The Effect of Photobiostimulation by Light Waves in the Blue Range of the Spectrum on Microcirculation Parameters and the Activity of Oxidative Homeostasis Enzymes in the Skin

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Abstract. The study employs laser doppler flowmetry and laser fluorescence spectroscopy to reveal the changes in microcirculation and activity of coenzymes of oxidative metabolism in the finger skin under the influence of photobiostimulation by monochrome incoherent low-intensity electromagnetic radiation with a wavelength of 470 nm. Photobiostimulation with light waves in the blue range has contributed to an increase in hemomicrocirculation during and 15 min after the termination of exposure, while the indicator lymph outflow, on the contrary, decreased during the irradiation period and recovered after its termination. The dynamics of changes within the parameters of blood microcirculation, the lymph flow in microvessels and the indicators of oxidative metabolism showed that the skin microcirculation system is an important acceptor of the photobiostimulating effect of light in the blue range of the spectrum. Photobiostimulation triggers the mechanism of activation of hemomicrocirculation by reducing myogenic vasomotion, thereby increasing the conductivity of cardiogenic biorhythm in the vessels of the microcirculatory bed. With an increase in the level of hemomicrocirculation, photobiostimulation is directly associated with the activation of tissue oxidative metabolism.

Keywords: laser doppler flowmetry; lymph outflow; blood microcirculation; myogenic vasomotion; oxidative metabolism; photobiostimulation with light waves in the blue range of the spectrum.

Paper #3531 received 15 Sept 2022; revised manuscript received 15 Dec 2022; accepted for publication 15 Dec 2022; published online 30 Mar 2023. doi: 10.18287/JBPE23.09.010309.

1 Introduction

One of the priority work areas of the Biomedical Optics technical group of the International Optical Association (OPTICA) is to study the mechanisms by which non-ionizing optical radiation in the visible and near infrared spectral range is absorbed by endogenous chromophores, causing photophysical and photochemical phenomena at various biological scales [1]. Making the basis of light therapy, photobiostimulation (PBS) involves the use of various light sources, including LEDs and broadband light in the visible and infrared spectrum resulting in physiological changes and therapeutic effects.

Human body has photoreceptors tuned to different light frequencies and associated with various cellular reactions. Human skin is the main target of various light waves. Visible radiation of light waves (400–750 nm) penetrates the dermis deeply enough, with a multiple

decrease in intensity every ~1 mm [2]. Part of the blue visible radiation spectrum is reflected from blood vessels and red blood cells moving in them back through the skin, so that the total radiation flux near the skin surface is greater than the incident light [2], which allows it to affect a much larger number of cells compared to the UV range of visible radiation.

For this reason, in recent years, light emission of blue diapason is actively used in dermatology. In particular, a number of studies [3] have shown that blue light has a positive effect on fibroblasts and can be used to treat keloids and fibrosis.

An experimental study focused on burn modeling [4] reports that under the influence of the blue light emitted by the light-emitting-diodes, laboratory rats consumed more food than the rats from the control group, the angiogenesis index increased after 7 days of treatment and the skin of irradiated animals began to reactivate [4].

Research that was performed on melanocyte cell cultures [5] showed that exposure to blue light significantly improved viability, proliferation and migration of melanocytes. Blue light also proved to be able to activate opsins that play an important role in healing skin wounds and restoring human epidermal barrier function [6].

For blue light (400–470 nm), the penetration depth into the tissues is 2 mm, however, taking into account the radiation scattered in the tissues, its penetration depth can reach as far as 2.5 cm. Moreover, since blue light can propagate in an aqueous medium without absorption, it is maximally absorbed by lymph, bile, tendons, and adipose tissue [7, 8].

Nowadays a number of chemical structures are considered to be acceptors of light emission in the blue portion of the spectrum, among which a large group of flavins (such as NAD-H dehydrogenases, succinate dehydrogenases, acyl-CoA dehydrogenases, D-amino acid oxidases, glucose oxidases and the cytochrome system) is considered the final photon acceptor for flavin dehydrogenases. The compounds having porphyrin structures (bilirubin, haemoglobin, protoporphyrin, and porphyrin) are good at absorbing the blue light. Light emission with the wavelength of 420–475 nm is absorbed by a large group of carotenoids (carotene, neurosporine, and carotenoids of cardiac homogenates) that are considered antioxidants [9].

For the in-depth study of PBS, the task is to identify the physiological effects of phototherapy and the mechanisms of involving the microcirculation system, which is directly concerned with ensuring the oxidative metabolism in tissues.

Laser doppler flowmetry (LDF) is widely used among various other methods of both direct and indirect recording microcirculation, including the lymphatic link [10]. The signal recorded during LDF characterizes the blood flow in the microvessels with the tissue volume of about 1 mm^3 [10], while in the lymphatic capillaries and microvessels, the LFD signal characterizes the mobility of lymph and lymphocytes [11].

It is well-known that the metabolic processes in the skin and other tissues are energy-dependent, which makes it possible to use the method of laser fluorescence spectroscopy (LFS) to assess oxidative metabolism. For this purpose, we propose to identify the fluorescence amplitude of the coenzymes nicotinamide adenine dinucleotide (NADH) and the flavinadenine dinucleotide (FAD) [12–14].

The aim of this study is to identify the changes in microcirculation and the activity of coenzymes of oxidative metabolism in the skin of fingers under the influence of photobiostimulation by monochrome incoherent low-intensity electromagnetic radiation with a wavelength of 470 nm.

2 Methods and Materials

The experimental study involved 40 men aged 19 to 28 (the average age is 20.5), conditionally healthy students of the *Medical Institute* of the *Peoples' Friendship University of Russia*, who voluntarily agreed to participate in the study and provided their Informed Consent. Their participation was also approved by the University's Ethics Committee.

The participants underwent transdermal photobiostimulation with electromagnetic radiation of the light range with the wavelength of $\lambda = 470$ nm (the blue spectrum) for 8 min using an autonomous light-emitting bracelet BASI (SPE "Poisk" Ltd, Russia) worn on the wrist region with the radiating matrix on the inner surface of the wrist in contact with skin. the illumination of light-emitting diode was 2000 lx, the power of the emitted blue light by the emitting matrix was 40 mW, the density of radiation on the skin was 4–5 mW/cm^2 (the skin area irradiated with laser diodes was 8 cm^2), the energy of the emitted light during 8 min was 20 J. When considering the time of transdermal (transcutaneous) exposure to blue light, we proceeded from the generally accepted recommendations and conditionally divided the area of influence of the light-emitting-diode matrix into four zones with the tentative exposure time for one zone being 2–5 min [15].

Synchronous registration of blood microcirculation and lymphocirculation indicators was performed using a multi-channel LDF probe, while the activities of redox coenzymes NADH and FAD were recorded by LFS using the Lazma ST device (SPE "LAZMA" Ltd, Russia).

The instrument probe was fixed on the palmar surface of the distal phalanx of the third finger of the left hand to register all the parameters when LDF and LPS were recorded. This was done in the following sequence: 1) before photobiostimulation for 4 min;

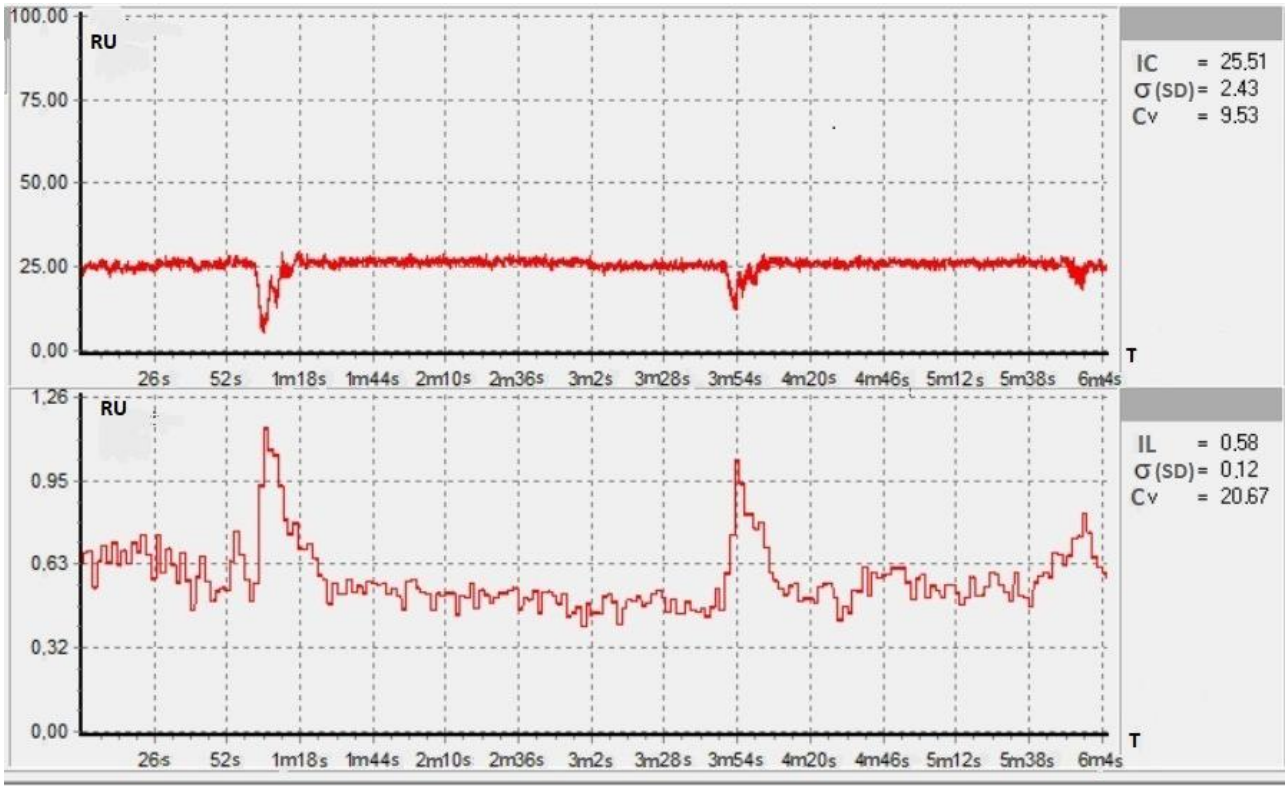
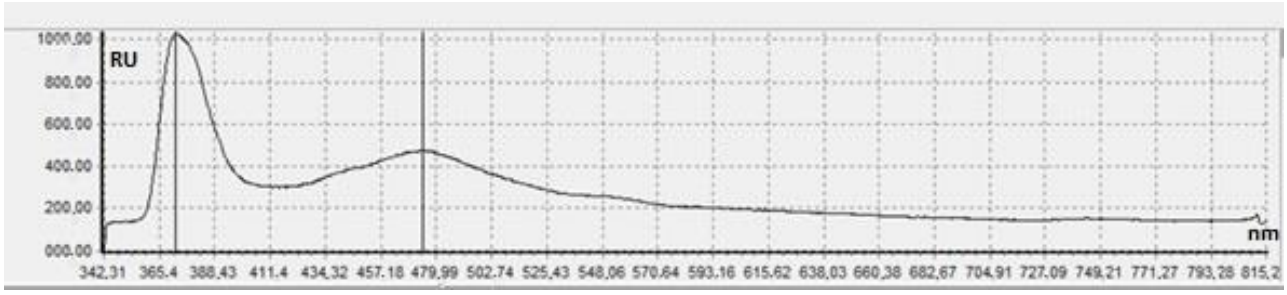
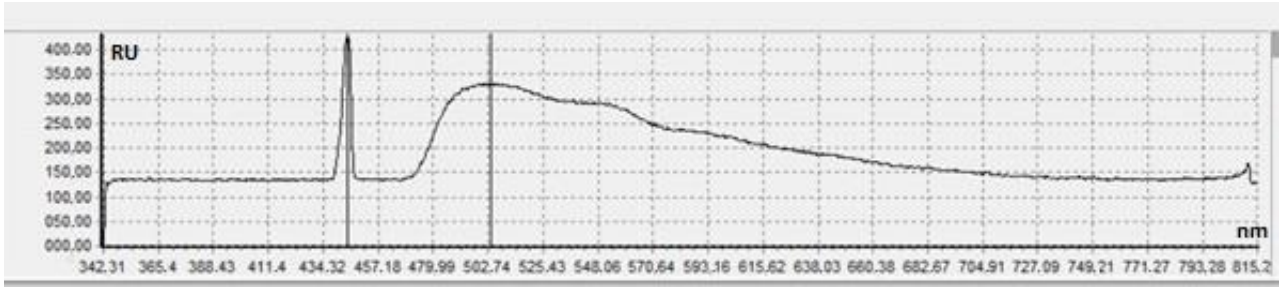


Fig. 1 An example of simultaneously detected diagnostic parameters: synchronous recording of the hemomicrocirculation and lymph flow; the changes are visible during involuntary breath retention (OX axis – recording time, (T); OY axis – relative units, (RU).



(a)



(b)

Fig. 2 An example of simultaneously detected diagnostic parameters: registration using LFS: (a) NADH, (b) FAD (OX axis – wavelength, nm; OY axis – in relative units, RU).

2) during photobiostimulation for 8 min; 3) 15 min after stopping photobiostimulation for 4 min. LDF and LFS were recorded when the test subjects were in the sitting position.

The indicator of blood microcirculation (IC) was determined by the LDF method (in the previous works on LDF, it was designated as PM). It is believed [16], that IC is determined by two factors: the concentration of red

blood cells in the probed tissue volume and their mobility (an averaged erythrocyte rate). IL is proportional to the product of the number of scatterers in the lymph flow by the average speed of their movement [11].

The LDF-gram analysis was used to assess the IC and IL indicators; the level of the flow fluctuation was evaluated by means of SD (standard deviation) or fluxes recorded in relative (perfusion) units (RU); whereas their coefficient of variation (Cv) was evaluated in % (Fig. 1).

The frequency-amplitude analysis of LDF-grams [10, 16–18] defined the contribution of the vasomotion-induced physiologically most significant blood flow fluctuations within the range of 0.1 Hz and its immediate vicinity (0.07–0.15 Hz). The vasomotor biogenic rhythm is secondarily influenced by modulations of neurogenic, respiratory and cardiogenic nature that were determined by their amplitude in the corresponding frequency ranges (A_{NF} neurogenic, A_{MF} myogenic, A_{HF} respiratory, and A_{CF} cardiogenic). The contribution of various biorhythms to the modulation of tissue blood flow was estimated by their power R_i as a percentage of the total power of the spectrum of M fluxmotions:

$$R_i = A_i^2 / M \times 100\%, \quad (1)$$

where $M = A_{NF}^2 + A_{MF}^2 + A_{HF}^2 + A_{CF}^2$.

To assess the oxidative metabolism, the amplitudes of fluorescence of NADH and FAD coenzymes (relative units, RU) were determined by the LFS method, while their ratio was determined by the redox ratio (NADH/FAD) [12, 13, 19] (Fig. 2). The fluorescence of the NADH and FAD coenzymes was excited using a Nichia NVSU233B D4 LED with a wavelength of 365 nm (NADH fluorescence wavelength is in the range of 460–470 nm) and an OSRAM PLT5 450B laser diode with a wavelength of 450 nm (FAD fluorescence maximum is in the range of 510–520 nm) [13]. The relationship between the state of microcirculation and oxidative metabolism in tissue was quantified by the indicator of oxidative metabolism (IOM) equal to IC/NADH+FAD [12].

The obtained data were processed using the methods of variation statistics, the reliability of differences was determined using the Student's criterion; the results were considered reliable at $p < 0.05$.

3 Results and Discussion

The calculated parameters of IC and IL, Cv and SD give an overall assessment of the state of hemomicrocirculation and lymph flow (Table 1). The results of the study indicate that during the time of exposure to light radiation, PBS increases the hemomicrocirculation indicators by an average of 26% compared to the baseline level. 15 min after the cessation of light exposure, the hemomicrocirculation indicators still exceed the baseline level by 22%.

IC (the indicator of hemomicrocirculation) has a complex nature, because it depends on the mobility of red blood cells, their concentration in microvessels and, to a certain extent, on the geometry of blood flow in tissues. Biomicroscopic studies of capillaries and other microvessels in human skin show that the bulk of erythrocytes is concentrated in postcapillary venules [10]. Because of this, approximately 50% of the value of the recorded LDF signal is due to the mobility of erythrocytes in the postcapillary segment of the microcirculatory bed. With ABS, the increase in IC is more likely to be due to increased level of the tissue blood flow. This is what light therapy using the blue range of the spectrum is designed for [7]. At the same time, it is possible that with the acceleration of the transition of erythrocytes from capillaries to microvessels of the postcapillary link, their local hematocrit increases.

The IC is subject to significant temporal and topological variations, which is clearly seen by the dynamics of the flux and SD. The results of the study of hemomicrocirculation show that during PBS these indicators decrease, and in the aftereffect period they are restored to their original values. The data obtained may indicate a decrease in the level of modulation of tissue blood flow during irradiation.

A very weak signal has been recorded from the lymphatic segment of the microcirculatory system, which is due to the low population of lymphatic capillaries and postcapillaries with stetho-reflective elements among which the lymphocytes are the most significant. Synchronous recording of IC and IL clearly shows that blood flow and lymph outflow at the level of the microcirculation system are closely functionally interconnected and are in antiphase.

Table 1 Indicators of hemomicrocirculation.

Parameters	Original value	Photobiostimulation	
		During	After
IC, RU	23.4 ± 2.94	29.4 ± 1.46*	28.1 ± 1.62*
SD, RU	4.01 ± 0.69	2.94 ± 0.40*	3.77 ± 0.62
Cv, %	17 ± 2.3	10 ± 1.4*	13 ± 2.8

* the differences are significant in comparison with the control data at $p < 0.01$.

Table 2 Lymph outflow indicators.

Parameters	Original value	Photobiostimulation	
		During	After
IL, RU	0.7 ± 0.12	0.5 ± 0.05	0.6 ± 0.09
SD, RU	0.14 ± 0.02	0.14 ± 0.01	0.16 ± 0.02*
Cv, %	20 ± 3.3	28 ± 3.8*	27 ± 5.3*

* the differences are significant in comparison with the control data at $p < 0.01$.

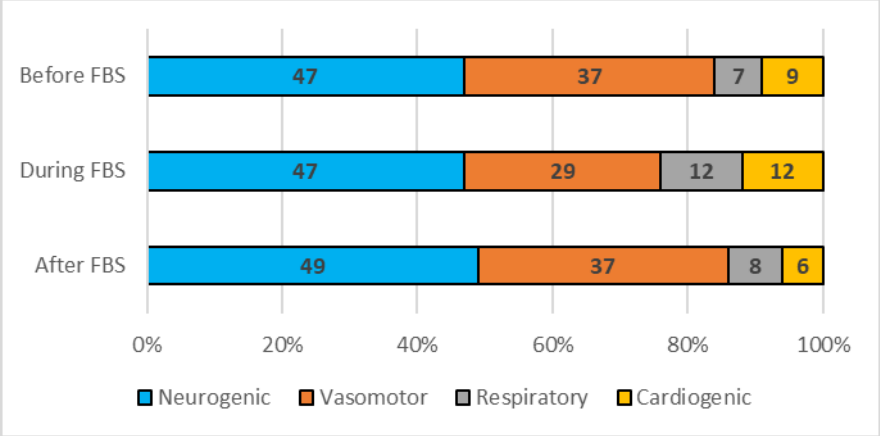


Fig. 3 The ratio of the main rhythmic components of fluxmotions in the LDF-gram by their contribution (in %) to the power of the spectrum and their changes due to PBS.

In PBS, the lymph outflow index, on the contrary, decreased by 19% compared to the baseline level, and although after the PBS it showed some increase, the IL was below the baseline level by 13% (Table 2). It should be noted that the variation of the IL was significantly different from the flux in the blood microvessels. It turned out that as the IL decreases with PBS, the temporal variability of the lymph flow increases markedly. This may be due to the activation of contractility of smooth myocytes in the initial links of lymphatic vessels that starts immediately after lymphatic postcapillaries.

The frequency-amplitude analysis of the LDF-gram is applicable to the assessment of the myogenic mechanism of modulation of tissue blood flow, because it most dynamically reflects the changes in hemomicrocirculation due PBS (Fig. 3). Among the local (within the area of optical sensing) microvascular biorhythms, the dominant rhythm is the myogenic one that accounts for 37% of the total power of the oscillation spectrum of tissue blood flow at the initial (before irradiation) level. Myogenic biorhythm lies in the frequency range of 0.1 Hz and its immediate vicinity. However, it is subject to secondary neurogenic influences that originate outside the microcirculation system but nevertheless have modulating effects on hemomicrocirculation.

During PBS, the activity of the myogenic mechanism somewhat decreases (up to 29% of the total power of the spectrum), which results in the increased conductivity of cardiogenic modulations through the capillary link of the microcirculatory bed. This is due to both an increase in the mobility of red blood cells and an increase in hematocrit in the postcapillary link of the microcirculatory bed. After the PBS is over (in 15 min), the myogenic vasomotion returns to the initial level. As the activity of the myogenic mechanism decreases, the efficiency of fluxmotion decreases by 27% (see Table 1).

Another important consequence of PBS is decreased vascular tone (VT) in the vessels of the microcirculatory bed. Vascular tone can be characterized by means of normalization of the recorded level of fluxmotion by the amplitude of myogenic biorhythm: $VT = COE/A_{MF}$ [10]. In some works [10], normalization according to the microcirculation index (IC) is applied. IC, as noted above, by its nature may have an ambiguous interpretation, since its increase may indicate both an increase in microcirculation due to increased mobility of red blood cells, and its deterioration in cases of increased hematocrit in the vessels of the postcapillary link. Therefore, normalization of the frequency-amplitude parameters of the LDF-gram by IC inevitably leads to an ambiguous interpretation of the LDF results. Our study has revealed that PBS leads to a decreased vascular tone in microvessels within 7% (from 2.9 to 2.7 conl. units), which basically has a decrease in the activity of myogenic vasomotion.

Table 3 Indicators of oxidative metabolism during photobiostimulation.

Indicators	Original value	Photobiostimulation	
		During	After
Amplitude NADH, RU	0.51 ± 0.01	0.48 ± 0.01	0.48 ± 0.01
Amplitude FAD, RU	0.78 ± 0.01	0.74 ± 0.01*	0.73 ± 0.01*
Redox ratio NADH/ FAD, RU	0.6 ± 0.01	0.65 ± 0.01	0.66 ± 0.01
Indicator of oxidative metabolism IC /(NADH+FAD), RU	8.35 ± 0.02	14.02 ± 0.03*	13.01 ± 0.04*

* the differences are significant in comparison with the control data at $p < 0.01$.

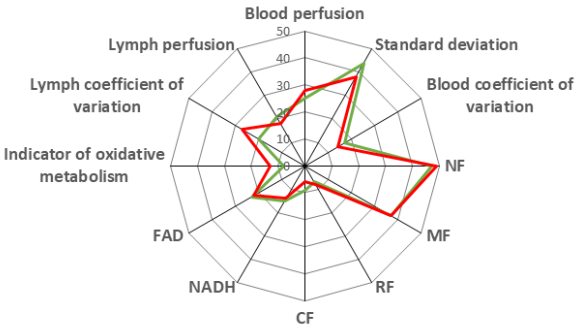


Fig. 4 Synchronous changes in skin microcirculation and oxidative metabolism during photobiostimulation, RU. (Cardiogenic Fluctuations (CF); Respiratory Fluctuations (RF); Myogenic Fluctuations (MF); Neurogenic Fluctuations (NF)).

The structure of temporary fluctuations of lymph flow in microvessels during PBS demonstrates an increased amplitude of myogenic oscillations compared to the baseline level. It is also noted here that the reaction of lymphatic microvessels to PBS is in antiphase with the reaction of blood vessels of the microcirculatory bed. The contour of the functional interaction of blood and lymphatic microvessels in the microcirculation system remains largely unclear. The data on the lymph flow rate relate mainly to the relatively large lymphatic vessels and are principally determined by the reduction of lymphangions. Spontaneous active contractions of lymphangions usually occur with a frequency of 2–3 to 10–18 vibrations/min. In humans, with local anesthesia, the lymphatic vessels of the foot contracted with a frequency of 4–5 in 1 min [20, 21]. The pressure drops that occur during the reduction of lymphangions have a sucking effect on the lymph flow in the lymphatic postcapillaries and capillaries.This means that the mechanisms activating the lymph flow lie outside the microcirculation system and, unfortunately, the possibility of their direct analysis by the LDF method must be considered limited.

Thus, photobiostimulation with light in the blue range of the spectrum activates the processes of microcirculation in its circulatory link. The indicators of lymph flow decrease, which may indicate a redistribution of interstitial fluid in the tissue microdistrict and activation of venous tissue drainage. Our data correspond with the data of other authors [22] examining the skin of mice after being irradiated with a low dose of blue light (< 300 mJ/cm^2), which indicates that irradiation with blue light triggers the synthesis of hydrogen peroxide in T-lymphocytes and enhances their mobility in the skin. These data give reason to believe that T-lymphocytes have photosensitivity in this range of the spectrum. The data we obtained on PBS are also confirmed by the data of a clinical study in which patients with peripheral nerve damage and the presence of neuropathic pain syndrome were exposed to monochrome incoherent low-intensity light radiation of the blue spectrum (470 nm) [23]. Their study showed a pronounced analgesic and decongestant effect as a result of the exposure, which may indicate a change in microcirculation and lymphatic drainage of tissues. Our observations are also consistent with the results of the study [24], which showed that when exposed to incoherent light radiation of red (633 nm, 70 mW/cm^2) and near infrared (830 nm, 55 mW/cm^2) range on the wrist skin for 5 min, arterioles dilated, leading to increased tissue perfusion in healthy people.

The components of the energy metabolism of the cell, which include glycolysis and oxidative phosphorylation, are associated with the processes of cellular respiration and ATP synthesis. The NADH and FAD cofactors act as electron donors and acceptors in ATP formation reactions that are present in the cell in oxidized (NAD^+, FAD) or reduced forms (NADH, $FADH_2$) [25]. Summary data on the dynamics of fluorescence of the NAD and FAD coenzymes, determined by means of LFS, are presented in Table 3.

The obtained results have shown that photobiostimulation causes a decrease in the amplitude of fluorescence of the oxidative NADH and FAD coenzymes, while the amplitude of FAD is significantly reduced to a greater extent. The change in the amplitude of fluorescence of the NADH coenzyme, and hence its concentration, is due to a change in oxidative metabolism in tissues. Our data have shown that an increase in the level of microcirculation triggers a mechanism for increasing the level of oxidative metabolism in tissues (Fig. 4).

Since all indicators are presented in units, for their comparability, a proportionality multiplier is introduced when constructing a diagram for extremely low indicators: ×10 for SD, ×30 for IL, NADH, and FAD.

As reported by Luo et al. [19], decreased amplitude of NADH fluorescence activates the oxidative

metabolism. If NADH is localized mainly in the mitochondria and participates mainly in the energy metabolism of the cell, then FAD is contained both in the cytoplasm and in the mitochondria and is involved in addition to oxidative phosphorylation in various biochemical processes such as glutathione utilization, lipogenesis, lipid peroxidation, synthesis of acetyl coenzyme A, the pentose phosphate cycle, etc., which significantly complicates data analysis [25]. The ratio of the oxidized electron carriers to the reduced ones is characterized by a redox ratio [26]. In our study, the redox ratio in PBS practically does not change, which may indicate the preservation of the processes of glycolysis and oxidative phosphorylation.

4 Conclusion

Synchronous recording of the dynamics of blood microcirculation, lymph flow in microvessels and indicators of oxidative metabolism showed that the microcirculation system in the skin is an important acceptor of the photobiostimulating effect of light in the blue range of the spectrum.

Photobiostimulation triggers the mechanism of activation of microcirculation by reducing myogenic vasomotion, thereby increasing the conductivity of cardiogenic biorhythm in the vessels of the microcirculatory bed and accelerating the movement of red blood cells from capillaries to the postcapillary link. The activation of tissue oxidative metabolism and the subsequent redistribution of interstitial fluid flows in the interstitial space are directly associated with an increase in the level of microcirculation during photobiostimulation.

Disclosures

The authors have no relevant financial interests in this article or potential conflicts of interest to disclose.

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