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Review

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Age-related hearing loss: the complex interaction of carbohydrate metabolism in auditory and cognitive dysfunction during aging

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Abstract

Age-related hearing loss (ARHL) is an extremely widespread form of age-related disease mainly characterized by high-frequency hearing loss and subsequent cognitive dysfunction. The pathological changes associated with ARHL involve both peripheral auditory structures and the central nervous system. Recent studies have focused on the aging mechanisms of peripheral auditory sensors, such as cochlear hair cells, spiral ganglion cells, and the stria vascularis. Additionally, the role of carbohydrate metabolic signaling pathways in ARHL has garnered attention, particularly the regulatory effects of glycolysis, the glycosylation pathway, and the pentose phosphate pathway. Additionally, cognitive dysfunction is a significant clinical symptom in the advanced stages of ARHL, and growing evidence suggests that ARHL may be closely linked to Alzheimer's disease, potentially serving as a risk factor for its development. In this review, we summarize the specific regulators and metabolic pathways of carbohydrate metabolism that contribute to ARHL. Furthermore, we discuss recent research progress on the relationship between carbohydrate metabolism, hearing loss, and cognitive dysfunction in ARHL. Finally, we explore novel therapeutic targets and future prospects for understanding the pathogenesis and clinical diagnosis of ARHL and related aging-associated diseases.

Keywords: Age-related hearing loss, carbohydrate metabolism, cognitive function, aging, neurodegenerative, deafness

INTRODUCTION

Age-related hearing loss (ARHL) is a high-incidence neurodegenerative disease characterized by peripheral auditory impairment and central neuropathy. ARHL is associated with cognitive dysfunction and is a potential modifiable risk factor for predementia and Alzheimer's disease (AD)[1-3]. ARHL refers to a gradual, age-associated decline in auditory function, typically presenting as a bilateral and symmetrical sensorineural hearing impairment. This condition initially manifests in the higher frequency ranges, leading to reduced auditory sensitivity (perceived as diminished sound intensity) and compromised speech clarity (resulting in distorted word recognition)[4-6]. ARHL not only severely affects patients' hearing and speech functions but also disrupts their cognitive abilities in the nervous system. Untreated ARHL may lead to the emergence of disabilities and have a tremendous impact on patients' future quality of life (QOL) as well as on the social productivity of the community[7]. Therefore, it is crucial to explore the pathogenesis of ARHL in depth for social stability and the improvement of physical and mental health for the elderly.

In recent years, metabolism has become increasingly prominent in research on ARHL. Carbohydrate metabolism, in particular, is a complex process involving different types of carbohydrates, including monosaccharides, complex carbohydrates, and glycoconjugates, such as glucose, fructose, or galactose, which enter glycolysis through distinct pathways[8]. Additionally, glucose can be synthesized via gluconeogenesis[9,10]. Glycogen and other complex carbohydrates can be metabolized through the glycolytic pathway. The hexosamine biosynthetic pathway generates essential biomolecules through the covalent attachment of glucose derivatives to proteins, forming glycoproteins, or to lipids, creating glycolipids. These glycoconjugates play crucial roles in cellular communication and contribute significantly to the structural integrity of cellular membranes[8,11]. Carbohydrate metabolism can be organized into catabolism and anabolism, including glycolysis in the absence of oxygen, oxidation in the presence of oxygen, the pentose phosphate pathway, glycogen synthesis and catabolism, and gluconeogenesis[12].

Emerging evidence indicates a significant association between abnormal glucose metabolism and auditory dysfunction. Studies have demonstrated that compromised glycolytic activity exacerbates alcohol-induced apoptosis in HEI-OC1 auditory cells, mediated through the suppression of epidermal growth factor receptor (EGFR) signaling pathways[13]. The pentose phosphate pathway has a significant effect on ARHL, and NQO1 enhances the level of cellular NAD+ to ameliorate age-related hearing impairment[14-17]. The pathophysiology of ARHL cannot be separated from aging impairment to the auditory center. The nervous system can produce adenosine triphosphate (ATP) from glucose metabolism to perform complex neurological functions, including neuronal signaling, such as action potentials, synaptic transmission, and glutamate cycling, and non-signaling activities, including resting potentials, axonal transport, and actin cytoskeleton remodeling[18,19]. Metabolic coupling between neurons with glia is important for normal brain function. Impaired glucose metabolism or damage to the action of brain insulin results in the degeneration of AD neurons that may contribute to pathological changes in this neurodegenerative disease[20,21]. Disturbances in glucose metabolism have been observed in the brains of AD patients and AD model mice, with a particularly reduced glucose utilization in the brain regions most affected by the disease[22]. Comorbidity of AD and type 2 diabetes mellitus (T2DM) occurs significantly more frequently than is expected by chance alone[23]. Therefore, investigating the role of carbohydrate metabolism in the development of ARHL may help relieve the grim situation and diagnose the aging-related disease early. This review examines the related regulators and pathways of carbohydrate metabolism in ARHL and summarizes current research on the relationship between ARHL and cognitive decline, with a focus on its potential mechanisms and clinical significance, in order to elucidate existing valuable theories targeting diagnostic

and therapeutic approaches in ARHL and related aging-associated diseases.

THE ROLE OF CARBOHYDRATE METABOLISM IN ARHL

Modulation of the pentose phosphate pathway in ARHL

Antioxidant systems are largely dependent on the reducing power provided by reduced nicotinamide adenine dinucleotide phosphate (NADPH), including isocitrate dehydrogenase 1 (IDH1), isocitrate dehydrogenase 2 (IDH2), malic enzyme 1 (ME1), malic enzyme 3 (ME3), glucose-6-phosphate dehydrogenase (G6PD), phosphogluconate dehydrogenase (PGD), and glutamate dehydrogenase (GLUD1)[24]. The most important antioxidant enzyme is G6PD in the pentose phosphate pathway, which is the first step and rate-limiting enzyme that catalyzes pentose phosphate[25]. G6PD is an enzyme that facilitates glucose metabolism and produces NADPH during metabolism, and it catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconic acid and nicotinamide adenine dinucleotide phosphate (NADP) to NADPH[26,27]. Inhibition of mitochondrial catalase by Bak expression reduces reactive oxygen species (ROS)-induced mitochondrial damage and attenuates ARHL in C57BL/6 mice[28]. Bermúdez-Muñoz *et al.* reported that G6PD is important for the maintenance of cochlear redox homeostasis and is a positive regulator of the inflammatory response and that G6PD-Tg mice act as antioxidants by counteracting age-related redox imbalance, oxidative-induced damage, and mitochondrial dysfunction, which in turn delays ARHL[29]. Nóbrega-Pereira *et al.* reported a clear association between increased G6PD activity, elevated NADPH and redox potentials, and antioxidant protection, which also had a positive effect on prolonging the lifespan of aged G6PD-Tg mice[30]. These results reveal the regulatory effect of glutathione metabolism from the pentose phosphate pathway that alleviates aging on the peripheral auditory system of ARHL.

Multipoint of glycolysis influence the pathologic changes in ARHL

Calorie restriction slows aging by increasing NAD+ and SIRT1 levels. Additionally, β-lapachone, a recognized regulator of cellular NAD+ that converts NADH to NAD+, significantly prevents ARHL in animals by lowering inflammation, decreasing oxidative stress, and mitigating mitochondrial damage[17]. In mice treated with MNAM, a sirt1 agonist, the expression levels of tricarboxylic acid cycle (TCA) intermediates, pyruvate, fumarate, and lactate were found to be increased during aging. Mitochondrial oxidation and metabolism levels in the inner ear also increased. The mice showed accelerated senile deafness[31]. LDHB plays a crucial role in maintaining high pyruvate levels in cells, and LDHB deficiency results in mitochondrial defects in auditory cells, because LDHB is a substrate for mitochondrial ATP synthesis and the end result of glycolysis[32,33]. One study revealed that increased adenosine signaling through ADORA2B regulates the process of ATP synthesis and activates AMP-activated protein kinase (AMPK). AMPK activation activates bisphosphoglycerate mutase (BPGM), the rate-limiting enzyme of the Rapoport-Luebering shunt, resulting in the formation of 2,3-bisphosphoglycerate (BPG). 2,3-BPG is an allosteric modulator of hemoglobin (HGB) that promotes O2 release under hypoxia[34]. Erythrocyte 2,3-BPG and ATP levels decrease during aging and are even lower in patients with AD[35-37]. eAdora2b-/- mice exhibit accelerated development of cognitive ability, memory ability, and auditory functional decline with an increased immune response in the brain and cochlea as young as 2 months after exposure to hypoxia[38]. These findings suggest that the impact of the recoding of glycolytic metabolism affects cognitive function and hearing dysfunction during aging. Cellular and tissue functions are determined by more than 50% of the various membrane-integrated proteins glycosylated (e.g., receptors, ion channels, and transporter proteins). Glycosylation affects Asn residues (N-glycans) or Ser/Thr residues (O-glycans) and highlights distinct N-glycans involved in regulating membrane proteins and protein stability[39,40]. The N-glycan structure of the cochlear stria vascularis was analyzed via three high-performance liquid chromatography (HPLC) methods and different modes of multistage mass spectrometry (MSn), and 79 different N-glycans were identified and characterized, identifying the heterogeneity of vascular stripe glycoproteins in deafness[41]. A noteworthy aspect is that auditory and vestibular epithelia may differ in their reliance on

glycolysis and oxidative phosphorylation. The quantification of proteins in chicken auditory and vestibular sensory epithelia by applying intensities in mass spectrometry experiments revealed a threefold enrichment of glycolytic enzymes in the auditory epithelium and at least a fourfold increase in enzymes responsible for oxidative phosphorylation in the vestibular epithelium[42]. As a crucial anabolic pathway, serine and glycine metabolism significantly influences key junctures in glucose conversion and one-carbon metabolism. Serine metabolism affects pyruvate production, which in turn regulates mitochondrial function and cancer cell growth[43]. Numerous metabolic enzymes have been found to exhibit high mRNA expression levels in tumor cells. Mitochondrial one-carbon metabolism plays a vital role in the rapid proliferation of cancer cells[44]. The above studies suggest that glycolysis affects both auditory and cognitive function through multiple targets. However, the dynamic changes in glycolysis during aging are unknown. Exploring how altered carbohydrate metabolism can be leveraged to delay the progression of ARHL may be an innovative direction for future research.

GENETIC SUSCEPTIBILITY TO DIABETES MELLITUS IS TIGHTLY LINKED TO ARHL

Genetic susceptibility to diabetes, a major disease characterized by defects in glucose metabolism, has received widespread attention. Globally, diabetes is the ninth leading cause of death, with 90% of those with diabetes having T2DM[45-47]. Type 2 diabetes is a metabolic disease caused by elevated blood glucose due to insufficient insulin secretion or insulin resistance[48]. The main role of insulin is to regulate metabolism, including promoting glycogen synthesis, inhibiting gluconeogenesis, promoting fatty acid synthesis and fat storage, and promoting protein synthesis[49]. Diabetes was widely recognized as a risk factor for hearing impairment in many early human studies[50-52]. The prevalence of deafness in patients with type 1 diabetes mellitus (T1DM) (44.4%) and T2DM (45.1%) is approximately twice as high as that in non-diabetic patients (20.0%)[53]. Thickening of cochlea basilar membrane and capillaries in the vascular stria and atherosclerotic stenosis of the internal auditory arteries in patients with diabetes mellitus (DM), including microangiopathy, advanced glycosylation end products (AGEs), the ROS surge, the downregulation of Na-K-2Cl cotransporter protein (NKCC) function, the accumulation of toxic glucose metabolism byproducts, altered perivascular striatal cell function, and auditory neural changes, which are not found in the population without DM, are found at autopsy[54,55]. Diabetic microangiopathy is a product of intimal glycoprotein accumulation and endothelial damage[56,57]. Increased levels of diglyceride (DAG), a byproduct of high glucose metabolism, activate the DAG/PKC signaling pathway, which increases endothelial permeability in the stria vascularis (an organ that is highly dependent on the microvasculature), leading to endolymphatic electrolyte disorders[58], which in turn affects hair cell (HC) transduction and signaling[59,60]. Disruption of microcirculation also leads to loss of spiral ganglion neurons (SGNs)[61]. Secondly, the cascade of reactions induced by hyperglycemia and PKC leads to the deposition of AGEs in collagen. When these AGEs accumulate in capsules, they promote fibrosis, leading to poorly connected HCs and compromised signaling[58]. Furthermore, the activation of the polyol pathway due to high sugar levels leads to the accumulation of toxic substances, which damage the structure of HCs and increase ROS levels[62]. An increase in ROS leads to DNA damage, lipid peroxidation, cascading reactions of apoptotic signaling, and protein degradation[63-66]. Therefore, an increase in ROS is a key factor in hearing loss. The Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) is located in the basolateral plasma membrane of endolymphatic fluid-producing striatal marginal cells[67,68], which influences the intracochlear potential (EP) of the endolymphatic fluid. Insulin resistance in T2DM is associated with decreased NKCC1; when the expression or function of the NKCC1 protein is reduced, the mitochondrial potential decreases, auditory transduction to receptors or HCs is underpowered, and transduction is impaired[69]. The production of glucose metabolic byproducts increases cytotoxicity[58,70]. For example, increased levels of the metabolic byproduct sorbitol lead to the oxidation of NADPH to NADP, resulting in reduced antioxidant capacity and cellular damage by ROS[71]. High glucose affects the mitochondrial membrane potential, leading to increased ROS levels and a

progressive rise in the expression of cleaved caspase-3 and Bax proteins in cochlear pericytes, causing apoptotic cell death[72]. The pericytes of the cochlear vascular stripe play important roles in angiogenesis, blood flow regulation, and barrier integrity[73,74]. Brain-derived neurotrophic factor (BDNF) and neurotrophic factor 3 (NT-3) are also important components of auditory development[75,76]. This may be a key signaling molecule that leads to diabetic neuronal degeneration, which can lead to impaired development of the spiral ganglion in the basal segment of the cochlea and reduced nerve conduction when both parameters decrease, leading to hearing loss[77]. The detailed mechanisms of diabetes-induced hearing loss are poorly understood. Possible treatments include: Restoring hearing loss by controlling blood sugar[78-80]. Additionally, antioxidant therapy, such as the use of astaxanthin (AST), has been explored. AST quenches unilinear oxygen, scavenges free radicals to prevent lipid peroxidation, and inhibits the expression of oxidative stress-related genes[81]. Alpha-lipoic acid (ALA) is a metabolic antioxidant that protects against hyperglycemic loss of HCs in a diabetic zebrafish model. ALA is protective against hyperglycemia-induced HC loss and may be effective in scavenging ROS and inhibiting apoptotic molecules[82].

Researchers have recently shown that genetic susceptibility accounts for a considerable proportion of the pathological component of functional variability in ARHL through single-cell RNA sequencing of the cochleae and brains of mice[83-85]. ARHL has genetic complexity, including genetic and epigenetic modifications[86]. For example, increasing susceptibility to ARHL in humans may be intimately connected to single nucleotide polymorphisms (SNPs) of the GRHL2, DFNA5, and KCNQ4 genes[87,88]. Studies of animal or human pathology have shown that DM causes damage to blood vessels, SGNs, afferent nerve fibers, the organ of Corti, and the stria vascularis of the inner ear[89,90]. Epidemiological studies reveal significant correlations between glucose metabolism disorders and auditory impairment. Specifically, diabetic patients demonstrate a two-fold increased prevalence of hearing dysfunction compared to non-diabetic individuals. Furthermore, subjects with prediabetic conditions exhibit a 30% elevated risk of developing auditory deficits. Notably, DM shows a distinct association with the progression of bilateral auditory impairment[47,72,90,91]. Diabetes-related microvascular hypertension is actively implicated in ARHL[92,93]. Clinical studies have demonstrated that individuals with diabetes exhibit an increased susceptibility to ARHL. The underlying metabolic mechanism is associated with the activation of the polyol pathway. In diabetic patients, excessive glucose is converted to sorbitol through aldose reductase, and subsequent sorbitol accumulation contributes to neuropathy and auditory dysfunction. Furthermore, clinical investigations have revealed a positive correlation between serum creatinine levels and the severity of ARHL in diabetic populations, suggesting that creatinine levels may serve as a potential biomarker for predicting the progression of hearing impairment[94]. However, the mechanism by which diabetes-related hyperglycemia and microvascular hypertension contribute to ARHL has not been fully elucidated, which is valuable for the prevention of ARHL.

THE EXTENSIVE CONNECTION BETWEEN ARHL AND OTHER NEURODEGENERATIVE DISEASES

AD and ARHL

In the Lancet Commission released in 2020, reports suggest that modifying 12 risk factors across the lifespan could significantly help reduce the global impact of dementia, and the most important risk factors are associated with ARHL[95]. The number of people suffering from ARHL is expected to reach nearly 2.5 billion globally by 2050. Dementia is an acquired intellectual impairment with cognitive deficits as a core symptom. AD is the most common type of dementia, accounting for 60% to 70% of all dementia cases[96]. The amyloid cascade hypothesis and the tau hypothesis are the two main hypotheses describing the pathogenesis of AD. The prevalence of dementia has increased and is likely to continue to increase in response to the rapid aging of the population[97]. The relationship between hearing loss and cognitive impairment has been confirmed

by many studies thus far, but there is little accurate neurophysiological evidence to support a link between hearing loss and cognitive impairment. There are several mechanistic hypotheses regarding the link between the ARHL and AD. Firstly, the cognitive load hypothesis states that hearing loss deprives individuals of the corresponding cognitive resources, leading to corresponding cognitive impairment[98-100]. Hearing loss alters cortical activity in the medial temporal lobe (MTL), which may be associated with AD pathology in the same region[101,102]. Secondly, the common cause hypothesis suggests that extensive neurodegeneration caused by inflammatory factors[103,104] may be a shared mechanism for hearing loss and cognitive impairment[105]. The early stages of neuroinflammation in AD are characterized by a vicious cycle of microglial activation, proinflammatory factor release, and neuronal injury week after week[106]. In elderly patients with ARHL, C-reactive protein (CRP) elevation, a circulating marker of inflammation, is strongly associated with decreased hearing sensitivity[107]. Reduced levels of VEGF may lead to Aβ deposition, which prevents the repair of inner ear hair cells (IHCs) and spiral ganglia, as well as the reconstruction of the cerebral vasculature, leading to AD or ARHL[108]. However, the order of precedence between the two is unclear. SIRT1 is a NAD+-dependent protein deacetylase located upstream of PGC-1α. It contributes to the regulation of neuronal survival and death, glucose metabolism, insulin sensitivity, and mitochondrial synthesis and plays a crucial role in maintaining cellular homeostasis[109]. PGC-1α plays an important role in the inhibition of neurodegeneration[110]. Decreased expression of SIRT1-PGC-1α may impair mitochondrial synthesis and respiration, leading to neuronal degeneration and apoptosis, which may trigger age-related deafness. Moreover, decreased expression of SIRT1-PGC-1α in the brain leads to increased Aβ production and decreased BDNF production, resulting in an increased incidence of AD[111,112]. LKB1 and the CaMKKβ/AMPK pathway: AMPK is a major regulator of cellular energy homeostasis and a central player in glucose and lipid metabolism[113]. Decreased AMPK activity also leads to decreased Aβ degradation and increased tau phosphorylation. LKB1 and CaMKKβ are required for AMPK activation and are important for the stability of stereocilia in HCs and for the protection of neurons in the auditory cortex, respectively[108]. AMPK may be chronically phosphorylated in response to changes in the intracellular environment in the brains of patients with attention deficit disorder, which may damage the auditory cortex and accelerate hearing loss[108]. Furthermore, a decline in auditory input capacity leads to increased dependence on cognitive resources. This results in information processing overload during cognitive processes and cognitive decline[114-116]. A study found that hearing loss in the APP/PS1 transgenic mouse model of AD inhibits the GDF1-AKT signaling pathway, leading to the progression of AD-associated pathology and cognitive impairment[117]. AD mice showed increased poly ADP-ribosylation and higher DNA damage marker expression in cochlear tissue. Conversely, quantitative analysis revealed substantial reductions in phosphoglycerate mutase 2 expression levels and a notable decrease in synaptic ribbon density within the presynaptic regions of inner HCs[118]. After hearing loss, social isolation, loneliness, apathy, and depression occur, leading to a decline in an individual's cognitive ability, and these harms create a cascading response that leads to cognitive impairment[119]. Hearing loss affects functioning and test performance to any degree on neuropsychological assessments; despite normal cognitive function, people with hearing loss remain vulnerable to overdiagnosis and even misdiagnosis of cognitive impairment[120-122]. Finally, long-term sensory deprivation due to ARHL leads to functional and structural changes in the auditory and cognitive systems in the brain, such as reduced cortical volume[123,124], leading to cognitive decline[125-127]. Concretely, pathological manifestations of AD follow an anatomical-temporal pattern starting in the temporal lobe and spreading to neocortical areas at later stages, and the progression pattern arises from trans-synaptic propagation of misfolded tau between established neural circuits[128-130]. Hearing worsening of ARHL was related to the increased burdens of β-amyloid and tau detected by PET, which were the AD pathological markers[131]. Further work to explore the potentially relevant links and mechanisms between hearing impairment and AD will be essential in the prevention and treatment of cognitive impairment in older adults.

ARHL can be intervened by avoiding noise, increasing exercise, preventive medication, and wearing hearing aids or cochlear implants[132] to reduce the disease risk caused by ARHL. In addition, the assessment of hearing level can be used as an early detection method for AD. For example, the peaks of distinct auditory event-related potentials (AERP), measured using surface skin electrodes non-invasively, have been used to objectively evaluate the central auditory function, hearing thresholds, and sensory processing[133,134]. The use of AERPs for measuring differences between AD patients and healthy older adults shows great promise, particularly in P50, N100, P200, N200, and P300 latency measures. In particular, the neural generators of the P300 response reflect cortical activity, participating in sensory processing, memory storage, cognitive function, and executive function[135]. AERP is crucial for screening as a biomarker of cognitive decline associated with AD[136,137]. Additionally, clinical doctors should regularly screen cognitive impairment in patients with ARHL, as early identification and timely intervention may effectively prevent AD.

Parkinson's disease and ARHL

Parkinson's disease (PD) is a neurodegenerative disorder caused by degeneration of midbrain dopaminergic neurons in the substantia nigra (SN), resulting in corresponding motor symptoms[138]. In addition to motor symptoms, PD can also result in a number of non-motor features (NMSs), such as ARHL, which is considered a novel NMS of PD[139]. However, the underlying pathophysiologic mechanisms have not been elucidated. The APOE ε4 allele is mostly observed in PD patients and is characterized by amyloidosis and nonmotor symptoms. PD patients with APOE ε4 have more extensive Lewy body brain accumulation, greater amyloid β plaque deposition, and α-synuclein pathology. It has also been shown that the presence of ε4 allows PD patients to experience more rapid cognitive decline and a greater risk of progression to dementia[140,141]. The dopaminergic nerve cluster is located in the lateral olivocochlear (LOC) bundle, which forms axonal synapses underneath inner HCs[142,143]. The asymmetry of hearing in PD patients reflects the asymmetry of motor symptoms in PD patients[144,145]. The pathological hallmarks of PD are the presence of Lewy bodies (LBs) and Lewy neurites (LNs) composed of α-synaptic nuclear proteins[146]. The possible links between the auditory system and degenerative processes in PD patients are as follows: first, asymmetrical hearing in PD disease patients reflects the asymmetry of motor symptoms in PD patients[145]. One study further suggested that cochlear dysfunction may have a lateralization effect, reflecting the course of asymmetric movement disorders, by examining the associations of striatal dopamine transporter (DAT) protein receptors with audiological variables assessed by pure tone audiometry (PTA) and DPOAE[147]. Second, the synuclein family includes three small, soluble, highly conserved neuronal proteins called α-synaptonemal, β-synaptonemal, and γ-synaptonemal proteins[148]. Lewy pathology (accumulation of misfolded α-synuclein) may be associated with hearing loss in PD, with α-synuclein located in the efferent prominence of outer HCs, the base of inner HCs (but in low amounts), and the vascular stria[149]. Although synaptic nucleolar proteins are not essential components of synaptic transmission, they may contribute to the long-term regulation or maintenance of presynaptic function through the modulation of transmitter release[150]. Furthermore, dopamine acts as an inhibitor to reduce the cochlear response, thereby protecting the cochlea from excessive excitotoxicity[151]. Dopamine receptor D2 knockout mice exhibit reduced levels of distortion product otoacoustic emission (DPOAE) and increased auditory brainstem response (ABR) thresholds[143,147]. Massive release of glutamate from IHCs has been shown to induce excitotoxic damage in primary auditory neurons[152]. In contrast, dopamine is released from LOC efferent fibers below IHCs and plays a significant role in modulating afferent dendrites, thus counteracting the excitotoxic effects of glutamate[142]. Decreased dopamine secretion in the inner ear leads to neurotoxic effects of glutamate, resulting in hearing loss[151,153]. Finally, the pathogenesis of hearing loss in PD patients may be related not only to cochlear involvement alone but also to impaired central auditory function in the cerebral cortex, such as impaired brainstem auditory evoked potentials (BAEPs) and vestibular evoked myogenic potential (VEMP) responses found in PD patients with hearing loss[154]. Three mechanisms explain auditory and vestibular dysfunction in PD, including dopamine modulation of excitability in the vestibular nucleus[155].

PD pathology disrupts the connections between the vestibular nuclei and other brainstem nuclei (especially the dorsal nucleus of the middle suture)[156,157], and PD pathology directly destroys the vestibular nuclei, leading to vestibular abnormalities[158]. PD patients often experience hyperglycemia and elevated levels of amino and fatty acids associated with the TCA and fatty acid beta-oxidation[48]. The use of hypoglycemic agents significantly ameliorated exercise injury and suppressed inflammation induced by microglial hyperactivation in the mouse model of PD. Metformin enhanced striatal dopaminergic levels through increased AMPK-mediated autophagy and ROS clearance[159,160].

Carbohydrate metabolic homeostasis is probably disrupted in the aging brain.

Functional neuroimaging studies indicate that glucose hypometabolism and mitochondrial dysfunction are early signs of age-related alterations in the brain during normal aging[161,162]. Excitatory synapses are subcellular locations with very high rates of energy consumption because large amounts of ATP are required to maintain the activities of neurotransmitter transporters and membrane Na^+ and Ca^{2+} pumps, which rapidly restore gradients of these ions following synapse activation[163]. Recent studies have shown that mice with the reduced glucose transporter GLUT1 levels exhibit age-dependent decreases in cerebral capillary density, blood flow, glucose uptake, and blood-brain barrier (BBB) leakage before dendritic spine loss in CA1 hippocampal neurons and associated behavioral impairments, and reduced BBB GLUT1 expression worsens cerebrovascular degeneration, neuropathology, and cognitive function in AD[164]. In PD patients, energy deficits may be a pathogenic factor for neurodegeneration progress. Studies have found that terazosin can stimulate glycolysis, thereby enhancing mitochondrial function to produce more cellular ATP and prevent the degeneration of dopaminergic neurons[165]. In addition, glycolysis is the primary target of astrocytes in regulating energy homeostasis at the center[166,167]. The glycolytic level of astrocytes in advanced AD has been observed to correlate with the degree of AD pathology and exerts neuroprotective effects in the disease[168,169]. These findings suggest that cerebral glucose homeostasis maintains the stability of the nervous system in terms of excitatory synaptic transmission and energy support that may contribute to the treatment of neurodegenerative diseases such as AD.

CONCLUSION

In brief, carbohydrate metabolic homeostasis contributes to the preservation of better auditory function and the correction of the progressive hearing loss and cognitive dysfunction that occur during aging. As a complex geriatric disease, ARHL is not considered a single individual; instead, it is an organism-wide aging lesion that includes metabolic abnormalities, oxidative stress, apoptosis, gene polymorphisms in the peripheral auditory sensor and nervous system, and even systemic diseases such as DM. Carbohydrate metabolism synergistically and antagonistically affects the aging mechanism, and further research on carbohydrate metabolism is indispensable in the exploration of ARHL. In addition, the potential relationship between central nervous diseases such as AD and PD with ARHL is still unclear. The interactions of multimodality between different brain regions, as well as the mechanisms of carbohydrate metabolism in auditory and cognitive functions, could be potentially important research directions for the clinical diagnosis and prognosis of ARHL in the future.

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Authors' contributions

Wrote the manuscript: Zou S, Liu Y, Xu B
Revised the manuscript: He Z, Li J
All the authors proofread the final version of the paper.

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Conflicts of interest
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