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Age-Related Hearing Loss and Aldosterone Treatment

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Hearing loss is a common cause of disability in the global population. The prevalence of hearing loss is estimated to dramatically increase in the next decades with an increase in the number of older people. The fact that hearing loss correlates with aging suggests that age-related hearing loss (presbycusis) will be a critical issue and hearing care will be required. Untreated hearing loss has negative effects at multiple levels, such as hearing loss affecting the quality of life of hearing-impaired individuals, deteriorating family relationships, and interfering with economic growth. Unfortunately, treatments for hearing loss are limited to the use of hearing devices. Studies have shown that the number of hearing aid users is approximately 20% of all hearing-impaired individuals. Therefore, having alternative treatments is critical to reduce the number of people with hearing loss and to prevent a dramatic increase in the number of hearing-impaired individuals. In the future, a potential medication may be aldosterone (ALD). Studies have reported positive effects of aldosterone treatments on hearing loss in aged mice. ALD treatment in aged mice shows an improvement in hearing sensitivity and a healthier cochlear structure. Although higher ALD concentrations are associated with better hearing sensitivity and hearing in noise ability than lower concentrations, there is no clinical trial in ALD treatment in human has been reported.

Keywords: Age-related hearing loss, Aldosterone, Hearing loss treatment, Older population

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Introduction

Speech and hearing are primary communication strategies in daily life. They are involved in almost every task for living, such as providing information (eg, in schools and workplaces), expressing needs (eg, asking for food and help), and saving life (eg, communicating with a doctor and listening to warning sounds). Unfortunately, poorer speech perception has been reported in the older population because of a decline in hearing sensitivity with advancing age, which is also known as age-related hearing loss (ARHL) or presbycusis.[1]

According to the World Health Organization (WHO), a recent statistical estimation showed that approximately 20% or 2 billion people among the global population of all ages reported hearing loss.[2] More than 5% of the world's population or approximately 432 million people worldwide are suffering from moderate or greater severity of hearing loss and require rehabilitative services to overcome a hearing disability. In Thailand, the prevalence of sensorineural hearing loss was also estimated between 3.5% to 5% of population.[3]

As life expectancy increases and people are living longer, the number of the population aged 60 years and older is increasing. In 2019, the number of the population aged 60 years and older was approximately 1 billion globally. This number of the older population is anticipated to dramatically increase to 1.4 billion in 2030 and to 2 billion in 2050.[4] An increasing age is typically associated with hearing loss. Therefore, the number of the older population with hearing loss will also greatly increase in the next decades. Undeniably, the requirement for intervention and aural rehabilitation will increase with an increase in the hearing-impaired population.

Hearing loss has a negative effect on individuals and families. Hearing-impaired individuals usually report a decreased quality of life, reduced social interactions, and feelings of loneliness. Moreover, they feel frustrated, embarrassed, and angry when they cannot understand an ongoing conversation. In the hospital setting, hearing loss also affects communication, where patients cannot completely understand the information from health care providers, which could hinder them from achieving effective treatments. Hearing loss is also associated with a higher risk of physical conditions such as falling. Studies have shown a strong relationship between hearing loss and the incidence of falls in older adults. This relationship might be explained by the combination of hearing loss and vestibular function disorders, poorer spatial perception, and shared attention between balance and hearing with limited neural resources.[5] Moreover, hearing loss also affects cognitive function and is associated with cognitive decline (eg, difficulty in focusing, confusion, and decreased self-esteem). However, the causal mechanism underlying the relationship between hearing loss and cognitive decline remains unclear.[6] The negative effect of hearing loss does not limit an impact only on hearing-impaired individual, but also affects family members or caregivers. Factors that affect families and caregivers when coping with a hearing difficulty include an increased burden of communication,[7] emotional conditions, and relationship problems.[8]

Hearing loss not only affects hearing-impaired individuals and family, but also global economics (eg, unemployment, special educational support, and financial support). An analysis of the annual cost of untreated hearing loss reported that it is approximately $750 to $790 billion globally.[9] The cost for untreated hearing loss was greater than the cost for treatment. Untreated hearing-impaired individuals are associated with higher medical costs and health care use than those with normal hearing. This finding might be explained by the fact that hearing loss is correlated with other factors, such as cognitive decline,[6] physical issues[5] (eg, falls), and psychosocial problems.[10] A study showed that untreated hearing-impaired individuals had a longer stay in hospital than individuals with normal hearing.[11] Additionally, outpatients with untreated hearing loss tended to have a greater number of hospitals visits than those with normal hearing.

Because of the negative effects of ARHL mentioned above, treatment plans for ARHL must be prepared and

accessible to improve the quality of life of hearing-impaired individuals and to provide a buffer to reduce the effects of hearing loss on society and economics. Even though there has been an improvement in medical technology, treatments for ARHL are still limited to only using hearing devices. Therefore, to expand the range of treatment options for ARHL, recent studies have been investigating alternative procedures for regaining or preserving hearing sensitivity in the older population.[12-15] Studies in animal and human models are being performed to identify potential medical treatment to slow the progress and reduce the prevalence of ARHL.

Age-Related Hearing Loss

ARHL or presbycusis is 1 of the 3 most common chronic medical conditions among the older population, along with arthritis and cardiovascular disease.[16] ARHL typically starts from the loss of hearing sensitivity in the high frequency range, which is the critical frequency range for carrying speech information. Therefore, older people with ARHL usually report that speech signals are audible, but they cannot understand the information. Hearing loss typically progresses and affects the low frequency range in later years.

ARHL can be classified by histopathology (ie, affected cochlear structure and cell type) into 5 different types of sensory ARHL, neural ARHL, strial ARHL, cochlear conductive ARHL, and mixed ARHL. Sensory ARHL is defined by the degeneration of the organ of Corti where the damage extends at least 10 mm from the basal part of the cochlea. This type of damage reflects abnormal hearing sensitivity at high frequencies. A study showed that sensory ARHL was the least common type, with an incidence of less than 10% of reported cases.[17] Neural ARHL refers to the loss of radial afferent neurons that innervate the inner hair cells. Research has shown that the incidence of neural ARHL is 15% to 30% of all cases.[17] Interestingly, progress of hearing difficulty due to neural ARHL usually occurs at a slow pace, where loss of afferent neurons of up to 50% might only show small clinical signs (eg, word discrimination).[18] Additionally, abnormal audiometry may not appear until there is almost 90% of afferent neuronal damage.[17] Strial ARHL refers to a type of hearing loss due to the degeneration of the stria vascularis, which leads to reduced endocochlear potential. Because the stria vascularis is an essential source of energy for inner ear function, degeneration of the stria vascularis leads to elevated hearing thresholds. The prevalence of strial ARHL is approximately 20% to 30% of all cases.[17] Cochlear conductive ARHL has not been clearly explained. The term cochlear conductive ARHL is used to describe hearing loss without obvious degeneration of any cochlear cells or structures. The incidence of cochlear conductive ARHL is approximately 15% to 20% of cases. Finally, mixed ARHL denotes hearing-impaired ears with multiple forms of degeneration. The incidence of this impairment is approximately 25% of all cases.

ARHL is associated with a decline in spectral and temporal cues important for speech perception, especially when listening in background competition. Spectral cues play a critical role in vowel identification and sound localization in the vertical plane. Temporal cues are important for consonant identification and sound localization and spatial perception. Older adults with hearing loss commonly report some degree of difficulty in poorer speech perception and spatial perception because of a considerable age-related decline in auditory temporal processing and spectral processing abilities compared with adults with normal hearing.[19]

Measurements of Temporal and Spectral Processing

ARHL leads to poorer spectral resolution as a reflection of loss of frequency tuning in the peripheral auditory system as typically shown in higher hearing thresholds recorded in an audiogram. A common consequence of reduced spectral resolution is a decrease in the perceptual ability of the unique spectral shape of each speech signal known as the speech envelope. Therefore, aging and hearing loss can greatly affect speech

perceptual ability, especially when listening to speech signals in competing background speech. A common behavioral measure to evaluate spectral envelope perception is called spectral modulation detection. The spectral modulation detection task is used to measure the smallest modulation depth (peak-to-valley difference) in a signal that is detectable. A smaller modulation depth indicates a better perceptual sensitivity for spectral modulation and is associated with greater speech perception. However, the spectral modulation detection performance is decreased in individuals with ARHL.[20]

Temporal processing also declines with advancing age. Common measures for temporal processing include measuring behavioral gap detection, which measures the ability to perceive a small silent gap in the signal. Gap detection thresholds represent the ability to perceive a temporal envelope of speech, which is important for speech identification.[21] A smaller duration of the gap (better gap detection threshold) reflects better temporal processing. Furthermore, a common electrophysiological measure for temporal processing is the auditory brainstem response (ABR).[22] The ABR is a measure of neural synchrony of auditory neurons along the auditory pathway from the auditory nerve up to the brainstem. A greater number of neurons that synchronously respond to a signal leads to larger ABR response components. The ABR can be analyzed by identifying 5 wave peak components of waves I to V. Each peak is generated at a different location along the auditory pathway and occurs at a certain time window (latency), usually with recording from 0 ms to 12.5 ms. Specifically, major peaks, such as I, III, and V, should occur at approximately 1.6 ms to 1.8 ms, 3.6 ms to 4.0 ms, and 5.4 ms to 5.8 ms, respectively. An abnormal ABR might be observed in patients with hearing impairment or auditory nerve dysfunction, and in the normal aging process. In older hearing-impaired listeners, ABR wave components might be prolonged and reduced in amplitude owing to poorer hearing sensitivity and reduced neural synchrony in the older auditory system.[23] In addition, the ABR can also be used for estimating the hearing threshold by decreasing the stimulus intensity to the lowest presentation level that the wave V response amplitude is still detectable.

Aldosterone

As mentioned above, ARHL clearly has a negative effect at multiple levels. Unfortunately, there is still no surgery or medication available to treat ARHL other than using hearing devices, such as hearing aids and cochlear implantation. Surprisingly, recent studies have shown that less than 20% of hearing-impaired individuals are using hearing aids[24] because of limitations, such as financial problems, limitations of hearing devices, and patients' preferences. Therefore, providing alternative treatments is important to reduce the number of untreated hearing-impaired individuals. A potential candidate for ARHL treatment may be a mineralocorticoid hormone secreted from the adrenal gland called aldosterone (ALD). Clinically, ALD plays a critical role in regulating blood pressure and salt balance in the body.[25]

In the mammalian inner ear, the stria vascularis is considered as a power supply for the cochlea. The main function of the stria vascularis is to secrete high potassium (K^+) concentrations into the scala media of the cochlea and maintain K^+ ion recycling. Those processes are essential for auditory signal transduction and active transportation enable the transfer of K^+ ion from the stria vascularis through spiral ligament fibers back into the scala media. There are 2 alternative K^+ pathways for recycling through the sodium-potassium (Na^+-K^+) pump and the sodium-potassium-chloride (Na-K-Cl) cotransporter (NKCC). Sodium-potassium adenosine triphosphatase (Na^+/K^+ ATPase) is an enzyme regulating Na^+/K^+ ion transportation against a gradient concentration, which maintains electrical ion concentrations across cell membranes. Evidence suggests that the inhibition of Na^+/K^+ ATPase increases cell depolarization and apoptosis.[26] NKCC transports $1Na^+$, $1K^+$, and $2Cl^-$ ions across cell membranes. There are 2 isoforms of NKCC called NKCC1 (secretory isoform) and NKCC2

(absorptive isoform). NKCC1 plays a key role in Na^+ movement into marginal cells, boosts Na^+/K^+ ATPase activity, and enables K^+ diffusion into the endolymph. The differences in electrical polarity between cell membranes within the cochlea called the endocochlear potential is essential for maintaining normal auditory function. Inefficiency of the K^+ recycling process leads to a decrease in cochlear amplification and eventually loss of hearing sensitivity. Strial presbycusis is a major type of ARHL and results from a decline in the endocochlear potential.

Corticoid hormones, especially glucocorticoids (eg, prednisone), have long been used to treat autoimmune and idiopathic sudden hearing loss. The 3 main functions of glucocorticoids are immune suppression, anti-inflammation, and an increase in Na^+ transportation. Similarly, naturally produced mineralocorticoids, such as ALD, have a primary role in increasing Na^+ transportation by upregulating the number of Na^+ channels and increasing Na^+/K^+ ATPase. ALD has been reported to have equivalent effects on regaining hearing from abnormal ionic balancing in the endolymph caused by autoimmune disorders without any inflammatory signs.[27] Therefore, ALD might restore hearing sensitivity after deconstruction and ionic imbalance in the inner ear.

Unfortunately, studies have reported that ALD concentrations decrease with advancing age.[28, 29] A relationship between presbycusis and serum ALD concentrations has been reported in animal and human models.[14, 15] Studies have shown that high serum ALD concentrations are associated with a better intact cochlear structure and healthier stria vascularis.[27] However, a decrease in ALD concentrations with advancing age can cause atrophy and deconstruction of the lateral wall of the inner ear, including the stria vascularis. This situation results in insufficient Na^+/K^+ recycling, reduced endocochlear potential, and poor neural transmission, all of which lead to reduced hearing sensitivity.

In brief, ALD is a naturally produced steroid hormone, which influences Na^+/K^+ ion regulation in the mammalian cochlea. Serum ALD concentrations decrease with advancing age. Therefore, an age-related decline in serum ALD concentrations might interrupt normal cochlear function and lead to reduced hearing sensitivity.

Age-Related Hearing Loss and Aldosterone Concentrations

ARHL affects speech perception and daily communication. Additionally, most reported ARHL cases are caused by the degeneration of the stria vasculitis in the cochlea.[17] Studies have reported relationships among aging, audition, and serum ALD concentrations. Animal studies have shown a relationship between ALD concentrations and auditory function where high serum ALD concentrations are associated with a better hearing sensitivity and more intact stria vascularis structure.[14] Recently, studies have investigated potential alternative treatment for ARHL using ALD treatment. These studies showed preventive effects of ALD on ARHL and improving hearing sensitivity after ALD treatment.[14, 30] Long-term treatment of ALD has been evaluated using electrophysiological measures, such as the ABR. Studies showed that ALD-treated mice had stable ABR thresholds and maintained peak I and IV amplitudes over the time course of treatment.[13] This finding suggested that ALD-treated mice did not show a significant effect of aging because hearing sensitivity remained stable over the course of the treatment. However, the control group showed a significant increase in the ABR threshold (poorer hearing sensitivity) and loss of amplitude robustness over time, which is compatible with poorer neural synchrony due to the aging processes.[13] Moreover, ALD implants were provided to aged mice to treat ARHL.[14, 30] Hearing sensitivity was evaluated using behavioral and electrophysiological measures. These studies showed that ALD treatment prevented ARHL and enhanced hearing sensitivity as measured by behavioral measures and ABR thresholds. The ALD treatment group showed better behavioral responses and greater ABR responses to sound stimuli than the non-treated control group.[14, 30] Additionally, in old mice, long-term treatment led to

increased serum ALD concentrations close to the normal range relative to normative data from control younger mice.[13, 30] This finding suggested that using ALD as a long-term treatment did not induce potential negative side effects (eg, hypertension). ALD treatment is also associated with reduced spiral ganglion cell damage in older mice. A study showed that the long-term ALD treatment group had a larger amount of intact spiral ganglion neurons than the age-matched control group.[30] In addition, ALD treatment is effective as commonly used prednisolone for regaining hearing sensitivity in autoimmune sensorineural hearing loss. A study reported that ALD-treated mice showed a restored normal appearance of stria vascularis morphology, while the untreated group showed degeneration with progressing disease and hearing loss.[29]

In humans, a cross sectional-design study showed the effects of serum ALD concentrations on peripheral and central auditory functions.[15] A significant correlation between low ALD concentrations and presbycusis was reported. Specifically, the low serum ALD concentration group had significantly higher pure tone detection thresholds (poorer hearing sensitivity) and poorer hearing in noise performance than the high serum ALD group. Furthermore, cochlear function as measured by transient evoked otoacoustic emission and temporal processing as measured by the gap detection task were not affected.[15] These findings suggest that low serum ALD concentrations affect central auditory processing as shown by poorer hearing sensitivity and greater difficulty of hearing in noise rather than affecting the cochlea. However, the location in the central auditory pathway that is affected by serum ALD concentrations remains unclear. Moreover, a long-term observation of the association between variations in ALD concentrations and changes in hearing levels with advancing age has not been reported. Therefore, how aging is associated with a change in ALD concentrations and a change in hearing sensitivity over time remain unclear.

On the basis of previous literature, ALD could be a strong candidate for a medication to treat ARHL.[15] Fortunately, ALD treatments may be the first medication to be approved by the US Food and Drug Administration. However, ALD treatment in human clinical trials has not been reported.

Discussions

Increasing numbers of senior citizens globally are associated with an increase in the incidence of hearing impairment. Many studies have reported the negative effects of hearing loss on daily living and society. Therefore, interventions and treatments are urgently required. At present, available treatment for hearing loss is only limited to hearing devices. However, research has shown potential medical treatment for ARHL using ALD treatment. ALD treatment has been well studied in animal models. This treatment shows promising outcomes, such as recovery of hearing sensitivity in aged mice, an intact cochlear structure in treated mice and no side effects of long-term treatment. Moreover, in humans there is a correlation between high ALD concentrations in the blood and better hearing sensitivity and hearing in noise performance.

In the future, ALD might be an alternative treatment for ARHL, since it has also shown equivalent effects for treatment of sudden hearing loss as a commonly used medication. However, number of literatures regarding hearing loss and ALD treatment in human are still limited. Therefore, it might be too soon to draw a conclusion about the effectiveness of ALD treatment in human at the moment. Fortunately, clinical trials for ALD treatment in humans are ongoing, and will hopefully provide promising outcomes.

Conclusions

ARHL or presbycusis is a critical issue globally. Nowadays, treatment for ARHL remains limited to only using of hearing devices. After completed clinical trial in human, an alternative treatment might be available in near future by using aldosterone hormone.

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ประสาทหูเสื่อมตามวัยกับการรักษาด้วยฮอร์โมนแอลโดสโตโรน

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การสูญเสียการได้ยินเป็นสาเหตุหลักของความพิการที่พบในประชากรโลก โดยในทศวรรษหน้าประมาณการว่าความชุกของการสูญเสียการได้ยินจะเพิ่มขึ้นอย่างมาก เนื่องจากจำนวนประชากรผู้สูงอายุที่เพิ่มขึ้น ซึ่งการสูญเสียการได้ยินมีความสัมพันธ์กับอายุที่มากขึ้น และจำเป็นต้องได้รับการช่วยเหลือ โดยหากไม่ได้รับการรักษาจะส่งผลเชิงลบหลายด้าน เช่น คุณภาพชีวิต ความสัมพันธ์ในครอบครัว และการเจริญเติบโตทางเศรษฐกิจ ปัจจุบันการช่วยเหลือผู้สูญเสียการได้ยินยังมีข้อจำกัดด้วยการใช้อุปกรณ์ช่วยการได้ยินเพียงอย่างเดียว และมีผู้สูญเสียการได้ยินน้อยกว่าร้อยละ 20 ที่ใช้เครื่องช่วยฟัง ดังนั้น การเพิ่มทางเลือกในการรักษาจึงมีความจำเป็น หนึ่งในวิธีการรักษาที่กำลังเป็นที่สนใจในอนาคต คือ การใช้ฮอร์โมนแอลโดสเตอโรน ซึ่งจากการศึกษาในหนูสูงวัยพบผลเชิงบวกในการรักษาการสูญเสียการได้ยิน โดยกลุ่มที่ได้รับฮอร์โมนมีการได้ยินดีขึ้นและมีหูชั้นในที่แข็งแรง แม้ว่าระดับฮอร์โมนที่สูงขึ้นมีความสัมพันธ์กับระดับการได้ยินและการฟังเสียงในที่ที่มีเสียงรบกวนดีขึ้น แต่ยังไม่มีการทดลองทางคลินิกเกี่ยวกับการใช้ฮอร์โมนแอลโดสเตอโรนในมนุษย์

คำสำคัญ: ประสาทหูเสื่อมตามวัย ฮอร์โมนแอลโดสเตอโรน การรักษาประสาทหูเสื่อมตามวัย ประชากรผู้สูงอายุ

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