NEUROLOGY

Cite as: Archiv EuroMedica. 2024. 13; 1: e1. DOI <u>10.35630/2024/14/1.107</u>

Received 29 January 2024; Accepted 19 February 2024; Published 21 February 2024

TRANSCRANIAL PHOTOBIOMODULATION IN NEUROLOGICAL AND PSYCHIATRIC PRACTICE: FUNDAMENTAL AND CLINICAL ASPECTS



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ABSTRACT

Photobiomodulation is a relatively young medical technology that integrates the efforts of physicists, engineers and specialists in the field of biomedicine and includes various methods of light exposure to cells and tissues of the body. The main options for such effects are light radiation of the visible and IR spectrum generated by LED sources, and low-intensity laser radiation (LILI), which requires the use of lasers with special characteristics. In recent years, there has been an avalanche of interest among neurologists and psychiatrists in transcranial photobiomodulation, However, a systematization of empirical data and the fundamental foundations of technology is required.

On this basis, the **purpose** of the review is to integrate ideas about the molecular-cellular and systemic effects of transcranial photobiomodulation and the prospects for its application in neurological and psychiatric practice. We have shown that intensive research in the field of studying the biological effects of low-intensity laser radiation, red and infrared light, which made it possible to decipher the main ways of responding to it at the molecular, cellular and tissue levels, created prerequisites for the formation of a new synthetic scientific direction - photobiomics. This translational discipline is focused on the development of pathogenetically sound technologies for the treatment of diseases of various profiles, including neurological and mental pathology. The results of experimental and clinical studies presented in the literature indicate the effectiveness of photobiomodulation in depression and post-traumatic stress disorder, nevertheless, extensive trials and meta-analyses are advisable for their full inclusion in international clinical recommendations.

Keywords: photobiomodulation, red light, infrared radiation, photobiomics, depression, post-traumatic stress disorder

BACKGROUND

Photobiomodulation (PBM) is a relatively young medical technology that integrates the efforts of physicists, engineers and specialists in the field of biomedicine and includes various methods of light exposure to cells and tissues of the body [4, 9, 12-15, 21-24, 37]. The main options for such effects are the light radiation of the visible and IR spectrum generated by LED sources [8, 18, 29, 36], and low-intensity laser radiation (LILI), which requires the use of lasers with special characteristics [3-5, 18, 29]. In this regard, previously, researchers considered only the effects of LILI. To this day, some publications identify it with PBM, despite the fundamentally large breadth of this concept. Among the light sources, the most commonly used for photobiomodulation are those that produce light with a wavelength corresponding to the red and near infrared regions (600-1100 nm) [1, 6, 11, 13, 15, 26].

Currently, there are various applications of photobiomodulation. In particular, for neurology and psychiatry tasks involving effects on the brain, intraoral, intranasal, intracranial and transcranial processing of brain tissue is distinguished [9, 15, 43]. At the same time, the potential range of applications of intracranial photobiomodulation is extremely limited, since it involves mandatory penetration into the skull, and intranal and intraoral effects allow only a small and narrowly focused area of the brain to be processed. On this basis, transcranial photobiomodulation is the most optimal and universal option. Transcranial photobiomodulation is a form of light therapy using monochromatic light in the visible and infrared ranges from non-ionizing radiation sources (lasers, LEDs), which are placed on the scalp, on the forehead or intranasally in such a way as to project a luminous flux directly onto the target areas of the brain [1, 6, 39, 47]. In recent years, there has been an avalanche-like increase in the interest of neurologists and psychiatrists in transcranial photobiomodulation, however, a systematization of empirical data and the fundamental foundations of technology is required.

Therefore, **the purpose** of our review is to integrate ideas about the molecular-cellular and systemic effects of transcranial photobiomodulation and the prospects for its application in neurological and psychiatric practice.

MOLECULAR AND CELLULAR MECHANISMS OF ACTION OF RED AND INFRARED RADIATION ON BIOSYSTEMS

It is known that the nature of the biological effects of light radiation is determined by its parameters, primarily wavelength, power and energy, and monochromaticity, coherence and collimation are also important for laser radiation [5, 42]. Most ranges of visible light (in particular, those recognized by human vision as blue and green) realize their effect through modification of the state of ion channels.

On the contrary, the light sources used in PBM have other "application points". Thus, the light of the red spectrum, which corresponds to wavelengths of 600-810 nm, has a predominant effect on the functioning of mitochondria [13, 22, 26, 36], whereas infrared radiation with a wavelength of 800-1100 nm changes the permeability of the calcium channels of cell membranes [13, 14, 28, 31, 34, 40]. According to M. Bathini et al. (2022), such modes of exposure to biological objects have a positive effect on cell survival by regulating apoptosis, anti-apoptotic and anti-inflammatory effects, relieving oxidative stress and restoring mitochondrial functioning [8]. In this case, it is assumed that a number of kinase intracellular cascades are involved, including ERK-, MAPK- and Akt-dependent pathways, as well as stimulation of neurotrophic factors and secretases [8, 26, 46]. Additionally, it is assumed that secondary cellular messengers (primarily cyclic AMP) are involved in the implementation of the effects of PBM [26].

In addition, the review by E. Colombo et al. (2021), based on the analysis of more than 50 experimental and clinical studies, provides information on the ability of PBM to eliminate endothelial dysfunction, and this effect depends on the characteristics of the applied light radiation [13]. For example, when treating the body with radiation with a wavelength of 800 nm and a power of 18 J, a decrease in the risk of restenosis was recorded, and in the case of using a wavelength of 645 nm with a power of 20 J, an increase in angiogenesis was recorded.

At the same time, mitochondria are the central cellular acceptor of radiation generated during photobiomodulation. L.F. de Freitas et al. (2016) indicate two relatively independent mechanisms of response of these organelles to the action of light radiation, mainly related to red and infrared light [13]. Red–band light is perceived by the fourth component of the mitochondrial electron transport chain, namely, cytochrome oxidase C [45]. When its activity is modulated, NO is released, provoking numerous molecular and cellular effects, including activation of the chain itself, changes in the membrane potential of mitochondria and an increase in the concentration of ATP in them. The effect of infrared radiation is realized in the opening of calcium channels and the launch of Ca2+-induced signaling using cAMP and stimulation of a number of transcription factors, simultaneously providing a steady increase in the concentration of reactive oxygen species [26, 40, 46]. This suggests that the perception of reactive oxygen species when exposed to physico-chemical agents [32]. In addition, there is evidence of light-induced modification of the activity of matrix metalloproteinases, which allows the factor to participate in the restoration of the extracellular matrix [7].

It should be emphasized that the above molecular cellular effects, including the release of NO, elimination of endothelial dysfunction, increased ATP concentration and calcium signaling, contribute to the stimulation of blood flow in the treated tissues.

THE SCOPE OF PHOTOBIOMODULATION

In recent decades, numerous reports have appeared on the experimental and clinical evaluation of the effectiveness of photobiomodulation, including descriptive and systematic reviews and the results of randomized placebo–controlled clinical trials [4, 38]. At the same time, the scope of the considered method

is extremely wide and includes neurological [1-3, 8, 17, 31, 39], traumatological and orthopedic [5, 48], ophthalmological pathology [20], a number of psychiatric diseases [6, 9, 11, 21, 29, 33] and others. In addition, there is information in the literature about the positive experience of using PBM technology in dentistry [37], regenerative medicine (in particular, for the treatment of wounds of various origins [7], the treatment of alopecia [24] and stimulation of osteogenesis [18]) and post-traumatic conditions [10, 23, 30, 34-36], sports medicine [4, 19, 28] and even the treatment of some forms of cancer [25]. Such an extensive range of clinical applications of the technology is due to the diverse effects of photobiomodulation, however, for a full understanding of the pathogenetic mechanisms of its action and targeted inclusion of the method in clinical recommendations, further disclosure of both fundamental aspects of the problem and large-scale clinical testing of the technology in various categories of patients is necessary.

POSSIBILITIES OF PHOTOBIOMODULATION IN NEUROLOGICAL AND PSYCHIATRIC PRACTICE

It should be noted that physical methods of treatment have been used for many decades in the practice of neurologists and psychiatrists with varying degrees of success. Thus, B. Guo et al. (2023) indicate that, for example, magnetic, electrical, electroconvulsive, vagal brain stimulation, as well as photobiomodulation are used in depressive disorders [21]. Currently (for 2023), the PubMed database contains 78 articles on the use of PBM in depression (since 2015), and 50 of them are devoted to the transcranial version of the technology. The researchers assume that the antidepressant effect of the method is due to the positive effect on the functioning of mitochondria and normalization of cerebral blood flow [6, 10, 13, 45]. In addition, data are provided on the possibility of stimulating synapto- and neurogenesis under the influence of red and infrared radiation [12]. Based on experimental modeling of depressive disorder in laboratory animals, it was shown that the use of PBM contributes to the optimization of oxidative metabolism (reduction of lipoperoxidation intensity, increase in total antioxidant activity, glutathione concentration and catalytic properties of superoxide dismutase) in the hippocampus and prefrontal cortex, reduces the level of neuroinflammation markers (NF-kB, p38, JNK, etc.) in the structures of the central nervous system, affects the parameters of apoptosis of neurons (reduction of Bax, Bcl-2, caspase 3 and 9), it also reduces the severity of stress reaction inducers (concentrations of cortisol, corticosterone, aTNF, IL-6) [40]. In addition, H. Zhao et al. (2023) provide data on a decrease in c-Fos in the infralimbic cortex [47], and D. Zhang et al. (2021) indicate stimulation of glutamatergic effects under the action of red and infrared light, mediated by GLT-1, as well as an increase in the preservation of astrocytes both in the cerebral cortex in the brain, as well as in the hippocampus [46].

The above molecular and cellular mechanisms of action of PBM determine its clinical effects. Thus, even in healthy volunteers in a placebo-controlled study, when exposed to red light, improved memory and attention, as well as response time to stimuli and optimization of delta waves on the EEG were shown [27, 28, 38]. At the same time, L. Yang et al. (2020) directly point to mitochondria as the main target for neuroprotection in clinical settings [45].

Numerous clinical studies have shown a reduction in symptoms of depression and anxiety under the influence of PBM, and these patterns have been established as primary (major depressive disorder) [6, 9, 11, 21, 33], as well as secondary (arising from somatic pathology, for example, in the framework of inflammatory bowel diseases) disorders [22, 29]. Similar information about the positive effects of red and infrared radiation is available in relation to neurodegenerative diseases (Alzheimer's disease [3, 8, 17, 31], Parkinson's disease [3, 8], etc.). A separate area of application of the technology is post-stroke rehabilitation, which promotes accelerated recovery of speech functions and verbal skills [2]. A number of publications are devoted to the effectiveness of using the method in the treatment of patients with traumatic brain injury [10, 23, 30, 34-36, 38]. The authors note a decrease in the severity of headache, sleep disorders, accelerated normalization of cognitive functions, elimination of symptoms of depression, anxiety and irritability. Similar data were obtained by W. Stephan et al. (2017) for patients with post-traumatic stress disorder [42], which was confirmed by later experimental studies by H. Zhao et al. (2023) [47]. An unusual clinical effect, considered by A. Valverde et al. (2023), is the positive effect of PBM on sleep parameters in various categories of patients [44].

In addition to the direct assessment of the clinical effectiveness of transcranial photobiomodulation, an aspect of the hardware of the technology should be highlighted. Currently, most of the technology implementation complexes are manufactured abroad and are focused on generating either red or infrared light, which requires optimization and unification of equipment and full-fledged import substitution. Company Eltorg has developed and registered in Russia and Kazakhstan transcranial phototherapy devices "Elmedlife H", which are actively used in clinical practice, including emitting modules of both red and infrared light (https://elmed.life/).

CONCLUSION

Intensive research in the field of studying the biological effects of low-intensity laser radiation, red and infrared light, which made it possible to decipher the main ways of responding to it at the molecular, cellular

and tissue levels, created the prerequisites for the formation of a new synthetic scientific direction - photobiomics. This translational discipline is focused on the development of pathogenetically sound technologies for the treatment of diseases of various profiles, including neurological and mental pathology. The results of experimental and clinical studies presented in the literature indicate the effectiveness of photobiomodulation in depression and post-traumatic stress disorder, however, extensive trials and meta-analyses are advisable for their full inclusion in international clinical recommendations.

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<u>back</u>