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Treatment of peripheral vestibular dysfunction using photobiomodulation

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Abstract. Gentamicin, which is still used in modern medicine, is a known vestibular toxic agent, and various degrees of balance problems have been observed after exposure to this pharmacologic agent. Photobiomodulation is a candidate therapy for vertigo due to its ability to reach deep inner ear organs such as the cochlea. Previous reports have suggested that photobiomodulation can improve hearing and cochlea function. However, few studies have examined the effect of photobiomodulation on balance dysfunction. We used a rat model to mimic human vestibulopathy resulting from gentamicin treatment and evaluated the effect of photobiomodulation on vestibular toxicity. Slow harmonic acceleration (SHA) rotating platform testing was used for functional evaluation and both qualitative and quantitative epifluorescence analyses of cupula histopathology were performed. Animals were divided into gentamicin only and gentamicin plus laser treatment groups. Laser treatment was applied to one ear, and function and histopathology were evaluated in both ears. Decreased function was observed in both ears after gentamicin treatment, demonstrated by low gain and no SHA asymmetry. Laser treatment minimized the damage resulting from gentamicin treatment as shown by SHA asymmetry and recovered gain in the treated ear. Histology results reflected the functional results, showing increased hair cell density and epifluorescence intensity in laser-treated cupulae. [DOI: 10.1117/1.JBO.22.8.088001]

Keywords: vestibular organ; photobiomodulation; protection; gentamicin; regeneration.

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1 Introduction

Vertigo is one of the most common medical complaints, affecting 15% to 35% of the general population.[1] The severity of vertigo varies, but many patients suffer from severe disability that can be long lasting. One of the primary causes of vertigo is dysfunction of the peripheral vestibular system. Unfortunately, there are no specific treatments to cure peripheral vestibular dysfunction, and most therapeutic approaches rely on vestibular rehabilitation that involves compensation from the central nervous system. Aminoglycosides are pharmacologic agents that are known to result in peripheral vestibulopathy.[2,3] Gentamicin, a type of aminoglycoside, can result in vestibular damage, but it is still widely used due to its effectiveness and low cost. The impact of gentamicin on the peripheral vestibular system can vary from minimal damage to complete loss of function.[4] Pathophysiology of gentamicin vestibular toxicity is known to relate to the reactive oxygen species (ROS) formation and it has been proved that several ROS scavengers can minimize its toxicity.[5] The agent affects both cochlea and vestibule but it is relatively more vestibular toxic; therefore, it is commonly used for ablation of vestibular function in cases of intractable Meniere's disease.

Photobiomodulation is the therapeutic application of light energy that is red and near-infrared at power levels that do not cause tissue heating. It promotes tissue regeneration, reduction of inflammation, and pain relief. The mechanisms of action are not fully understood, but are thought to involve a photochemical effect, where light is absorbed by mitochondrial chromophores and stimulates the respiratory chain and adenosine 5'-triphosphate (ATP) production.[6] Several previous studies have shown that photobiomodulation has positive effects on acute and chronic pathologic conditions.[6] Long wavelength red/NIR light, which is typically used in photobiomodulation, enables deeper penetration, less scattering, and reduced harm to living tissue compared to ultraviolet (UV) or blue/green light (UV) or visible light.[7] This means that photobiomodulation can be used to treat deep organs such as those in the inner ear. The inner ear comprises the cochlea (hearing organ) and the vestibular organ (balancing organ), which are located adjacent to one another and form a fluid-filled cavity with a bony wall. Several recent studies have shown promising effects from photobiomodulation of the cochlea;[8–13] however, the effect of photobiomodulation on the vestibular organ is not well understood.

In this study, we used an animal model to examine the effects of photobiomodulation on vestibular function after damage by gentamicin treatment. The results showed that photobiomodulation resulted in a faster recovery of vestibular function and recovered vestibular hair cells in the cupula.

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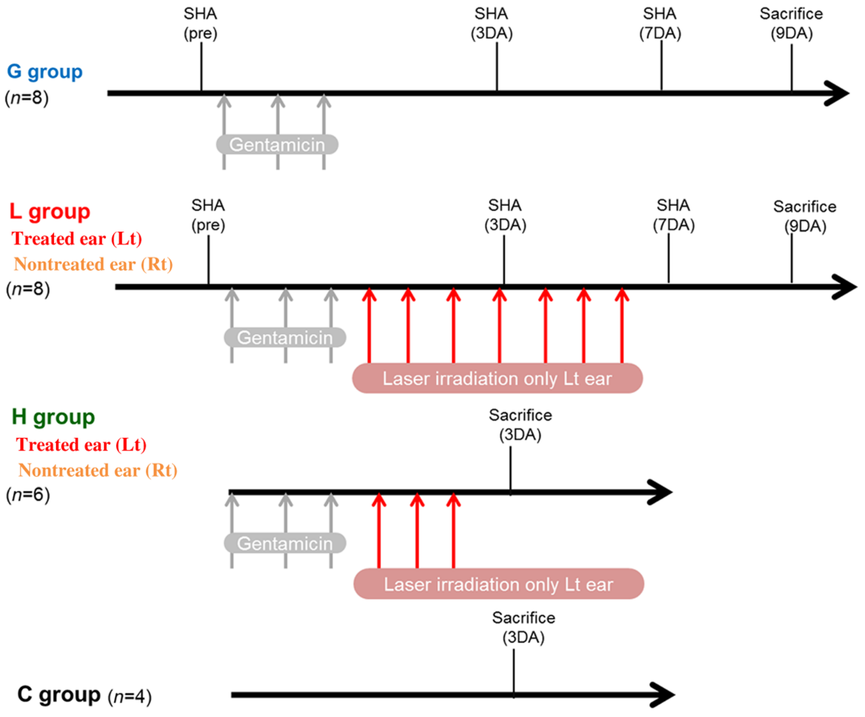

Fig. 1 Experimental groups and schedule. Animals were divided into four groups. Function and histology were evaluated in two groups each. Group G received gentamicin only and group L received gentamicin and laser treatment in the left ear only. Group C was untreated, and group H received gentamicin plus laser treatment in the left ear only.

2 Materials and Methods

2.1 *Animal Model and Experimental Protocols*

All animal experiments were authorized and performed in accordance with Dankook University College of Medicine Animal Use Committee guidelines. Twenty-six Sprague-Dawley rats (male; 12 weeks old; 300 to 400 g), supplied by Narabio Laboratories (Seoul, Korea), were used. The functional test used in this study is relatively stressful, restraining the animal in the platform without anesthetics. Therefore, we separated functional and histologic study so that the functional test process cannot intervene in the histologic outcome. For functional testing, the animals ($N = 16$) were treated with intravenous gentamicin (110 mg/kg daily) (Shinpoong Pharmaceutical Co., Korea) for 3 days to induce vestibular dysfunction and were divided into gentamicin (G group; $N = 8$) and laser groups (L group; $N = 8$) (Fig. 1). The rotating chair testing method (described later) was performed multiple times on each animal, and the results were averaged and compared between the groups. Ten animals were used for histological examination, including six exposed to gentamicin (group H) and four controls (group C) (Fig. 1).

The animals were anesthetized for gentamicin injection and laser irradiation. Zoletil (Virbac Laboratories, France) and Rumpun (Bayer Korea, Korea) were mixed in a 4:1 ratio for anesthesia. A combined solution (0.1 ml/100 g) was administered by intramuscular injection and boosted with one-fifth of the original dose when required.

2.2 *Slow Harmonic Acceleration Rotating Platform Testing*

A vestibular function test designed for rats was used to evaluate the vestibular ocular reflex. Vestibular ocular reflex is the reflex for animals to see the target while they are moving. Sensory input of head rotation results in the movement of the eye and this reflex happens with and without a target or light.[14] An animal rotator (Jeil Co., Seoul, Korea) that records slow harmonic acceleration (SHA)-induced nystagmus and controlled by a computer system was used. Animals were placed on the animal rotator mounting plate in a prone position to align the horizontal semicircular canals and the plane of rotation (Fig. 2). The animals were firmly fixed to reduce displacement during rotation. The animals underwent sinusoidal oscillation around a vertical axis at oscillation frequencies of 0.02, 0.04, 0.08, 0.32, and 0.64 Hz, with a peak angular velocity of 60 deg/s at all frequencies. The platform rotates in one direction and reaches its maximal speed, which is 60 deg/s, then reduces speed, changes direction, reaches 60 deg/s, and stops. This cycle is repeated for five times and averaged. The animal's horizontal eye movements were monitored, and the relationship between eye and head movement was examined. All eye movements were recorded with a magnetic search coil system in darkness. The animal's horizontal nystagmus was recorded and analyzed using a computer program. SHA testing was performed before gentamicin injection and at 3 and 7 days after initial laser irradiation (Fig. 1). The test outcomes were averaged and compared between groups and sides.

2.3 *Photobiomodulation*

Animals were anesthetized for the laser irradiation using the same protocol as mentioned above. Transmeatal laser irradiation was performed using an 830-nm diode laser (Won Tech, Daejeon, Korea). Irradiation was performed for 30 min at a power of 200 mW (297 J; 165 mW at the tip of the fiber; fiber tip diameter, 6.5 μm) every day for 7 days (3 days for the histologic analysis) starting the next day of gentamicin treat-

Fig. 2

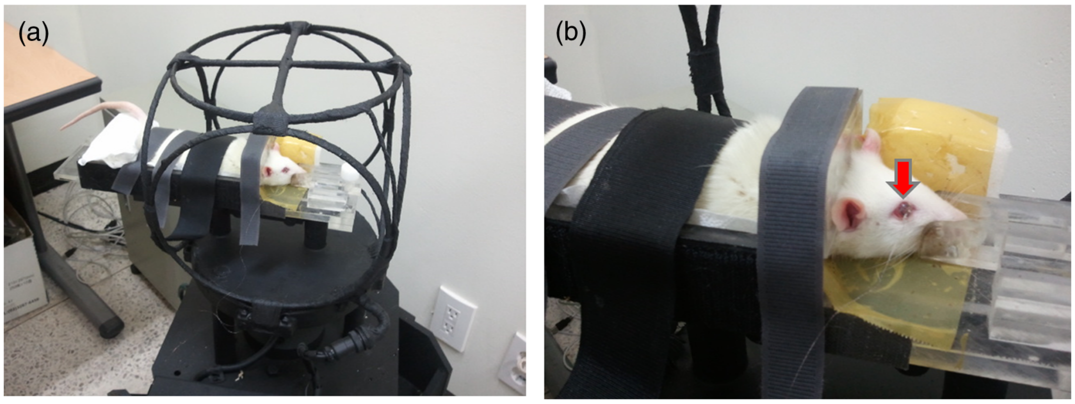

Fig. 2 Animal SHA system. (a) An orthogonal magnetometer was mounted on the rotator, and animals were placed in the rotator on the magnetometer. (b) Search coils to record the eye movement were placed on the right eye (red arrow). Animals were not sedated to record reflex eye-movement.

ment. The laser fiber was delivered into the left external auditory canal. The irradiation was performed as previously described.[8–12] Only the left ear was irradiated in groups H and L, and groups G and C did not receive photobiomodulation (PBM). PBM parameters were determined considering the penetration rate and the safety of the peripheral sensory organ. Its penetration rate and safety are addressed in previous literature.[11,15]

2.4 Histology and Cell Counting

Group H animals received gentamicin injections i.m. for 3 days, and laser treatment was administered the next day, once daily for 3 days into the left ear. The temporal bones were harvested on the sixth day for histopathologic examination. Horizontal semicircular canal ampullae were embedded in optimal cutting temperature compound (Sakura Finetek, Torrance, California). The ampulla was cut into 5-μm-thick sections and stained with DAPI and Phalloidin (Sigma, St. Louis, Missouri). The prepared slides were examined, and imaging was obtained with an LSM-510-META apparatus (Carl Zeiss confocal microscope, Oberkochen, Germany). Six representative images from each 50-μm segment (section of ampulla was 50 μm long and cut into 5 μm section, among them six representative sections were randomly selected and analyzed) were used to quantify the number of hair cells. The number of hair cells was counted without distinguishing cell type (i.e., type 1 or type 2 hair cells). Counted sections accounted for ~10% of the whole crista ampulla. The number of cells was compared among normal ears (group C), laser irradiated left ears, and nonlaser irradiated right ears (group H).

2.5 Statistical Analyses

Data are presented as the mean ± standard deviation (SD). Values of $p < 0.05$ were considered statistically significant. Data were analyzed (Wilcoxon signed-rank test) using SPSS software ver. 18.0 (SPSS, Inc., Chicago, Illinois).

3 Results

3.1 Functional Test Outcomes

3.1.1 SHA asymmetry

Groups G (gentamicin only) and L (gentamicin and laser) were tested. The average gains during the right and left rotations were compared at each frequency. Group G showed symmetric gain (values close to 0), with no differences between the right and left ears, at day 3 and day 7. Group L showed asymmetric gains at both days 3 and 7 time points, indicating vestibular imbalance. Asymmetry values were statistically higher in group L compared to group G at all frequencies (Fig. 3). These results suggest that laser irradiation resulted in vestibular imbalance and an increase in vestibular function in the treated ear. To determine the exact improvement resulting from laser treatment, the gains in the treated ear were compared to the gains in the untreated ear in group G.

3.1.2 SHA gain comparison

Group G had decreased gain values at all frequencies at 7 days after initial gentamicin injection (3 days after initial laser irradiation), and the gain values had recovered slightly after 10 days. These results suggest that systemic injection of gentamicin decreased vestibular function and that partial recovery of vestibular function had occurred by 10 days after initial injection. Average bilateral ear function values were compared to the vestibular function of the laser-treated ears. The gain values of the laser-treated ears of group L were significantly higher than those of group G at all frequencies 3 days after completing gentamicin infusions, and at 0.02, 0.04, 0.08, and 0.16 Hz 7 days after completing infusions (Fig. 4). The laser-treated ears had significantly higher gain values compared to the untreated ears in group L at all frequencies 3 days after gentamicin infusions, and at all frequencies except 0.02 and 0.08 Hz 7 days after infusion (Fig. 5). These results suggest that laser treatment ameliorated the vestibular dysfunction induced by gentamicin infusion.

3.2 Histological Evaluation

3.2.1 Balance organ morphology

In normal vestibular organs, rotation stimulates the cupula, a hill-like structure composed of sensory hair cells and other supporting cells. Ears treated with lasers showed an increased number of surviving cells near the surface [Fig. 6(a), upper right] compared to the no laser group [Fig. 6(b), upper right]. In addition, there was increase in phalloidin intensity in the cupula- and stereocilia-like structures on the surface area [Fig. 6(a) upper left], suggesting that photobiomodulation has a protective effect

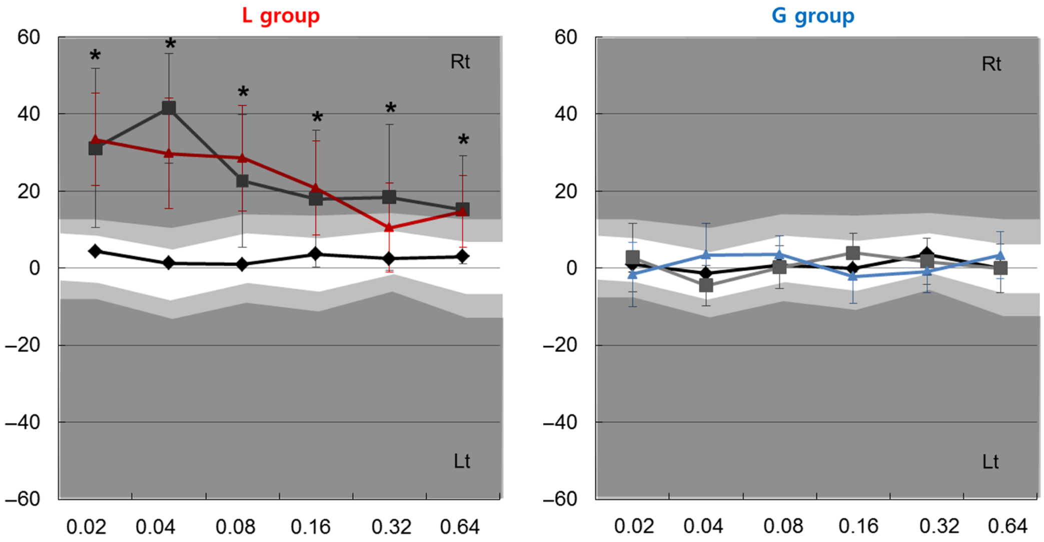

Fig. 3 Functional outcome: SHA asymmetry. Group G (gentamicin only) showed symmetric outcomes at all tested time points, all dots and lines were within the white area. Group L (gentamicin and laser-treated group) showed symmetric outcomes initially for pretreatment measurements (black line with small diamonds). After 3 days of laser treatment, group L showed significant asymmetry at all frequencies (black line with large rectangles). This asymmetry was maintained 7 days after initiation of gentamicin treatment (red line with small triangles) ($*p < 0.05$, group L versus group G). Units of the x-axis are Hz. White areas indicate normal range, light gray shadow indicates mean ± 1 SD, and dark gray shadow indicates mean ± 2 SD.[16] Diamonds represent baseline, rectangles represent 3 days of laser treatment, and triangles represents 7 days of laser treatment.

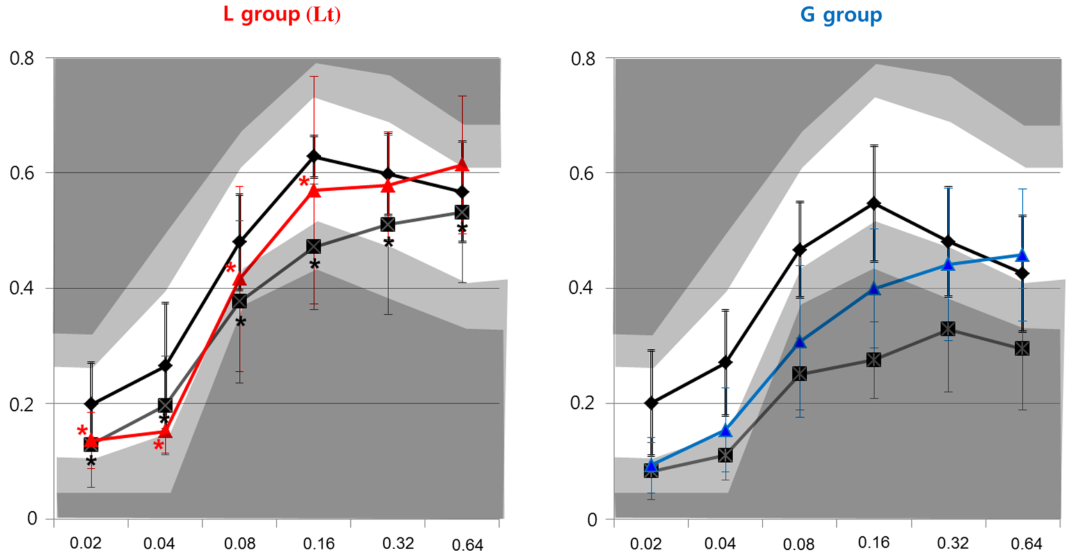

Fig. 4 Functional outcomes: SHA gain comparison between groups. Group L gain values (laser-treated ear) were statistically higher than group G gain values (gentamicin treated) at all frequencies after 3 days of laser treatment, and at 0.02, 0.04, 0.08, and 0.16 Hz after 7 days of laser treatment. ($*p < 0.05$, group L versus group G). Units of the x-axis are Hz. White areas indicate normal range, light gray shadow indicates mean ± 1 SD, and dark gray shadow indicates mean ± 2 SD.[16] Diamonds represent baseline, rectangles represent 3 days of laser treatment, and triangles represents 7 days of laser treatment.

against gentamicin. On the other hand, the intensity of phalloidin (actin) staining was reduced in the cupula after gentamicin treatment without laser, suggesting a decrease in stereocilia, which initiates balance signal transduction [Fig. 6(b) upper left].

3.2.2 *Quantification of cellular density*

The cells near the cupula surface were quantified to determine hair cell density. Gentamicin-treated animals (group H, no laser ear) without laser therapy had a lower number of hair cells at every location of the cupula compared to laser-treated ears (group H, laser-treated ear). There was little difference in hair cell density between the control (group C) and laser-treated groups (group H, laser-treated ear) [Fig. 7(a)]. The total number of cells was also compared between groups, and cupulae from ears treated with gentamicin alone (group H, no laser ear) had a lower number of hair cells compared to both control and laser-treated ears [groups C and H (laser-treated ear), respectively].

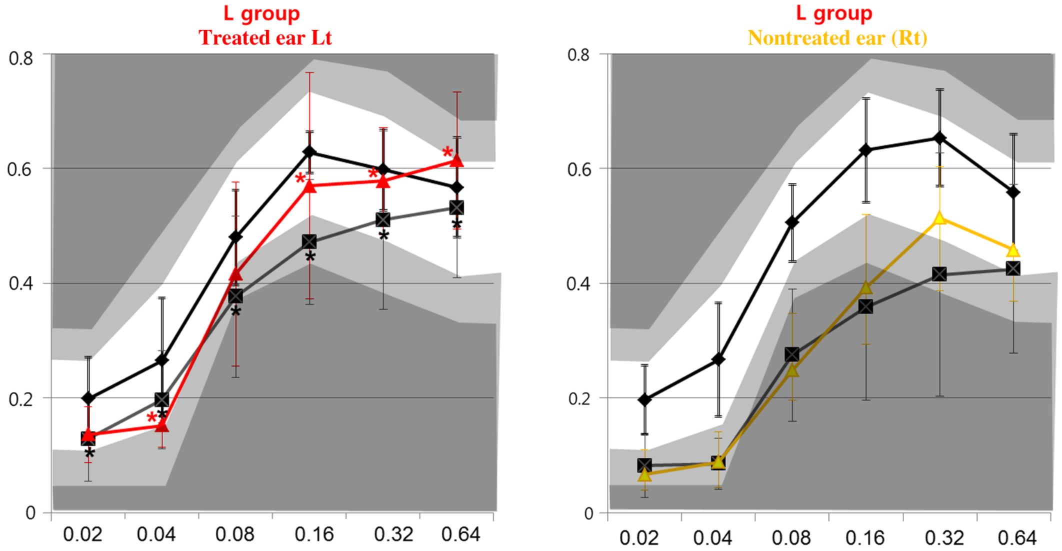

Fig. 5 Functional outcome: SHA gain comparison between ears. Group L (laser-treated) gain values were compared between ears. Laser treatment resulted in statistically higher gain values compared to the untreated ear at all frequencies after 3 laser treatments, and at all frequencies except 0.02 and 0.08 Hz after 7 laser treatments ($*p < 0.05$, treated versus nontreated ears). Units of the x-axis are Hz. White areas indicate normal range, light gray shadow indicates mean ± 1 SD, and dark gray shadow indicates mean ± 2 SD.[16] Diamonds represent baseline, rectangles represent 3 days of laser treatment, and triangles represents 7 days of laser treatment.

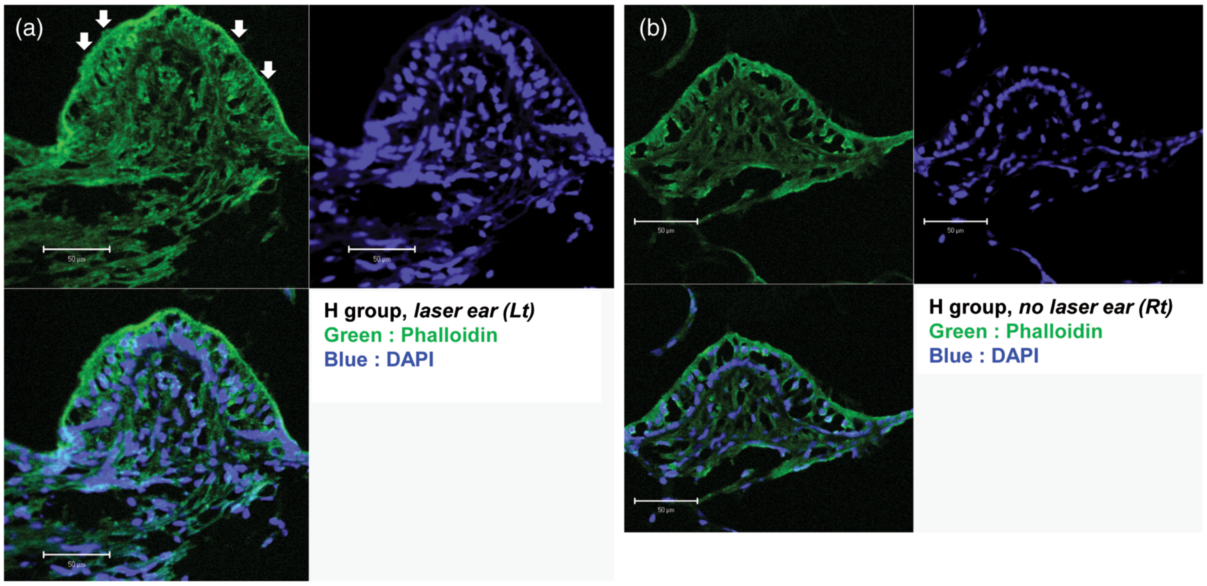

Fig. 6 Histological outcomes: cupula morphology. Epifluorescence analysis using confocal microscope was done. Harvested tissues were stained by phalloidin (actin) and DAPI (nucleus staining). Upper right image in each subfigure is stained by phalloidin, upper left images are stained by DAPI, and lower images are merged. Two representative sections were both at 200 μm distance from lateral wall. Overall height of the two specimens was different. (a) H group with laser was taller than (b) H group without laser. Ears treated with lasers showed increased number of nuclei (DAPI) near the surface [(a) upper right] compared to no laser group [(b) upper right]. There was increase in phalloidin intensity in the cupula- and stereocilia-like structures (white arrow) on the surface area [(a) upper left]. The intensity of phalloidin (actin) staining was reduced in the cupula after gentamicin treatment without laser [(b) upper left]. Scale bar is 50 μm.

In addition, in group H, the ear that received laser treatment had a significantly higher number of cells compared to the untreated (laser treated: 188 ± 17; untreated: 149 ± 16). Finally, there was no difference in cell count between laser-treated and control ears [Fig. 7(b)].

4 Discussion

In this study, we demonstrated that photobiomodulation has a regenerative effect on a vestibular organ damaged by gentamicin treatment. Gentamicin treatment resulted in a reduction of function and cells in the inner ear, but laser treatment resulted

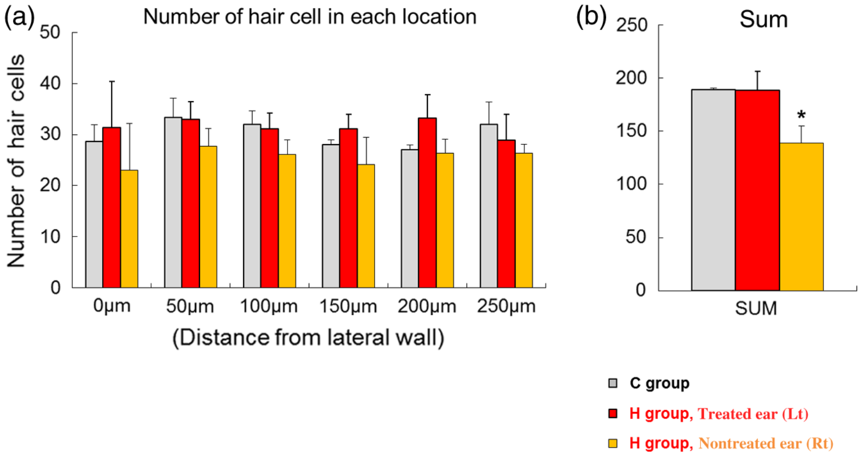

Fig. 7 Histological outcomes: quantitative analysis. The gentamicin-treated cupulae (group H, untreated-ears) had the lowest number of cells throughout the cupula compared to control and laser-treated ears. (a) The difference in cell density between the control (group C) and laser-treated groups (group H; laser-treated ear) varied between locations. The total number of cells across all locations was significantly lower in the unirradiated ears (group H) compared to laser-treated ears (group H) and control ears (group C). (b) There was no difference in the number of cells between the laser-treated ears and control ears (asterisk: $p<0.05$, C group versus H group nontreated ears).

in almost total functional recovery and a return to near-normal histology. However, there were slight discrepancies between the histological and functional recovery. Functionally, recovery was incomplete at the 3 day time point and complete recovery was observed at the 7 day time point. In contrast, histological results showed almost complete recovery at the 3 day time point. Therefore, the 7 day time point histologic analysis (analysis of H group) was not necessary.

It is still unclear whether the effect of photobiomodulation on vestibular function is due to regeneration of hair cells or recovery of function. Cochlear hair cells cannot regenerate once damaged,[17] but vestibular hair cells spontaneously regenerate after toxic damage.[18,19] Therefore, it is possible that the increase in hair cell number seen after laser treatment was due to a hair cell regeneration. This effect may also be due to a recovery of hair cells from the apoptosis process by an increase in ATP. Increase in ATP leads to the downregulation of proapoptotic proteins and upregulation of antiapoptotic proteins and this could be responsible for this recovery, which would be a similar process to that found in neural cells.[20,21] Otherwise, it could be due to low level stress that is induced by photobiomodulation. This low level cellular stress might activate the protective pathways of vestibular hair cells. Considering the current research outcomes from the studies of neural cells, "recovery" of the hair cell better explains the results of this study, but further studies are necessary to elucidate the exact mechanism of increased hair cell density and balance functions after photobiomodulation.

Determining vestibular function is complicated due to its connectivity to the brain and other sensory organs such as the eye balls. In clinical settings, diagnosis of vestibular function relies on the measurement of eye movement in response to stimuli such as rotation. Sensory information from rotation is provided by the cupula, which is located in the semicircular canal. The cupula is likely the key organ responsible for vestibular function tests. Any future research studies on vestibular dysfunction should focus on cupula histology. However, due to its three-dimensional structure and its inaccessibility, animal experiments on the cupula are limited, and research tends of be performed on otolith organs that are more easily accessed, such as the utricle.[10,22] Several studies from the authors have shown that photobiomodulation can have both preventative and regenerative effects.[12,13] However, these studies were performed in *ex vivo* organ culture systems using the utricle, and they lack functional outcomes.[23,24] In this study, rats were used as a model animal, and function and morphology were examined using the SHA test and cupula histology, respectively. As to the result, photobiomodulation was associated with improved functional and histologic outcomes after gentamicin treatment, and had a positive effect on the cupula.

Therapeutic approaches to vestibulopathy rely on vestibular rehabilitation that results in central compensation from the brain.[25,26] Surgical approaches are not available, and medical treatment is limited to the vascular circulatory agents or steroids.[26,27] The majority of patients suffering from vestibulopathy may spontaneously recover partially, but a large number of patients suffer from long-term disability. In addition, reducing the symptoms and intensity of vestibular dysfunction could result in a significant reduction in the socioeconomic burdens resulting from vertigo. Thus, innovative strategies to treat vertigo are needed, but little research on ways to enhance functional recovery has been performed to date. Application of photobiomodulation, which is noninvasive and has minimal complications, could be a promising new treatment for vestibulopathy that allows for functional recovery. Clinically, transmeatal photobiomodulation could be applicable to ototoxic bilateral vestibulopathy.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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