Application of Photobiomodulation in Hearing Research: Animal Study

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Hearing organs have unique characteristics and have a role in processing external sensory signals. Sensory hair cells and nerve fibers in the organ of Corti can be damaged by various causes and they do not regenerate themselves. Medication used for clinical treatment for the inner ear is limited due to the anatomical structure of the inner ear. Photobiomodulation (PBM) is a therapeutic approach that uses various sources of light and the success of PBM therapy is highly reliant on the parameters of the light sources. The positive effects of PBM have been reported in various clinical fields. This paper summarizes the previously reported research on PBM for the treatment of hearing damage in animal models.

Key words

Photobiomodulation; Hearing research; Hair cell protection; Nerve regeneration; Diode laser

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INTRODUCTION

Photobiomodulation (PBM) is a type of therapy using light source including laser and light emitting diodes (LED). More than 1,000 research papers have reported that its positive effect in pain relieving,¹⁻³ neuronal regeneration,⁴ inflammation reducing,^{5,6} tissue repairing,^{7,8} and nerve promoting.⁹ Application and effect of PBM is highly rely on its parameters. These parameters including power density, wavelength, beam spot size, irradiation time, total energy, and number of repetitions are directly related with success of therapy. Combining of laser sources or delivery method can be additional factor to control the effect of PBM.

Hearing problems are the one of three most general social problem in aging society.¹⁰ Several cohort studies reported that over 45% of population in the world have hearing problems.¹¹⁻¹³ Recently, the prevalence of hearing problems in young generation is increasing,^{14,15} and this could be resulted in communication dysfunction and social burden which also affect their family.¹⁶ Hearing aid and cochlear implant could be alternative way to compensate this problem but these approaches have clear limitation since these only aid remnant hearing function without treatment.

Diverse applications of PBM were reported after it approved by the United States Food and Drug Administration (FDA). Several studies performed PBM on patient with hearing dysfunction, especially for tinnitus.¹⁷⁻²⁰ PBM has also been used in pre-clinical hearing research for treatment after damage in both in vitro and vivo (in review).²¹ In this paper, we shortly review the previous result using PBM for hearing dysfunction in animal models. We discuss what kind of PBM parameters was used and how is applied to animal.

MATERIALS AND METHODS

Strategy for article identification

Research was conducted using the following databases: PubMed, Google Scholar, and Springer

Keywords used: Photobiomodulation, hearing, LLLT, regeneration, hearing, recovery

The titles, abstracts, and conclusions were screened and unrelated articles were excluded. Total 38 articles were included and were summarized. Evaluations of collected articles were performed by three reviews.

PARAMETERS OF PBM FOR HEARING RESEARCH

Wavelength

To apply PBM on the cochlea, penetration depth of wavelength is critical. Anatomically, cochlea is position inside of the temporal bone and light can be attached through tympanic membrane (Fig. 1). To compensate this hurdle, red and near-infrared (NIR) light of wavelength 600-1000 nm which has greater penetration depth than other wavelengths is generally used.²²⁻²⁷

Laser power and total intensity

Tympanic membrane which is first terminal of light for hearing treatment could be damaged depending on the total power of light. Since total power is composed with laser power, beam spot size, and irradiation time, appropriate parameters for each animal model is needed. Too strong power could lead pathological changes on the tympanic membrane and middle ear.²⁸ According to previous study, around 10% of light energy can reach to the cochlea in animal model.^{24,25}

Irradiation and repetition time

Irradiation times of PBM in previous hearing researches are separated into two times (30 and 60 minutes). Since animal should be anesthetized during PBM irradiation, too long irradiation time is not appropriate for animal study. Furthermore, burning of tympanic membrane or pathological changes in the middle ear tissue caused by long duration of irradiation could occur in animal model.²⁸

Fig. 1. Laser irradiation in the ear. Laser reaches to the cochlea through several obstacles. Curvy ear canal and tympanic membrane should be considered for photobiomodulation (PBM) in hearing research.

EFFECT OF PBM IN HEARING RESEARCH

Several papers reported various regenerative and protective effect of PBM in hearing research. Information of researches with PBM and parameters of PBM is summarized in Table 1.

HAIR CELL PROTECTION

Rhee et al. (2012) firstly reported the protective effect of PBM on cochlear hair cell after traumatic noise exposure.²⁶ PBM treated animal showed significant hearing threshold recovery with less hair cell loss in the middle turn of cochlear after 8 days of treatment. The wavelength and power of PBM in this study have been used as a standard PBM parameter for hearing research with animal model. Tamura et al. (2015) reported similar recovery of hearing threshold and similar hair cell protection in animal model with similar parameters of PBM in Rhee et al. (2012).²⁷ Their further study found that these positive effect of PBM occurred though modulation of Reactive oxygen species (ROS) and activation of NF- κ B.²² Furthermore, simultaneous PBM irradiations in both ears showed better recovery and protective effect than unilateral PBM in noise overexposed animal.²⁴

Protective effect of PBM on cochlear hair cell after ototoxic drug damage was also reported. Rhee et al. (2012) reported that survival of hair cell increased in PBM group after gentamycin treatment.²⁹

NEURONAL PROTECTION

Protective effect of PBM had reported in the neuronal structures in the cochlea. PBM using 808 nm protected damage of ribbon synapse between inner hair cell and spiral ganglion neuron against traumatic noise exposure.³⁰ Number of post synaptic receptor were also signif-

icantly less damaged by neurotoxic drug application after PBM. Moreover, higher number of spiral ganglion neuron survived in neurotoxin with PBM group than neurotoxic damage only group.²⁵

POSSIBLE MECHANISM OF PBM IN HEARING RESEARCH

Molecular mechanisms of PBM can be categorized as chromophores, signaling molecules, and activation of transcription factors. Cytochrome c oxidase (Cox), which is the terminal enzyme of the electron transport chain, has known as typical chromophore related with PBM mechanism.³¹ Cox performs as a photo-receptor and transducer of photo-signals of light with red and near infrared regions. Reduction of oxygen in the Cox leading increment of mitochondrial membrane potential and the level of ROS and ATP as well.³² PBM can increase Cox activity to modulate cellular, resulting in reduction of nitrite.³³

There are several light sensitive ion channels in the cochlea. Transient receptor potential (TRP) channels have various isoforms with seven sub families.³⁴ In the neurons, infrared light is able to generate laser-evoked neuronal voltage and TRPV4 channels were demonstrated to be the primary effectors of the chain reaction.³⁵ Recent study supported this hypothesis by reporting the result that TRP channels involved in hair cell protection.³⁶

PBM also can activate signaling molecule. PBM can initiate mitochondrial ROS changes leading to activation of the transcription factor nuclear factor kappa B (NF- κ B), which can sense the redox signaling.³⁷ The fact that the addition of antioxidants inhibits the activation of NF- κ B by 810 nm light reinforces this assumption.³⁸ Protective of PBM in noise induced hair cell loss by NF- κ B signaling was support this assumption.²²

Table 1. PBM treatment parameters of previous animal studies

Laser type	Wavelength (nm)	Animal	Power (mW/cm ²)	Irradiation time (minutes)	# of treatment (# per day)	Total laser energy (J/cm ²)	Year	Reference number
Diode laser	830	SD Rat	200	60	10 (1)	7200	2013	[27]
Diode laser	808	SD Rat	110, 165	30	5 (1)	1980, 2970	2015	[25]
Diode laser	830	SD Rat	200, 250, 300	30	14 (1)	10080, 12600, 15120	2016	[26]
Diode laser	808	SD Rat	165	60	7 (1)	4158	2019	[28]
Diode laser	830	SD Rat	200	30	7 (1)	297	2017	[21]
Diode laser	830	SD Rat	100 to 165	60	12 (1)	4320 to 7128	2012	[24]
Diode laser	808	SD Rat	165	30	5 (1)	1485	2016	[20]
Diode laser	808	Gerbil	200	60	7 (1)	4158	2016	[23]
Diode laser	808	SD Rat	165	60	15 (1)	8910	2016	[22]

CONCLUSIONS

PBM is a therapeutic approach with potency in hearing research. Non-invasive access without side effect of PBM therapy is the most efficient characteristic for clinical application. In this review, we summarized previous studies with PBM therapy in animal models. The success of PBM therapy in hearing research highly rely on the parameters of light source. For clinical application, more studies should be followed to address molecular mechanism of PBM therapy in the hearing area.

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