Literature Review

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Photobiomodulation therapy in ophthalmology

O. S. Zadorozhnyy, A. R. Korol, I. O. Nasinnyk, T. B. Kustryn, A. O. Nevska; N. V. Pasyechnikova

SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine";
Odesa (Ukraine)

Photobiomodulation (PBM) therapy is a form of light therapy that utilizes non-ionizing forms of light sources in the far-red to near-infrared spectrum to produce non-thermal photochemical reactions in different biological structures. The paper reviews the experience of implementing (a) PBM in different fields of medicine (e.g., ophthalmology) and (b) the known mechanisms of PBM-induced effects on cells and tissues.

Keywords:
photobiomodulation therapy, far-red to near-infrared light spectrum, retina, mitochondria

Photobiomodulation (PBM) therapy is a form of light therapy that utilizes non-ionizing forms of light sources, including lasers, light-emitting diodes, and broadband light, in the visible and infrared spectrum. It is a nonthermal process involving endogenous chromophores eliciting photophysical (i.e., linear and nonlinear) and photochemical events at various biological scales [1].

The term PBM combines some medical approaches to light application, previously referred to by other names (phototherapy, photobiostimulation, low-intensity laser therapy, low-level laser therapy, and laser stimulation).

PBM uses mostly light in the far-red to near-infrared light spectrum (600 to 1,000 nm).

The healing effect of the red light has been well-known since ancient times [2]. The utility of red light appears to be "re-discovered" at the end of the 19th century by Finsen who later became to be known as the "father of contemporary phototherapy" for his astonishing achievements of curing skin disorders using red light. These successes won him the 1903 Nobel Prize in Medicine and Physiology [3]. New opportunities for treatment applications of far red and near IR light appeared after the invention of the laser in the 1960s. This was due to an unexpected study results when Mester and colleagues found that 694 nm ruby laser radiation caused accelerated fur growth in mice compared to a control group that didn't receive laser light exposure [4]. It was the first documented demonstration of laser stimulation.

Mester and colleagues later used a He-Ne laser lightto stimulate wound healing in animals [5].

Linnik and colleagues [6] conducted animal and clinical studies to investigate biological effects of laser radiation on the eye and demonstrated the stimulating effect of low-energy laser on retinal functions. In their experimental studies, the fundus of the animal received a threshold laser irradiation through the pupil (i.e., retinal laser coagulation was performed). Thereafter, electron microscopy and cytochemical studies were conducted. The signs of active biosynthesis (like an increased RNA synthesis and increased numbers of mitochondria) were found at the sites remote from laser coagulation foci. The examination of the effects of laser irradiation on the anterior segment of the eye revealed the signs of increased functional activity of corneal epithelial cells and lens epithelial cells. These findings were used in the development and clinical application of the method for treating human retinal and corneal disorders [7].

The mechanism of action of PBM

The biochemical mechanism underlying photobiomodulation is still not completely understood. It is believed that PBM therapy approach exploits the photochemical conversion potential of low-intensity far-red to near-infrared light (FR/NIR), with mitochondria being implicated as the subcellular targets of FR/NIR [8-11]. Mitochondria contain chromophores which absorb photons from PBM. In the cellular level, PBM acts on mitochondria to increase adenosine triphosphate (ATP) production, modulation of reactive oxygen species and leading to a change in transcription through transcription factor activation [12-14]. Transcription factor activation causes protein synthesis that triggers further effects like increased cell proliferation and migration, modulation in

the level of cytokines, growth factors and inflammatory mediators, and increased tissue oxygenation [15-17]. It is believed that cytochrome C oxidase (CcO) inside mitochondria functions as the photoacceptor [3]. CcO is the enzyme that represents a transmembrane protein complex essential for the sustained availability of energy inside cells [18-20]. Cell culture studies demonstrated directly that PBM enhances the activity of CcO [21,22]. Activation of CcO triggers a series of biochemical cascades. The stimulation of cytochrome C oxidase by FR/NIR light is reported to lead to an increase in the energy generation by mitochondria, increase in the metabolic rate, proliferation and migration of cells [23-26].

Photobiomodulation also stimulates the release of nitric oxide (NO) from intracellular stores such as heme-containing proteins [27,28]. It is assumed that PBM leads to the photo-dissociation of NO from the cytochrome C oxidase heme. Since NO displaces oxygen from CcO, inhibiting mitochondrial respiration and reducing ATP production, its dissociation from CcO restores oxygen consumption by mitochondria. This should enhance the energy production and thus increase cellular metabolism [29]. NO is probably the most important and best-characterised mediator with a potent vasodilating function. It has been hypothesized that photobiomodulation may cause photodissociation of NO, not only from CcO, but from intracellular stores such as nitrosylated forms of both hemoglobin and myoglobin, leading to vasodilation [27, 30]. Nawashiro and colleagues [31] demonstrated an increase in cerebral blood flow after treatment with transcranial PBM. Vasodilation increases the availability of oxygen to treated cells, and also allows for greater traffic of immune cells into tissue. These two effects contribute to accelerated healing. Studies have demonstrated that PBM can reduce cell death and mitigate oxidative stress and retinal immune response in cell culture [32-34]. The processes described above are almost certainly only part of the story needed to explain all the effects of PBM on biological tissues.

CcO is a key enzyme in the bioenergetics of the cells, especially retinal neural and brain cells [35]. The retina is highly dependent on energy and is particularly vulnerable to mitochondrial dysfunction.

The retinal neurons, photoreceptors, and ganglion cells contain the highest density of mitochondria and therefore present as potential therapeutic targets for PBM [36].

In addition to the effect of PBM on the metabolism of photoreceptor cells, the effect of photobiomodulation on Muller cells, which protect photoreceptors, was also found. Albarracin and V alter [37] demonstrated that pretreatment with 670 nm light (in the rat model of lightinduced retinal degeneration) prior to damaging light exposure resulted in reduction of the light damage-induced changes in Müller cells.

Tang and colleagues [38] reported that PBM therapy protects retinal ganglion cells. Fuma and co-authors [39] demonstrated that PBM caused an increase in phagocytosisin human retinal pigment epithelial cells.

A scheme of retrograde mitochondrial signaling pathways has been proposed to explain the way in which a solitary and short-duration exposure to light may induce a biological effect lasting hours, days and even weeks [40].

Given that the mechanisms of actions of the FR/NIR light have been scientifically grounded, further research and application of biological effects of PBM are of sustained interest to the medical community [17,41,42].

Medical applications of PBM

PBM has been widely used for the therapy of numerous human diseases. One of the first fields of therapeutic application of PBM was low-energy He-Ne laser irradiation for wound healing [42,43]. PBM has been demonstrated to have effects on all the three phases of wound healing [44,45]. It is believed to promote wound healing by inducing the local release of cytokines, chemokines, and other biological response modifiers that reduce the time required for wound closure [46,47]. This result is achieved by increasing the production and activity of fibroblasts and macrophages, improving the mobility of leukocytes, promoting collagen formation, and inducing neovascularization [16,17,48].

Over the years, the number of conditions amenable to PBM has greatly increased. The use of PBM for pain control for neurologic pain has been reported. A study of randomized controlled trials [49] indicated that PBM can significantly reduce pain and improve health in chronic joint disorders such as osteoarthritis, patellofemoral pain syndrome, and mechanical spine disorders. PBM has also been shown to relieve periodontal pain during orthodontic tooth movement [50]. A review of clinical trials found that PBM reduces acute neck pain immediately after treatment, and up to 22 weeks after completion of treatment in patients with chronic neck pain [51].

A profound cardioprotective effect of PBM on chronic infarcted myocardium has been demonstrated in animals. This phenomenon was partially due to significant elevation in the number of undamaged mitochondria and ATP content in the cardiomyocytes in the ischemic zone after PBM [52-55]. PBM treatment consisting of intravascular delivery of low-level laser irradiation has been reported [56].

It has been demonstrated that impaired mitochondrial oxidative metabolism is associated with neuronal dysfunction, neurological impairment, and neurodegeneration [57]. Therefore, interventions aimed at improving mitochondrial metabolism are hypothesized to benefit the function of both the diseased and normal brain [41].

In addition to its effects in increasing mitochondrial activity and activating transcription factors, PBM could benefit traumatic brain injury patients by inhibiting apoptosis, stimulating angiogenesis, and increasing neurogenesis [58-61].

Neuroprotective effects of PBM in brain ischemia have been demonstrated [62, 63]. Animal studies have shown promise for transcranial PBM for reduction of neurological damage in animal stroke models [64-66]. Transcranial PBM significantly improved outcome in human stroke

patients [67]. Studies indicated that transcranial PBM therapy had shown initial safety and effectiveness for the treatment of neurological diseases.

PBM has also been considered as a candidate for treating degenerative brain disorders such as familial amyotropic lateral sclerosis, Alzheimer's disease, and Parkinson's disease [68-72]. Evidence of early cerebral metabolic decline in subjects predisposed to senile development of Alzheimer's disease (especially, evidence of reduced CcO metabolism) has been reported, which may be employed in the use of PBM in these subjects [73, 74].

Transcranial PBM produces beneficial cognitive and emotional effects in humans, and may be effective in the treatment of cognitive and emotional disorders. Antidepressant effects of transcranial PBM therapy, with improvements in attention and memory, have been reported [75, 76].

Anders and colleagues [77] and Gigo-Benato and colleagues [78] reported that PBM promoted regeneration and functional recovery of injured peripheral nerve. PBM has been successfully used in the treatment of male androgenetic alopecia [79].

Ophthalmological applications of PBM

Mitochondrial dysfunction and oxidative damage are involved in the pathogenesis of different retinal disorders [80]. Reduced mitochondrial function, oxidative damage and inflammation are signs of ageing retina and characteristic for age-related macular degeneration (AMD) [81]. It has been demonstrated that PBM at 670 nm increased mitochondrial membrane potential and reduced complement activity in the aging retina [82-85]. Studies have shown that PBM can improve visual acuity, contrast sensitivity, and fixation stability, reduce drusen volume and thickness, and has beneficial effects on macular pigment density but no adverse side effects in patients with AMD [86-91].

The application of PBM for the treatment of diabetic retinopathy and diabetic macular edema has been reported. Cheng and colleagues [92] demonstrated that daily administration of PBM induced by 670 nm light for 8 months significantly inhibited the diabetes-induced increase in vascular permeability and capillary degeneration that is characteristic of diabetic retinopathy [92]. Others also have reported that PBM inhibited early changes in the retina in pigmented mice in diabetes-induced retinopathy [93]. PBM treatment showed promise for improving patients with diabetic macular edema, with a post-treatment reduction in retinal thickness [94, 95]. Kim and colleagues [96] conducted a randomized trial of PBM for center-involved diabetic macular edema (CI-DME) with good visual acuity. They concluded that 670-nm light-emitting PBM as given in that study, although safe and well-tolerated, was not found to be effective for the treatment of CI-DME in eyes with good vision.

PBM applications for hereditary retinal degenerations have been reported. There have been a few case reports on successful use of transconjunctival PBM for the treatment of retinitis pigmentosa [97]. Scalinci and colleagues [98] used a light emitting diode (LED) of 10 Hz and wavelength 650 nm for PBM treatment of 45 patients with Stargardt Disease, and demonstrated that best corrected visual acuity (BCVA), MP-1 microperimetry, and pattern electroretinography (PERG) amplitude significantly improved one year after treatment [98].

Some authors have pointed to neuroprotective potential of PBM in the treatment of mitochondrial optic neuropathies. Leber's hereditary optic neuropathy is accompanied by mitochondrial alterations and can result in retinal ganglion cell dysfunction and loss, leading to bilateral loss of vision [3, 99]. Rojas and colleagues [63] conducted a rat study and demonstrated that 650-nm LED for PBM treatment can prevent neurotoxic effects of rotenone, a natural mitochondrial complex I inhibitor. They concluded that PBM might be used in the treatment of neurodegenerative disorders associated with mitochondrial dysfunction [63].

PBM might also be effective for reducing phototoxic damage to the retina. Pre-treatment with 670 nm light (prior to damaging light exposure in the rat model of light-induced retinal degeneration) resulted in a reduced loss of photoreceptor cells, amelioration of the light-induced alterations in the expression of specific markers for stress, and reduction of microglial and macrophage invasion [37]. In addition, preconditioning with PBM was more effective than treatment with PBM during or after exposure to damaging white light for reducing the phototoxic effect of light [100]. Eells and colleagues [101] reported on therapeutic PBM for methanol-induced retinal toxicity, and showed that PBM treatment protected the retina from the histopathologic changes induced by methanol-derived formate. Linnik and colleagues [7] used a subthreshold argon laser in a rabbit model of toxic cataract and demonstrated the resistance of rabbits to cataractogenesis.

In studies by Ivandic and Ivandic [102] and Guzun and colleagues [103], PBM improved visual acuity in patients with amblyopia.

Beneficial effects of PBM for optic nerve damage have been demonstrated [41]. Schwartz and colleagues [7] showed effects of low-energy He-Ne laser irradiation on posttraumatic degeneration of adult rabbit optic nerve. It has been hypothesized that PBM improves the function of preserved nerve fibers rather than induces the restoration of neurons [105].

Conclusion

PBM is an effective and safe treatment for a wide range of disorders of human tissues and organs, including neurological and eye diseases. Although the mechanisms underlying the action spectrum of PBM (e.g., the action exerted on the retina) are still not completely understood, the actions of the FR/NIR light on mitochondrial metabolism have been scientifically grounded. Further research on developing (a) novel equipment for conducting PBM and (b) standard PBM treatment protocols is warranted.

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Corresponding Author: *O. S. Zadorozhnyy, e-mail: zadoroleg2@gmail.com*

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Abbreviations*. PBM, photobiomodulation; LLLT, low-level laser (or light) therapy; FR/NIR, far-red/near-infrared light; ATP, adenosine triphosphate; CcO, cytochrome C oxidase; NO, nitric oxide; AMD, age-related macular degeneration; CI-DME, center-involved diabetic macular edema; LED, light emitting diode; BCVA, best corrected visual acuity; PERG, pattern electroretinography.*