Published in final edited form as:
Hear Res. 2010 June 1; 264(1-2): 98–107. doi:10.1016/j.heares.2009.09.001.

Age-related hearing loss: Is it a preventable condition?

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Abstract

Numerous techniques have been tested to attempt to prevent the onset or progression of age-related hearing loss (ARHL): raising the animals in an augmented acoustic environment (used successfully in mouse and rat models), enhancing the antioxidant defenses with exogenous antioxidant treatments (used with mixed results in mouse and rat models), raising the animals with a calorie restricted diet (used successfully in mouse and rat models), restoring lost endocochlear potential voltage with exogenous electrical stimulation (used successfully in the Mongolian gerbil model), and hypothetical enhancement of outer hair cell electromotility with salicylate therapy. Studies of human ARHL have revealed a set of unique hearing loss configurations with unique underlying pathologies. Animal research has developed models for the different forms of age-related peripheral pathology. Using the animal models, different techniques for prevention of ARHL have been developed and tested. The current review discusses ARHL patterns in humans and animal models, followed by discussions of the different prevention techniques.

Keywords

presbycusis; Fischer 344 rat; age-related hearing loss; antioxidant

1. Human Age-related Hearing Loss

Age is the factor most commonly associated with acquired hearing loss in the adult population. As our society matures, there are more people living into their 60’s, 70’s, 80’s and beyond due to factors such as improved nutrition and health care. Within the elderly segment of our society, hearing loss is only second to arthritis as a handicapping condition (CDC, 2003). The causes of presbycusis are not well understood. Certainly, age-related hearing loss (ARHL) is a reflection of the genetics of the individual (Gates et al., 1999) as well as the accumulation of noise exposures, ototoxic drugs, and disease (Hefzner et al., 2005). For example, when humans are highly screened (subjects with no history of significant noise exposure or diseases that affect the ear), hearing acuity declines with age and the rate of decline accelerates with age (ISO1999 Annex A). The interactive effects of age and experience of life and work that damage the ear increase ARHL and are documented in Annex B of ISO1999. When compared to the highly screened population of Annex A, the population of Annex B that is unscreened for noise exposure, ototoxic drug exposure, and otologic disease history develops ARHL earlier and to a greater extent than Annex A, but both screened and unscreened subjects develop a hearing

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loss that begins at the highest frequency measured (6 kHz) and, with increasing age, expands both in the magnitude and extent of the loss. It should be noted that there are some limitations to the ISO1999 data, in that the data are not longitudinal. Each age group represents different populations of people, instead of the same population as they aged from 30–60 years-old. So, because these data points are from different populations of humans, other factors beyond simple aging could influence the course of the ARHLs.

After studying the audiograms and the temporal bones of many elderly patients, Schuknecht (1964) proposed four types of presbycusis: (1) Sensory – a high-frequency hearing loss caused primarily by missing outer hair cells (OHCs); (2) Neural – broad hearing loss with high-frequency emphasis and degeneration of the VIIIth nerve; (3) Strial – flat hearing loss with degeneration in stria vascularis (StV) (Representative audiograms of patients with hearing losses consistent with patterns that were identified by Schuknecht as fitting the parameters of sensory, neural, and strial ARHL are displayed in Fig. 1); and 4) Cochlear Conductive – an evenly-sloping hearing loss hypothetically associated with changes in the stiffness properties of the basilar membrane. In a later study, Schuknecht and Gacek (1993) studied a series of 21 human temporal bones with diagnosed presbycusis. Several of the cases had evidence of classic strial or neural presbycusis. However, 5 of the 21 example temporal bones showed hearing loss consistent with sensory presbycusis, but showed no underlying pathology consistent with sensory, strial, or neural presbycusis. These samples were labeled “indeterminate” presbycusis. Schuknecht and Gacek speculated on a number of possible pathologies that might underlie the hearing loss, including: dysfunction of cells in the cochlea, alterations in intracellular organelles that would impair cell metabolism, diminished numbers of synapses on the hair cells, chemical alterations in the endolymph, and alterations in the auditory pathways in the brain. Schuknecht’s work was ground-breaking, but it remains difficult to determine the extent to which the categories accurately describe large populations of human ARHL patients, or if the selected cases on which the categories were based reflect rare patients who demonstrate unique audiometric findings coincident with unique cochlear pathology findings.

Prevention of ARHL is a relatively new area of research study. Until the last several years, little experimental data had been collected on the prevention of ARHL. Since an individual’s ARHL was determined largely by genetics and history of deleterious auditory exposures, the only way to prevent ARHL was minimizing ototraumatic exposures during the lifespan. Such a notion was confirmed in Mongolian gerbil animal model of ARHL (described below). Raising the animals in quiet, versus a moderate noise level of 85 dB SPL, led to lower hearing thresholds, less OHC loss, and greater preservation of tone-tone suppression, as compared with animals raised in the noisy condition (Schmiedt et al., 1990). In humans, minimizing noise exposure, and living a generally healthy lifestyle with respect to stress and diet can lead to minimal ARHL compared to populations in which noise exposure was common, stress higher, and diet poorer (Rosen et al., 1962; Goycoolea et al., 1986). Even with the promising potential of the preventative techniques described below, minimizing noise exposure and maintaining a healthy lifestyle are still the most effective accepted routes to limiting ARHL in the human clinical population.

Development of effective techniques for prevention of peripheral ARHL requires an understanding of mechanisms underlying the age-related cochlear changes. Given the limitations inherent in the study of ARHL in humans (genetic heterogeneity, duration of time for onset and progression of ARHL, difficulty in controlling deleterious auditory exposures), an understanding of the mechanisms of ARHL (as well as possible points of intervention) is best achieved with animal models of aging, despite the limitations of animal models of aging. The challenge with the commonly-used animal models of aging is determining the extent to which the animal models aspects of human auditory aging, and identifying the aspects of the animal model that cannot be generalized to the common human ARHL patient. Because

laboratory animals are maintained in controlled environments, they are exposed to few, if any, of the environmental hazards that can affect the course of human ARHL, including: high-level noise, disease pathogens, medications, and others. In addition, numerous animal models are inbred strains, limiting the genetic heterogeneity of the models and making it more likely that they can be generalized to only a fraction of the diverse human population. Furthermore, animals model an average eight decade human lifespan in the 2–4 year life spans of the animals.

2. Animal Models of ARHL

Mouse models of ARHL have been used frequently in aging research. Mouse strains have shown evidence of spiral ganglion neuron (SGN) degeneration (Saitoh et al., 1994; Dazert et al., 1996; McFadden et al., 2001; Bao et al., 2005; Kujawa and Liberman, 2006; Lang et al., 2006). Although it is unknown if the pathology is indicative of primary neural ARHL, or if it is secondary to the loss of HC, examples of 129S6/SvEv mice have been found that have SGN loss without loss of inner hair cells (IHCs) (Ohlemiller and Gagnon, 2004). Mouse strains have also been used to model strial ARHL (Ohlemiller et al., 2006; Ohlemiller et al., 2009). In addition, a large amount of research has been performed on knockout mice to elucidate the mechanisms underlying ARHL (see review by Ohlemiller, 2006).

Two mouse strains have been used frequently to model sensory ARHL and have been used for analysis of loss of hearing sensitivity and concomitant loss of hair cells (HCs), the CBA/Ca mouse and C57BL/6 mouse. The CBA/Ca mouse retains most of its hearing sensitivity up to 18 months of age (in a 30-month average lifespan), after which hearing declines progressively beginning in the high frequencies and moving to the lows (Li and Borg, 1991). Underlying the loss of hearing sensitivity late in its lifespan, the CBA/Ca mouse is thought to undergo progressive loss of HCs (Li and Hultcrantz, 1994; Spongr et al., 1997), although the data are not completely confirmed. The C57BL/6 mouse has been used as a model for accelerated ARHL. The C57BL/6 mouse demonstrates a much more rapid onset of hearing loss and more rapid decline than the CBA/Ca mouse (Li and Borg, 1991). HC degeneration also happens more rapidly, with potentially complete loss of HC by one year of age (Li and Hultcrantz, 1994; Sponger et al., 1997). The DBA/2J mouse is also used as a model of accelerated ARHL. The mouse strain develops hearing loss by age three weeks (Willott, 1981 and Willott et al., 1982). By 2 months of age, high frequency hearing is severely impaired, and by age 55 days, low-frequency hearing is also significantly impaired (Willott et al., 2005). The underlying pathology is progressive loss of cochlear sensory cells.

The Mongolian gerbil develops an ARHL that is consistent with a pattern of strial ARHL. By 36 months of age, the Mongolian gerbil shows a 15–35 dB threshold shift, with greater damage in the high frequencies (Mills et al., 1990). The hearing loss is associated with underlying damage to the cochlear blood supply structures, including the StV (Thomopoulos et al., 1997; Gratton and Schulte, 1995) and spiral ligament fibrocytes (Spicer and Schulte, 2002). The damage to StV is associated with a possible reduction in mitochondrial adenosine triphosphate (ATP) supply in the strial marginal cells due to loss of the marginal cell processes (Spicer and Schulte, 2005). The loss of ATP supply is thought to lead to a loss of Na, K-ATPase activity and a decrease in the endocochlear potential (EP) (Schulte and Schmiedt, 1992; Gratton et al., 1997). The loss of EPs in aged Mongolian gerbils is thought to be the causative factor in the Mongolian gerbils' loss of hearing sensitivity with age.

The Fischer 344 (F344) is an inbred, albino rat strain with a median life span of as low as 22 months (Chesky and Rockstein, 1976) to as much as 28–31 months (Rao and Boorman, 1990). Its limited inter-animal variability makes it a useful candidate for ARHL study. The F344 rat develops a progressive hearing loss that begins in the high frequencies and includes lower frequencies as the animal ages. Recent studies on the F344/DuCrl substrain, which is

used in research in Europe, found that its ARHL is related to changes in middle ear impedance (Popelar et al., 2006), and strial degeneration leading to possible loss of EP and/or K^+ cycling (Buckiova et al., 2006; Buckiova et al., 2007), as well as OHC loss. The F344/NHsd rat substrain, which is used for research in the United States, develops a progressive high-frequency hearing loss in a pattern very similar to the F344/DuCrl substrain. The F344/NHsd rat develops its hearing loss starting in the 20–40 kHz range at 12 months of age, and progresses through its lifespan (~27–30 months) to include the 5–10 kHz range. The threshold shift follows a pattern that is qualitatively consistent with the pattern of human hearing loss in ISO1999 Annex A (Fig. 2). In addition, the F344/NHsd rat's hearing loss follows a pattern consistent with sensory ARHL, as it is associated with a progressive, age-related loss of distortion product otoacoustic emissions (DPOAE) (Fig. 3). The assumption with the F344/NHsd rat was that the underlying pathology of the ARHL was indeed a loss of OHCs. However, OHC examination in 24-month-old rats showed a significant disconnect between the OHC loss and the hearing loss. There is less than 20% OHC loss in the region corresponding to the 6–24 kHz frequency range, a range with threshold shifts of 20–45 dB (re: 3-month-old subjects) (Fig. 4). Additionally, loss of SGNs in the basal and middle turns of the cochlea has been reported (Keithley et al., 1992), although the SGN loss may be secondary to loss (Fig. 4.) or damage (see below) to the OHCs. The EP was found to be intact in the aging F344/NHsd rat (Bielefeld et al., 2008). Therefore, the disconnect between depression of DPOAE and loss of OHCs prompted investigation of the prestin levels in the OHC of the aged F344/NHsd rats. In the basal turn of the cochlea, prestin staining intensity levels were dramatically lower in the OHCs of the aged rats compared to young (2 month-old) rats (Fig. 5 from Chen et al, 2009), suggesting the possibility that prestin levels in the OHCs may themselves be reduced. The elevated hearing thresholds, reduced DPOAE, intact OHCs, intact EP, and reduced OHC prestin staining intensity levels may be a clue that the category of "indeterminate' presbycusis, as hypothesized by Schuknecht and Gacek (1993), may indeed be OHC damage that was undetectable with their microscopy. The damage may lead to OHC dysfunction, resulting in hearing loss that is identical to sensory ARHL. Prestin loss may be one of the forms of subtle OHC pathology that leads to the hearing loss that Schuknecht and Gacek initially had summarized as "indeterminate" ARHL.

Each of the above models has been used for the study of ARHL, and for the study of techniques to protect against the onset and progression of ARHL. Those studies are described below.

3. Strategies for Preventing or Treating ARHL

The first two strategies for preventing ARHL address the cochlea's antioxidant defense system. In 1972, Harman hypothesized that the body's continued creation of toxic free radicals was a common process responsible for aging and death. The cause of these free radicals can be influenced by genetics and environmental factors. Although there are a number of potential sources of reactive oxygen species (ROS), the most important during normal aging is the generation of the superoxide radical $0_2^{\bullet-}$ during cellular respiration in the mitochondria. The rate of $0_2^{\bullet-}$ generation increases with both aging and metabolic activity (Harman, 1972), leading to conditions of oxidative stress. There have been many studies showing an organism's life span can be extended by diminishing oxidative stress (see review by Finkel and Holbrook, 2000). Thus, increasing the body's antioxidant defenses against oxidative stress may prove to be an effective way to slow the progression of age-related damage to the body. The effectiveness of antioxidant prevention of hearing loss from ototoxic drugs or noise is well documented (Hoffman et al., 1987; 1988; Hu et al., 1997; Hight et al., 2003; Lautermann et al., 1997; Rybak et al., 1999). Since oxidative stress has been implicated as a factor in ARHL (Staecker et al., 2001; Sha et al., 2001; Jiang et al., 2007), enhancing the cochlea's antioxidant defense may render that cochlea less susceptible to ARHL. Studies that attempted to enhance

the cochlea's antioxidant defense with both endogenous (augmented acoustic environment) and exogenous (antioxidant supplementation) treatments are described below.

Augmented Acoustic Environment (AAE)

ARHL progresses steadily during the lifespan, and we now know that the noise level in the environment can influence the progression of ARHL (Turner and Willott, 1998; Willott and Turner, 1999; Willott and Bross, 2004; Willott et al., 2005, 2006; Tanaka et al., 2009). Interestingly, augmented acoustic environment (AAE) can be more conducive to minimizing ARHL than aging in a quiet environment. AAE is a complex background noise at a level that is clearly audible, but not high enough to cause threshold shift. Turner and Willott (1998) exposed DBA/2J mice to an AAE (70 dB SPL broadband noise for 12 hours per day) at various times after the onset of their accelerated ARHL. They found, compared to controls aged in a normal quiet environment, that animals raised in the AAE had reduced auditory brainstem response (ABR) threshold shifts, and enhanced central auditory function as indexed by pre-pulse inhibition of the acoustic startle reflex. The peripheral and central protective findings were further supported by reduced anatomic damage in the cochlea and cochlear nucleus of DBA/2J mice raised in the AAE (Willott et al., 2005, 2006). The findings were also replicated in C57BL/6J mice (Willott and Turner, 1999; Willott and Bross, 2004).

The protective effect of AAE has also been demonstrated to influence the progression of ARHL in the F344/NHsd rat. 16-month-old F344/NHsd rats were divided into two groups: an AAE group and a quiet environment group. The AAE group was exposed to a wide-band noise (4–20 kHz) at 80 dB SPL for 12 hours/day (5 pm to 5 am), 5 days/week for 13 weeks. The quiet group was housed in the same environment as the AAE group, but without sound exposure. ABR thresholds were measured before the start of the AAE, and at several points (2, 6, 9 and 13 weeks) during the AAE exposure. ABR thresholds of the two groups are displayed in Figure 6. The results indicate that the progression of ARHL at 20–40 kHz in the enriched group was stopped for the 3-month period after initiation of AAE while the ABR thresholds in the quiet group continued to deteriorate.

Hypothesized putative mechanisms of prevention against ARHL with AAE include enhancement of the antioxidant profile of the cochlea, alterations in blood flow patterns to the cochlea, and changes in excitotoxicity patterns in the auditory system (Willott, 2009). Studies on the effectiveness of AAE in promoting recovery from traumatic noise (Niu et al., 2004; Norena and Eggermont, 2005) support the notion that a cochlea under oxidative stress can be protected by exposure to AAE. Increases in antioxidant enzyme levels in the cochlea after sound conditioning (in which animals were given non-traumatic noise exposures at regular time points prior to a traumatic exposure in order to reduce the permanent hearing loss from the traumatic exposure) support the possibility that AAE increases cochlear antioxidant activity (Jacono et al. 1998). The study (Jacono et al., 1998) tested antioxidant enzyme levels in three experimental conditions: animals exposed to the conditioning noise only, animals exposed to the traumatic noise only, and animals exposed to the conditioning noise followed by the traumatic noise. The results showed that all three conditions elevated the antioxidant enzymes in the cochlea, but that the conditioning noise followed by the traumatic noise elevated the enzymes the most, suggesting that the conditioning effect was related to increased antioxidant profile in the cochleae of the conditioned animals.

The interesting experimental results with AAE may have important clinical implications. The AAE has a direct effect on the auditory system without altering the aging of the entire body. For this reason, effects of sound enrichment on ARHL are likely to occur independently of changes in lifespan. What remains unclear about AAE is the extent to which the clinical human population receives AAE-liked noise exposures as part of their normal lifestyles. The typical human is not raised in the quiet laboratory conditions of the rodents used in the experiments

describes above, but nor does the typical human receive a controlled AAE-like noise exposure on a daily basis. It seems likely the typical human's daily sound exposure is somewhere between quiet control conditions and the AAE to which experimental rodents are exposed. If this is indeed the case, it is unclear how much the typical human's sound exposure is limiting his/her ARHL already, and therefore, how much additional benefit more AAE could provide. Further complicating the issue is the damaging effect higher-levels of noise exposure to which many humans are exposed have on hearing.

Antioxidant Enhancement

The effectiveness of AAE may be an indication that enhancing the cochlea's antioxidant defenses can prevent the onset, or slow the progression, of ARHL. Numerous studies have tested exogenous antioxidant treatments to prevent ARHL, with mixed results. Seidman (2000) used a variety of antioxidant treatments to prevent ARHL in the F344/NHsd rat. He found significant protection with Vitamin C, Vitamin E, and melatonin. A weaker protective effect was detected with lazaroid, a free radical scavenger. Seidman et al., (2000) then tested the protective effect of oral supplementation with acetyl-l-carntine (ALCAR) on F344 rats as they aged from 24 to 26 months. ALCAR is used to improve mitochondrial membrane energetics, and has been used successfully to prevent noise-induced hearing loss (Kopke et al., 2002). Over the two-month period, the hearing sensitivity thresholds of the treated animals actually got lower, while the placebo-treated animals thresholds elevated 3–7 dB. The effective prevention of ARHL with ALCAR could not be replicated in a study by Bielefeld et al., (2008) that tested oral doses of ALCAR in F344/NHsd rats for three months starting at 15 months of age, for three months starting at 18 months of age, and for one month starting at 24 months of age. Seidman et al. (2002) followed up the previous studies by examining lecithin, a compound that enhances membrane antioxidant responses in an attempt to reduce oxidative stress at the mitochondrial level. Six months of oral supplementation with lecithin reduced ARHL in F344 rats as they aged starting from 18 months. In the frequency range 3–18 kHz, the control animals sustained an average of 35–40 dB threshold shifts after the 6-month interval, while the treated animals' mean threshold shifts were 12–17 dB. Along with the reduced threshold shifts, the lecithin-treated rats showed less degradation in mitochondrial membrane potentials and fewer mitochochondrial DNA deletions of $mtDNA^{4834}$ (Seidman et al., 2002), suggesting a reduction in oxidative stress in the animals that received the lecithin treatment.

The antioxidant n-acetyl, l-cysteine (L-NAC), a pro-glutathione and free radical scavenger molecule, has been used extensively in studies of protection against noise-induced hearing loss (Kopke et al., 2000; Duan et al., 2004; Kopke et al., 2005; Bielefeld et al., 2007; Kopke et al., 2007). Yet it has not been utilized successfully in protection against ARHL in either the C57BL/6J mouse (Davis et al., 2007) or the F344/NHsd rat (Bielefeld et al., 2008). It must be noted, though, that unsuccessful studies of pharmacological protection from acquired hearing loss are complicated by numerous factors related to dosing levels, frequency of dosing, etc, and do not extinguish the possibility that a particular drug (in this case, L-NAC) can be used as a successful prevention against ARHL.

Perhaps even more powerful and relevant are the findings of exacerbated ARHL in animals that lack antioxidants and/or antioxidant enzymes. A study (Keithley et al., 2005) of mice with genetic deletion of Cu/Zn superoxide dismutase 1 (SOD1) showed that complete loss of SOD1 led to accelerated ARHL with underlying pathologies of severe spiral ganglion cell loss and reduced size of the stria vascularis. Another study showed accelerated OHC loss in mice with genetic deletion of SOD1 (McFadden et al., 1999). Animals heterozygous for SOD1 (Keithley et al., 2005) or manganese SOD (SOD2) (Le and Keithley, 2007) produced 50% of the amount of SOD1 or SOD2 that wildtype mice did, and those heterozygous mice showed normal patterns of ARHL. The implications are that reducing SOD did not have significant effects on ARHL,

but completely eliminating SOD led to acceleration of ARHL. Interestingly genetic overexpression of SOD has not been shown to provide a protective benefit against ARHL (Coling et al., 2003; Keithley et al., 2005). A similar finding of increased ARHL (as well as increased susceptibility to noise damage) was found in knockout mice that lacked the gene for production of the antioxidant enzyme, glutathione peroxidase (Ohlemiller et al., 2000). A study of C57BL/6 mice that were albino, and thus lacked melanin pigment, found that the albino mice showed greater age-related strial degeneration (loss of strial thickness, loss of strial marginal cells) and subsequent loss of EP than the pigmented C57BL/6 mice (Ohlemiller et al., 2009). The implications of these studies of ARHL in animals with reduced antioxidant capability suggest that maintaining proper antioxidant/oxidative stress balance is indeed important for ARHL.

The findings of a lack of benefit from overexpression of SOD suggest that the body has an antioxidant capacity that should be maintained to minimize ARHL, but that exceeding the body's antioxidant capacity may not provide any additional benefit. Such a conclusion would imply some benefit for exogenous antioxidant supplementation, specifically that it will help the individual reach his/her antioxidant capacity. But for those individuals who are already at their antioxidant capacity through proper diet and exercise, there may be no additional benefit from antioxidant supplementation, at least as it pertains to ARHL.

Caloric Restriction (CR)

It is well established in the literature that an organism's lifespan can be extended with calorie restricted diets (Weindruch and Sohal, 1997; Howitz et al., 2003; Wood et al., 2004). The most robust and reproducible pro-longevity intervention is seen in reducing caloric intake by ~40% below that of *ad libitum*-fed animals (Ingram et al., 2004, Sinclair, 2005). Moreover, CR has been reported to delay in animal models the onset of many age-related diseases such as cancer (Hursting et al., 1994), cardiovascular diseases (Minamiyama et al., 2007), diabetes (Lane et al., 1999), and neurodegeneration (Mattson, 2000). Numerous putative mechanisms have been hypothesized as being responsible for the decrease in age-related disease and increased lifespan with CR, including: 1) reduction in oxidative stress and glucoregulation; 2) decreased metabolic rate; 3) stress response-induced upregulation of heat shock proteins; 4) reduced dietary fat; 5) prevention of age-related reductions in protein turnover; 6) upregulation of the sirtuin pathway. In addition to increasing lifespan, CR has been shown to reduce/delay ARHL. Willott et al. (1995) showed that the rapid ARHL of the C57BL/6J mouse could be significantly delayed with CR. Sweet et al. (1988) reported that dietary restriction starting from midlife until death in CBA/J mice showed reduced ABR thresholds compared to the control animals. Seidman (2000) demonstrated delayed ARHL in the F344/NHsd rat using CR. Since CR affects all systems of the body, it is likely that the delayed ARHL is simply a consequence of the prolonged lifespan. In addition to using CR to prevent ARHL, another intriguing possible approach is mimicking CR with resveratrol. Resveratrol (*trans*-3, 5, 4′-trihydroxystibene) is a naturally occurring phytoalexin produced by a wide variety of plants (Burns et al, 2002). Resveratrol has been reported to have numerous health benefits, among the most prominent of which is an anti-aging effect (Aggarwal et al, 2004). Resveratrol supplementation in a high-calorie diet in mice can lead to expansion of lifespan (Baur et al., 2006) and increased mitochondrial biogenesis (Lagouge et al., 2006). According to Barger et al. (2008), dietary supplementation of *trans*-resveratrol (4.9 mg/kg/day) in mice starting at middle age (14 months of age) showed a striking transcriptional overlap between CR and resveratrol-supplementation in different organs (heart, skeletal muscle, and brain) examined by gene microarray analysis. A number of different molecular targets are known to be influenced by resveratrol treatment, but the key mechanism for resveratrol's anti-aging effects may be its activation of the Sir2 and sirtuin (SIRT) pathway (Howitz et al., 2003). The Sir2 family of genes helps regulate gene silencing, DNA repair, rDNA recombination, apoptosis (Tang and Chua, 2008; Pallas et al.,

2008), and mitochondrial energetics (Guarante, 2007). In mammals, there are seven members of Sir2 family. Mammalian SIRT1 is located in the nucleus and exerts a regulatory effect on p53 (Luo et al, 2001; Vaziri et al, 2001), a key apoptosis signaling molecule. Increasing SIRT1 *in vitro* has been found to protect cells against amyloid-beta-induced ROS production and DNA damage, thereby reducing apoptotic death. In the auditory system, resveratrol has been shown to effectively reduce noise-induced hearing loss in the F344/NHsd rat model (Seidman et al., 2003). It represents an intriguing avenue for prevention of ARHL, and is currently being tested in the F344/NHsd rat model.

Electrical Stimulation to Restore the Endocochlear Potential

For strial (or metabolic) ARHL, the Mongolian gerbil is an excellent model, showing progressive loss of EP voltage, along with a concomitant loss of lateral wall tissue. Since the animals show relatively low hair cell loss, the potential would seem to exist to restore lost hearing sensitivity by enhancing EP voltage. Indeed, studies in which DC voltage is introduced into the scala media have demonstrated the ability to increase a low EP by as much as 55 mV. When the EP is enhanced with DC voltage, hearing sensitivity could be restored by as much as 40 dB in the aged Mongolian gerbils (Schmiedt et al., 1993).

Salicylate Therapy

A novel hypothetical approach to limiting ARHL is salicylate therapy. Salicylate can cause reversible hearing loss, DPOAE loss, and tinnitus (Boettcher and Salvi, 1991; Brien, 1993; Cazals, 2000). Mechanisms of salicylate-induced temporary threshold shift include reversible elimination of OHC electromotility by competitively binding to prestin, the OHC motor protein (Zheng et al. 2002). Despite the temporary hearing loss, recent studies have shown that salicylate can protect against ototoxicity induced by noise, cisplatin, or gentamicin (Chen et al., 2007; Kopke et al., 2000; Sha and Schacht, 1999; Sha et al., 2006). Recently, two studies have shown that high doses of salicylate can increase prestin levels in the cochlea by inducing increased prestin gene expression. Yang et al. (2009) reported that twice daily intraperitoneal injections of 200 mg/kg for two weeks in rats increased prestin mRNA by 3–6 fold. This interesting result was also found by Yu et al. (2008) in guinea pigs. They showed increased DPOAE levels and a 2-fold increase in prestin gene expression. Both of these studies used young, normal-hearing animals. The implications of the results are that salicylate-induced prestin gene expression can enhance OHC electromotility, as indexed by enhanced DPOAEs. We hypothesize that aged F344/NHsd with suppressed prestin levels in their OHCs might benefit from salicylate therapy, and that salicylate therapy could restore lost prestin, restore OHC electromotility, and potentially restore hearing sensitivity in the aging rats. The possibility of actually improving hearing in an ear with ARHL is an exciting idea with significant clinical implications. Investigations into the effectiveness of salicylate therapy in the F344/NHsd rat model are currently ongoing.

Conclusion

While the population of patients with ARHL continues to grow, identification and development of potential protective or therapeutic treatments becomes more and more potentially clinically significant. While the basic principles of minimizing ototoxic exposures and living a generally healthy lifestyle are still the best ways to prevent ARHL, the variety of techniques that were reviewed here are the subjects of ongoing research investigations using animal models of ARHL. As the techniques are refined and their potential clinical application evaluated, they may make the transition into clinical use in the human population.

List of abbreviations

ARHL	age-related hearing loss
OHCs	outer hair cells
StV	stria vascularis
IHCs	inner hair cells
HCs	hair cells
SGN	spiral ganglion neurons
EP	endocochlear potential
F344	Fischer 344
DPOAE	distortion product otoacoustic emissions
AAE	augmented acoustic environment
ROS	reactive oxygen species
ALCAR	acetyl-l-carnitine
ATP	adenosine triphosphate
L-NAC	n-acetyl, l-cysteine
SOD1	Cu/Zn superoxide dismutase
SOD2	manganese superoxide dismutase
CR	caloric restriction
ABR	auditory brainstem response
SIRT	sirtuin

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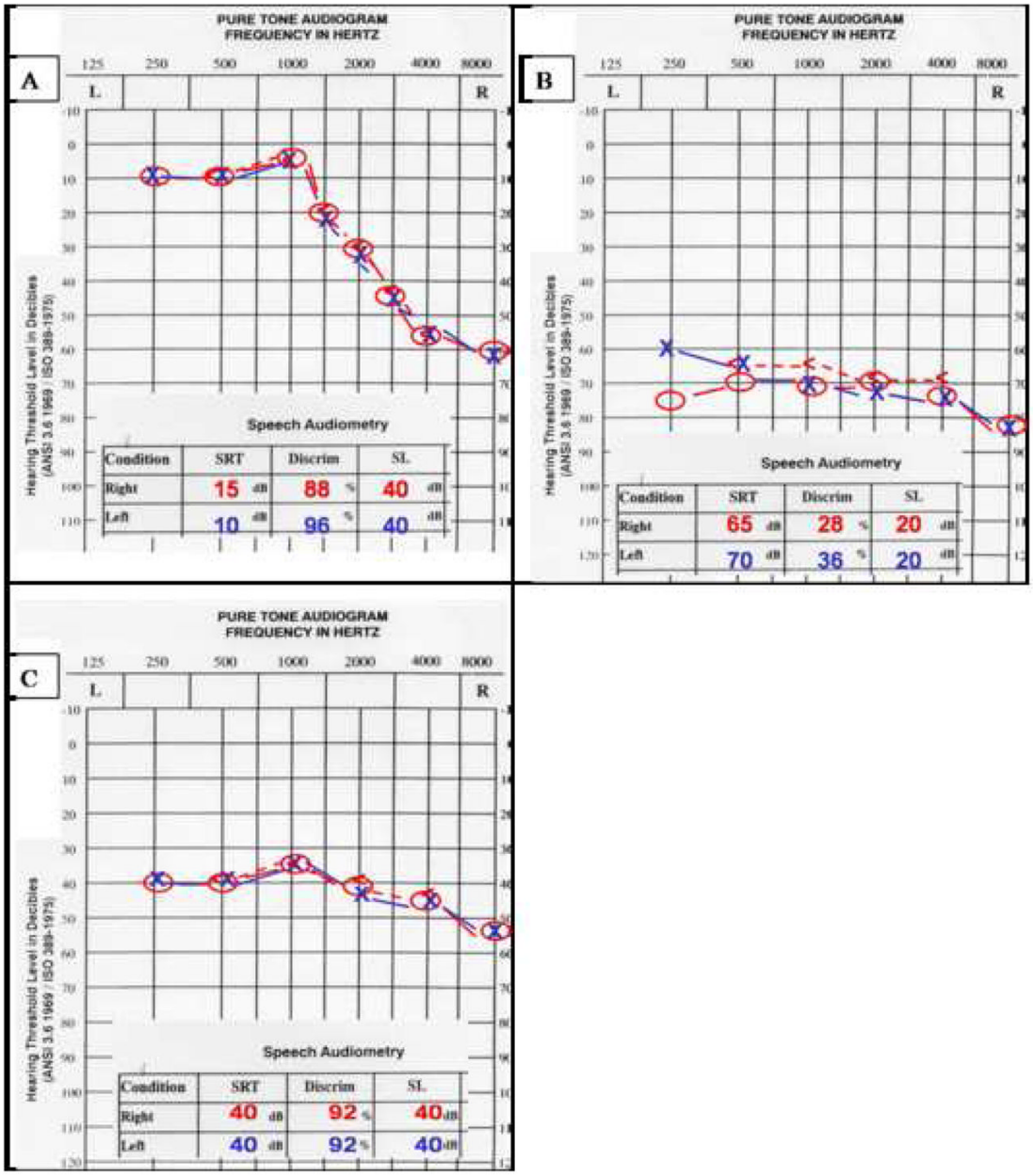

Figure 1.

Audiograms that are representative of hearing loss patterns that are consistent with three different forms of Schuknecht's category of ARHL: A) Sensory; B) Neural; C) Strial.

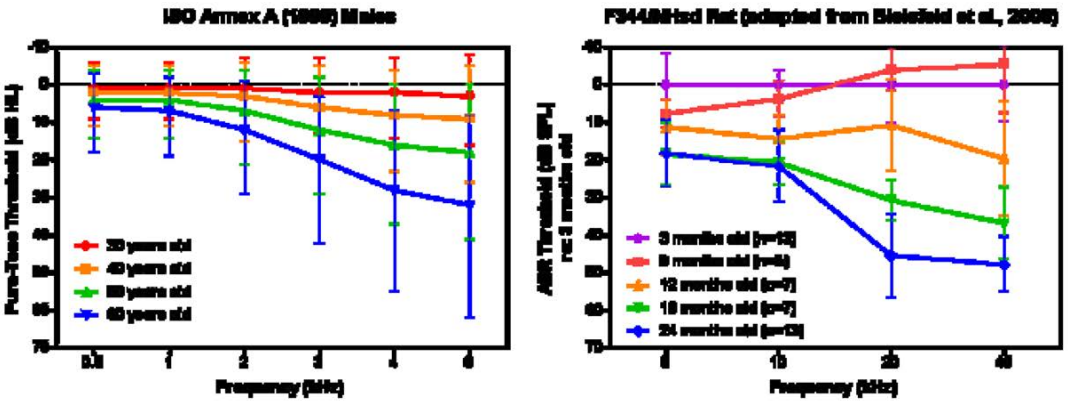

Figure 2.
Comparison of the age-related ABR threshold in the F344/NHsd rat to the age-related hearing loss in humans as indexed by ISO (1999) Annex A.

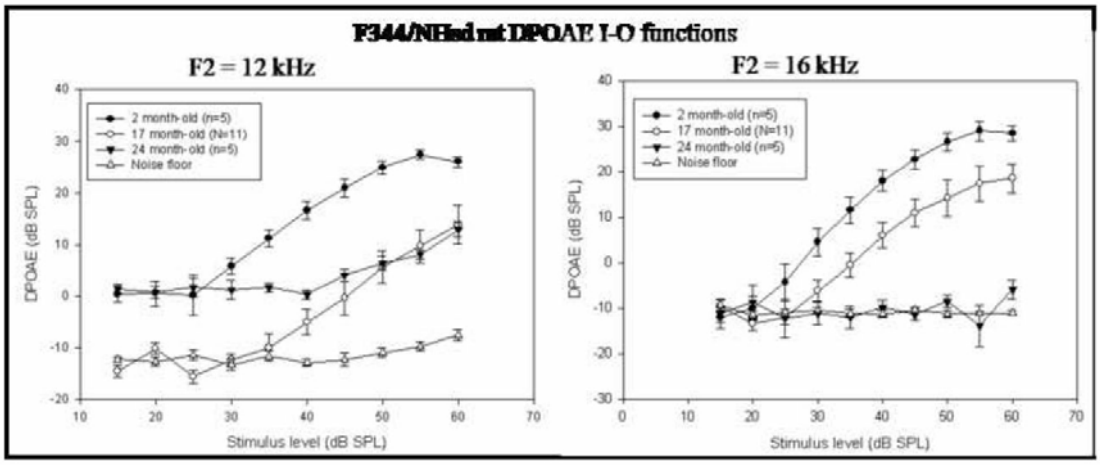

Figure 3.
Mean DPOAE amplitude input-output functions at 12 and 16 kHz for 2, 17, and 24 month-old F344/NHsd rats. Error bars are +/− 1 SEM.

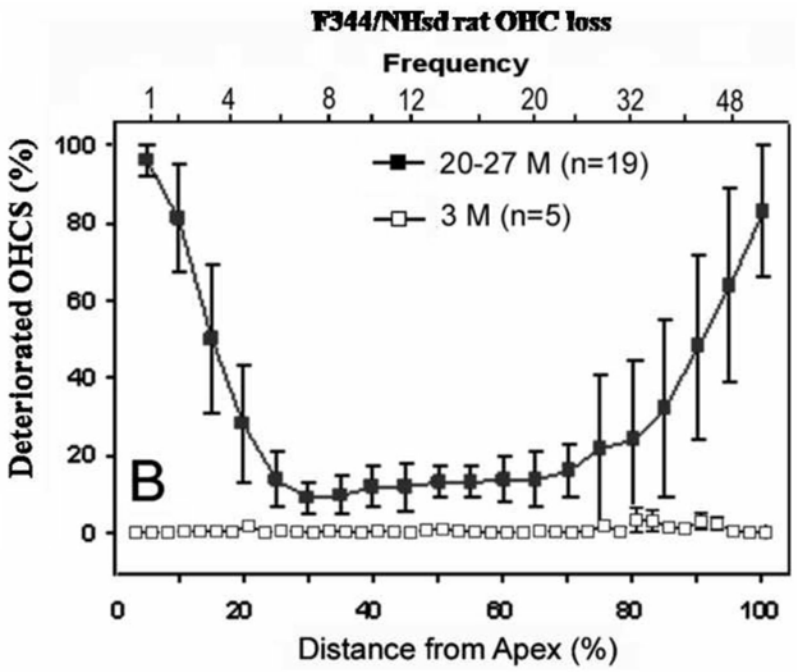

Figure 4.
Mean OHC cochleograms for F344/NHsd rats aged 3 and 20–27 months. Dying and missing OHC were grouped together under the label “deteriorated OHC” as presented on the y-axis. Reprinted with permission from Bielefeld et al., (2008) in Hearing Research.

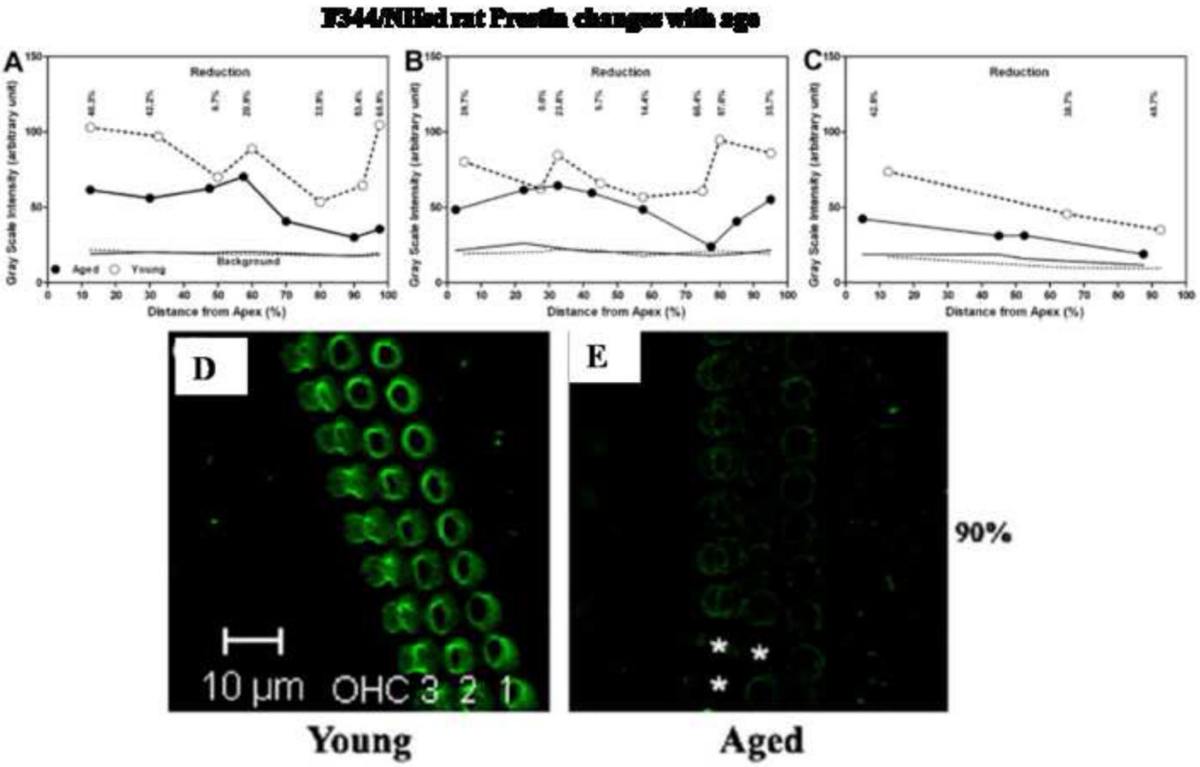

Figure 5.

Prestin changes in 2 month-old and 24 month-old F344NHsd rats. Panels A, B, and C are from three separate pairs of animals' organ of Corti samples. Each pair includes on 2 month-old and one 24 month-old rat's organ of Corti sample. The panels display much lower gray scale staining intensities for prestin in the 24 month-old rats (dark circles) than the 2 month-old rats (open circles). Panels D and E display representative organ of Corti sections for a 2 month-old (D) and 24 month-old (E) rat. The green fluorescence is prestin staining. Clear, consistent prestin staining can be seen in the outer walls of the OHCs in the young animal while very little staining in visible in the intact OHCs of the older animal. Asterisks in Panel E represent locations of missing OHCs. Most of the OHCs in the sample are present, but have reduced prestin staining intensity (From Chen et al., 2009).

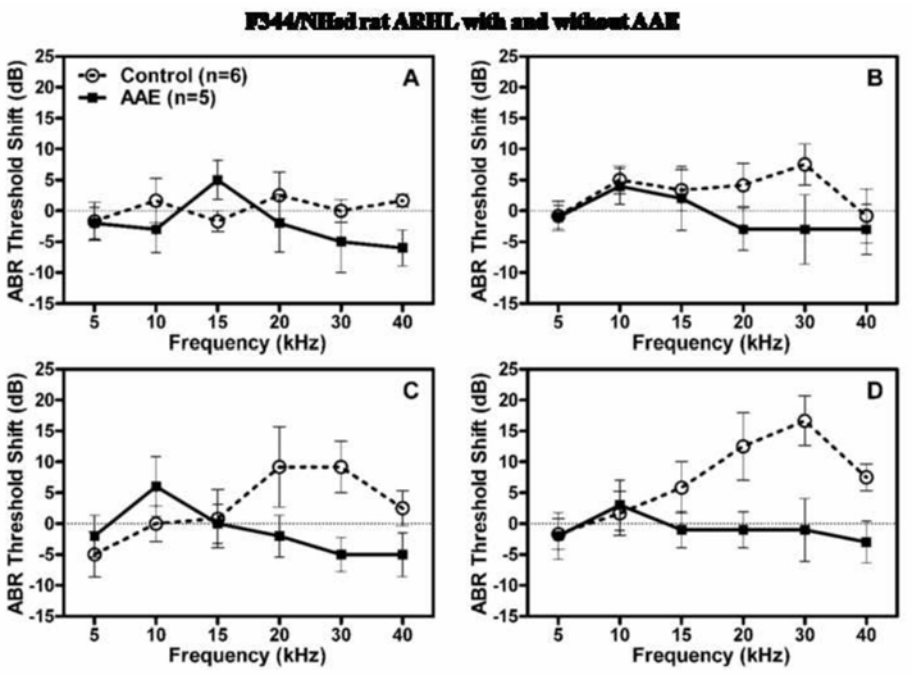

Figure 6.

Results of AAE treatment in aging F344/NHsd rats. Treatment was begun at 16 months of age. Panel A is ABR threshold shift after 2 weeks of treatment. Panel B is after 6 weeks. Panel C is after 9 weeks. Panel D is after 13 weeks. Dark circles are the mean threshold shifts in rats treated with AAE. Open circles are the control rats. The control rats underwent progressive ABR threshold shift over the 13-week period, while the AAE-treats did not show the threshold shift. Reprinted with permission from Tanaka et al. (2009) and Laryngoscope.