AJA

Research Forum

Physiological and Neurobiological Bases of Age-Related Hearing Loss: Biotherapeutic Implications

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Purpose: The aim of this study was to highlight growing evidence of interactions between hormones and the structure and function of the auditory system.
Method: Recent studies implicating sex hormones and other natural hormones in the modulation of hearing status in age-related hearing loss were reviewed.
Results: Progesterone, a sex hormone, has been shown to have negative effects on the hearing of older women and aging mice, whereas, in contrast, estrogen was found in some cases to have a positive influence. Aldosterone, used in studies of animal models of autoimmune hearing loss, slowed the progression of hearing loss. Follow-up studies in humans revealed that auditory measures varied as serum aldosterone levels shifted within the normal range, in otherwise healthy older subjects. This was true for simple as well as complex auditory tasks (i.e., sound spatial processing), suggesting benefits of aldosterone to postperipheral auditory processing as well. In addition, evidence suggests that this functional hearing improvement occurred in association with anatomical improvements to the stria vascularis—an important site of anatomical change in presbycusis.
Conclusions: Audiology is now at the point where the search for biomedical interventions to modulate or prevent age-related hearing loss can move forward. Such interventions would require multidisciplinary collaborative initiatives by researchers in such areas as drug development, anatomy, auditory physiological and perceptual testing, and drug microdelivery systems.

Key Words: audiology, presbycusis, stria vascularis, aging, hearing loss, deafness, cochlea, brain

Hearing loss and deafness affect more than 10% of the population of most countries, which translates into some 30 million people in the United States alone. In association with the recent expansion of the aged segment of our populace, age-related hearing loss—*presbycusis*—constitutes a large proportion of those with permanent hearing loss. Elderly listeners with presbycusis not only have a loss in sensitivity to sound, but also have significant difficulties understanding speech in background noise at suprathreshold, conversational levels (e.g., Frisina & Frisina, 1997). Currently, there are no biomedical treatments for permanent hearing loss or deafness, notwithstanding the fact that management of communication aids for persons with hearing impairment (e.g., hearing aids, auditory rehabilitation/training, or cochlear implants) is a significant component of the U.S. health care system. Clearly, there is an imperative to pursue translational research pathways for developing biomedical interventions to prevent, delay, or reverse cases of permanent hearing loss or deafness.

Perspective: Why Study Hormones and Hearing?

There is growing evidence that interactions between hormones and sensory systems are sometimes beneficial, but oftentimes detrimental. Recently, Canlon and Frisina (2009) edited a special issue of *Hearing Research* that focused on the effects, sometimes quite dramatic, of sex hormones on the peripheral (inner ear–cochlea) and central (parts of the brain used for hearing) auditory systems. One "take-home" message from that special issue is evidence indicating that progesterone can often negatively affect hearing in older women, whereas in some cases, estrogen may have positive effects (Guimaraes et al., 2006). In addition, sex hormone variations can significantly alter auditory temporal processing in the central auditory systems of fish (Sisneros, 2009) and amphibians (Arch & Narins, 2009) for neuroethologically important mating behaviors.

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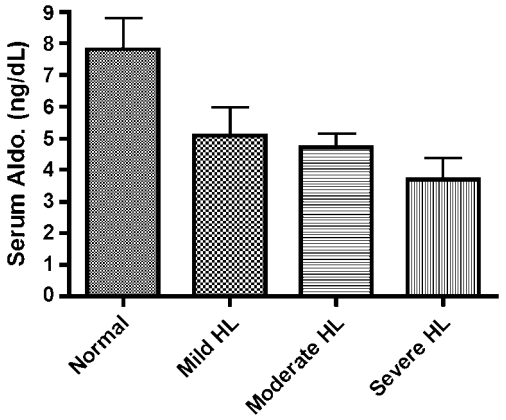
Aldosterone Can Reduce Autoimmune Hearing Loss in an Animal Model

Not surprisingly, other natural hormones can also affect the functionality of sensory systems. For example, Trune pioneered some early mouse model experiments, demonstrating convincingly that aldosterone can have positive effects on slowing the progression of autoimmune hearing loss (Trune, 2010; Trune, Kempton, & Kessi, 2000). Aldosterone is the steroid hormone that exerts the primary hormonal physiological control of Na+ and K+ ion concentrations in the body (e.g., Eisen, Meyer, Christ, Theisen, & Wehling, 1994; Fuller & Young, 2005; Le Moellic et al., 2004). Specific to hearing, for 2 months, Trune added aldosterone to the water supply of an inbred mouse strain that exhibited accelerated autoimmune hearing loss with aging. After administration of aldosterone for 2 months, the treated mice showed significantly less hearing loss than the mice that did not receive steroid treatment (10- to 20-dB improvement in auditory brainstem response (ABR) thresholds for 16–32 kHz), as well as improvement over treatment with prednisone, another steroid hormone. Moreover, the reduction in age-linked hearing loss following the aldosterone treatments was accompanied by anatomical improvements in the cochlear stria vascularis in contrast to the untreated mice. The *stria vascularis* is the specialized organ on the lateral wall of the cochlear scala media, which produces the potassium-rich fluid called *endolymph* that bathes the apical surfaces of the cochlear hair cells (Salt & Thalmann, 1987; Wangemann, 2002; Weber, Cunningham, & Schulte, 2001). The special ionic composition of the endolymph is critical for proper transduction of sound into the code of the nervous system carried out by cochlear hair cells. Age-linked degeneration of the stria vascularis, also referred to as the *cochlear battery,* has been implicated as a primary cause of presbycusis (Schmiedt, 2010; Schmiedt, Lang, Okamura, & Schulte, 2002; Schulte & Schmiedt, 1992).

Clinical Research Discovery: Low Aldosterone Levels Are Linked to Accelerated Age-Related Hearing Loss in Old Listeners

Given the seminal aldosterone discoveries of Trune (2010; Trune et al., 2000), Tadros and colleagues (Tadros, Frisina, Mapes, Frisina, & Frisina, 2005) conducted a clinical hearing research study to ascertain the existence of relations between aldosterone levels and hearing abilities for an otherwise healthy group of older listeners (age 58–84 years). They conducted a comprehensive battery of hearing tests on each listener, which included audiograms, hearing-in-noise tests, gap detection measures, and otoacoustic emissions. After this array of classical and experimental auditory tests, the team collected a blood sample from each subject, which was quantitatively analyzed for serum aldosterone levels. The team found a positive relation between subjects' hearing abilities and blood levels of aldosterone: Subjects with aldosterone levels near the top of the normal clinical range had lower pure-tone thresholds (see Figure 1) and improved abilities to pick out speech in the presence of loud background noise than subjects who had aldosterone levels near the bottom of the normal clinical range. Because the improvements in hearing of the subjects with higher levels of aldosterone occurred for threshold measures, as well as for suprathreshold hearing tests involving spatial processing (e.g., hearing-in-noise tests), Tadros and colleagues concluded that the benefits of higher levels of aldosterone can occur in both the peripheral and central auditory systems.

Figure 1. For elderly subjects, significant differences in serum aldosterone concentrations were found between normal-hearing and mild, moderate, and severe presbycusic subject groups. Main finding: The lower the serum aldosterone (Aldo.) levels within the normal clinical range, the higher the hearing thresholds. Subjects were retrospectively classified into two main groups: The normal-hearing group (average pure-tone thresholds < 23.0 dB HL) consisted of 16 subjects with normal audiometric thresholds (flat audiometry), 10 women and six men, age 58–73 years (mean age = 64.6 years). The hearing loss (HL) group (average pure-tone thresholds ≥ 23.0 dB HL) consisted of 31 subjects with a high-frequency hearing loss (sloping audiometry) characteristic of presbycusis, 20 females and 11 males, 59–84 years (mean age = 71.4 years). The HL group was further subdivided: the mild-to-moderate HL group (average pure-tone thresholds = 23.0–40.0 dB HL) consisted of 20 subjects, 13 women and seven men; and the severe HL group (average pure-tone thresholds > 40.0 dB HL) consisted of 11 subjects, seven women and four men. If there was a difference in pure-tone thresholds between the two ears, the average of the better ear was used to categorize the subject. Error bars represent *SEM*. Adapted with permission from Elsevier.



Experiments in Aging Mice Show Similar Findings

One of the crucial steps along a drug discovery translational research pathway is to determine the adequacy of animal models to be used for the development and testing of novel uses of compounds—in this case, the hormone aldosterone. To accomplish this in the present context, Zhu, Walton, Ding, Peterson, and Frisina (2011) measured hearing capabilities and serum aldosterone levels in CBA/CaJ mice, one of the mouse strains that has proved quite useful in investigating the biological underpinnings of presbycusis.

They found that old CBA mice, which characteristically have elevated tone thresholds and complex sound processing deficits, have reduced levels of serum aldosterone relative to young adult members of this same mouse strain that have normal hearing.

Implications for a Biomedical Intervention to Reduce Presbycusis

Utilizing a multidisciplinary approach of coordinated cell line (in vitro) and animal model (mouse, in vivo) experimentation, we are pursuing critical questions along biotherapeutic pathways aimed at using aldosterone as a component of interventions to prevent or slow down the progression of age-related hearing loss in mammals: Does the expression of the key stria vascularis ion channels/pumps that produce endolymph change with age? Can aldosterone modulate the expression (up-regulate) of the two key ion channels/pumps found in the stria vascularis? Will increasing the expression of these ion channels/pumps improve hearing in old mice, as relations have been observed between hearing thresholds, strial function, and endocochlear potential levels in aging mammals (Gratton, Schmiedt, & Schulte, 1996; Lang et al., 2010; Marcus, Wu, Wangemann, & Kofuji, 2002)? Can novel microelectromechanical cochlear drug delivery systems be utilized to deliver therapeutic compounds to the mammalian cochlea (Borkholder et al., 2010; Johnson, Frisina, & Borkholder, 2011; Johnson, Waldron, Frisina, & Borkholder, 2010), circumventing problems of unstable dosage levels and systemic side effects?

Summary and Conclusions

It is well established that age-related hearing loss—presbycusis—exists in a large proportion of the ever-increasing number of aging persons worldwide. On the positive side, notable strides have been made in the treatment of presbycusis, in large measure through innovative applications of communication access technology. And yet, we have fallen short on parallel advances in biomedical treatments of age-related hearing loss. Here we report on initiatives in biotherapeutics focused on discovering translational research pathways for developing biomedical interventions that prevent, delay, or reverse age-related hearing loss. We begin by recognizing that interactions between sex hormones and sensory systems can be beneficial or detrimental to the peripheral (inner ear) and central (parts of the brain used for hearing) auditory system. For example, progesterone can negatively affect hearing in older women, whereas in some cases, estrogen may have positive effects. The natural hormone, aldosterone, was shown to slow the progression of autoimmune hearing loss in animal models. It was then determined that this functional hearing discovery was associated with anatomical improvements to the stria vascularis, a primary site of anatomical changes of presbycusis. The next important step was the demonstration of positive relations between serum aldosterone levels and hearing abilities in a group of older listeners. We are now at the point where a biomedical intervention to reduce presbycusis can be carried out more fully. This involves multidisciplinary advances in the areas of drug development, anatomy, auditory physiological testing, and drug microdelivery systems.

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