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Density difference between perilymph and endolymph: A new hypothesis for light cupula phenomenon

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A B S T R A C T

Light cupula is an emerging concept accounting for positional nystagmus. It can be diagnosed when persistent geotropic direction-changing positional nystagmus (PG DCPN) is observed in a head-roll test. Although hypotheses explaining light cupula phenomenon such as “light debris”, “lighter cupula”, and “heavier endolymph” have been proposed, the mechanism underlying light cupula has not been clearly elucidated yet. In the present study, we proposed a new hypothesis accounting for light cupula, i.e., density difference between perilymph and endolymph could elicit characteristic PG DCPN in a head-roll test. We also discussed the mechanism how membranous canal containing endolymph became buoyant within the perilymphatic space under constant influence of gravity when the density of perilymph was higher than that of endolymph.

Introduction/background

Light cupula phenomenon

Since the first report of light cupula in the English literature [1], many studies have been conducted on light cupula phenomenon [2–24]. Clinical characteristics in patients with light cupula are very similar to those with benign paroxysmal positional vertigo (BPPV), the most common cause of positional vertigo. Patients with light cupula complain of positional vertigo and exhibit persistent geotropic direction-changing positional nystagmus (PG DCPN) in supine head-roll test. Distinction between light cupula and canalolithiasis involving lateral semicircular canal (LSCC) was confused when the concept of light cupula was first introduced because both conditions could show DCPN during a head-roll test. However, DCPN of LSCC canalolithiasis is transient while that of light cupula is persistent with a null plane. Considering the nature of positional nystagmus which changes its direction according to a relative directional arrangement between the cupula and the gravitational force and persists under constant influence of gravity, researchers have postulated that the light cupula phenomenon occurs when densities of the cupula and the surrounding endolymph that are the same under normal condition become different from each other. While the percentage of patients with geotropic DCPN due to light cupula has been reported to be as high as 14.2% [6], the pathophysiology of light cupula remains unclear.

Characteristics of positional nystagmus need to be determined to expedite the diagnosis of light cupula. Knowledge about the orientation of the LSCC plane within the temporal bone and the axis of the cupula within LSCC is an essential prerequisite for such characterization. LSCC cupula is slightly tilted laterally from the sagittal plane. LSCC is anteriorly up-tilted approximately 30° from the horizontal plane, although individual variations may exist anatomically [11]. The nystagmus observed in the unilateral light cupula is characterized as follows [6]: ① spontaneous nystagmus weakly beating toward the healthy side is observed in a sitting position, ② bowing nystagmus beating toward the affected side is observed in a nose-down position, ③ leaning nystagmus beating towards the healthy side is observed in a head-up position, [4] PG DCPN is observed in a supine head-roll test, and [5] a null plane is identified when the head is ipsilaterally turned to approximately 30° in a supine position.

PG DCPN has also been observed in patients with comorbid central nervous system (CNS) diseases or inner ear disorders. Patients with CNS disorders such as vestibular migraine (VM) [25,26], cerebellar tumor [27], brainstem stroke [27], and human immunodeficiency virus encephalopathy [28] may also exhibit PG DCPN. PG DCPN in patients with VM is characterized by symmetrical intensity in head-rolling to both sides, and has low slow-phase velocity. Dysfunction of inhibitory GABAergic connections from the vestibulocerebellum to the vestibular nuclei has been suggested as a cause of PG DCPN [26]. A patient with meningitis exhibited PG DCPN which developed in association with increased protein in the cerebrospinal fluid (CSF) due to meningitis [16]. The authors suggested that increased CSF protein might have elevated protein content in the inner ear fluid because CSF is connected to the perilymphatic fluid through the internal auditory canal and

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cochlear aqueduct. This can make the specific gravity of the endolymph higher, resulting in light cupula [16]. PG DCPN has been reported in patients with inner ear diseases such as sudden sensorineural hearing loss (SSNHL) with vertigo [2,3,29–33], acute otitis media (AOM) complicated by serous labyrinthitis [34], Ramsay Hunt Syndrome with vertigo [35], and Meniere's disease [36]. PG DCPN in Meniere's disease can be observed both during an acute vertigo attack and at the interictal period. Geotropic DCPN can change to apogeotropic DCPN in some cases of SSNHL with vertigo and AOM with vertigo. PG DCPN may last for more than several months in SSNHL with vertigo.

When PG DCPN is observed without comorbid CNS or inner ear disorders, the time constant of slow-phase velocity (SPV) in PG DCPN is comparable to that of LSCC cupulolithiasis and the relationship between SPV of PG DCPN and the angle of head rotation is linearly symmetrical to that of LSCC cupulolithiasis [23,37]. Thus, PG DCPN of peripheral origin ("light cupula") is a counterpart of LSCC cupulolithiasis ("heavy cupula") when a null plane is identified. The objective of the present study was to propose a new hypothesis accounting for PG DCPN of peripheral origin, i.e., light cupula.

Previously proposed hypotheses for light cupula phenomenon

Three hypotheses have been proposed to explain the light cupula phenomenon: [1] "light debris" hypothesis, [2] "lighter cupula" hypothesis, and [3] "heavier endolymph" hypothesis. However, none of these three hypotheses has been proven yet.

"Light debris" hypothesis

The light cupula phenomenon can be observed when "light debris" adheres to LSCC cupula and lowers the specific gravity of the cupula (Fig. 1A). Although light debris has not been identified yet, degenerated and swollen cells in the endolymph and products from chemical reaction of otoconial particles have been proposed as candidates of light debris [21,2]. Clinical observations supporting the "light debris" hypothesis are: ① only horizontal component of DCPN is induced in many light cupula patients, ② positional vertigo shows abrupt onset, ③ usually only one side is affected [3,19,21–23]. However, "light debris" detaching maneuver does not show any additional therapeutic effect [9].

"Lighter cupula" hypothesis

The "lighter cupula" theory was first introduced to explain persistent geotropic DCPN in positional alcohol nystagmus (PAN) [38]. It is assumed that diffusion of ethanol (specific gravity = 0.79) from capillaries occurs more rapidly into the cupula than into the surrounding endolymph after alcohol intake, which makes the density of the cupula lower than that of endolymph, resulting in persistent geotropic DCPN (Phase I of PAN). This hypothesis is supported by observations that heavy cupula is elicited by ingestion of heavy water (deuterium oxide) [39] or glycerol (specific gravity = 1.25) [40]. It has been suggested that altered homeostasis of macromolecules such as sulfated proteoglycans that are synthesized in the cupula and secreted into the endolymph may cause relative density change between endolymph and the cupula [3].

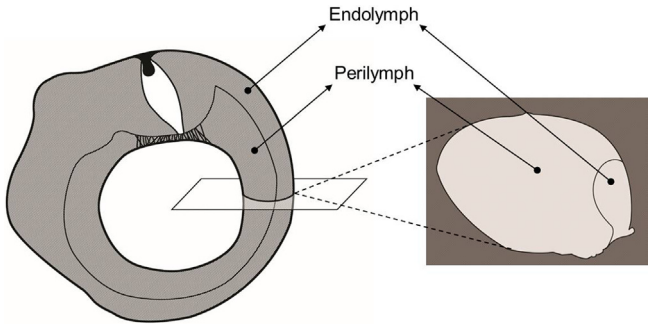

Fig. 1. Membranous ducts of semicircular canals assume an eccentric position and course along external walls of bony semicircular canals.

"Heavier endolymph" hypothesis

The "heavier endolymph" theory is based on the assumption that density of the endolymph may increase due to alteration of chemical composition of the endolymph attributed to acute insult on inner ear caused by labyrinthine hemorrhage, inner ear hypoperfusion, inflammation, or hormonal imbalance [6]. A patient with light cupula after stellate ganglion block (SGB) has been reported [2]. The authors speculated that inner ear hypoperfusion after SGB caused alteration of endolymph density [2]. Kim et al. have reported SSNHL patients with PG DCPN [6,30]. They proposed that leakage of plasma proteins into the endolymph caused by breakdown of blood-labyrinthine barrier (BLB) might increase density of the endolymph [6,30].

Hypothesis

A light cupula phenomenon develops due to density difference between the perilymph and the endolymph. When the density of perilymph becomes higher than that of endolymph, buoyant force can be implemented on the endolymphatic membrane which is immersed in perilymphatic fluid, causing PG DCPN in a head-roll test.

Case presentation and evaluation of hypothesis

A previously healthy 51-year-old woman visited emergency department complaining of acute onset of vertigo that was aggravated by change of head position. The patent did not report any accompanying auditory symptoms such as hearing loss, ear fullness, or tinnitus. She denied previous history of vertigo. The patient was subsequently referred to our dizziness clinic. Bedside head impulse test was negative for refixation saccade bilaterally. Gaze-evoked nystagmus or skew deviation was not observed. Cerebellar function test was normal, and no other neurologic deficit was found on a neurologic examination. Pure tone audiometry showed no hearing loss on either side. Diffusion-weighted magnetic resonance imaging of the brain did not reveal acute infarct. In a seated position, weakly right-beating spontaneous nystagmus was observed. In a supine position, very weak nystagmus with vertical and torsional components was observed instead of horizontal nystagmus (Supplemental Video 1). We then performed supine head-roll test on the patient. When the patient's head was turned to the right and left at 90°, persistent geotropic DCPN was observed (Supplemental Video 2). A null plane, at which the nystagmus would disappear, could not be identified in this patient. Under the diagnosis of light cupula, the patient received vestibular suppressants and antiemetic drugs. Two days later, the patient was followed up. She reported alleviation of vertigo symptom. Left-beating nystagmus was persistently observed in a supine position. Supine head-roll test elicited PG DCPN. A null plane was identified when the patient's head was slightly turned to the right in supine position. Three days later, the patient revisited our clinic, and nystagmus was not observed in the supine head roll test.

While PG DCPN was observed in our patient at the initial examination, a null plane was not identified on either side, although null plane was identified on the right side later. Identification of a null plane has been suggested to be one of the most characteristic nystagmus findings in light cupula that can provide important cues in determining the affected side [6,7,11]. Our patient exhibited weak nystagmus with vertical and torsional components instead of horizontal nystagmus in a supine position. These findings may suggest that all three semicircular canals might be involved in the light cupula phenomenon, and "heavier endolymph" hypothesis may be more plausible than "light debris" hypothesis in this case because inner ear organs are interconnected and inner ear fluids are circulated within them [10]. The "heavier endolymph" hypothesis assumes that the density of endolymph becomes

higher than that of cupula. Leakage of plasma protein into the endolymph due to impairment of BLB function has been suggested as a cause [6,29]. However, the endolymphatic space is strictly separated from the perilymphatic space by epithelial barrier function of tight junctions in the endolymphatic membrane [41], while BLB is a barrier between inner ear capillaries and perilymphatic space [42]. Considering that light cupula takes a clinical history of sudden onset in most cases, the possibility that the light cupula phenomenon is caused by change in chemical composition of the perilymph can be raised because alteration of endolymph density is likely to be preceded by alteration of perilymph density. Indeed, studies about inner ear fluid dynamics have been focused on endolymph fluid under the assumption that a precise balance between cupula and endolymph densities is essential to proper sensing of angular acceleration by semicircular canals. It has been reported that a density difference as small as $\sim 10^{-4}\,g/cm^3$ between endolymph and cupula is sufficient to make semicircular canals sensitive to gravity [43]. Due to such high sensitivity of semicircular canal sensory receptors, even little difference of density can evoke significant semicircular canal response. In the present study, we discuss the possibility that density difference between perilymph and endolymph can elicit semicircular canal response causing PG DCPN which is characteristic nystagmus observed in the light cupula phenomenon.

The membranous canal is bounded by endolymphatic membrane, and contains endolymph. It is completely immersed in perilymph fluid. Because endolymphatic membrane is thin (approximately 0.02 mm) and deformable [44], mechanical indentation of membranous duct can drive endolymph flow, leading to cupula deflection [45,46]. Mathematical modeling has demonstrated that pressure-driven membranous duct deformation by acceleration-driven flow of perilymph can elicit cupula displacement [44]. If the density of perilymph becomes higher than that of endolymph by any causes, the endolymphatic space will become buoyant within the perilymphatic space under constant influence of gravity. Membranous duct of the lateral semicircular canal (LSCC) assumes an eccentric position within the bony canal (Fig. 1). It is attached to crista ampullaris and the opposing wall in the area of ampulla (Fig. 1) [47–50]. When perilymph density is higher than endolymph density, endolymphatic membrane of the right LSCC at the ampulla is utriculopetally indented (Fig. 2A, long arrows in the right panel) when the patient's head is turned to the right (lesioned) side in a supine position (Fig. 2A, left panel). It is utriculofugally indented while head-rolling to the left (healthy) side in a supine position (Fig. 2B). Because adhesion between the cupula and endolymphatic membrane at the ampulla separates the endolymphatic space into medial and lateral to the cupula, endolymph fluid does not traverse through the cupula-membrane attachment [51]. The buoyant force that elicits indentation of endolymphatic membrane is directly delivered to the cupula causing cupular deflection (Fig. 2A and B, short arrows right panels). Thus, the presence of PG DCPN in our patient might be explained by increased density of perilymph over endolymph.

Questions concerning what conditions elevate perilymph density should be addressed. It is known that the density (g/cm^3) or specific gravity of the endolymph is equal to that of the perilymph under normal condition. The specific gravity or density is proportional to both the number of solute particles and the weight of solute particles whereas osmolality is determined only by the number of particles present in a solution [52]. Plasma osmolality is primarily determined by plasma Na^+ concentration. Normal plasma osmolality usually held within narrow limits is 275 to 290 mosmol/kg [52]. It has been demonstrated that perilymph is normally close to osmotic equilibrium with blood [53]. Although plasma osmolality is strictly regulated, water deficit or systemic disorders such as hormone imbalance, diabetes mellitus, uremia, and neurologic catastrophes can result in hyperosmolality. Since BLB is permeable to water [54], water can move from the perilymph to plasma through BLB and cause the increase in perilymph density (Fig. 3A). Although plasma proteins do not move across

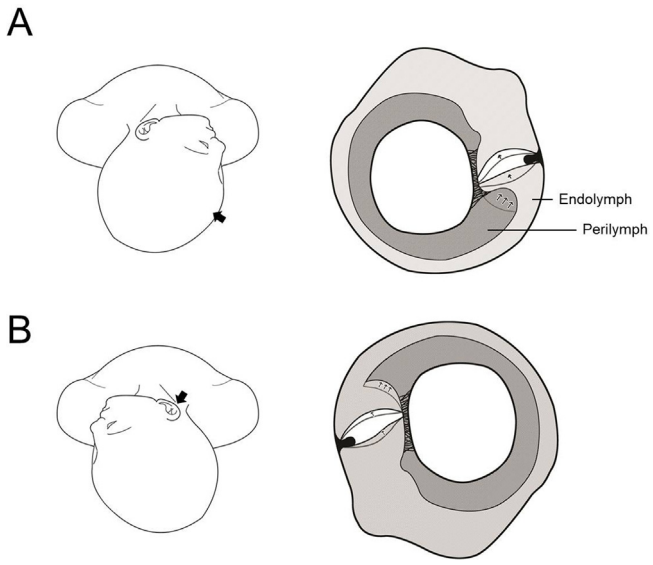

Fig. 2. Mechanism underlying persistent geotropic direction-changing positional nystagmus when perilymph density becomes higher than that of endolymph. The view from the top of the patient's head in a supine position is depicted in the left panels, and the right lateral semicircular canal is depicted in the right panels. When specific gravity or density of the perilymph is elevated excessing that of the endolymph, the membranous duct containing endolymphatic fluid will become buoyant by gravity. (A) In a right head-roll position, the continuous buoyant force is utriculopetally applied to the endolymphatic membrane at the ampullary region (long arrows in the right panel), causing cupula displacement (short arrows) which elicits persistent right-beating (geotropic) positional nystagmus. (B) In a left head-roll position, the continuous buoyant force is utriculofugally applied to the endolymphatic membrane at the ampullary region (long arrows in the right panel), causing cupula displacement (short arrows) which elicits persistent left-beating (geotropic) positional nystagmus.

the BLB under normal condition, leakage of plasma proteins such as serum albumin can occur if dysfunction of BLB develops (Fig. 3B). In such condition, density of perilymph may become higher than that of endolymph because these proteins have high molecular weights (serum albumin, 66.5 kDa).

Questions concerning why only LSCC is involved in most of light cupula patients should be addressed. This issue has long been debated, and more evidences will be needed for the clear explanation about this. We speculate that vertical canals would also be involved if density difference is a cause of light cupula phenomenon, and in this case, torsional or vertical component of nystagmus would be observed during positional nystagmus test. Because geometry and exact location of the crista and cupula of anterior semicircular canal is not clearly known even though those of posterior and lateral canals are relatively straightforward [47,55], it is difficult to exactly figure out which of vertical or torsional component of nystagmus is observed at specific head position with regard to the direction of gravity. In Supplemental Video 1, we can observe weak vertical nystagmus in a supine position, which may indicate the involvement of semicircular canals other than lateral semicircular canal. Then, why is horizontal nystagmus is predominantly observed during head-rolling? Although it is difficult to answer clearly, we assume that when horizontal nystagmus is strong vertical and torsional components may be weakened or concealed. Similar examples may be observed in nystagmus induced by magnetic vestibular stimulation. While pure horizontal nystagmus seems to be observed during 7T MRI scanning in a healthy volunteer [56], three-dimensional analysis of nystagmus induced by magnetic vestibular stimulation during 7T MRI scanning in other healthy volunteers demonstrated that anterior and lateral canals are equally activated [57].

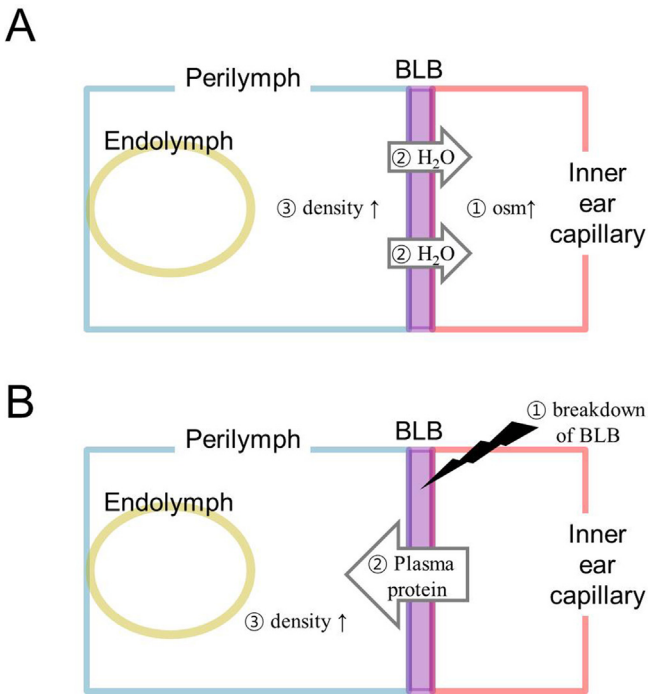

Fig. 3. Schematic illustrations showing the hypothetical mechanism on how the perilymph density is elevated. (A) If plasma osmolality increases by any cause, H_2O moves across the blood-labyrinth barrier from the perilymph to blood, which elevates the density or specific gravity of the perilymph. (B) If blood-labyrinth barrier function becomes impaired, plasma protein such as serum albumin are leaked into the perilymph through the blood-labyrinth barrier, which elevates the density or specific gravity of the perilymph. BLB, blood-labyrinth barrier.

Conclusion

We proposed density difference between the perilymph and endolymph as a new hypothesis accounting for light cupula phenomenon. When the density of perilymph becomes higher than that of endolymph by any cause, the membranous canal containing endolymph becomes buoyant within the perilymphatic space under constant influence of gravity, thus eliciting characteristic PG DCPN in a head-roll test.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.12.017.

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