Role of Nitric Oxide in the Visible Light-Induced Rapid Increase of Human Skin Microcirculation at the Local and Systemic Levels: II. Healthy Volunteers

Kira A. Samoilova, Ph.D., Natalia A. Zhevago, M.D., Ph.D., Nicolai N. Petrishchev, M.D., Ph.D., and Alexander A. Zimin, M.D.

Abstract

Objective: The aim of this study is to evaluate the skin microcirculation increase seen in healthy volunteers after a single exposure to polychromatic visible (pVIS) light, and to prove the role of nitric oxide (NO) in the development of this effect.

Background Data: Improvement of microcirculation is one of the most important effects of laser and pVIS light therapy; however, its mechanism of action remains unknown. A main role in the regulation of vascular tone is known to be played by NO. It is produced by NO-synthase (NOS) located in membranes of many cells, including endothelial and blood cells. NOS, a bioprotein, absorbs pVIS light, resulting in its activation.

Materials and Methods: The central area of the dorsal side of the right hand (24 cm²) of 42 volunteers was irradiated for 5 min with pVIS light from a Q-light (385–750 nm, 95% polarization, 40 mW/cm², 12 J/cm²). Then for 90 min, the blood flow rate (Qas) was measured eight times, both in the area of the irradiation (local effect) and in the non-irradiated left hand (systemic effect) by using a high-frequency ultrasound Doppler device, recording Qas in human skin to a depth up to 5 mm. In the central area of the right hand of 14 volunteers an NOS inhibitor, N-monomethyl-L-arginine (L-NMMA, 0.1% solution), was iontophoretically administered prior to exposure, whereas in 10 other subjects it was administered to the left hand with subsequent exposure of the right hand.

Results: As soon as 2 min after exposure, Qas in the irradiated area rose on average by 32%, and in 20 min by 45%; it then decreased and in 90 min returned to the initial level. A statistically significant Qas increase in the non-irradiated hand was recorded in 5 min (+9%), and in 20 min it reached a maximum level (+39%), and 90 min later it decreased to the initial values. The presence of L-NMMA in the light-exposed area completely blocked the photoinduced rise of microcirculation, both in the irradiated and in non-irradiated hand; however, its administration to the non-irradiated hand did not prevent these effects.

Conclusion: The increase in skin microcirculation produced by pVIS light at the local and systemic levels is due to activation of NO synthesis in the irradiated area.

Introduction

Improvement in microcirculation is one of the most important effects of laser therapy; however, its mechanism of action have yet to be elucidated. In a previous study, we showed that polychromatic visible (pVIS) alone or pVIS + near-infrared (nIR) light, by acting on a small area of the body surface of diabetic patients nearly immediately enhanced skin microcirculation in the upper and lower extremities at the local and systemic levels, with a parallel marked decrease of reactivity of microvessels to the vasodilators acetylcholine (ACH) and nitroglycerine (NG). The former is known to stimulate vascular endothelium to synthesize nitric oxide (NO), a gaseous compound that is an effective regulator of vascular tone, whereas NG itself is an NO donor. The fact that for the first 2 min the effect of light exceeded that of NG, and its maximal value 30 min later was comparable with the maximal effects of both NG and ACH.
allowed us to suggest that NO plays an important role in the light-induced enhancement of microcirculation, both in the area of irradiation (locally) and in distant areas (at the systemic level).

To prove this theory, in this study we explored the pVIS light–induced increase in microcirculation after local intracutaneous iontophoresis of an inhibitor of NO-synthase (NOS), the enzyme that synthesizes NO from L-arginine and surrounding oxygen. NOS is located in the superficial membrane of many cells, including endothelial cells, platelets, and leukocytes. As a biopteroflavohemoprotein, it absorbs light in the pVIS part of the spectrum. Thus, upon penetrating the skin into the dense network of superficial microvessels, pVIS light can activate NOS of endothelial and blood cells, and thereby enhance synthesis of NO. The formation of NO by these cells under the effects of light in vitro has already been shown by a number of authors.\(^2\text{–}^6\)

For ethical reasons, we carried out this study with an inhibitor of synthesis of NO not on patients with vascular pathology, but instead on healthy volunteers. The study design was approved by the Ethics Committee of Academician I.P. Pavlov St. Petersburg Medical University in 2005.

### Materials and Methods

#### Volunteers

The participants in this study were 42 apparently healthy volunteers aged 40–80 y (85% women and 15% men with a mean age of 54 y ± 5 y). In each subject, the microcirculation was measured in the skin of the dorsal side of both hands, then the right hand was irradiated and the blood flow rate changes were evaluated for 90 min, both in the irradiated area (local effect) and in the non-irradiated left hand (systemic effect). The volunteers were randomly divided into five groups. In the 11 subjects of group I, irradiation of the entire dorsum of the right hand (120 cm\(^2\)) was performed without NOS inhibitor. In the 8 subjects of group II, 1 min prior to irradiation the NOS inhibitor was injected by iontophoresis into the skin of the central area (24 cm\(^2\)) of the dorsum of the right hand. The effect of the inhibitor was evaluated both in the irradiated area and in the non-irradiated left hand. In the group III (7 subjects), only the central area of the dorsum of the right hand (24 cm\(^2\)) was irradiated, while the rest of the dorsal hand surface was covered with a 5-mm-thick cardboard shield. Volunteers of group IV (6 subjects), 1 min before irradiation of the central area of the right hand, were intracutaneously given NOS inhibitor. In group V (10 subjects) the inhibitor was applied to the left hand to evaluate its effect on the enhancement of systemic microcirculation following irradiation of the right hand.

#### Study of microcirculation

Assessment of microcirculation was performed using a high-frequency ultrasound Doppler device (Minimax Doppler-K; Minimax AG, St. Petersburg, Russia), that analyzed the local microvessel network with a high-frequency sensor and measured the blood flow rate (mL/sec/cm\(^2\)) to a depth of up to 5 mm. The features of this device are described in the greater detail by its designers.\(^7\)

### Iontophoresis

A solution (0.1% in water) of N-monomethyl-L-arginine (L-NMMA) (Sigma, St. Louis, MO), an inhibitor of constitutive and inducible NO-synthase, was administered for 1 min intracutaneously into the skin of the central area of the dorsum of the hand, and 1 min later irradiation was performed. Preliminary determinations showed that the inhibitor acted only in the areas occupied by electrodes (i.e., the 24-cm\(^2\) area), while in intact skin the microcirculatory blood flow was not suppressed by the inhibitor.

#### Light sources

A phototherapeutic device (Q-light; Biotechnology & Photomedicine AG, Rorschacherberg, Switzerland) emitting over the entire spectrum of visible light with a high degree of polarization (385–750 nm, 95% polarization) was used. The power density used, 40 mW/cm\(^2\), resulted in light levels similar to those present at noon on a cloudless day in Central Europe. The time of exposure was 5 min and energy density was 12 J/cm\(^2\); the area irradiated was either 120 cm\(^2\) or 24 cm\(^2\).

### Statistics

Evaluation of the statistical significance of changes was performed with a parametric method for matched (dependent) pairs of results (Student’s t-test). The statistical significance of the differences in the results seen in healthy volunteers and those seen in diabetic patients was performed with the Student’s t-test for independent samples.

### Results

The initial blood flow rate values (Qas) in the microvessels of the central zone of the dorsum of the hand varied in the examined volunteers from 9–15 × 10\(^{-4}\) mL/sec/cm\(^2\); in the subjects in group I it was on average 11.85 × 10\(^{-4}\) mL/sec/cm\(^2\) (Fig. 1). Whereas in late autumn and winter (November–February) it was somewhat lower (11.23 × 10\(^{-4}\) mL/sec/cm\(^2\)), in summer (May–July) it rose, on average, by 10%, to 12.32 × 10\(^{-4}\) mL/sec/cm\(^2\).

As seen in Fig. 1, as soon as 2 min after irradiation of the entire dorsal surface of the right hand of 11 volunteers (group I), the Qas value rose to 14.80 × 10\(^{-4}\) mL/sec/cm\(^2\) (by 26%), and reached its maximum (17.80–18.20 × 10\(^{-4}\) mL/sec/cm\(^2\)) 15–30 min later, and decreased gradually for 90 min after irradiation. Thus, the local microcirculation in the irradiation zone rose maximally by 51–54%, and for 90 min of observation exceeded the initial level, on average by 38% ± 5.7%.

Five minutes after the right hand was irradiated, a statistically significant increase in blood flow, on average by 16%, was also recorded in the microvessels of the non-irradiated left hand, which indicated the development, with a slight delay, of a systemic effect (Fig. 1). Its maximal value was seen after 20–30 min and amounted to an increase of 44–45%. The mean increase in systemic microcirculation for 90 min of observation reached was 24% ± 6.4%, with a statistically significant difference in the degree of increase of local and systemic microcirculation being seen only at the earliest time points after irradiation, at 2 and 5 min (Fig. 1).

Iontophoretic administration of the inhibitor of NO synthase (L-NMMA) into the central area of the right hand (24
cm²) of the subjects in group II, with subsequent irradiation of the entire hand, prevented a rapid rise in local microcirculation (Fig. 2A). A statistically significant increment (by 13%) was found only at two time points: at 10 and 15 min after irradiation. According to the data from the eight time points of testing of the local blood flow rate, the increase seen in the 90 min after irradiation did not exceed 8% ± 1.6%.

Meanwhile, the systemic effect of the light, as assessed by the increase in microcirculation in the non-irradiated left hands of the subjects, was not suppressed, and moreover, at 2 and 5 min after inhibitor administration and right-hand irradiation, it statistically significantly exceeded the systemic effect seen in group I subjects, who did not receive the inhibitor (Fig. 2B); the maximal effect was seen only at the earlier time points. Its absolute value (+38%) and the mean increase in systemic microcirculation for the 90-min period (+26% ± 4.1%) did not differ from these parameters in group I subjects, although the degree of changes in blood flow rate at 20 and 30 min turned out to be lower. It is likely that the development of such a pronounced systemic effect of the light energy in the non-irradiated hand, together with the marked inhibition of the effects seen in the irradiated area, are due to the inhibition of NO synthase in the small central skin area of the right hand dorsum, but there was still the possibility of the enzyme’s photoactivation in the remaining nearly fivefold larger area of the right hand dorsum.

To prove that the increase in blood flow rate at the systemic level was the direct consequence of photoactivation of NO synthase in the light-exposed area, in the next two series of experiments we irradiated only the small area (24 cm²) of the right hand that was previously administered L-NMMA. In the subjects in group III, this area was irradiated without the inhibitor, while in group IV it was irradiated after administration of the inhibitor.

As can be seen in Fig. 3A and B, the presence of the NO synthase inhibitor in the irradiated zone completely blocked any increases in both the local and the systemic microcirculation. At none of the post-irradiation time points did the blood flow rate in the right and left hands exceed their initial values.

As an additional argument that the key event in light-induced microcirculation increases at the systemic level are activated by NO synthase in the irradiated area, it is worth considering the results of testing of the rate of blood flow in the subjects in group V, to whom L-NMMA was iontophoretically administered into the skin of the non-irradiated left hand. As seen in Fig. 4, the blood flow rate in this group did not decrease and remained as high as that seen in

FIG. 1. Local (1) and systemic (2) changes in blood flow rate (Qas) in skin microvessels of both hands of healthy volunteers after irradiation of the entire dorsal surface of the right hand (1) with polychromatic visible light. *Differences with the Qas initial values were not statistically significant (p > 0.05). The other differences were statistically significant (p < 0.05). #Differences in the local microcirculation changes were statistically significant (p < 0.05). The other differences were not statistically significant (p > 0.05).

FIG. 2. Local (A) and systemic (B) changes in blood flow rate (Qas) in skin microvessels of both hands after irradiation of the entire dorsal surface of the right hand (120 cm²) without the NOS inhibitor (1) and following intracutaneous iontophoresis of the NOS inhibitor into the irradiated area (2). #Differences with the Qas initial values were not statistically significant (p > 0.05). The other differences were statistically significant (p < 0.05). *Difference with the light’s effect without the NOS inhibitor was not statistically significant (p > 0.05). The other differences were statistically significant (p < 0.05).
A statistically significant \((p < 0.05)\) difference with the Qas initial values were not statistically significant \((p > 0.05)\). The other differences were statistically significant \((p < 0.05)\). *Differences of the light’s effect without the NOS inhibitor were not statistically significant \((p > 0.05)\). The other differences were statistically significant \((p < 0.05)\).

The data obtained demonstrate for the first time the possibility of enhancement of skin microcirculation in healthy volunteers after treatment with full-spectrum visible light. Since the method used in the present work is identical to that used in our previous study, that was carried out on patients with type 2 diabetes mellitus (DM), we can compare the light-induced microcirculation changes in healthy subjects with those in ill subjects.

It is obvious that in both cases the blood flow rate (Qas) in skin microvessels increased not only in the area irradiated (both at the right hand, but also in the non-irradiated left hand, i.e., both at the local and at the systemic level). The stimulatory effect of pVIS and nIR laser light on local microcirculation has long been known to accelerate wound healing and induce pain relief, but the possibility of such treatment to improve tissue perfusion in organs distant from the irradiated site has only recently been recognized. The data detailed here and in our previous work, demonstrate this effect of irradiation with pVIS and pVIS + nIR light. Some authors indicate that light treatment promotes improvement of microcirculation not only in distant skin areas, but also in visceral organs. Indeed, irradiation with laser light (633 nm) of a small area of a laboratory animal’s body stimulates blood flow in mesentery arterioles, as well as coronary and cerebral blood vessels.

**Discussion**

The data we obtained demonstrate for the first time the possibility of enhancement of skin microcirculation in healthy volunteers after treatment with full-spectrum visible light. Since the method used in the present work is identical to that used in our previous study, that was carried out on patients with type 2 diabetes mellitus (DM), we can compare the light-induced microcirculation changes in healthy subjects with those in ill subjects.

It is obvious that in both cases the blood flow rate (Qas) in skin microvessels increased not only in the area irradiated (both at the right hand, but also in the non-irradiated left hand, i.e., both at the local and at the systemic level). The stimulatory effect of pVIS and nIR laser light on local microcirculation has long been known to accelerate wound healing and induce pain relief, but the possibility of such treatment to improve tissue perfusion in organs distant from the irradiated site has only recently been recognized. The data detailed here and in our previous work, demonstrate this effect of irradiation with pVIS and pVIS + nIR light. Some authors indicate that light treatment promotes improvement of microcirculation not only in distant skin areas, but also in visceral organs. Indeed, irradiation with laser light (633 nm) of a small area of a laboratory animal’s body stimulates blood flow in mesentery arterioles, as well as coronary and cerebral blood vessels.

**Activation by light**

By irradiating different sizes of the hand dorsum areas in the subjects in groups I and III, we have established that the fivefold decrease in area irradiated reduced the systemic blood flow twice as much as the local blood flow. Results of this comparison are presented in Table 1. It can be seen that the local blood flow increase after irradiation of the entire dorsum of the right hand (120 cm²) after 90 min reached, on average, 38%, while with irradiation of only the central area (24 cm²), this figure was 32%, whereas changes in blood flow in the non-irradiated hand were 24% and 17%, respectively.
ROLE OF NO IN LIGHT-INDUCED INCREASE OF MICROCIRCULATION

TABLE 1. DEPENDENCE OF LOCAL AND SYSTEMIC CHANGES OF SKIN MICROCIRCULATION IN HEALTHY SUBJECTS ON THE SIZE OF THE LIGHT-IRRADIATED AREA

<table>
<thead>
<tr>
<th>Effect on the back of the hand</th>
<th>Size of the irradiated area (cm²)</th>
<th>Mean change in the blood flow rate (Qas, Δ, % of the initial value) at different time points (min) post-irradiation</th>
<th>Average for 90 min (mean ± SE)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>120</td>
<td>+26 +39 +46 +53 +54 +51 +24 +10 +38 ± 5.7</td>
<td></td>
<td>1-2</td>
</tr>
<tr>
<td>Local</td>
<td>24</td>
<td>+32 +38 +38 +46 +45 +37 +17 +5³ +32 ± 5.0</td>
<td></td>
<td>p = 0.04</td>
</tr>
<tr>
<td>Systemic</td>
<td>120</td>
<td>+2³⁺ᵇ +16ᵇ +30 +40 +45 +44 +16 +1³ +24 ± 6.4</td>
<td></td>
<td>3-4</td>
</tr>
<tr>
<td>Systemic</td>
<td>24</td>
<td>+1³⁺ᵇ +9ᵇ +19ᵇ +34 +39ᵇ +28ᵇ +8ᵇ 0³ +17 ± 5.3</td>
<td></td>
<td>p = 0.005</td>
</tr>
</tbody>
</table>

ᵃDifferences with the Qas initial values were not statistically significant (p > 0.05). The other differences were statistically significant (p < 0.05).
ᵇDifferences with the corresponding local effects were statistically significant (p > 0.05). The other differences were not statistically significant (p < 0.05).

density of tissue blood flow at the systemic level correlates well with the systemic characteristics of photostimulation of wound healing processes.¹⁹,²³ Moreover, as shown by our studies, local treatment with pVIS + nIR radiation of the human body, due to transcutaneous photomodification of a small amount of blood in skin microvessels, induces changes in cells and plasma that develop rapidly in the entire volume of circulating blood. It also induces structural and functional changes in red blood cells, causes platelet deaggregation and modulation of the functional status of all types of leukocytes, and changes the plasma content of cytokines and growth factors.¹⁸–²²

An important aspect of the systemic effects of pVIS light is their high rate of development, which is sometimes underestimated by specialists analyzing the mechanisms behind phototherapy. We have shown that a statistically significant increase in local blood flow is seen both in healthy subjects and in diabetic patients as soon as 2 min after a 5-min irradiation period, while at the systemic level it is seen after 5 min in healthy subjects and after 2 min in diabetic patients with (Table 2). In the latter group, with their initially lower microcirculatory parameters, the systemic effect develops faster and lasts longer (until the next day). Similar differences in the changes seen in microvascular blood flow rates at the systemic level in healthy individuals and in patients with atherosclerosis of the lower extremities after laser irradiation (890 nm) have also been described by Briskin et al.²³ A common mechanism of pathogenesis of both DM and atherosclerosis is known to be a disturbance of endothelial function, which leads to a decrease in microcirculation and regional blood flow.²⁴,²⁵ The endothelial dysfunction is characterized by insufficient production of nitric oxide. As shown by our results, pVIS light immediately activates NO synthesis and improves blood microcirculation, and these develop faster and last longer in sick subjects than in healthy ones. By studying microcirculation in the forefoot skin of patients with diabetic microangiopathy using thermography, Schindl et al.¹² found a statistically significant increase in microcirculation after irradiation with a He-Ne laser 20 min after it is begun, and it reached maximum levels 15 min after the end of treatment. The local changes in blood flow rate developed more quickly than did the systemic ones, a fact also confirmed by our data. In experiments on rats, distant activation of microcirculation by laser light (633 nm, 2.5 J) was

TABLE 2. COMPARISON OF MEAN CHANGES IN BLOOD FLOW RATE (Qas) AT THE LOCAL AND SYSTEMIC LEVEL IN SKIN MICROVESSELS OF THE EXTREMITIES IN HEALTHY VOLUNTEERS AND DIABETIC PATIENTS AFTER IRRADIATION WITH VISIBLE LIGHT

<table>
<thead>
<tr>
<th>Type of blood flow</th>
<th>Study groups</th>
<th>Irradiated area</th>
<th>Area of blood flow rate testing</th>
<th>Mean Qas initial value (mL/sec/cm³ × 10⁻⁴)</th>
<th>Mean change in Qas (Δ, % of the initial value) at four time points post-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Volunteers</td>
<td>Back of the right hand</td>
<td>Back of the right hand</td>
<td>11.9</td>
<td>+26</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>Dorsal surface of the right foot</td>
<td>Dorsal surface of the right foot</td>
<td>9.6</td>
<td>+39</td>
<td>+41</td>
</tr>
<tr>
<td>Systemic</td>
<td>Volunteers</td>
<td>Back of the right hand</td>
<td>Back of the left hand</td>
<td>11.9</td>
<td>+2ᵃ</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>Lumbar/sacral area</td>
<td>Back of the left hand</td>
<td>10.9</td>
<td>+20ᵇ</td>
<td>+32</td>
</tr>
</tbody>
</table>

ᵃDifferences with the Qas initial value was not statistically significant (p > 0.05). The other differences were statistically significant (p < 0.05).
ᵇDifference with the effects seen in healthy volunteers was statistically significant (p < 0.05).
seen as soon as a few seconds after irradiation begun. These authors also found indirect proof that the distant effects of He-Ne laser light consisted of an increase in the endothelium of non-irradiated arterial vessels in synthesis of prostacyclin responsible both for vasodilation and for atherogenesis of vascular walls. Some authors explain the rise seen in tissue blood perfusion in laser-treated areas as being due to dilation of arterioles, involvement of once non-functioning microvessels, and opening of collaterals, all of which are considered to be a consequence of the direct effects of light energy on endothelial and smooth muscle cells of the vascular walls, as well as mast-cell release of histamine and heparin during photoactivation.16,26–28

According to the current theory, dilation of skin vessels is mediated primarily by three factors: nitric oxide, endothelial-derived hyperpolarizing factor (EDHF), and prostacyclin, which are produced predominantly by endothelial cells.24,25 By acting via different mechanisms on vascular wall smooth muscle cells, these compounds produce relaxation and subsequent vasodilation. It has been suggested that the vasodilatory properties of nitric oxide synthesized by constitutive and inducible NO synthase are of significance in the arteries, whereas in arterioles with diameters >100 μm, the contributions of NO and EDHF are equal, but in arterioles with diameters <100 μm NO plays a secondary role, and the main vasodilator is EDHF. The latter is shown to be produced by endothelium due to the effects of the same factors as is NO, but production of EDHF is preserved after blockade of synthesis of NO and prostacyclin. An important role in the formation of NO, EDHF, and prostacyclin is played by hemodynamic factors, including increased blood flow rate and improvement in the blood’s rheologic properties. Intravenous prostacyclin administration has been shown to lead to vasodilation at the systemic level. However, it is also wise to take into account that other factors participate in the production of NO, including other cells that contain NOS, such as vascular wall smooth muscle cells, mast cells, platelets, leukocytes, and skin cells (keratinocytes and fibroblasts).

To date, several studies have shown that light from laser sources in vitro produces relaxation of rat portal veins, and this effect is dependent on the initial level of NOS activity, and it is completely blocked by an inhibitor of NOS, L-NMMA.2,3 On the other hand, Klebanov et al.5,6 have shown the red light of the He-Ne laser induces NO synthesis in rat peritoneal macrophages, and they have proven that the polymorphonuclear leukocytes isolated from rat wound exudates, 1–3 d after irradiation with the same type of laser, produce 2–3 times more NO than that present before irradiation. This same effect was revealed in murine immune cells after exposure to red laser light.4

In the present work the light-induced rise in skin microcirculation has been demonstrated to be completely inhibited by the NOS inhibitor L-NMMA, and this inhibition occurs both in the irradiated area and also in distant sites. This proves the key role of NO in the initiation of vasodilation of microvessels under the direct and distant actions of pVIS light. This conclusion agrees well with the results of our previous work, that showed that pVIS light-irradiated subjects experienced a decrease in the reactivity of skin microvessels to intracutaneous administration of NO donors, and showed similar effects on microcirculation of pVIS light and of the vasodilating substances NG and ACh.1 Since nitric oxide participates in regulation of tonus of almost exclusively arterial, rather than venous, vessels, the inhibitor L-NMMA blocks constitutive NOS forms more than inducible NOS forms.25 The rapid increases in local blood flow may be caused by the action of light on the constitutive NOS forms found in arteriolar walls. To what degree the light treatment induces formation of other forms of NO, particularly in blood cells, is still to be elucidated.

The complete blockade of light-induced enhancement of microcirculation at the systemic level after administration of the NOS inhibitor in the irradiated body area indicates involvement of NO synthesis in the initiation of these distant effects of light energy. However, these systemic effects may occur without participation of NO synthesis, as administration of an NO inhibitor into an area distant from the irradiated site did not prevent improvements in microcirculatory blood flow. It is possible that an important role is played by EDHF and prostacyclin in the arteriolar vasodilation seen in tissues distant from the irradiated area. The latter, as mentioned above, are believed to play an important role in changing microcirculation at the systemic level. The stimulus for the rapid synthesis of prostacyclin and EDHF in the non-irradiated endothelium may be a result of a tension shift due to improvement of the blood’s rheologic properties,18 as well as an increase in blood flow rate in the irradiated area. Other mechanisms also cannot be ruled out.

On the whole, the proof of the participation of pVIS light in induction of rapid NO synthesis in vivo opens new approaches to the study of the mechanisms behind phototherapy. Over the last 15 y, NO has been shown to play a significant role in the functioning of cells, tissues, and the organism as a whole. NO is a gaseous compound that dissolves well in water and lipids, and diffuses rapidly across cell membranes and biological fluids, and participates in the transduction of regulatory signals inside cells, as well as in the formation of intercellular signaling networks. NO has unpaired electron, therefore it is a highly active free radical, and the main mechanism behind its physiological effects is related to its actions on protein nitrosylation. These properties of NO help to explain why the responses to pVIS light develop so rapidly. Thus, it is possible that NO causes rapid signal transduction, and that systemic effects may result from irradiation of only a small volume of blood. In our opinion this phenomenon, which is also described in other studies,18–22 is the main mechanism behind the light energy’s systemic effects, both physiological and therapeutic.

Conclusion

In conclusion, the significance of the results reported here is not restricted to the proof of the participation of NO in the functional responses seen in humans to pVIS light energy. It is apparent that the increases in microcirculatory blood flow and the positive changes seen in the cells and plasma of the entire circulating blood pool, reported both here and in earlier studies,18–22 indicate that the therapeutic effects of terrestrial solar radiation are much more significant than once thought.

Disclosure Statement

No competing financial interests exist.
References


Address reprint requests to:
Dr. Kira A. Samoilova
Head of Photobiology Unit
Institute of Cytology of the Russian Academy of Sciences
4 Tikhoretsky Ave.
St. Petersburg 194064, Russia
E-mail: samoilova3@yandex.ru
This article has been cited by:


2. Delia B. Roberts, Roger J. Kruse, Stephen F. Stoll. 2013. The Effectiveness of Therapeutic Class IV (10 W) Laser Treatment for Epicondylitis. Lasers in Surgery and Medicine n/a-n/a. [CrossRef]

3. Rodrigo Leal de Paiva Carvalho, Ernesto Cesar Pinto Leal-Junior, Maria Carla Petrellis, Rodrigo Labat Marcos, Maria Helena Catelli de Carvalho, Gilberto De Nucci, Rodrigo Alvaro Brandão Lopes-Martins. 2013. Effects of Low-Level Laser Therapy (LLLT) and Diclofenac (Topical and Intramuscular) as Single and Combined Therapy in Experimental Model of Controlled Muscle Strain in Rats. Photochemistry and Photobiology 89:2, 508-512. [CrossRef]

4. Dong-Hee Choi, Kyoung-Hee Lee, Ji-Hye Kim, Moon Young Kim, Jeong Hoon Lim, Jongmin Lee. 2012. Effect of 710nm visible light irradiation on neurite outgrowth in primary rat cortical neurons following ischemic insult. Biochemical and Biophysical Research Communications. [CrossRef]


8. Debora G. Minatel, Marco Andrey C. Frade, Suziele C. França, Chukuka S. Enwemeka. 2009. Phototherapy promotes healing of chronic diabetic leg ulcers that failed to respond to other therapies. Lasers in Surgery and Medicine 41:6, 433-441. [CrossRef]