ejpmr, 2016,3(10), 17-22.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

DIABETES MELLITUS IN THE INNER EAR

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Article Received on 27/07/2016 **Article Revised on 17/08/2016** **Article Accepted on 07/09/2016**

ABSTRACT

Information about the inner ear repercussions of diabetes mellitus is scattered and not so well recognized. Variable findings have been reported when testing the auditory or the vestibular function of both animal models and patients with either type 1 or type 2 diabetes mellitus. In the cochlea there is evidence of microangiopathy with loss of outer hair cells, while the vestibular maculae seem to be less predisposed to vascular damage, with derangement of the electrical transmission of both the auditory and the vestibular pathways. However, differences among the cochlea and the 5 vestibular organs have to be considered (eg. energy production, resistance to ischemia and insulin signaling). To better understand the functional meaning of the diverse damage of the inner ear organs related to diabetes mellitus, multidisciplinary studies on the specific vestibular organs and detailed studies on the effects of diabetes mellitus on the auditory and vestibular central pathways are still required.

KEYWORDS: Diabetes mellitus, ear/ inner, hearing, vestibular.

INTRODUCTION

According to World Health Organization Global Report on Diabetes 2016, the age-standardized prevalence of diabetes mellitus (DM) has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population,[1] increasing the prevalence of its complications as a major source of multiple organ disease, with an impact on quality of life.[2]

Although, those who provide care to patients with diabetes are aware of the risk of multisensory deficits, information about the inner ear repercussions of DM is scattered and not so well recognized, as retinopathy or neuropathy. The purpose of this brief review is to summarize core implications of DM on the inner ear function.

The main metabolic mechanisms of the inner ear organs

The inner ear provides sensory information: hearing from the cochlea and orientation and equilibrium from the 5 vestibular organs (utricular macula, saccular macula and the 3 semicircular canals). All of them have cells with hair-like extensions organized in bundles, which perform the mechano-electrical transduction process, in order to convert sound and head acceleration (including gravity) into electrical signals.

Mechano-electrical transduction occurs when stimuli deflects the hair bundle, increasing tension on extracellular tip link proteins to open cation-selective transduction channels (calcium channels).[3-4] Although metabolic energy apparently is not required for mechano-transduction itself, parallel mechanisms require it and the major consumer of ATP in hair bundles is the plasma membrane calcium pump (PMCA2),[3-4] which is also relevant for frequency tuning, neurotransmitter release and efferent synaptic signaling. The creatine kinase circuit is responsible for maintaining bundle ATP levels, despite high PMCA2 activity;[5] apart from the energy demands from the specialized tissues required to create and preserve the adequate environment for the transduction.

Cochlear cells convert sound into electrical signals and also amplify the mechanical stimulus by active contraction.[6] In the cochlea, transcripts for a number of anti-angiogenesis factors are upregulated inhibiting vascularization, with reliance on glycolytic energy production[7] and increased resistance to oxygen depletion under ischemic conditions (compared to the vestibular organs and the stria vascularis), while the stria is the most sensitive to ischemia.[8-9] Accordingly, the cochlea prefers glycolytic energy production, while the utricle predominantly relies on the oxidative phosphorylation pathway.[7] Then, glucose and glycogen are much higher in the cochlea compared to the sacculus, the utricle and the semi-circular canals.[8]

The local metabolic rate of glucose utilization for the rat vestibular end organs is similar within the utricle and saccule and significantly higher than that for the superior, posterior, or lateral canal ampullae.[10] However, the capillary diameter in the rat utricular

macula is smaller than that of the posterior canal ampullae, while the capillary length is greater and the end organs are similar with respect to neuroepithelial volume, capillary surface area and blood flow,[11] suggesting that delivery of metabolites is not a primary regulating force for vestibular blood flow.[10]

In cats, comparison of glucose concentration in fluids from various inner ear compartments has shown almost identical concentration in perilymph of the scala vestibule, perilymph from the scala tympani and cerebrospinal fluid (circa 80 mg/100 ml), while utricular endolymph glucose level is lower (41.9 mg/100 ml) than the above three fluids and cochlear endolymph is the lowest of all (11.2 mg/100 ml).[12]

In most tissues, glucose uptake is regulated by the level of expression of glucose transporters on cellular surfaces.[13] In the cochlea, tissues may differ in their expression of glucose transporter isoforms, which suggests differences on the effect of glucose and insulin between cell types.[14] In the cochlea of guinea pigs, insulin stimulates protein synthesis and phospholipid signaling systems, but does not regulate glucose uptake, with a phospholipid-based trans-membrane signaling system mediating the effects of insulin.[15] In cats, at 90 minutes after intravenous regular insulin (30 units/kg), glucose concentrations in cerebrospinal fluid and the perilymphs decrease, but during hypoglycemia there is no significant change in cochlear microphonics.[12] Although knowledge about the effects of insulin and insulin signaling in the vestibular organs are scarce, a recent study showed that insulin receptor, insulin signaling components and selected cAMP signaling components are expressed in the human saccule:[16] insulin receptor substrate 1 and calcium-sensitive cAMP/cGMP phosphodiesterase 1C are selectively expressed in sensory epithelial hair cells whereas other components are expressed in sensory epithelial supporting cells or in both cell types, insulin-sensitive glucose transporter and aquaporin 2 are expressed in the peri-nuclear area of stromal cells.

Experimental diabetes mellitus

Histopathology

Type 1 DM is caused by the loss of beta cells, with reduction of production of endogenous insulin, leading to hyperglycemia and hypoinsulinemia. On the other hand, type 2 DM is associated with insulin resistance or relative insulin deficiencies. Accordingly streptozocine-induced diabetes is an experimental model frequently used to study type 1 DM,[17-18] while diet-induced diabetes is a model frequently used to study type 2 DM, which includes hyperglycemia, hyperinsulinemia, and a mild hypertriglyceridemia.[19]

In the cochlea of rats with streptozocine- induced diabetes, there is thickening of the basement-membrane of the stria vascularis and basilar membrane, which is consistent with diabetic microangiopathy.[20] However, in the microvasculature of the saccule and the utricle of rats with streptozocine- induced DM, no changes related to diabetic microangiopathy have been found.[17] Similar results have been reported in rats with diet induced DM, where DM alone may not be a cause of statistically significant thickening of the basement membrane, but the combination of DM with obesity and/or noise exposure may be related to significant thickening and the combination of all three may provoke the greatest thickening.[21]

In rats with streptozocin-induced diabetes, compared to controls, electron microscopic examination of the saccular and utricular nerves, showed differences related to myelin sheaths:[22] a variety of osmiophilic inclusion bodies, often associated with disrupted myelin-sheath lamellae, lysosomal bodies and periaxonal expansions of Schwann cell cytoplasm, with no evidence of demyelination/ remyelination or neuronal degeneration. In the same animal model, other study showed an increased incidence of secondary lysosomes within the connective tissue cells, as well as an accumulation of intracellular lipid droplets, which were related to hyperglycemia.[18]

Function

In animal models of both type 1 and type 2 DM, auditory evoked responses and otoacoustic emissions have shown similar hearing threshold shifts and latency delays, supporting hair cell dysfunction, although animals with type 2 DM also had severe damage to the central auditory pathway and a greater degree of cochlear hair cells dysfunction.[23] Additionally, in a model of type 2 DM, dysfunction of both auditory and vestibular organs were observed on the electrical responses to auditory stimuli and to linear acceleration, respectively.[19] The prolonged latency and decreased amplitude of the first wave of the electrical responses to linear acceleration suggested dysfunction of the vestibular maculae.[19]

Studies in human beings

Histopathology

Studies in human temporal bones from patients with DM are scarce and those on the vestibular organs are even scarcer.

Assessment of the relationship of the pathological findings in the cochlea with the audiometric and clinical histories, of eight patients with diabetes and ten normal controls (matched for age and sex), showed microangiopathy in the stria vascularis of the patients:[24] those with microangiopathic involvement of the endolymphatic sac had significantly greater hearing loss than patients without such involvement and patients with basilar membrane microangiopathy had significantly lower percentages of histologically normal hair cells.

Examination of 26 cochleae from patients with type 1 DM (compared to 30 age-matched controls) showed atrophy of the stria vascularis in all turns, spiral ligament

cell loss in upper turns and outer hair cell loss in the lower basal turn; the longer the duration of DM, the greater the damage of outer hair cells, with no significant difference in the number of spiral ganglion cells between patients and controls.[25]

The neuroepithelium and microvasculature of the saccule of patients with DM (16 type 1 & 23 type 2) showed a lower density of type I hair cells in the saccules of subjects with DM, with no evidence of microangiopathy than that of 40 age-matched controls.[26] In the semicircular canals, comparison between temporal bones from 14 patients and 28 age-matched controls showed that type 1 DM may be associated with cupular and free-floating deposits.[27]

Epidemiological studies

Evidence suggests that patients with type 2 DM may not be aware of their sensory dysfunction or balance decline. Even intentional questioning may not be enough to detect hearing or visual deterioration, but suggest somatosensory or vestibular dysfunction.[28-29] Then, studies in human beings with no specific testing of the auditory or vestibular systems may provide inaccurate information about the prevalence of inner ear dysfunction in patients with DM.

Hearing

The information available from population studies are mainly focused on the elderly. In the Framingham Heart Study Cohort, using a definition of hearing loss as threshold levels greater than 20 dBnHL for at least one frequency from 0.5 to 4 kHz, age was by far the most critical risk factor for hearing loss, with no association with diabetes.[30]

In population-based longitudinal studies of aging, conducted in Wisconsin, in the United States, in which hearing thresholds were determined by audiometry and DM was identified by self-report of physician-diagnosed diabetes or by elevated glucose or glycated hemoglobin levels at examination, when controlling for potential confounders, the results supported a weak association between type 2 DM and hearing loss.[31] These results are consistent with a 5-year follow-up of 342 veterans with DM and 352 non-diabetic veterans, from Oregon in the United States, showing that patients with DM who were 60 years old or younger had an early high-frequency hearing loss, but after age 60, differences in hearing between patients with/without DM were reduced.[32]

In Korea, assessment of hearing loss as a function of aging and diabetes mellitus was performed in 37,773 individuals who visited a Health Promotion Center for health screening examinations.[33] Hearing loss was defined as a hearing threshold >25 dB and diabetes was identified by fasting blood glucose concentration or glycated hemoglobin levels. After subjects with specific ear disorders were excluded, aging and DM were related with the prevalence of hearing loss; and after adjusting for age and DM, no statistically significant association between hypertension and hearing loss was found. In all age groups, mild hearing loss was the most common form of hearing loss, with higher thresholds at the high frequencies. The findings support that the prevalence of hearing loss increases with age, as well as being higher in subjects with than without DM.[33]

Vestibular function

In adult subjects from the United States, aged 40 years and older, who participated in the 2001-2004 National Health and Nutrition Examination Survey, balance assessment with no specific vestibular testing, but a modified Romberg test showed higher prevalence of balance deterioration in patients with longer duration of DM, with greater glycated serum hemoglobin levels and other diabetes-related complications.[34] In non-frail older people from the English Longitudinal Study of Ageing, impaired balance was associated with age, diabetes, arthritis, eyesight and grip strength, when static balance was evaluated in three separate and progressively more difficult tests:[35] side-by-side stand, semi-tandem stand, and full tandem stand.

Clinical Studies

Variability among studies precludes definitive assumptions. However, some findings have been consistent among different studies and populations.

Hearing

Patients with type 1 DM may have normal hearing thresholds with variable auditory brainstem responses,[36-37] but altered otoacoustic emissions.[37] In patients with type 2 DM with no other otological disease, evidence has shown altered cochlear micromechanics,[38] subclinical hearing loss and impaired auditory brainstem responses, independent of peripheral neuropathy, retinopathy or nephropathy, with increased perception thresholds at high frequencies,[38-40] which may be related to age and to the time elapsed since the diabetes was diagnosed.[39-40]

Vestibular function

In adult patients with type 1 DM with no vestibular symptoms, those with recent diagnosis and no chronic diabetic complications showed normal responses to caloric vestibular stimulation.[41] However, young patients with type 1 DM and peripheral neuropathy, but no retinopathy or nephropathy, showed decreased responses to horizontal canal stimuli.[36] In children and young adults with type 1 DM, peripheral and central vestibular dysfunction has been observed, with influence from metabolic control, disease duration and hypoglycemic episodes.[42]

In adult patients with type1 DM, patients with type 2 DM and non-diabetic controls, comparison of the vestibulo-ocular reflex and optokinetic reflex supported that DM may be related to deficits in gaze-holding, the vestibule-ocular reflex and the optokinetic reflex.[43] Accordingly,

various measures of visual–vestibular interaction in subjects with type 1 DM or type 2 DM, compared to controls, showed altered gaze-holding in darkness with some differences between groups on the optokinetic response.[44]

In patients with type1 DM and type 2 DM, with or without polyneuropathy, cervical vestibular evoked myogenic potentials has not shown consistent evidence of peripheral saccular dysfunction.[45-46] However, findings suggest central rather than peripheral dysfunction in patients with type 2 DM.[47]

In 101 patients with type 2 DM, receiving primary health care, with/ without a history of falls and 51 healthy volunteers with no history of dizziness, vertigo, unsteadiness, hearing loss or neurological disorders, utricular function was impaired in the absence of horizontal canal dysfunction, independently from age, peripheral neuropathy or a history of falls.[48]

DISCUSSION

Although the basic mechanism to transduce mechanical signals into electrical signals is similar in the cochlea and the 5 vestibular organs, the metabolic differences among the specific sensory organs are striking. The reliance on glycolytic or oxidative phosphorylation pathways for energy production is different in the cochlea than in the vestibular organs,[7] as well as their resistance to ischemia[9] and the insulin signaling.[15-16] In addition, the different implications of hyperinsulinemia versus deficient insulin have to be considered. More studies are needed to comprehend the functional implications of all these differences. As a consequence, variable findings may be found when testing the auditory or the vestibular function of patients with either type 1 or type 2 DM.

Epidemiological studies support that chronic hyperglycaemia is the main aetiological factor for the development of microvascular complications.[49] The link between chronic hyperglycemia and vascular damage has been established by several biochemical abnormalities including increased polyol pathway flux, increased formation of advanced glycation end-products, activation of protein kinase C and increased hexosamine pathway flux and oxidative stress.[50-52] Even further, advanced glycation end-products accumulate in extracellular matrix proteins during aging;[53] in patients with DM, compared to subjects with no DM, this accumulation seems to happen earlier.[53-54]

Accordingly, pathological studies have shown variable vascular consequences of DM within the inner ear organs. In the cochlea of both, animal models and human beings, there is evidence of microangiopathy with loss of outer hair cells,[20,24-25] which in turn may explain deterioration of the otoacoustic emissions.[37-38] On the other hand the maculae of neither animal models nor human beings have shown microangiopathy, even if loss of type I hair cells has been described.[17, 26]

In spite of the evidence of microangiopathy in cochlear tissues, epidemiological and clinical studies have shown no hearing loss or just mild hearing loss affecting mostly the high frequencies,[30-32]and altered cochlear micromechanics.[37-38] Several explanations can be conceived, the cochlea seems to resist hypoxia[9] and viability of isolated outer hair cells varies with the place of their origin from the base or the apex.[55] Vulnerability to trauma has been related to the evidence of an intrinsic susceptibility to free radicals among different cochlear cell populations.[55] Of note, inner hair cells are required for the onset of auditory function while mature outer hair cells are necessary for the more discriminative properties of the cochlea;[57] the outer hair cells develop latter than the inner hair cells, receive a small percentage of the cochlear innervation (circa 10%) and are more susceptible to insult.[58]

Although information about the vestibular system is scarce, the vestibular organs seem to be less predisposed to vascular damage than the cochlea, even if damage to the vestibular nerves and the connective tissue cells has been reported.[18, 22] Studies in patients with any of both type 1 and type 2 diabetes have shown derangement of the electrical transmission of the auditory and the vestibular pathways. In animal models, DM complications in the Central Nervous System have been related to structural, hemodynamic, biochemical and physiological change.[59]

To better understand the functional meaning of the diverse damage of the inner ear organs related to DM, more multidisciplinary studies on the specific vestibular organs and detailed studies on the effects of DM on the auditory and vestibular central pathways are still required.

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