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Research Article

Development of Photobiomodulation and its Application in Retinal Diseases

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Abstract: Photobiomodulation (PBM) is a therapeutic approach that utilizes low-energy laser or light to regulate biological tissues. The mechanism is to promote cytochrome C oxidase (CCO) through low energy light, regulate the REDOX of mitochondria, and then regulate the biological functions of tissues and cells. Compared with traditional laser, it has a higher safety. There are a large number of mitochondria in retinal tissue, and studies have shown that PBM has a good protective and regulatory effect on the mitochondrial functions of retina and optic nerve. Therefore, PBM is clinically applied to treat age-related macular degeneration, diabetic retinopathy and retinitis pigmentosa and other retinal diseases. In order to provide a new direction for the treatment of retinal diseases, this paper reviewed the main parameters, mechanisms and the research progress of PBM in the fundus indications.

Key words: Photobiomodulation; Mechanism; Cytochrome C oxidase; Parameters; Retinal disease

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1 Introduction to PBM

1.1 Introduction to PBM

Photobiomodulation (PBM) refers to the irradiation of biological tissue with low intensity far red/near infrared (FR/NIR) light generated by laser, LED and other light sources, and the adjustment of biological tissue with endogenous chromophore. The corresponding therapy is low energy phototherapy. In 1968, Endem Mester[1] first discovered the effect of Low Lever Laser Therapy (LLLT) on accelerating hair growth and wound healing in tumor mice. In 2014, the North American Phototherapy Association changed the name of low-energy laser therapy to the bioregulation of light[2]. In addition, Eells et al[3] studied the direct relationship between the function of PBM on mitochondria and retinal protection, and proved for the first time that PBM has the potential to treat retinal diseases. Up to now, PBM has a history of 52 years. As a safe and new medical method, PBM has achieved beneficial effects in Alzheimer's disease, vestibular dysfunction, osteoarthritis and other medical fields, as well as reducing inflammation[4]. Recent studies have also shown the positive effect of PBM in improving fundus metabolism, providing a new choice for the clinical treatment of retinal diseases[5].

1.2 Dose-response relationship of PBM

The efficacy of PBM was closely related to light quantity parameters, and it was intensity - and dose-dependent. In recent years, bidirectional dose response has been used to explain this phenomenon, pointing out that when the amount of light is very low, there is often no therapeutic effect. As the amount of light increases, the positive effect will

gradually appear until it reaches a plateau state, and the therapeutic effect corresponding to this amount of time is the most obvious. With further increase in the amount of light, the corresponding therapeutic effect will gradually decrease until it has no effect, at which point the continuous increase in the amount of light will begin to cause damage to tissues[6]. Hamblin et al[7] also showed that low (0.001-10 J/cm2) flux enabled tissue to receive photostimulation while high (gt; 10 J/cm2) flux induced photoinhibition in tissues. Biological effects generated by different parameters vary greatly. Therefore, at present, clinical workers should standardize the application of parameters of PBM related to specific diseases, including further clarifying the optimal wavelength, light amount and other large-sample data, for better clinical application and promotion.

2 The mechanism of PBM

Some progress has been made in the mechanism of low-energy light mediated Photobiomodulation stimulation. At present, most studies take mitochondrial pathway as the main mechanism of PBM mediated action, which considers that Cytochrome C Oxidase (CCO) in mitochondria is the main receptor for low-energy light in the human body[8]. CCO is catalytic electronics from the enzyme cytochrome C transferred to molecular oxygen, to maintain the normal operation of the mitochondrial respiratory chain, is critical to ensure the energy metabolism in cells, when under low intensity light CCO, inspire electrons, and then from the primary electronic excited state occurs photochemical reaction, increase the mitochondrial membrane potential (MMP) and cyclic AMP, causing secondary interface body such as calcium ions and nitric oxide, the tertiary reaction for activation of transcription factors, and then adjust with cell proliferation and migration, inflammation, and resistance to apoptosis related gene expression[9]. Retina is a tissue with a large number of mitochondria and high metabolic activity. PBM treatment improves mitochondrial function, regulates oxidative stress and inhibits the inflammatory process, so low-energy light has a good protective function on retinal cells and retinal function[10,11]. In recent years, related studies have proved that PBM therapy acts on mitochondria-mediated signaling pathways to protect mitochondrial function, regulate oxidative stress and chronic inflammation, and prevent neuronal death. However, the deeper mechanism still needs to be explored and clarified.

3 Application of PBM in retinal diseases

3.1 Treatment of age-related macular degeneration by PBM

More and more evidence indicates that mitochondrial dysfunction, chronic inflammation, oxidative stress and genetic susceptibility play an important role in the pathogenesis of age-related macular degeneration (AMD)[12]. PBM can eliminate chronic inflammation of AMD and slow down the formation of new blood vessels under the retina.

Koev et al[13] used 633 Nmhe-Ne laser for the treatment of AMD patients at various stages, and found that after PBM treatment, the visual acuity of patients was improved, with the reduction of deformation and dark spots, and the edema and bleeding of wet AMD patients were alleviated.

A clinical trial conducted by Markowitz[14] evaluated the safety and efficacy of PBM in 30 patients with middle and advanced dry AMD. After two intervention studies a year, it was found that no adverse events occurred during the treatment process, visual improvement and reduction of the volume and thickness of hyrenoid warts, indicating the efficacy and safety of PBM.

3.2 Treatment of Diabetic Retinopathy by PBM

Diabetic retinopathy (DR) is one of the most common eye diseases causing blindness, which is affected by retinal inflammation, oxidative stress and other factors.

At present, the only treatment for vision protection is retinal laser photocoagulation, but it is often accompanied by retinal injury. The emergence of PBM can better improve this situation. Shen et al[15] developed a 670nm low-energy laser PBM for the phase IIa clinical trial of DME. Compared with before and after treatment, the CMT of DME patients treated with three intensity gradients of PBM was significantly reduced.

In addition, Tang et al[16] developed a portable and miniatured PBM device for DR patients, which

significantly reduced NCDME of non-central diabetic macular edema in diabetic patients after treatment, with good safety, economy and efficacy, providing evidence-based medicine for clinical use. PBM delays the occurrence and development of DR and reverses the elevation of retinal CMT in DME patients, showing a good application prospect for the prevention and treatment of diabetic retinopathy. However, relevant clinical evidence is insufficient, and large randomized clinical trials are still needed to verify its long-term efficacy. The above clinical studies have shown that PBM can effectively improve the visual function and pathological changes of animal models and patients with retinal diseases. It is safe, economical and easy to operate, which is convenient for clinical promotion and application.

In addition, PBM is expected to be developed into a non-invasive and portable physiotherapy method due to its regulation of inflammation and oxidative stress and non-damage to normal tissues.
However, the dose-response relationship and treatment parameters in the current studies are not unified, and clinical evidence is insufficient.

Therefore, it is urgent to develop the equipment that meets the clinical needs, carry out large-scale clinical and animal experiments, and clarify the mechanism of action of PBM in the treatment of retinal diseases and standardize the treatment plan.

4 Conclusion

Relevant animal and clinical experiments have verified the efficacy of PBM for AMD, DR, etc., indicating the possibility of PBM becoming an effective alternative therapy for the above-mentioned diseases. Because of its safety and economic advantages, its ability to be used as an adjuvant therapy for these diseases, and even as a preventive physiotherapy, PBM has shown great promise in the prevention and treatment of retinal diseases.

At present, there are still many challenges in this field. Large-scale clinical and animal experiments are needed to explore the efficacy and potential mechanism of PBM in the prevention and treatment of various ophthalmic diseases, clarify the dose-effect relationship, and develop new clinical PBM devices, so as to better promote the application of PBM in retinal diseases.

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