Outcomes of Endolymphatic Shunt Surgery in Ménière's Disease Indicate Potential Contribution of Shear Stress Instead of Relieving the Endolymphatic Hydrops

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Abstract

Believing that the attack of Ménière's Disease (MD) resulted from overpressure of the endolymphatic fluid, Georges Portmann introduced a surgery on the endolymphatic sac for the control of vertigo through releasing the endolymphatic hydrops in 1927. Since then, different types of ES surgery have been sued to treat MD all over the world for more than 80 years and the endolymphatic shunt surgery by inserting drainage tubing into the ES became a standard procedure in treating MD. However, this therapeutic theory was challenged by a specifically designed study performed in Denmark. A recent temporal bone study of MD patients who underwent surgery showed that endolymphatic sac surgery did not relieve hydrops in patients with MD but did relieve vertigo in some patients.

In this review, we provided a novel hypothesis on the endolymphatic shunt surgery in MD, which is that potential shear stress induced by the endolymphatic shunt surgery in MD patients may modulate activities of the afferent system of the vestibular end organ, enhance plasticity of the vestibular system, and result in symmetric sensitivity in the vestibular system. TRPV may be involved in the molecular mechanism in endolymph cationic ion circulation affected by shear stress. Matrix maintenance in the vestibule may also be enhanced after shear stress. Shear stress-promoted differentiation of BMSC toward certain cell types may have beneficial effects on the vestibular system in MD.

Keywords: Ion channel; Menieres disease; Plasticity; Reactive oxygen species; Shear stress; Vestibular stimulation

Introduction

Ménière's disease (MD) is a symptom complex characterized by vertigo, fluctuating hearing loss, tinnitus, and aural fullness. MD significantly affects patients' quality of life and work performance. As a chronic illness, MD affects approximately 190 per 100,000 patients, according to a U.S. health claims database; however, population studies have shown a prevalence as high as 513 out of 100,000 [1]. The most descriptive pathologic feature of MD is endolymphatic hydrops, which can be observed in histopathology studies. Endolymphatic hydrops may be caused by endolymphatic malabsorption in endolymphatic duct and sac, with consequent dysfunction of the hydro-ionic homeostasis and disrupted endocochlear potential [2].

Endolymphatic hydrops can be visualized using gadolinium-enhanced MRI, which provides an objective diagnosis of MD [3,4]. Immune reactions, viral infections, inflammation, and vascular insufficiency are suspected to contribute to the progress of MD. Current therapy for MD includes betahistine, diuretics, corticosteroids, vasodilators, anti-inflammatory and antiviral medicines, intratympanic gentamicin injections (chemical vestibulectomy), the use of a MeniettR device, endolymphatic shunt surgery, and vestibular nerve section for untreatable MD.

The effect of endolymphatic shunt surgery on MD has been argued and no explanation was delivered. In this review, we provided a novel hypothesis on the endolymphatic shunt surgery in MD, which is that the shear stress potentially involved in the therapeutic effect according our previous studies. Since the inner ear including the vestibule is composed of nerve, vascular, and bone tissues, progresses in shear stress in these tissues were also reviewed.

Endolymphatic Shunt Surgery Relieves Vertigo but not Hydrops

The theory behind the endolymphatic shunt surgery for MD treatment is that an artificial endolymph opening is used to replace the nonfunctional endolymphatic sac and release the endolymphatic hydrops. After surgery, the vestibular end organ and Corti's organ regain function once normal or near normal hydrostatic pressure is restored. However, this therapeutic theory was challenged by a specifically designed study performed in Denmark [5]. In that study, the placebo effect was investigated by comparing the effect of a regular endolymphatic shunt with the effect of a placebo operation (regular mastoidectomy).

Thirty patients with typical MD participated in the study. They were selected for surgery because of unsuccessful medical treatment and were randomly assigned to a treatment group. The patients filled in daily dizziness questionnaires for 3 months before and 12 months after surgery, registering nausea, vomiting, vertigo, tinnitus, hearing

impairment, and pressure in the ears. Minor differences between the active and placebo groups were found, but the greatest difference in symptoms was found when the pre- and postoperative scores were compared, and both groups improved significantly. Approximately 70% of the patients in both groups achieved lasting improvement, and no significant differences between the two groups were found during a 9-year follow-up [6]. The nonspecific effect of endolymphatic shunt surgery in MD treatment was supported by a study of the temporal bones of 15 MD patients who had undergone shunt surgery [7]. The surgery failed to expose the sac in 5 cases; nonetheless, 4 of these 5 patients had relief from vertigo. In 8 cases, the sac was exposed, but the shunt failed to reach the lumen; still, 4 of these 8 patients experienced relief from vertigo. The shunt was successfully placed within the lumen of the sac in 2 cases, but both cases failed to experience relief from vertigo.

Endolymphatic hydrops was present in all 15 cases. The authors concluded that while endolymphatic sac surgery does not relieve hydrops in patients with Ménière's syndrome, it does relieve vertigo in some patients; however, the mechanism of this relief is unknown [7]. We suspect that endolymphatic hydrops is not attributable to the attack of vertigo, which is supported by our recent MRI study showing that endolymphatic hydrops does not always accompany MD [8]. Drilling the mastoid itself instead of artificial endolymph opening may induce therapeutic effect on vertigo.

Shear Stress in the Inner Ear

On the interface of fluid and solid structures, there exists tangential force acting on the surface: the shear force. It produces, for example, shear stress (SS) on the endothelium when blood is flowing in the artery. The generated mechanical forces on the cells of the vascular wall are expressed in units of force / unit area (N/m^2 or Pascal [Pa] or $dyne/cm^2$). Abnormal SS often leads to atherosclerotic lesions [9,10]. The nature of fluid flow in the vessel is dependent on the velocity of flow and might be either laminar or oscillatory (turbulent) [9]. Laminar flow induces anti-atherogenic gene expression, whereas oscillatory flow results in a pro-atherogenic reaction [10,11].

In the auditory system, sound waves are transformed with the middle ear mechanisms from air media to fluid oscillation in the cochlear compartments, and the Corti organ converts the mechanical vibration into sensory inputs. The cochlear structures, especially the components in the Corti organ are always undergoing an oscillatory shear, which is a highly energy-demanding process [12-14].

Stimulation pattern in the vestibular system is different from that of the auditory system and no fluid oscillation is evoked at the static status. However, fluid oscillation occurs when the head motion is induced, i.e. the vestibular end-organs are stimulated to maintain the balance. Shear stress in the cochlea was first addressed by Zou et al. in 2005, which is that intensive hitting (a linear acceleration of 6 m/s^2) the bulla of the guinea pig at the bony external ear canal at 250 Hz for 15 min that is delivered from an electromagnetic shaker upregulated expressions of tumor necrosis factor-α (TNF-α) and vascular endothelium growth factor (VEGF) and receptors in the cochlea [15].

We hypothesize that shear stress may also occur in the vestibular system by drilling the temporal bone during the endolymphatic shunt surgery. The positive outcomes of endolymphatic shunt surgery in Menie`re's disease are potentially contributed by the shear stress instead of relieving the endolymphatic hydrops. The literature reports support that skull vibration stimulates the vestibular end organs. In

1973, Lucke reported the first clinical observation of nystagmus induced by bone vibration in unilateral vestibular lesions [16]. Hamann and Schuster observed a similar phenomenon in vestibular schwannomas [17]. Dumas et al. described Videonystagmography (VNG) recordings in patients with various vestibular diseases and studied the effect of the stimulus frequency on the response [18].

The frequency that elicited the strongest nystagmus was 100 Hz, which is the frequency to which muscular receptors are reportedly sensitive. Young et al. observed squirrel monkeys' peripheral vestibular neuron responses to head vibration and airborne sound at frequencies from 50 to 400 Hz. The responses were measured in terms of the phase-locking in discharge and changes in firing rate. The lowest phase-locking thresholds for vibration were -70 to -80 dB re 1 g, and the median values in the most sensitive frequency range (200 to 400 Hz) were -20 to -40 dB re 1 g; the minimum and median thresholds for sound were 76 and 120 to -130 dB SPL, respectively. The rate-change thresholds were 10 to 30 dB above the phase-locking thresholds. The squirrel monkey sacculus has no special sensitivity to vibration compared with the other vestibular end organs; the median phase-locking threshold to sound for the saccular neurons exceeded 100 dB SPL. Using extracellular single neuron recordings from a large number of primary vestibular neurons identified by their location and their response to natural stimulation, Curthoys et al. [19] found that there is a very clear preference for irregular otolith afferents to be selectively activated by bone-conducted vibration stimuli at low stimulus levels and that bone-conducted vibration stimuli activate some irregular utricular afferent neurons.

Manzari et al. observed ocular and cervical vestibular-evoked myogenic potentials for bone-conducted vibration in MD patients during quiescence vs. during acute attacks. The researchers found that during MD attacks, dynamic utricular function in the affected ear (as measured by the n10 wave of the ocular vestibular-evoked myogenic potential at 500 Hz) is enhanced, whereas dynamic saccular function in the affected ear (as measured by the p13 of the cervical vestibular-evoked myogenic potential to 500-Hz bone-conducted vibration) is reduced [20]. We hypothesize that the constant and intensive shear wave generated during temporal bone drilling overstimulates the vestibular end organs and raises the threshold of response in a similar way to a hearing threshold shift. When the thresholds of the oversensitive vestibular end-organs are raised to levels near those of the less-sensitive vestibular end-organs, vertigo in MD patients may be directly resolved. Meanwhile, the nonsensorineural cells of the vestibular end-organs undergo shear stress and gene transcriptions are modulated accordingly. The biological responses induced by vestibular shear stress may also modify the progress of MD, producing beneficial effects in patients.

Shear Stress-Induced Biological Responses in Different Tissues

Vessels

Krajnak et al. [21] assessed the frequency-dependent responses of the peripheral vascular system (rat tail) to repeated bouts of vibration using 62.5, 125, or 250 Hz vibrations (constant acceleration of 49 m/s^2) for 4 h/d for 10 d. Vascular responses indicative of dysfunction (e.g., remodeling and oxidative activity) became more pronounced as the frequency of the exposure increased. Vibration at frequencies >100 Hz that induced the greatest stress and strain on the tail [21]. The authors

also investigated the effects of shear stress on vascular function using an animal model of metabolic syndrome (the obese Zucker rat).

The tails of lean and obese Zucker rats were exposed to vibration (125 Hz, 49 m/s^2 r.m.s.) or control conditions for 4 h/d for 10 d. Vibration exposure generally reduced the sensitivity of the rats' arteries to acetylcholine (ACh)-induced vasodilation. This decrease in sensitivity was most apparent in obese rats. Vibration also induced reductions in vascular nitric oxide (NO) concentrations and increases in vascular concentrations of ROS in obese rats. These results indicate that vibration interferes with endothelial-mediated vasodilation and that metabolic syndrome exacerbates these effects [22].

Nerves

Krajnak et al. [21] studied sensory nerve function in rats after acute exposure to vibration. They found decreased Aβ nerve fiber sensitivity in association with reduced expression of nitric oxide synthase-1 and a modest increase in calcitonin gene-related peptide (CGRP) transcript levels in tail nerves 24 h post-exposure to 4 h of continuous sinusoidal vibration at 125 Hz with a constant acceleration of 49 m/s^2 rms. These transient changes in sensory perception and transcript levels induced by acute vibration exposure may be indicators of more prolonged changes in peripheral nerve physiology [23].

In the inner ear, VEGF signaling was upregulated in the spiral ganglion cells and other cell populations' post-shear stress [15]. Shear stress-induced VEGF production in human adipose tissue mesenchymal stem cells has been reported to be mediated by NO. This response was partially inhibited by treatment with 5 mM of l-NAME, a nonspecific inhibitor of nitric oxide synthases (NOS), suggesting the participation of NOS enzymes (neuronal [nNOS], inducible [iNOS], or endothelial [eNOS]) [24].

The mechanism and significance of VEGF signaling modifications in the vestibular end- organs in response to shear stress need to be clarified. CGRP, choline acetyltransferase, and GABA are transmitters in the efferent pathways of the vestibular end organs. An animal model of transient bilateral vestibular input blockage with tetrodotoxin showed an obvious increase in the number of CGRP-immunoreactive fibers within the neurosensory epithelia of the maculae and cristae, indicating the plasticity of the impaired vestibular nervous system [25]. We suspect that CGRP in the vestibular end-organs might be upregulated by shear stress and could play an important role in MD rehabilitation.

Bone

Bacabac et al. [26] investigated bone cells' (MC3T3-E1 osteoblastic cells) responses to vibration at a wide frequency range (5 to100 Hz). NO release positively correlated with vibration, whereas prostaglandin E2 (PGE2) release negatively correlated with the maximum acceleration rate of the vibration. Cyclooxygenase2 (COX-2) mRNA expression increased in a frequency-dependent manner, which relates to the increased NO release at high frequencies [26]. Another study was performed on the same cell line, which was exposed to vibrational force originating from the NASA-designed amplifier-controlled shaker head that simulates the vibrations of a space shuttle launch (5 to 2,000 Hz). The mRNA levels of two growth-related protooncogenes, c-fos and c-myc, were upregulated significantly within 30 min after vibration, whereas those of osteocalcin and transforming growth factor-1 decreased significantly within 3 h after vibration [27].

When exposed to low amplitude strain vibration with broad frequency components up to 50 Hz, the MC3T3-E1 cell line upregulated osteocalcin mRNA 2.6-fold after 7 d of sinusoidal strain combined with broad frequency vibration stimulation, and MMP-9 mRNA increased 1.3-fold after 3 d of vibration alone. The expression of adipogenic genes, such as PPAR-γ and C/EBP-α, markedly increased in response to SSV at 20 Hz and 30 Hz during maturation [28].

The proliferation of sarcoma osteogenetic-2 (SAOS-2) cells was slowed down, so the acceleration perceived by the cells' mechanosensors may change the cellular cycle by blocking duplication to differentiate the cells toward bone tissue. After microvibration treatment (magnitude: 0.3 ×g, frequency: 40 Hz, amplitude: ±50 μm, 30 min/12 h), bone marrow-derived mesenchymal stromal cell (BMSC) proliferation was decreased on Days 7 and 10; however, the numbers of genes and proteins expressed during osteogenesis, including Cbfa1, ALP, collagen I and osteocalcin, increased substantially. ERK1/2 activation was involved in microvibration-induced BMSC osteogenesis [29].

TRPV Is the Potential Molecular Sensor in Shear Stress in the Vestibule Induced By Endolymphatic Shunt Surgery

The Transient Receptor Potential (TRP) ion channel family consists of 28 ion channels. It can be divided into six subgroups based on the structure and activation characteristics of the channels. The TRP subfamilies are canonical (TRPC, seven channels), melastatin (TRPM, eight channels), ankyrin (TRPA, one channel), vanilloid (TRPV, six channels), polycystine (TRPP, three channels), and mucolipin (TRPML, three channels). The vertebrate TRPV channels have been shown to be sensitive to many forms of physical and chemical stimuli. All vertebrate TRPV members are calcium-permeable channels, with TRPV Groups 1 through4 characterized as moderately calcium-selective cation channels, while TRPV-5 and TRPV-6 are highly calcium-selective channels.

In the mouse inner ear, TRPV-1, -2, and -3 are coexpressed in the hair cells and supporting cells of the organ of Corti and in spiral ganglion cells, sensory cells in vestibular end organs, vestibular ganglion cells, and sensory nerve fibers. TRPV-2 has also been detected in the stria vascularis, dark cells, and endolymphatic sac. TRPV-4 is expressed in hair cells and the supporting cells of the organ of Corti and in the marginal cells of the stria vascularis, spiral ganglion cells, vestibular sensory cells, vestibular dark cells, vestibular ganglion cells, and the epithelial cells of the endolymphatic sac [29]. TRPV4 expression in the mouse inner ear is not influenced by vitamin D receptor knockout [30]. Hypotonic stimulation and 4-alpha-phorbol 12,13-didecanoate, a TRPV4 synthetic activator, increased the intracellular Ca(2+) concentrations in wild-type outer hair cells, whereas in TRPV4(-/-) mice, the outer hair cells failed to exhibit a Ca(2+) response to either stimulation. TRPV4 may function as an osmosensory and a mechanosensory receptor in the cochlea. TRPV4 was expressed predominantly in the apical membrane of mitochondria-rich cells, and cell volume regulation by TRPV4 was observed in a tissue culture of the rat endolymphatic sac. TRPV4 was also present in the endolymphatic sacs of patients with vestibular schwannomas and Ménière's disease.

TRPV4 is assumed to act as an osmoreceptor in cell and fluid volume regulation in the human endolymphatic sac [30]. At 8 weeks of

age, TRPV4 knockout mice appeared normal, but at 24 weeks, they revealed significantly higher auditory brainstem response thresholds. TRPV4 knockout mice are more susceptible to noise exposure than TRPV4+/+ mice [31]. TRPV4 has a role in aminoglycoside uptake and retention in the cochlea. After kanamycin (KM) treatment, TRPV1 was significantly upregulated in both the spiral and vestibular ganglia, while TRPV4 was downregulated in the inner ear ganglia. As a therapeutic agent for MD, gentamicin treatment also upregulated TRPV1 and TRPV2 expression in sensory and ganglion cells of the inner ear, while TRPV4 expression in the stria vascularis and vestibular dark cells decreased [32]. Downregulation of TRPV4 in the inner ear may restore the Ca(2+) concentration in the endolymph. However, this hypothesis together with the impact of shear stress on TRPV expression and activities in the vestibule should be investigated in future research.

Conclusion

To summarize, potential shear stress induced by the endolymphatic shunt surgery in MD patients may modulate activities of the afferent system of the vestibular end organ, enhance plasticity of the vestibular system, and result in symmetric sensitivity in the vestibular system. TRPV may be involved in the molecular mechanism in endolymph cationic ion circulation affected by shear stress. Matrix maintenance in the vestibule may also be enhanced after shear stress. Shear stress-promoted differentiation of BMSC toward certain cell types may have beneficial effects on the vestibular system in MD.

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