral ligament of a young adult gerbil. The spiral ligament under outer sulcus cells (OSC) of a young adult gerbil exhibits congregated type IIc fibrocytes containing many mitochondria. Abundant processes of these rather stellate cells intermingle in loose stroma devoid of the dense bands that border IIb fibrocytes. Magnification × 4800. Apical region. (Reproduced from Spicer and Schulte, 2002.)

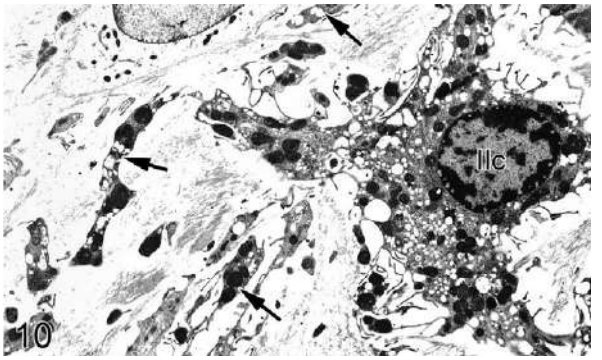

Fig. 20.9. Spiral ligament pathologies of an aged gerbil. An empty-looking zone encircles the stellate profile of a type IIc fibrocyte from a gerbil. Numerous small to large vacuoles populate the cytosol in the cell body and in nearby cell processes (arrows). Magnification × 4800. Basal region. (Reproduced from Spicer and Schulte, 2002.)

presbycusis. Unfortunately, this type exhibits no consistent audiometric patterns.

Cochlear conductive presbycusis

Cochlear conductive presbycusis is based on both clinical and pathologic criteria. It can be considered an interesting hypothesis of a mechanism leading to sensorineural hearing loss, but there is, however, no convincing evidence of a cochlear conductive defect. Hence this remains an unproven theory. Schuknecht described age-related thickening and hyaline degeneration of the basilar membrane and deposition of calcium salts in the basal portion of the membrane. A possible

explanation concerning these findings will be considered in the section below, focusing on the role of fibrocytes and inner-ear homeostasis.

Even though the classic types of presbycusis, i.e., sensory, neural, and strial persbycusis could be correlated with defined shapes of audiograms (Figs 20.1–20.3), a clear pathophysiologic explanation or pathohistologic pattern for the other types is lacking. Hence, Schuknecht's classification is considered vague and imprecise because most aging human and animal cochleas exhibit a mix of pathologies; furthermore, it was somewhat criticized because the classification concentrates on morphology of the peripheral hearing organ, excluding many functional and central aspects of hearing processing (Ohlemiller, 2004).

Therefore, and due to the fact that several causes overlap and interfere with each other, further explanations may be given by molecular biology and genetic analyses, opening a vast field in the modern area of research on ARHL.

A brief overview of some of these mechanisms is presented in the next section, with the aim of contributing some insights to the underlying cellular processes, which may lead to the above-mentioned histopathologic alterations of the cochlea.

AGING OF THE PERIPHERAL AUDITORY SYSTEM

Aging is not only determined by genetics, but also influenced by oxidative stress (Fig. 20.10). Several factors, e.g., infection of the middle ear, noise, and systemic diseases, cause oxidative stress that damages inner-ear structures and leads to premature aging (Fig. 20.11). Based on the above-mentioned histologic changes, some of the cellular parts of the inner ear are pointed out with respect to age-related changes. First, the role of oxidative stress and the damaging free radicals is highlighted and then some genetic aspects are summarized with respect to the damage caused by the oxidative stress. Furthermore some mechanisms of inner-ear homeostasis and metabolic factors that influence cell aging are described.

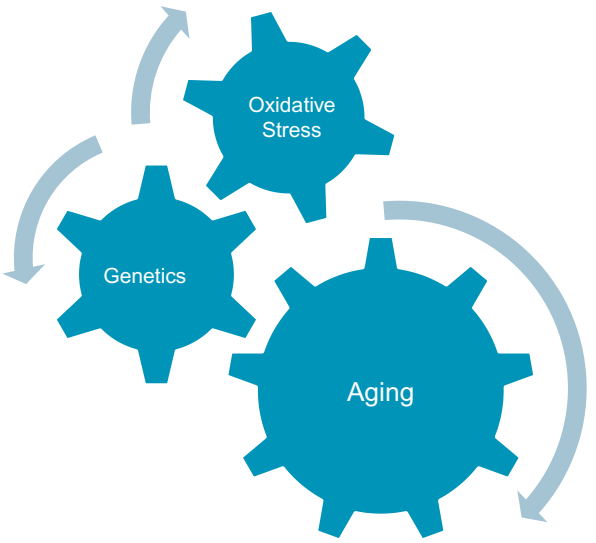

Fig. 20.10. Aging is a lifelong process which can be visualized as a wheel that is promoted by genetics. Various endogenous and exogenous factors lead to oxidative stress, which may overwhelm compensatory mechanisms and accelerate aging.

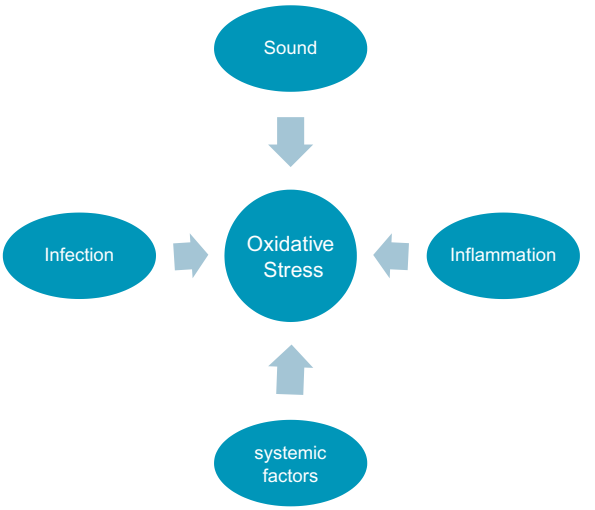

Fig. 20.11. Causes of oxidative stress in the inner ear. Many factors lead to disturbed intracellular homeostasis and therefore to oxidative stress. Overexposure to sound causes oxidative stress in the inner ear as well as systemic factors, e.g., diabetes, vascular and rheumatic factors, and some medication. Furthermore, infection, chronic inflammation, and irradiation therapy have a negative effect on inner-ear homeostasis.

Oxidative stress

Oxidative stress is determined by the imbalance between the production of oxygen metabolites and the cellular ability to detoxify reactive metabolites. These reactive oxygen metabolites and free radicals are highly toxic to many cellular components, even though some of them act as cellular messengers. Thus, if the cell is unable to repair the damage or to restore normal homeostasis, oxidative stress disturbs normal cellular signaling and leads to cell injury or even to cell death (Fig. 20.12).

Mitochondria exhibit an important function in maintaining the production and consumption of these toxic metabolites. Reduced activity of mitochondria increases the reactive metabolites and causes DNA damage that in turn reduces the mitochondrial activity on its own (Seidman, 2000).

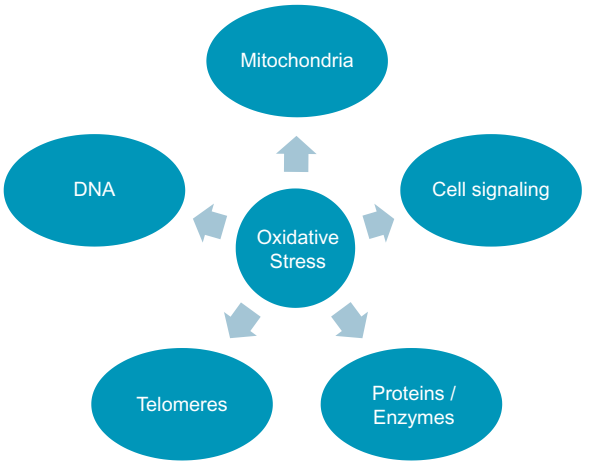

Fig. 20.12. Oxidative stress is due to the accumulation of free radicals during cell respiration. When the cell is unable to detoxify, cell metabolism is injured by these free radicals, leading to cell aging or even cell death. Mitochondria have an important role in detoxifying the cell, but mitochondria on their own are vulnerable to overwhelming oxidative stress. The disturbed calcium regulation due to mitochondrial injury leads to altered cell signaling with adverse effects on the surrounding cells.

Many factors cause oxidative stress (Fig. 20.11). In terms of cochlear pathology, bacterial toxins and noise overexposure cause acute oxidative stress in the cochlea and labyrinth and disturb inner-ear homeostasis with subsequent cell damage, resulting in sensorineural hearing loss and vertigo. Chronic inflammation or infection leads to oxidative stress and negatively affects the cochlea. The accumulation of free radicals in stressed cells on one hand has a toxic effect to bacteria that is advantageous for survival of the organ, but on the other hand damages cellular structures and in some way accelerates the genetic process of aging.

Genetics

As mentioned above, progeria as well as other pathologies, e.g., muscular dystrophies, scleroderma, and cardiomyopathies, belong to the group called laminopathies. They are determined by a genetic defect of the LMNA gene, producing aberrant nuclear proteins (lamin). These proteins lead to abnormal shape of the cellular nucleus and, therefore, have a wide range of effects on cellular function, leading to a broad presentation of clinical symptoms and the manifestation of premature aging (Zhang et al., 2013). To date, no studies are available in the literature investigating the effect of laminopathies on the inner ear.

Another protein, called klotho, was discovered in 1997 and acts as an aging suppressor gene (Kuro-o et al., 1997). It was named after the Greek goddess who spins the thread of life. The gene mutation in the klotho mouse exhibited multiple disorders resembling human premature aging (Kuro-o, 2008), but the protein acts in a different manner than those causing the syndromes of laminopathies. The klotho gene encodes for a secreted protein and has therefore an extracellular function which seems to be involved in the regulation of oxidative stress and senescence.

Klotho is expressed predominantly in tissues involved in the regulation of calcium homeostasis and was found in the stria vascularis and the vestibular dark cells of the inner ear (Kamemori et al., 2002; Takumida et al., 2009). Due to the distribution of klotho close to the Na-K-Cl co-transporter and the involvement of klotho with other proteins that regulate calcium homeostasis, e.g., transient receptor potential (TRPV), it was suggested that klotho participates in the regulation of the ionic composition of the endolymph; furthermore, the expression of klotho in the inner-ear sensory cell of the mouse led to the hypothesis that klotho is involved in signal transduction in the inner ear (Takumida et al., 2009). The expression of klotho was found to be closely related to the lifespan of the organism and klotho seems to have a protective effect against oxidative stress and to increase cell resistance to the subsequent damage (Yamamoto et al., 2005; Ikushima et al., 2006).

Telomeres consist of a series of non-coding, hexanucleotide repeats found at the end of chromosomes, and serve to ensure genomic stability during cell division. Telomeres and telomerase have been investigated not only in cancer development but also in their role of cellular senescence in mitotic cells (Smith et al., 2013). The corresponding enzyme, telomerase, is responsible for maintaining telomere length. It has been reported that telomeres and telomerase are a preferential target of DNA damage under oxidative and genotoxic conditions (Hewitt et al., 2012). Hence, defective DNA leads to a defective cell cycle, with the well-known adverse effects that gradually affect cell and organ structure and function, including cellular aging as well.

Mitochondria

As a consequence of the mechanisms mentioned above, an important aspect of aging can be attributed to mitochondria. Mitochondria exhibit a key role in cell cycle: on the one hand they provide energy and on the other hand they clean reactive oxygen species.

Mitochondria are involved in the aging process. Their interaction with calcium homeostasis and their important role in reducing oxidative stress lead to the mitochondrial clock theory of aging, also referred to as the membrane hypothesis of aging (Seidman et al., 2004).

Mitochondria have a high transmembrane gradient that is vulnerable to oxidative stress. Thus, oxidative stress not only damages the mitochondrial membrane but also leads to a disturbed calcium regulation and hence to altered intracellular signal processes that entail disturbed cell metabolism and finally lead to cell death (Smaili et al., 2013).

Mitochondrial pathologies play an important role in both inherited and acquired hearing loss. Genetic mutation of mitochondria, e.g., the MELAS syndrome (syndrome of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) presents clinically in a high percentage with sensorineural hearing loss caused mainly by dysfunction of the stria vascularis, which accounts for the cochlear battery, as mentioned above (Takahashi et al., 2003).

ARHL seems to be caused by mitochondrial dysfunction. Several factors cause oxidative stress that leads to the accumulation of acquired mitochondrial DNA mutations. With preponderance of DNA damage, mitochondria are damaged and the cell becomes bioenergetically deficient (Fischel-Ghodsian et al., 2004). Prior to hair cell injury, mitochondria seem to be affected by oxidative stress first. Altered mitochondria were found in the afferent nerve endings (Omata and Schätzle, 1984), and elevation of reactive oxygen species was observed after acute noise exposure (Ohlemiller et al., 1999).

Furthermore, mitochondria are providing the energy for the transmembrane ion pumps that maintain the high endocochlear potential.

Endocochlear potential

Histological changes in ARHL are predominantly in the basal end of the cochlea, progressing to the upper base. They were investigated with particular interest in the stria vascularis (Ohlemiller et al., 2008). The stria vascularis shows a high density of mitochondria and contains marginal cells, which are characterized by a unique complement of potassium channels and pumps responsible for maintaining the high endocochlear potential. The potassium exchange is supported by fibrocytes, which exhibit an important function in inner-ear homeostasis (García Berrocal et al., 2008). Typically, ARHL is combined with degeneration of the stria vascularis and reduced endocochlear potential (Fig. 20.13) (Schuknecht et al., 1974; Ohlemiller, 2009).

The changes in the stria vascularis are not only marked by loss of marginal cells and fibrocytes, but also in reduced density of mitochondria. Both these changes lead to reduced endocochlear potential. Given the observation that all these parts of the stria vascularis, i.e., mitochondria, fibrocytes and endocholear potential, are reduced in ARHL, this suggests that a closely related and interdependent connection meticulously tunes the electrolyte exchange, particularly sodium, potassium, and calcium (Fig. 20.14) (Goto et al., 1999; Ichimiya et al., 2000; Wangemann, 2002; Spicer and Schulte, 2002; Ohlemiller et al., 2006; Mann et al., 2009; Smaili et al., 2013).

Reduced endocochlear potential itself influences inner-ear homeostasis by increasing oxidative stress, causing further cell damage and thereby accelerating the aging process. This age-related alteration is most apparent in the basal turn of the cochlea, the region with the highest density of mitochondria. Whether the basal turn has high energy demands or is the most important and powerful region in inner-ear homeostasis is a difficult question to answer.

In addition to the mitochondrial aging theory or other local cellular factors, strial insufficiency may also be caused by microvascular pathologies due to systemic changes, such as hypertension, diabetes mellitus, hyperlipoproteinemia, hyperlipidemia, or autoimmune diseases, which all have an impact on ARHL. Correlated with age and duration of diabetes, significant changes in the cochlea were described: thickening of the vessels and basilar membrane and atrophy of stria vascularis were seen in all turns of the cochlea, while loss of outer hair cell was found only on the lower basal turn (Fukushima et al., 2005).

In a similar manner, acute otitis media with labyrinthitis shows a decreasing slope in higher frequencies in the tone audiogram, similar to Figure 20.1. This is explained by bacterial toxins and inflammatory mediators penetrating through the oval window and leading to oxidative stress and consequently to a disturbed homeostasis damaging the adjacent structures, i.e., in the basal turn of the cochlea (Cureoglu et al., 2004). The destruction depends on bacterial virulence and local immune conditions.

Independently of the pathophysiologic origin of energy loss, it seems conceivable that age-related reduction of the endocochlear potential will be particularly distinctive in the basal turn due to the high density of mitochondria. This corresponds with the clinical observation that many entities affecting the inner ear, e.g., inflammation, noise, or infection, lead to a sensory hearing loss (Fig. 20.1). The significant histopathologic changes of the cochlea, i.e., decrease in outer and inner hair cells and decrease in stria vascularis and the spiral ligament in the basal turn, were shown to be induced by chronic otitis media (Cureoglu et al., 2004). Cochlear inflammation is supposed to disrupt fibrocyte function of the spiral ligament; the stimulated fibrocytes produce chemoattractant mediators that induce prolonged inflammation and consequently lead to structural

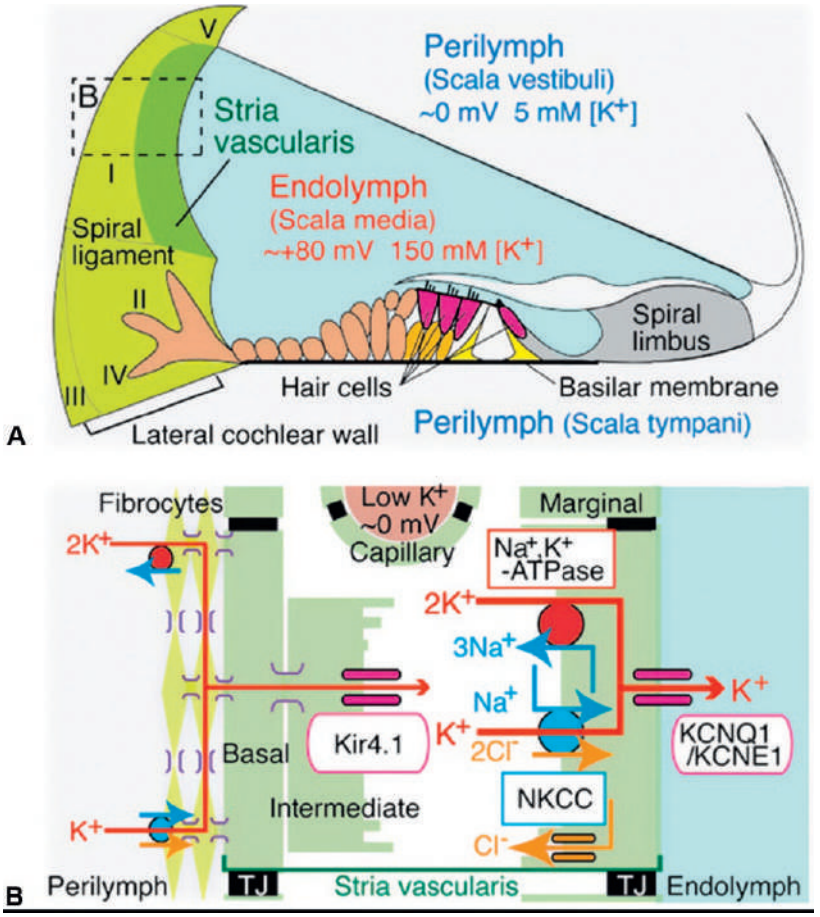

Fig. 20.13. Potassium exchange in the lateral wall of the cochlea. Reprinted from Ohlemiller (2009) and Nin et al. (2008), with permission. Copyright (2008) National Academy of Sciences, U.S.A. Schematic structure of the cochlear duct with the lateral wall. (**A**) Appropriate ionic composition of the endolymph and the endocochlear potential (EP) require that an ion barrier line scala media, the intrastrial space, and strial capillaries. A nearly continuous cellular network guides K^+ from the organ of Corti through finger-like root cells into (primarily) type II and I fibrocytes. Fibrocytes must take up K^+ from the extracellular space around root cells. Locations of five major types of fibrocytes are indicated by roman numerals. (**B**) Schematic enlargement of the boxed area in (**A**) depicts the cells and components required to generate the EP. Type I fibrocytes, strial basal cells, intermediate cells, as well as capillary pericytes (not shown) are joined by gap junctions composed mostly of connexins 26 and 30. K^+ enters the intrastrial space through Kir4.1, then through marginal cells via Na^+/K^+-ATPase, the NKCC ion exchanger, and KCNQ1/KCNE1 channel complexes. TJ, tight junction. (Reproduced from Ohlemiller, 2009 and Nin et al., 2008.)

changes, as mentioned above (Ichimiya et al., 2000; Moon et al., 2006).

The reduced endocochlear potential not only affects the sensory part of the inner ear but also leads to alteration of the supporting structures, e.g., fibrocytes and connective tissue.

Fibrocytes and fibroblast growth factor

Fibrocytes are not only important in the embryologic development of the cochlea; they continue to exhibit a crucial function in "backstage work," providing inner-ear homeostasis; as mentioned above, they are involved in potassium ion exchange. Five different types of fibrocytes are present in the spiral ligament, enabling the Corti organ to conduct signal transduction (Suko et al., 2000) (Fig. 20.15). Moreover, fibrocytes are involved in repairing function during acute or chronic inflammation (Ichimiya et al., 2000); their mediating role in inflammation seems to be decreased and inhibited by corticosteroids (Moriyama et al., 2007).

Fibrocytes are important contributors to forming and supporting cochlear structures, such as delivering components of microtubules to the hair cells (Szarama et al., 2012). Microtubules of the Corti organ also show age-related changes and may contribute to the alteration of micromechanical properties in signal transduction (Saha and Slepecky, 2000). Normal ciliar function

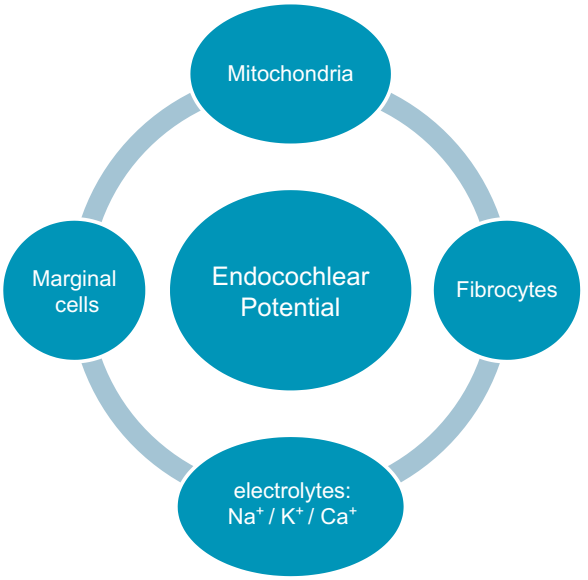

Fig. 20.14. The maintenance of the endocochlear potential demands a high quantity of energy that is supplied by mitochondria. Mitochondria are particularly present in the marginal cells. Marginal cells and fibrocytes are also supporting the high potassium gradient of the inner ear.

depends also on calcium homeostasis (Lumpkin and Hudspeth, 1998). Disturbed function of the cilia in hair cells contributes to altered signal transduction and consequently to hearing difficulties.

Age-related altered fibrocytes not only have decreased efficiency in maintaining inner-ear homeostasis with respect to the demanding endocochlear potential, but probably secrete altered microfilaments and other microstructures, which may influence cochlear dynamics by reducing the mechanical elasticity of the basilar membrane (Spicer and Schulte, 2002). Given these observations, it may be hypothesized that these changes are primarily due to altered function of supporting inner-ear cells, e.g., fibrocytes. It may explain Schuknecht's difficulties in correlating the audiogram with the variable histopathologic changes leading to the somewhat unclear or unproven classification of indeterminant, mixed, or cochlear-conductive hearing loss.

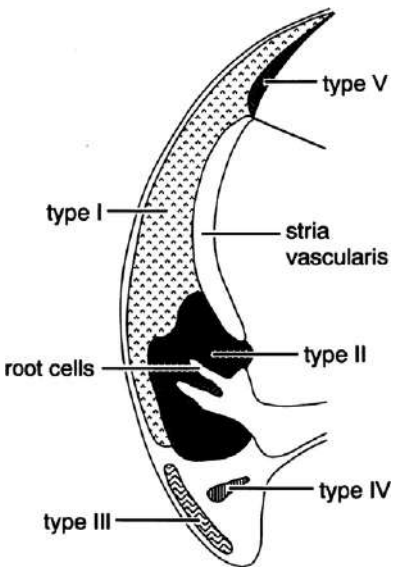

Fig. 20.15. Schematic showing localization of the spiral ligament fibrocyte types, as classified by Spicer and Schulte. The type II and type V fibrocytes shown here are both considered type II fibrocytes according to the Takahashi and Kimura classification system. (Reproduced from Ichimiya et al., 2000.)

Fibroblast growth factor (FGF) is expressed by neurons in the spiral ganglion and in the cochlear nucleus. FGF is not only responsible for normal fibrocyte differentiation and function, but also exhibits an important role in myelination of the cochlear nerve. Two cell types are involved in myelination: Schwann cells myelinate the peripheral part and oligodendrocytes the central part of the cochlear nerve (Wang et al., 2009). Disturbed function of myelination, independently of central or peripheral origin, leads to reduced signal transmission in the cochlear nerve visible in longer latencies of auditory evoked potentials (Makary et al., 2011).

Furthermore, FGF has an important role in hair cell differentiation and repairing function of the inner ear after injury (Jacques et al., 2012). Due to the production of FGF in spiral ganglion cells, it may be hypothesized that spiral ganglion loss results in hypo- or demyelination of the cochlear nerve and has adverse effects on sensory and supporting cells of the cochlea. Loss of spiral ganglion cells was also shown to be a direct result of acoustic overexposure, not just a consequence of hair cell loss (Makary et al., 2011).

Gender and hormones

Epidemiologically, men are more affected by ARHL than women. Consequently, hormones, especially estrogen, have to be considered not only in presbyacusis but also in other pathologies. Gender differences have been reported in auditory brainstem response, showing that women have shorter latencies than men. Women with Turner's syndrome, being biologically estrogen-deficient, have longer latencies in auditory brainstem response and show early presbyacusis (Hultcrantz et al., 2006). Hormone replacement therapy was supposed to have a slightly positive effect on hearing thresholds in menopausal women, but contradictory observations exist, reporting that contraceptive medication and hormone replacement therapy are associated with sudden hearing loss (Hanna, 1986; Strachan, 1996). Moreover, the known prothrombotic effect of

conceptive pills might play a role. Nevertheless, human studies investigating the effect of sex hormones on hearing show an influence of estrogen (Horner, 2009).

The estrogen receptors, alpha and beta, are localized where electric impulses are transmitted (inner and outer hair cells, spiral ganglion) and where inner-ear homeostasis is maintained (stria vascularis, spiral ligament) (Stenberg et al., 2002); therefore, estrogens seem to have a role in signal transmission and cochlear homeostasis.

AGING OF THE CENTRAL AUDITORY SYSTEM

Auditory cortex

Speech recognition is a frequent complaint of older adults, particularly in complex and demanding listening conditions. When differentiated hearing is impaired, the age-related changes not only involve the above-mentioned cellular structures of the cochlea, but also affect the central nervous system, in particular the auditory cortex and the frontal lobe. The latter seems to be progressively involved with increased age and to exhibit an important role in speech recognition when central auditory regions show a declining structural integrity (Eckert et al., 2008).

ARHL has been described as correlating with age-related changes in the auditory cortex (Eckert et al., 2012). A lower gray-matter volume of the auditory cortex has been observed in older adults with mild to moderate hearing loss (Husain et al., 2011), but it remains a question for further research whether these findings are causatively connected. A study investigated the gender-related morphologic symmetries of brain structures and described differences in the auditory cortex volume, which was less in men than in women (Rademacher et al., 2001). Given the epidemiologic observation that women are less affected by ARHL than men, the question about causality between epidemiology and the structural difference in the auditory cortex arises and the role and influence of sex hormones have to be considered.

Theory of cortical disconnection

Before the era of functional imaging the classic model of hearing was focused on the Broca's and Wernicke's area on the left hemisphere. The hemispheric specialization of language was supported for many years by differences in dichotic listening paradigms. But recent studies using functional neuroimaging revealed that speech recognition is not restricted to the left hemisphere, but seems to be bilaterally organized (Rogalsky et al., 2008). Furthermore, speech perception is not only confined to the temporal lobe, but also involves the frontal lobe. These findings open the discussion about a new and more sophisticated concept than the classic model of understanding human language and central auditory system (Poeppel et al., 2012).

Despite the controversies concerning the hemispheric asymmetry or connectivity and the modulating role of the frontal lobe, it has been shown that, in elderly patients, particularly in patients with Alzheimer's disease, the asymmetry in dichotic listening is accentuated (Bouma and Gootjes, 2011). These observations of age-related and pathologic changes of the brain with progressive decline of structural areas and tracts may lead to partial or gradual intrahemispheric and interhemispheric disconnectivity, due to disturbed signal transmission. Thus, the theory of cortical "disconnection," i.e., the disruption of subcortical white-matter tracts, has been put forward as a mechanism of age-related cognitive decline. The cortical disconnection seems to involve the central auditory system and impair speech perception (Gootjes et al., 2007).

Calcium homeostasis

Calcium was shown on the one hand to have an important function in intracellular processes and cell signaling and on the other hand to be closely involved in genetics of aging (Takumida et al., 2009; Smaili et al., 2013). Furthermore, calcium not only provides the synaptic potential that permits a finely tuned signal transmission, but also has an important impact on neural viability and synaptic plasticity (Foster, 2007).

As mentioned above, calcium is intimately linked to the activity of mitochondria that are implicated in the clearance of reactive oxygen metabolites. The high membrane potential of mitochondria is maintained by a calcium gradient that is tightly regulated by specific calcium transport mechanisms. Oxidative stress leads to defective mitochondrial membrane proteins and in turn to a disturbed calcium homeostasis and changed intracellular activity with its pathophysiologic consequences.

Contrariwise, age-related reduced calcium regulation alters mitochondrial activity that increases oxidative stress, leading to cell damage (Ouda et al., 2012; Smaili et al., 2013). Calcium dysregulation decreases neural transmission properties and leads to impaired or disrupted information exchange between the connected brain areas

The connection between mitochondrial activity and intracellular calcium regulation points to the importance of both components in aging.

Progressive demyelination of the central nervous system due to age-related changes in calcium homeostasis or mitochondrial activity impairs precise and rapid signal

transmission. Impaired signal transduction reduces the viability of synapses and neurons. As explained in the section above, loss of spiral ganglion cells disturbs the activity of fibrocytes, affecting the endocochlear potential and the highly differentiated microstructures of the Corti organ.

Comprehension of these interacting and interconnected mechanisms is important to understand the age-related changes in the clinical examination, discussed in the section below.

DIAGNOSIS AND CLINICAL MANIFESTATION

Patients often complain about hearing loss in a nonspecific way, but a detailed history can point out the circumstances or the social environment where hearing poses a problem. Given the above-mentioned age-related changes of the entire auditory pathway from the peripheral organ to the auditory cortex, all parts of the auditory system have to be considered and analyzed separately, but none the less, in relation to the entire auditory system. According to the site of the lesion, patients' complaints may vary in degree and characteristics. The clinical evaluation of ARHL should not focus only on the cochlea but also pay attention to the central nervous system. Additionally, psychologic aspects have to be considered, together with social personal activities when aiming to provide comprehensive holistic medical care.

One of the main characteristics in ARHL is the progressive difficulty in speech recognition, particularly in noisy environment. Some patients note that intelligibility depends on the frequency and phonetic resonance of the speaker's voice. This complaint may correspond to the above-mentioned age-related changes in the cochlea with its altered structures, mainly in the basal turn of the Corti organ. But diminished speech recognition may also be a sign of affected auditory cortex. It is quite a demanding clinical task to differentiate the involved site of ARHL and to determine whether the peripheral, the central, or both parts are predominantly affected.

Several clinical tests are used in the topodiagnostic evaluation of hearing loss. These are complemented by other tests, such as auditory evoked potentials, functional magnetic resonance imaging, and motor evoked potential, which can document slowing of the central nervous system.

There are two main components of the central nervous system that are affected by age: cognitive ability and temporal processing. Temporal processing becomes slower and cognitive ability decreases progressively. The latter is mainly influenced by altered central selection mechanisms, consisting of impairment of information transduction. In the aging central nervous system these modulating mechanisms, apart from being slower and less efficient, are shifted to the frontal cortex and hence, associative or memory function becomes more important in hearing processing and speech recognition.

The tone audiogram is the basic test to determine hearing loss (Figs 20.1–20.3). ARHL is typically characterized by symmetric high-frequency loss. This test depends on the patient's attention and cooperation. The tone audiogram provides quite a good evaluation of peripheral audition, including its mechanical components.

A central component is included in speech audiometry, since speech recognition depends on central auditory pathways and requires cognitive abilities. Central auditory testing by dichotic sentence or digit identification is recommended in the evaluation of elderly with hearing impairment (Gates et al., 2008).

Otoacoustic emissions play a less important role in the clinical evaluation of ARHL, because they exhibit an individual variability and therefore it is impossible to get a standard reference (Probst et al., 1991). It represents a dynamic exam that only with longitudinal testing can reveal age-related changes of the individually measured cochlear mechanisms. These changes are less prominent compared with threshold level and seem to depend on the decreasing endocochlear potential that is not measurable in clinical routine exam.

Auditory evoked potentials give important information about the central component of the auditory system. According to the age-related changes mentioned above, latencies are prolonged and the potential diminished. In the clinical exam they are mainly used to answer the question of whether there is a retrocochlear hearing disturbance. As with otoacoustic emissions, there is no standard reference, for the same reason of individual variability.

REHABILITATION

Current hearing rehabilitation is focused on the peripheral auditory part by applying hearing aids. With the continuous development of technical possibilities, the industry tries to improve the fine-tuning of the devices to compensate for age-related deficits. Unfortunately, they show limited success due to the above-mentioned variety of structural changes in the hearing pathway. The more the central auditory pathway and central nervous system are affected by structural changes, the less the success of hearing aids. In contrast, peripheral deficits respond well to the application of hearing aids.

In case of profound hearing loss unamenable to standard hearing aids, a cochlear implant (CI) can be evaluated. CIs in the elderly showed satisfying results, even if the difference in hearing improvement was less marked

than in children. Hence, if the peripheral auditory deficit can be compensated for sufficiently by CI, the central part of auditory deficit seems to be of less importance (Lenarz et al., 2012; Blamey et al., 2013).

When age-related changes mainly affect the central components, peripheral efforts will fail and auditory training should be attempted together with psychomotor or general daily activity.

CONSEQUENCES OF ARHL

Based on the above-mentioned epidemiologic considerations, ARHL is the most common chronic disabling condition in older adults. Hearing loss affects one of the most important human capabilities: verbal communication.

The disabling severity of ARHL is shown by a wide range of negative consequences caused by difficulties in understanding. These age-related changes in hearing lead to a reduced quality of life that affects all parts of human activity. Social isolation, emotional frustration, cognitive dysfunction, and behavioral changes may be further consequences of hearing impairment.

Moreover, the central nervous system, social activity, or lifestyle and psychologic factors have to be considered when dealing with hearing impairment. Patients with hearing impairment risk being isolated and isolating themselves, and therefore are prone to developing depression.

Premature aging of the central nervous system seems to affect the hearing process, on the one hand due to declined psychomotor activity and social interest, and on the other hand because reduced central activity may have a negative impact on auditory processing and possibly also on the peripheral auditory organ.

Hearing loss also affects negatively work productivity and has an impact on the economy. In this context, hearing loss seems to entail negative consequences for the social state, health, and survival (Barnett and Franks, 1999). Furthermore, ARHL is estimated to have a considerable economic weight in the public healthcare system.

For all these reasons, prevention (for example, through public health campaigns and work legislation on noise exposure), early identification, and appropriate management of AHRL are all important.

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