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The Potential of Mineralocorticoid Nanohydrogels as a Treatment for Metabolic Presbycusis

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ABSTRACT

Background & Aims: Presbycusis is the most prevalent neurodegenerative disorder in the elderly and causes communication difficulty. Metabolic presbycusis is a type of presbycusis caused by degeneration of the stria vascularis, which shows pathology in the form of atrophy. To date, pharmacological therapy continuously developed to achieve the optimum treatment of metabolic presbycusis. Drug delivery to the inner ear is one of the challenges in treating presbycusis. Anatomical location and physiological barriers, such as the blood labyrinthine barrier (BLB), are the main obstacle to attaining a high drug concentration in the inner ear. This paper aims to summarize the potential of mineralocorticoid nanohydrogels as a metabolic presbycusis treatment.
Material & Methods: Literature review was conducted with keywords "presbycusis", "mineralocorticoid", "nanoparticle", and "nanohydrogel" on PubMed, Google Scholar and ResearchGate. There were 52 articles were appropriate for this purpose.
Results: Mineralocorticoids show potential effect as an agent therapy for presbycusis due its action balancing mechanism of the Na^+–K^+–$2Cl^-$ cotransporter (NKCC1) ion pump, which can further increase spiral ganglion neuron (SGN) density and mineralocorticoid receptor (MCR) excretion. Furthermore, using nanohydrogel technology as a delivery vehicle has potency to increase contact time with round window membrane (RWM). This nanohydrogel meets the ideal characteristics drug delivery system to the inner ear, namely stable, intact delivery, specific to the desired target, and having good biocompatibility so the drug can work optimally for the target.
Conclusion: Mineralocorticoids encapsulated with hydrogel technology can potentially be a therapeutic option in metabolic presbycusis.

Keywords: Presbycusis, Mineralocorticoid, Nanoparticle, Nanohydrogel

INTRODUCTION

Age-related hearing loss (ARHL), often referred to as presbycusis, ranks first as a neurodegenerative disease in the elderly population and results in communication disorders. Presbycusis is one of three chronic conditions besides arthritis and cardiovascular disease.[1–3] The condition of presbycusis that occurs in patients is often associated with social isolation, weakness and cognitive decline, psychological and medical morbidity, and even depression.[4,5]
The prevalence of hearing loss is 3.7% in the 55-64 year age group. This incidence increases with age.[6] Presbycusis was reported to be detected at over 80 years in

all healthy subjects in a study conducted in Madrid, Spain. The prevalence of presbycusis will increase by 100% when someone is 80 years and over.[7] More than half of the adult population with an age range of over 75 years and almost the entire adult population over 90 years are reported to have presbycusis.[8]

Metabolic presbycusis is a commonly reported type of presbycusis.[1] Based on a study conducted on 429 presbycusis sufferers at the Hearing and Speech Impairment Clinic, ENT Health Sciences Padjajaran Medical School, West Java, Indonesia/Dr. Hasan Sadikin Bandung General Hospital found that 77 patients (17.9%) had presbycusis of the metabolic/strial type. The most common presbycusis was found in the age group >65 years, namely 259 patients (60.4%). This study found that the metabolic type of presbycusis sufferers experienced the most severe degree of hearing loss, namely, 29 patients (6.8%).[9] It was found that most patients who experienced presbycusis were male, with the most common type being the metabolic type of presbycusis (57.69%) and in the age group of 60-70 years.[10]

The most common treatment given to patients with metabolic presbycusis is hearing aids which can only help facilitate communication and improve the quality of life of sufferers without any improvement to normal hearing function. A cochlear implant is an operative procedure that can restore normal hearing function. However, cochlear implants are expensive, and patients must meet several specific criteria before carrying out cochlear implantation.[11] Meanwhile, pharmacological therapy for metabolic presbycusis is still limited, and there are few clinical studies related to this.[12] Until now, there is no pharmacological therapy that aims to treat or prevent the occurrence of presbycusis.[13]

The treatment for metabolic presbycusis that are now starting to be widely researched is related to targeting cellular, genetic, or pharmacotherapy that can increase the regeneration of damaged hair cells in the cochlea. One of those modalities that can be developed is hormone therapy. Mineralocorticoid hormones are hormones that are reported to maintain normal hearing function.[14]

Mineralocorticoids need to be packaged in an efficient, effective, and localized drug delivery strategy so can deliver the active molecules of these mineralocorticoids to their targets, namely in the deepest part of the ear. The smaller the particle size, the easier it is to transport the drug.[15,16]

Various drug delivery strategies have been developed to reduce obstructions in the inner ear. Nanohydrogel is one of the potential options to provide continuous drug delivery capabilities to its target in the inner ear. Mineralocorticoids packaged in nanohydrogels can potentially deliver their active molecules to targets in treating metabolic presbycusis by extending the contact time on the RWM and reducing clearance by the pharyngotympanic tract.[17]

Based on this explanation, the authors are interested in summarizing the potential of mineralocorticoid nanohydrogels as a treatment in cases of metabolic presbycusis.

MATERIALS & METHODS

Using the literature review method with the keywords "presbycusis," "mineralocorticoid," "nanoparticle," and "nanohydrogel" to obtain the sources used. Source from databases such as PubMed, ResearchGate, and Google Scholar. The selected articles are articles that meet the inclusion criteria. The inclusion criteria included all articles that discussed the potential of mineralocorticoid nanohydrogels as a treatment for presbycusis. The exclusion criteria from this literature review are publications in more than the last ten years unless there are no relevant new studies or updates to the article. There are 52 articles that fit the purpose of this writing. Existing information was collected, summarized, and compiled into a review of scientific literature.

RESULT

Pathophysiology of Metabolic Presbycusis

Currently, presbycusis is classified into six categories based on the pathology of the temporal bone and the results of audiometric tests. The six categories in question are sensory conductive presbycusis, nervous type presbycusis, metabolic or strial type presbycusis, cochlear type presbycusis, mixed and indeterminate type of presbycusis.[18]

Metabolic presbycusis or strial presbycusis is presbycusis which indicates a pathological condition in the form of atrophy of the stria vascularis. The stria vascularis in the cochlea and the organ corti are the parts responsible for the normal function of the auditory system. The stria vascularis, which consists of basal, intermediate, and marginal cells, functions to maintain the ionic composition of the endolymph and generates the endocochlear potential on the media scale.[19]

A common pathological feature is patchy atrophy of the stria vascularis in the middle and apical bends of the cochlea, which shows a flat pattern on audiometry. Atrophy is also reported in the lateral wall of the cochlea, in the middle scale of the stria vascularis. Loss of some or all of the strial cells indicates the presence of basophilic deposits or cystic structures that occur. The stria vascularis atrophy in metabolic presbycusis can occur in up to 30% or more of stria vascularis tissue and causes a decrease in the hearing threshold. The loss of the stria vascularis network will affect the endolymph's quality, resulting in physical and chemical energy processes in the hearing organs through disruption of K+ recycling.[15,20] This results in dysfunction of the ion pump Na-K-ATPase and NKCC1 in the stria vascularis.[1] The stria vascularis undergoes morphological changes in its lateral wall as well as decreased expression and activity of Na, and K-ATPase, which are two factors that together contribute to the pathogenesis of metabolic presbycusis (Figure 1).[21]

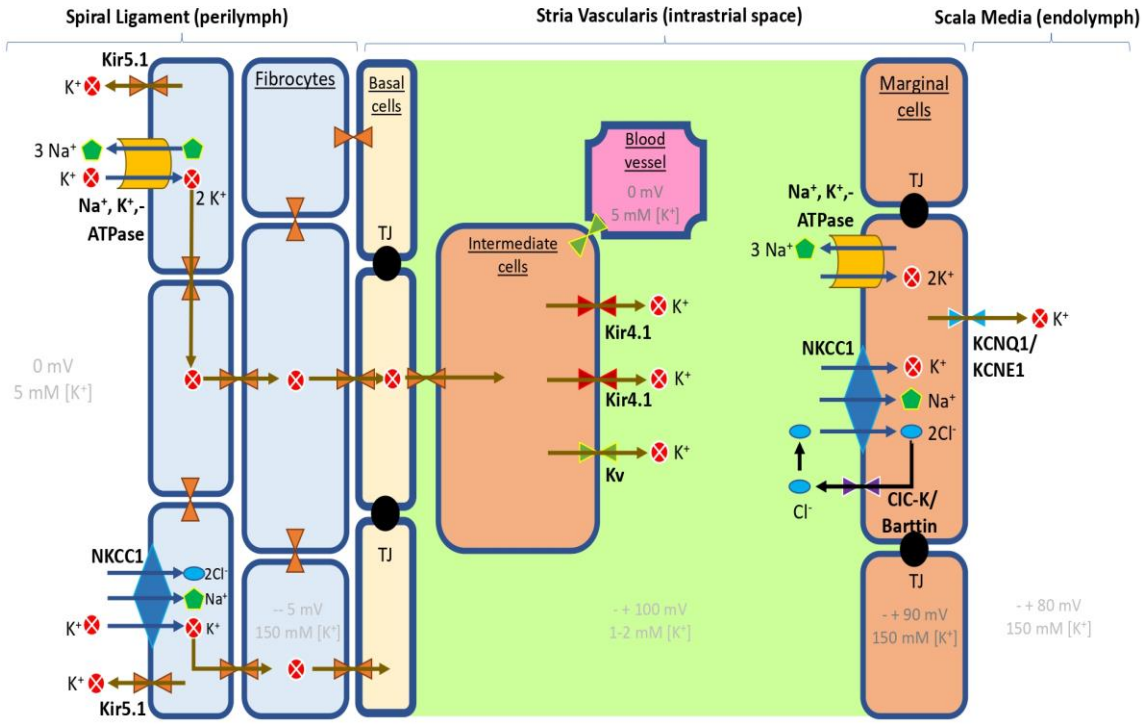

Figure 1. Some Ion Transporter Channels (NKCC1, Na, K, Atpase, KCNQ1, Kir4.1, Kir 5.1, and Kv) Expressed in the Stria Vascularis and Spiral Ligament that Play a Role in K+ Balance and Production of Endochlear Potentials.[22]

Presbycusis Therapy

One of the treatment options given is hearing aids. Hearing aids have a significant positive effect on improving quality of life and communication. However, using these aids only amplifies sound and does not improve normal hearing. The obstacle in using this tool is that it often causes discomfort and requires cognitive adjustments. Another treatment option is invasive therapy in the form of cochlear implants, which is generally recommended for patients with bilateral hearing loss who do not improve with hearing aids.[11] Until now, no pharmacological therapy has been reported that is clinically proven and accepted by the Food and Drug Administration (FDA) to cure presbycusis.[1,12] Several therapeutic agents are being developed using coenzyme Q10 (CoQ10) formulations, tanakan, antioxidant combination therapy, and hormone therapy.[12] The increase in the hormone aldosterone has a positive effect on hearing function. However, the treatment target in the middle ear makes it challenging to administer drugs given orally to achieve the treatment target and possibly has a systemic effect.[23,24] Also, drugs administered intratympanic have a low contact time with RWM and increased clearance through the pharyngotympanic canal.[17]

Mineralocorticoids

Mineralocorticoids are steroid hormones that play a role in regulating water and electrolyte balance.[20] Aldosterone is one of the main mineralocorticoids that is synthesized in the zona granulosa of the adrenal cortex. Mineralocorticoids work by binding to the mineralocorticoid receptor (MCR) in the cytoplasm of target cells. Activation of this receptor causes increased expression of Na+/K+- ATPase and Epithelial sodium channel (EnaC).[25]

Mineralocorticoid pharmacokinetics involves the release of the drug from the pharmaceutical preparation. Then the drug must pass through the RWM or the annular oval window (OW) ligament to reach the middle ear.[15]

Drugs administered intratympanically do not last long in the middle ear and are excreted rapidly into the pharyngotympanic tract, thereby reducing drug absorption. Mineralocorticoids are distributed in the endolymph and perilymph slowly, and this is because the process of diffusion and fluid volume flow only influences the distribution.[23] The shape/organization of drugs in smaller molecules is one of the efforts to increase the distribution and effectiveness of drugs.[26]

Furthermore, the drug is metabolized in the lymph or bound to the tissues. Elimination of mineralocorticoids through the vascular system, through the cerebro spinal fluid (CSF), then to the middle ear due to perilymph leakage through RWM or OW.[23]

Clinical Effects of Mineralocorticoids as Treatment of Presbycusis

Mineralocorticoids have the potential as presbycusis treatment by binding to mineralocorticoid receptors in the cytosol to increase the expression of NKCC1. In vitro study by Bazard et al. showed the mechanism of action of aldosterone through complex binding with mineralocorticoid receptors. In cells treated with aldosterone and eplerenone (EPL-20M), selective mineralocorticoid receptor antagonists showed no change in NKCC1. The semi-quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR) showed no differences in mRNA expression, which means that the increase in NKCC1 protein expression occurred in the post-transcriptional phase.[27]

Based on examination of NKCC1 protein expression in a study by Halonen et al. demonstrated up to a two-fold reduction in NKCC1 protein expression and a significant upregulation of NKCC1 in mice treated with aldosterone. The examination was carried out using the Western Blot method by comparing the expression of proteins on the lateral wall of the cochlea in groups of young rats, old rats, and rats with

aldosterone intervention for four months. In Auditory Brainstem Response (ABR) Audiometry, mice treated with aldosterone showed a stable noise threshold (± 1 dB), while the control rat group showed an increase from 39 dB to 49 dB. Then, measurements of the amplitudes of the P1 and P4 peaks at 80 dB SPL WBN were performed to assess the drive of peripheral to central excitability. There was a positive shift in the P1 and P4 amplitudes in the intervention group compared to the control group rats, which showed a greater peak ABR amplitude.[3] Cochlear hematoxylin/eosin (H&E) staining showed decreased spiral ganglion neurons (SGN) in old rats and a therapeutic effect at the modiolus level in the intervention group. A statistically significant correlation was found between SGN density and ABR shifts of 24 and 36 kHz, suggesting that worsening hearing was associated with a decrease in the number of SGNs. In testing the expression of Mineralocorticoid Receptor (MCR) in SGN cell bodies, with positive control RNA from the liver and heart.[1]

Nanohydrogel

Nanoparticles are particles with sizes 1-1000 nm that have been developed since the 1950s, but their use as drug delivery agents has begun to be used in the last two decades.[28] The small size of these nanoparticles allows access to cells and various cellular compartments, including the nucleus. In addition, this nano-size has the potential to cross various biological barriers in the body, such as the barrier in the inner ear.[24]

Treatment of the inner ear is one of the challenges in the health problem due to its anatomical location, which is difficult to reach, and there is a physiological barrier, namely the BLB, as a barrier or filter for substances that enter the inner ear. The nanoparticles carry therapeutic agents and can transport them across membranes such as RWM in the inner ear. Nanoparticles can reach inner ear hair, SGN, various structures in the organ of Corti, and up to the central auditory pathway in the brainstem. Nanoparticle delivery can be utilized to stabilize drugs, control drug release, and modify surfaces to achieve specific targets.[20,24]

The recommended nanoparticle size for the inner ear is smaller than 200 nm to avoid opsonization and elimination by the host's immune system. Research being conducted on nanotechnology-based hearing loss therapy that is currently being developed focuses on drug delivery systems that are stable, specific to the target, and slow-release. In addition, researchers are also focusing on treatments that are not only capable of delivering the drugs but also safe and do not damage the integrity or function of the inner ear structures.[29]

Various methods have been used to deliver nanoparticles to the inner ear. One of the methods used is using a nanohydrogel such as chitosan-glycerophosphate (CGP), which is an efficient local drug delivery system with the advantage of slow controlled drug release because the material is gradually degraded by enzymes such as the chitosanase enzyme present in the middle ear. Drug delivery using nanoparticles with CGP hydrogel-based nanoparticles (nanohydrogels) can increase the contact time with RWM, which has an impact on improving the effectiveness and success of the delivery of nanoparticles to the inner ear. Hydrogels coupled with nanoparticles have been used to deliver antibiotics and corticosteroids into the perilymph of the inner ear. Research conducted by Lajud et al. using nanohydrogel in vivo in a mouse model showed that nanohydrogel can deliver nanoparticles intact/intact to the perilymphatic system and can reach cellular structures in the media scale of the inner ear.[25,30]

Nanohydrogels are rich in water content and have good biocompatibility, so they are recommended to overcome the drawbacks of drug delivery systems using intratympanic injections, a method considered unstable.[24] In addition, nanohydrogels respond well to external

stimuli, such as light and magnetic fields. By applying external stimuli, nanoscale chemical and physical properties can be controlled remotely to achieve the desired administration.[28]

Therefore, nanohydrogel as a drug delivery system has great potential to produce controlled and continuous therapy from the middle ear to the inner ear without changing the inner ear structure.[29] The characteristics of nanohydrogel are in accordance with the characteristics required as a drug delivery system to the inner ear, including stability, specific to the desired target, safe without damaging the inner ear structure, good biocompatibility, intact delivery, and easily degraded so that drug delivery becomes more effective to the inner ear. [20,23–25]

Mechanism of Construction, Administration, and Distribution of Mineralocorticoid Nanohydrogels

Construction Mechanism

The method commonly used to prepare natural polymer nanocomposite formulations is chemical cross-linking of the polymers to alter the interaction and form mechanically and chemically stable hydrogels.[31] The nanoparticles are fluorescently labeled, namely rhodamine, and then loaded onto a CGP based hydrogel to form nanohydrogels then applied directly to RWM.[29,30] The CGP hydrogel was freshly prepared on the same day for use by dissolving 2% w/v ultrapure chitosan 95/1000 (91.7% DDA; Biosyntech, Quebec, Canada) into 0.1M HCl prepared by stirring (magnetic/vortex) overnight at room temperature. This solution was stored at 4°C until use.[29,32]

Administration and Distribution Mechanisms

The nanoparticles were fluorescently by rhodamine and then loaded into a CGP-based hydrogel to form a nanohydrogel which was then applied directly to the RWM via intratympanic injection (Figure 2). Nanohydrogels are used to deliver antibiotics or corticosteroids into the perilymph of the inner ear. The nanohydrogel is slowly released and traverses the RWM into the inner ear fluid until it reaches the inner ear cells to deliver the therapeutic agent it carries.[29,33] Incorporation of the nanoparticles into the gel slows the slow release of the drug for more than 72 hours. When embedded in a gel, drug release from NPs-CS/GP is significantly prolonged, mainly due to the obstructive effect of the gel matrix based on narrower and fewer aqueous channels, which makes the diffusion pathways longer and thicker.[33]

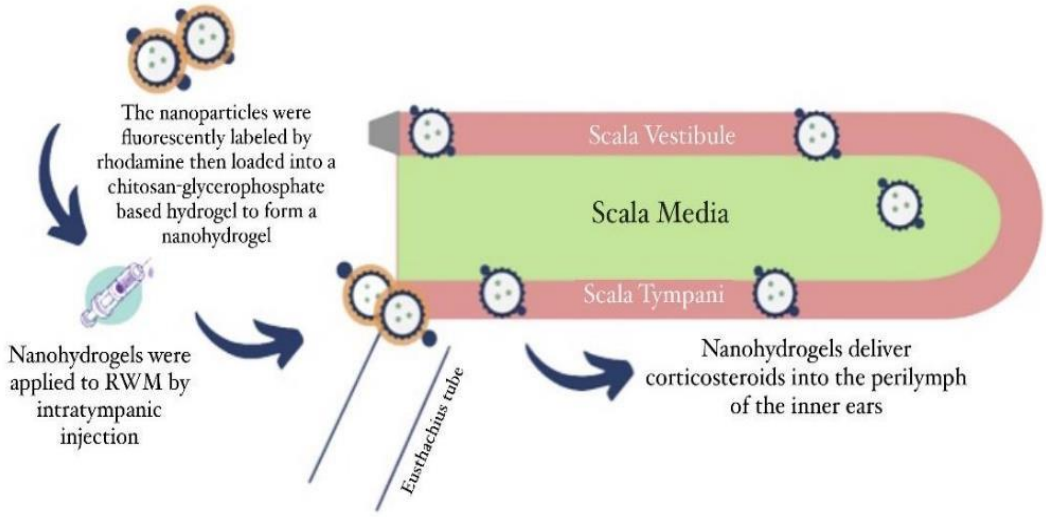

Figure 2. The Administration and Distribution Mechanism of Nanohydrogel to deliver corticosteroid into the perilymph of the inner ear by intratympanic injection to the RWM. [30]

Potential Mechanism of Action of Mineralocorticoid Nanoparticles in Patients with Metabolic Presbycusis

Aldosterone, as the main hormone of the mineralocorticoids, will produce an aldosterone receptor complex if it binds to the mineralocorticoid receptors in the cytosol and is regulated by ALD-SGK-1. This bond will regulate the activation and function of the balance of ions, including Na, Ca, Mg, and K ions, and the activation of K by Ca.[27] Hearing threshold was found to be significantly increased by aldosterone therapy in a study conducted on rats. The underlying cause of this event is related to the mineralocorticoid receptor, which is regulated through post-translational protein changes. The survival of spiral ganglion cells was found to be significantly increased, as well as the inhibition of extrinsic and intrinsic apoptotic pathways.[34] Mineralocorticoid receptors are distributed more limitedly in the central nervous system, unlike glucocorticoid receptors. Until now, there has been no research that explains the expression of these two receptors in the entire central auditory nervous system.[35]

Aldosterone has a major impact on gene expression in the auditory organ by controlling ion balance. Many genes regulated by mineralocorticoid receptors are affected by glucocorticoid administration.[36] Aldosterone regulates K and Na ion balance by regulating the protein expression NKCC1 and Na-K-ATPase.[35,36] Aldosterone will be released by the adrenal cortex to regulate the expression of NKCC1 and Na+/K+-ATPase proteins through modification of mRNA/protein synthesis in the inner ear.3 Na+/K+-ATPase is an integral membrane protein that functions to maintain the electrochemical gradient of Na+ and K+ ions that cross the cell membrane and regulate cell volume. Changes that occur in the regulation of Na+/K+-ATPase protein expression in the inner ear have an impact on increasing ion mobilization and reducing extracellular fluid.[34] Meanwhile, NKCC1 is a protein that can mediate the active transport of Na, K, and Cl ions across the cell membrane. Na+–K+–2Cl− cotransporter (NKCC1) becomes a protein that plays a role in the formation of endolymph which is rich in K ions in the inner ear as a support for normal hearing function.[27] Aldosterone can increase the stability of NKCC1 protein without increasing NKCC1 mRNA synthesis.[37]

Endocochlear potential (EP) is responsible for normal hearing and cochlear function. Endocochlear potential is created by the high concentration of K+ ions in cells within the stria vascularis. Endocochlear potential, which continues to decrease with age, will result in metabolic presbycusis, which shows degeneration of the stria vascularis. Na+–K+–2Cl− cotransporter (NKCC1) plays an important role in the production of endolymphatic fluid, which contains lots of K ions in the stria vascularis layer, namely in the marginal strial cells. Mineralocorticoid receptors regulate the regulation of the NKCC1 protein by aldosterone. Aldosterone is a form of a hormone that helps the expression of NKCC1, which has an important function in the balance of Na+, K+, and acid-base ions in the deepest part of the hearing organ.[38]

Decreased expression of NKCC1 as an ion channel transporter is associated with ion balance dysfunction in metabolic presbycusis. NKCC1 plays a role in the cochlea's normal physiological function and in the hearing loss associated with aging. Based on the research by Freeman et al., it was reported that prolonged administration of systemic aldosterone could increase the expression of NKCC1 protein in cell membranes caused by the presence of mineralocorticoid receptors and NKCC1 co-transporters.[3,38] This is supported by studies conducted on mice with decreased expression of NKCC1 on the lateral wall of the cochlea, which resulted in a decrease in ion balance regulation that can be slowed down by long-term aldosterone administration. Na+–K+–2Cl− cotransporter (NKCC1) expression was found to increase

after the administration of aldosterone, which was observed in the stria vascularis.[3] The increase in NKCC1 expression after aldosterone administration ultimately increases the auditory threshold and maintains the normal function of the spiral ganglion neurons. Treatment with aldosterone as a form of mineralocorticoid hormone in animals was found to have a positive impact on presbycusis cases through cellular stabilization of the NKCC1 protein structure in cells present in the lateral wall of the cochlea, specifically in the marginal cells of the stria vascularis.[3] Early aldosterone therapy can regulate mineralocorticoid receptor expression in spiral ganglion cells by preventing post-transcriptional modifications.[1]

Mineralocorticoid hormones have good potential in the treatment of presbycusis. The endocochlear potential produced by Na+/K+-ATPase and NKCC1, which is located on the basolateral membrane of the stria vascularis, has an important role in normal hearing transduction through hair cells. Therefore, the administration of aldosterone as a form of mineralocorticoid hormone aims to increase aldosterone hormone levels so that it can restore the regulation of the NKCC1 protein and Na+/K+-ATPase. Based on this, mineralocorticoid hormone supplementation is one of the therapeutic options that can be given in cases of presbycusis.[1,3,37,38]

Mineralocorticoids with therapeutic preparations in nanoparticle technology are a potential strategy to increase the efficiency of therapy, especially those that target the inner ear. Nanoparticles allow a drug to reach specific targets on auditory hair cells and maintain a sustainable concentration.[37] The mechanism of action of mineralocorticoid nanoparticles will initially be delivered to the middle ear, then it will diffuse through the RWM and eventually be released into the cochlea.[39,40] There are several advantages if the drug can be delivered directly to its target, which include a more efficient local effect, minimizes systemic toxicity, maintaining sufficient concentration at the target, and can pass through the BLB. Blood labyrinthine barrier (BLB) themselves can be a barrier when drugs are administered systemically.[23]

Nanoparticles can be conjugated to peptides that can pass through cells, and changes can be made related to their surface to increase the contact of mineralocorticoids with RWM. The increased contact that occurs will have the effect of delivering the drug to a more efficient target. The surface of these nanoparticles can be formed according to a specific target structure through ligand conjugation using bioconjugation techniques. One form of nanoparticle technology preparation is hydrogel nanoparticles. [1,3,44,45,13,35,37,39–43]

Chitosan-glycerophosphate hydrogel nanoparticles are an efficient drug delivery strategy to local targets through a controlled and slow drug release mechanism. This is caused by the enzyme chitosanase, which is found in the middle ear. Research reports that hydrogel nanoparticle preparations have been proven to deliver corticosteroid-class drugs to the perilymph in the inner ear with lower side effects compared to drug administration via intratympanic injection.[24] Drugs delivered via nanoparticle technology provide more advantages than intratympanic injection alone. In intratympanic injection, the concentration of the drug will be determined according to the amount exposed to the RWM, whereas with the help of nanoparticle technology, the drug preparation can be maintained for its release to the target continuously through the RWM.[23,44]

Mineralocorticoid hydrogel nanoparticles have the ability to pass BLB so that they will increase the release of molecules in the perilymph, prolong their contact time in the middle ear, deliver drug particles to target cells, increase exposure time with RWM, increase cellular uptake, and reduce clearance or clearance by the eustachian tube.[46–49] Mineralocorticoids packaged in hydrogel nanoparticles can have neuroprotective benefits and have the

potential to minimize systemic exposure to fludrocortisone so as to reduce side effects that have the potential to inhibit.[13,50–52] The advantages provided by mineralocorticoid hydrogel nanoparticles in RWM will increase the potential of mineralocorticoid particles to reach its target to the deepest part of the ear, especially in the stria vascularis, which is the basis of the pathogenesis of metabolic presbycusis, this can be a therapeutic breakthrough with preparations that have been packaged with hydrogel nanoparticle technology as a therapeutic modality to inhibit or treat metabolic presbycusis

CONCLUSION

Mineralocorticoids have the potential to be an option for metabolic presbycusis treatment by maintaining the balance of the NKCC1 ion pump, which can further increase SGN density and MCR excretion. Mineralocorticoids are administered using nanohydrogel technology, which can increase contact time with RWM and reduce clearance by the pharyngotympanic tract so that the drug can work optimally on its target. Nanohydrogel encapsulation minimizes the potential for systemic mineralocorticoid effects such as hypertension.

Declaration by Authors

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