Adv Exp Med Biol - Clinical and Experimental Biomedicine (2018) 1: 41–52
https://doi.org/10.1007/5584_2018_188

Published online: 24 March 2018

Perspective on Broad-Acting Clinical Physiological Effects of Photobiomodulation

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Abstract

Research into photobiomodulation reveals beneficial effects of light therapy for a rapidly expanding list of medical conditions and illnesses. Although it has become more widely accepted by the mainstream medicine, the effects and mechanisms of action appear to be poorly understood. The therapeutic benefits of photobiomodulation using low-energy red lasers extend far beyond superficial applications, with a well-described physics allowing an understanding of how red lasers of certain optimum intensities may cross the cranium. We now have a model for explaining potential therapeusis for applications in functional neurology that include stroke, traumatic brain injury, and neurodegenerative conditions in addition to the currently approved functions in lipolysis, in onychomycosis treatment, and in pain management.

Keywords

Cold laser · Laser therapy · Lipolysis · Neurodegeneration · Onychomycosis · Pain · Photobiomodulation · Photobiostimulation · Stroke

1 Introduction

Photobiomodulation or low-level laser therapy, low-intensity laser therapy, low-power laser therapy, cold laser, soft-laser, or photobiostimulation has been studied for over 50 years (Anders et al. 2015; Mester and Jászsági-Nagy 1971), with new clinical applications of light therapies growing exponentially. Unfortunately, this has resulted in a growing confusion about the clinical effectiveness of this technology due to the diverse assortment of lasers and light-emitting diode (LED) devices employing different light wavelengths, each purportedly treating conditions from hair loss (Avci et al. 2014) to cancer and neurodegenerative disease (Santana-Blank et al. 2016). To alleviate some of this confusion, "photobiomodulation" (PBM) has recently been added to the Medical Subject Headings of the National Library of Medicine thesaurus for PubMed indexing. The

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purpose of introducing a new term was to distinguish the PBM from other light-based devices that rely on thermal effects for some or all of their mechanisms of action.

Among the characteristics of PBM, including wavelength, power, and energy density, an emphasis has been placed on the ability of light to penetrate tissue (Hamblin 2017). Although PBM is well established as a beneficial treatment for numerous conditions, skepticism exists among those who think that light therapy, and particularly low-energy red lasers, can only be used to treat superficial conditions due to non-penetration of light energy in the body and bone. Far-red and near-infrared light waves do penetrate tissue to some extent. However, red lasers are capable of producing beneficial effects extending beyond treatment of superficial conditions (Grover et al. 2017; Maksimovich 2016; DeTaboada et al. 2006). It is apparent that the mode of therapeutic action of PBM is as complex as the pharmacokinetics of many medications. In the editorial in Photomedicine and Laser Surgery, Tiina Karu (2013) has asked a question: "Is it time to consider photobiomodulation as a drug equivalent?" She cited the use of PBM for treating a wide range of disorders including Parkinson's (Shaw et al. 2010) oral mucositis (Bjordal et al. 2011), peripheral nerve damage (Moges et al. 2011), ischemic tissue injury (Lapchak 2010), and other disorders (Santana-Blank et al. 2016).

The objective of this review is to provide perspective on the physiologically modifying properties of PBM, with potential application extending far beyond superficial applications including the evolving applications in functional neurology.

2 Photobiomodulation Effects

PBM employs non-ionizing light, including lasers, light-emitting diodes, or broadband light in the visible red (600–700 nm) and near-infrared (780–1100 nm) spectra to achieve therapeutic effects (de Freitas and Hamblin 2016). PBM is a nonthermal process beginning when a chromophore molecule is exposed to a suitable wavelength of light. Chromophores are responsible for the color associated with biological compounds such as hemoglobin, myoglobin, and cytochromes (Cotler et al. 2015). When a chromophore absorbs a photon of light, an electron transits to an excited state. A common target chromophore for PBM is the iron- and copper-containing enzyme cytochrome C oxidase in the mitochondrial respiratory chain, which absorbs light in the near-infrared spectrum (Avci et al. 2013; Karu and Afanasyeva 1995). The physiologic effects of PBM occur when photons dissociate the inhibitory signaling molecule of nitric oxide (NO), from cytochrome C oxidase, increasing the electron transport, mitochondrial membrane potentials, and the production of mitochondrial products such as ATP, NADH, RNA, and cellular respiration (Wang et al. 2016; de Freitas and Hamblin 2016).

Other effects include increases in the antioxidant enzyme activity, such as catalase and superoxide dismutase (Martins et al. 2016) or mitochondrial NO synthase, release of NO, also a potent vasodilator (Adamskaya et al. 2011), and the production of reactive oxygen species (ROS). ROS play an important role in cell signaling, cell cycle progression regulation, enzyme activation, and nucleic acid and protein synthesis (Holmström and Finkel 2014). ROS also activate transcription factors, leading to cellular proliferation, migration, and production of cytokines and growth factors (Farivar et al. 2014). Alternatively, light-sensitive ion channels can be opened to permit calcium ion entry into the cell.

Based on these complex characteristics, PBM possesses physiologically modifying properties associated with specific light characteristics, such as wavelength and irradiance, varied by exposure parameters, such as energy density, irradiation duration, and treatment frequency. Similarly to pharmacological agents, BPM displays a biphasic dose-response described by the Arndt-Schulz law (Huang et al. 2009). Increasing the PBM dose, based on exposure time or energy density, increases the response to a maximum effect, after which a further exposure increase results in decreased response or bioinhibition.

The biphasic dose-response of BPM has been demonstrated in in vitro (Solmaz et al. 2017; Hawkins and Abrahamse 2006) and in in vivo studies (de Lima et al. 2014; Hsieh et al. 2014; Rojas and Gonzalez-Lima 2013). These properties of BPM are sharply contrasted with infrared radiation (780–3000 nm), which heats tissues, resulting in physical changes.

PBM has been demonstrated to be beneficial for treating chronic joint disorders (Bjordal et al. 2003), musculoskeletal (Cotler et al. 2015), chronic low back (Huang et al. 2015) and neck pain (Gross et al. 2013; Chow et al. 2009), herniated disks (Takahashi et al. 2012), adhesive capsulitis (Ip and Fu 2015), and in wound healing (Aragona et al. 2017; Heidari et al. 2017; Yadav and Gupta 2017; Arany 2016; Kuffler 2016). PBM has even been determined to be promising for treating psychiatric and neurodegenerative disorders (Berman et al. 2017; Salehpour and Rasta 2017; Cassano et al. 2016; Hamblin 2016).

To date, clinical trials have demonstrated the therapeutic effects of PBM leading to the US-FDA clearance of devices for body sculpting (Roche et al. 2017; Thornfeldt et al. 2016; Suarez et al. 2014; McRae and Boris 2013; Jackson et al. 2012; Nestor et al. 2012; Jackson et al. 2009), cellulite (Jackson et al. 2013), pain (Roche et al. 2016), and, most recently, onychomycosis (Zang et al. 2017). There have been no reports of treatment-related adverse events.

3 Potential Clinical Applications

3.1 Lipolysis

Activation of cytochrome C oxidase triggers cellular events including an increase in ATP synthesis, with upregulation of cAMP and cytoplasmic lipase activation. Activated lipase breaks down intracellular triglycerides into fatty acids and glycerol (Karu and Afanasyeva 1995). An additional effect of cytochrome C oxidase activation is a transient formation of pores in the cell membrane of adipocytes, allowing the newly formed fatty acids and glycerol to pass into the extracellular space (Solarte et al. 2003). Electron microscopic images have demonstrated pore formation in the cell membranes of adipose cells exposed to low-level laser light. Upon entering the extracellular space, lipids released following PBM treatment are transported to lymph nodes, where lysosomal acid lipase hydrolyzes the released triglycerides to generate non-esterified free fatty acids (Neira et al. 2002). Alternatively, released lipids may be transported via the lymphatic system to the liver where they undergo normal fatty acid oxidation. Clinically, the use of PBM has been associated with decreased plasma triglycerides and cholesterol (Jackson et al. 2010; Rushdi 2010). Importantly, PBM does not result in necrosis, the endocrine function of adipose tissue is preserved (Poulos et al. 2010), and it prevents inflammatory effects of high-intensity focused ultrasound (Burks et al. 2011; Biermann et al. 2010) and cryolipolysis (Avram and Harry 2009).

3.2 Pain

A well-controlled trial has assessed PBM efficacy for treating chronic shoulder and neck pain and improving the upper body range of motion (ROM) (Roche et al. 2016). Participants received PBM using a diode laser emitting a divergent 635 nm (red) laser light (energy output of 1 mW) or sham treatment. After 48 h, 28 out of the 43 PBM-treated subjects (65.1%) demonstrated a greater than 30% improvement in pain scores vs. six (11.6%) in the sham-treated group.

The mechanism whereby PBM decreases pain is unknown (Hamblin 2017; Holanda et al. 2017). The analgesic and anti-inflammatory effects of PBM are associated with increased antioxidant glutathione and decreased expression of P2X3

receptor subunits in C- and Aδ-fiber afferent neurons (Janzadeh et al. 2016), significant reductions in cyclooxygenase-2 (COX-2) mRNA (Prianti et al. 2014), activation of endogenous opioids (Pereira et al. 2017), reductions in pro-inflammatory cytokines and glutamate, increases in endogenous analgesic prostatic acid phosphatase (Pires de Sousa et al. 2016), and the expression of bradykinin receptors (de Oliveira et al. 2017).

3.3 Onychomycosis

Zang et al. (2017) have reported on the use of PBM for treating onychomycosis. Fifty affected toenails were treated for 12 min weekly for 2 or 4 weeks with a 635/405 nm dual-diode laser device. Most treated toenails (67%) achieved individual treatment success. The extent of clearing at the nail baseline increased by a mean of 4.8 ± 5.2(SD) mm after 6 months. Nearly all treated toenails (89%) demonstrated an increase in the area of clear nails over the 6-month study period. Based on the safety and efficacy, this nonthermal laser PBM device received FDA 510 (k) market clearance for a temporary nail clearing in patients with onychomycosis caused by dermatophytes or yeasts.

PBM also exhibits antimicrobial effects on biofilms formed by *Streptococcus mutans* and *Candida albicans* (Basso et al. 2011) and activity against *C. albicans* cultures (Maver-Biscanin and Mravak-Stipetic 2005). It also is effective against oral *C. albicans* infections in mice and humans in vivo (Seyedmousavi et al. 2014; Scwingel et al. 2012) and against the fungus *Paracoccidioides brasiliensis* in both in vitro and in vivo (Burger et al. 2015).

The mechanisms of antifungal effect of PBM are unclear. Exposure of cytochrome C oxidase in the mitochondrial respiratory chain to suitable wavelength of light results in increased production of mitochondrial ATP, NADH, and RNA and increased cellular respiration (de Freitas and Hamblin 2016; Wang et al. 2015; Chung et al. 2012). Consistent with these effects, neutrophils from PBM-treated mice become more metabolically active and have higher fungicidal activity (Burger et al. 2015). When stimulated by PBM in vitro, human neutrophils show a greater production of ROS and increased fungicidal capacity against *C. albicans* (Cerdeira et al. 2016).

In contrast, thermal lasers used for treating onychomycosis emit light in the near-infrared spectrum (780–3000 nm) and exert their effect by simply heating the target tissue (Nenoff et al. 2014). In vitro studies have demonstrated a thermal killing effect on fungal mycelia when treatment temperatures exceed 50 °C (Carney et al. 2013; Paasch et al. 2013). The mean peak temperatures associated with an 808 nm laser is 74.1–112.4 °C and that of a 980 nm laser is 45.8–53.5 °C (Paasch et al. 2014). Consequently, the use of thermal lasers has been associated with moderate pain or burning sensations (Helou et al. 2016; Moon et al. 2014; Noguchi et al. 2013) and darkening under the nail (Lu et al. 2016). Discomfort is minimized by using a pulsed-wave laser instead of continuous-wave laser (Anderson and Parrish 1983).

4 Functional Neurological Applications

4.1 Photobiomodulation and the Cranial Vault

A significant literature exists on the ability of PBM to penetrate the skull in both diagnostic and therapeutic applications. Low-energy laser passes the skull and a therapeutic effect likely exists. Low-energy laser systems employ the so-called quantum optical induced transparency (QIT) effect (Weis et al. 2010; Harris et al. 1990). Quantum interference in the amplitude of optical transitions in atomic media can lead to strong modification in optical properties. This effect, electromagnetically induced transparency, controls optical properties of dense media and can enhance transparency contrast by a factor of five (Scherman et al. 2012). Therefore, the skull, spine, or joints can be penetrated even with moderate intensity light. Due to the QIT effect, the

radiation should reach deep tissue layers in muscles, connective tissue, and even bone, enabling noninvasive transcranial treatments for neurodegenerative diseases, stroke, or traumatic brain injury (TBI) (Tedford et al. 2015; Stemer et al. 2010; Oron et al. 2006). Litscher and Litscher (2013) have reported that laser emission in the yellow band of the light spectrum could penetrate the human cranium making PBM a promising option for treating neurodegeneration or stroke, TBI, and other neurologically based conditions. A central constraint controlling the depth of penetration of laser light past the cranium is wavelength. Both absorption and scattering coefficients of living tissue are greater at lesser wavelengths with near-infrared light penetrating more deeply than red light. It also is argued that pulsed-wave lasers penetrate more deeply into tissue than continuous-wave lasers with the same average energy power.

Let us suppose that at a wavelength of 810 nm, the depth of tissue at which the laser intensity is reduced to 10% of its value at the skin surface is 1 cm. A laser, with a power density (irradiance) of 100 mW/cm^2 at the skin, would have a power density of 10 mW/cm^2 1 cm below the skin and of 1 mW/cm^2 2 cm below the skin. Now, suppose that a threshold power density, a minimum number of photons *per* unit area *per* unit time, at the target tissue is necessary to have a biological effect and that this value is 10 mW/cm^2. The effective penetration depth of continuous-wave laser may be, say, 1 cm. By contrast, let us consider a pulsed-wave laser with a 10 ms pulse duration and frequency of 1 Hz (direct current (DC) =1 Hz × 0.010 s = 0.010) and the same average energy power. The peak power and power densities are now 100 times higher (peak power = average power/DC = average power × 100). With a peak power density of 10 W/cm^2 at the skin, the tissue depth, at which this peak power density attenuates to the threshold level of 10 mW/cm^2, is now 3 cm rather than 1 cm in the continuous-wave mode. However, it should be taken into consideration that the laser is on only for 1% of the time, so that the total fluence delivered to 3 cm depth in the pulse-waved mode is 100 times less than that delivered to 1 cm depth in the continuous mode.

The use of PBM to treat diseases, disorders, and injuries of the brain requires a detailed understanding of the nature of light propagation through tissues including the scalp, skull, meninges, and brain. Tedford et al. (2015) have investigated light penetration gradients in the human cadaver brains using a transcranial laser system with a wavelength of 808 nm and wavelength dependence of light scatter and absorbance in intraparenchymal brain tissue using 660, 808, and 940 nm. Those authors demonstrate that the 808 nm wavelength light has a superior brain tissue penetration.

4.2 Photobiomodulation (PBM) Application for Neurodegenerative Diseases

Peptide fibrillization is associated with the creation of amyloid fibers in Parkinson's and Alzheimer's diseases (Luo et al. 2000). Hanczyc et al. (2012) have shown that amyloids demonstrate robust nonlinear optical absorption that is not extant in native non-fibrillized proteins. Pérez-Moreno et al. (2008) have found that lysozyme β-amyloids, insulin, and α-synuclein display two-, three-, or multiphoton absorption processes, depending on the wavelength of light. Olesiak-Banska et al. (2012) have suggested that a heightened multiphoton absorption is the outcome of a mechanism comprising dipolar through-space pairing between excited states of aromatic amino acids compacted in fibrous assemblies (Figs. 1 and 2).

Moro et al. (2014) have investigated neuroprotection offered by PBM in the mouse model. Mice were treated with PBM 20 times over 4 weeks and Alzheimer's disease-related histochemical markers were examined in the neocortex and hippocampus. Those authors show that PBM treatment decreases neurofibrillary tangles, hyperphosphorylated tau protein, and oxidative stress markers, as well as restores cytochrome C oxidase, which suggests that it may potentially be

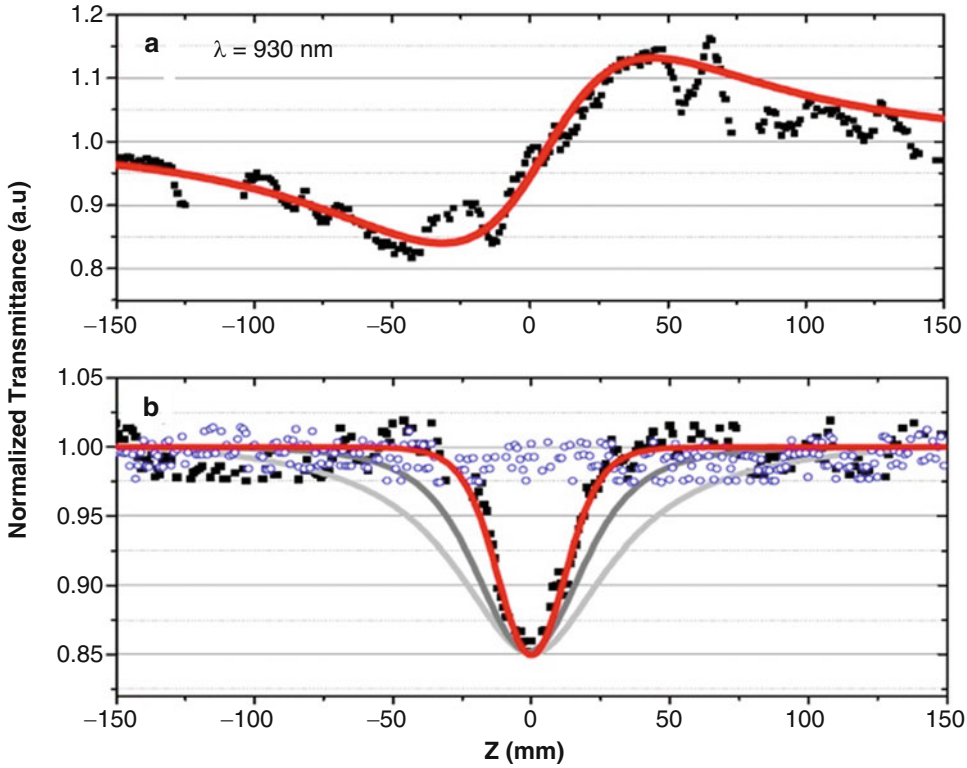

Fig. 1 (**a**) Z-scan example measurement of nonlinear refractive index and (**b**) nonlinear absorption coefficient of amyloid sample. Femtosecond Z-scan using 100 GW/cm^2 irradiation at 930 nm with closed (**a**) and open openings. (**b**) Amyloid fibrils (squares) are compared to native protein (circles). Theoretical fits are shown for two-photon absorption (2PA, light-gray solid curve), three-photon absorption (3PA, dark-gray solid curve), and five-photon absorption (5PA, red solid curve) (With permission from Olesiak-Banska et al. 2012)

an effective, minimally invasive intervention for progressive cerebral degeneration.

As downregulation of hippocampal brain-derived neurotrophic factor (BDNF), necessary for neuronal survival and dendritic sprouting, occurs in early Alzheimer's disease, BDNF upregulation may provide a mechanism to save dendritic atrophy in the disease course. Meng et al. (2013) have found that PBM reverses a decline in dendritic atrophy and in the number of neurons by means of BDNF upregulation. The PBM, through modulation of the transcription factor cAMP response element-binding protein (CREB), increases BDNF, mRNA, protein expression, as well as dendrite growth (dendritic spine length, density, and branching in hippocampal neurons).

4.3 Stroke

In an early study with transcranial-PBM (T-BPM) for stroke treatment in the rat model, Zhang et al. (1997) have obtained significant results. T-BPM at 808 nm, a previously alluded to important wavelength, significantly improves recovery 3 weeks after ischemic stroke. The regimen included one treatment on the contra-lesional side (power density: 7.5 mW/cm^2) 24 h post-stroke, with a good result in terms of neurogenesis stimulation.

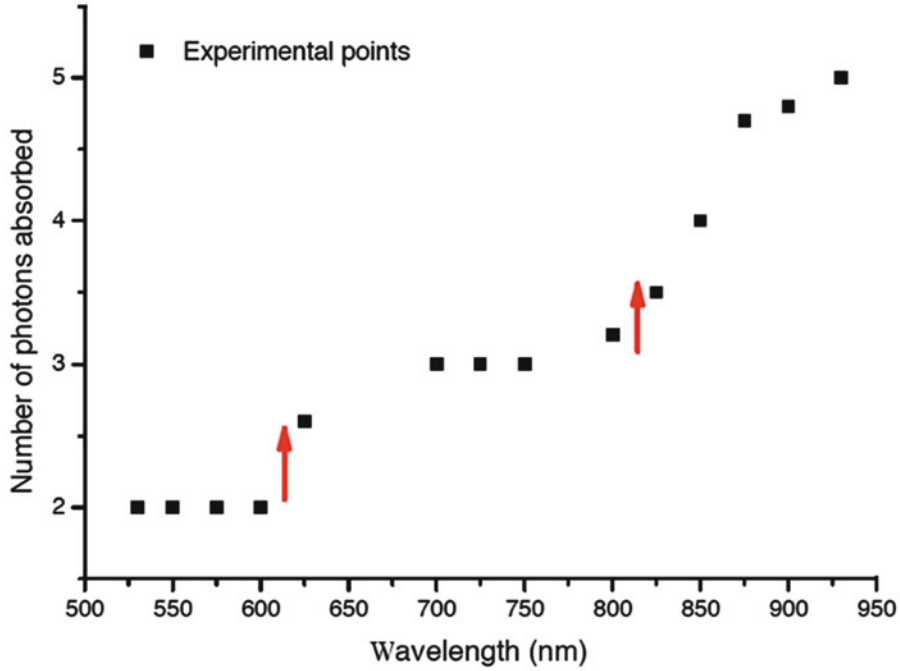

Fig. 2 Wavelength dependence of exponent n (the apparent number of photons taking part in the nonlinear absorption process) defined from dI/dz = -kIn with z denoting propagation distance I denoting light intensity. Steps marked with vertical arrows: below 625 nm, two-photon absorption and below 850 nm, three-photon absorption (From Olesiak-Banska et al. 2012 with permission)

A study in embolized rabbits has shown a direct relationship between cortical fluence (energy density, J/cm^2) and cortical ATP (Lapchak and DeTaboada 2010). Five minutes following embolization, rabbits received a 2-min PBM using 808 nm laser on the skin surface. Continuous-wave (CW) PBM (7.5 mW/cm^2, 0.9 J/cm^2) produced a 41% increase in cortical ATP. A 100 Hz pulse wave (PW) PBM (37.5 mW/cm^2, 4.5 J/cm^2) produced a 157% increase in cortical ATP. The authors suggest that even a greater improvement potential might be achievable by treatment length and mode (PW, at approximately 100 Hz) optimization.

T-BPM has been shown to significantly improve outcome in human stroke patients, when administered 18 h post-stroke, over the entire head surface, regardless of stroke localization (Lampl et al. 2007). Significant improvements are observed in the moderate and moderate–severe patients, but not in severe stroke patients (Zivin et al. 2009).

4.4 Traumatic Brain Injury (TBI)

Mild traumatic brain injury (mTBI) patients demonstrate cognitive and memory difficulties for at least 6 months or later after an episode. There is a significant requirement for effectual methods to foster cognitive recovery (Cicerone et al. 2006). mTBI from single and multiple events has been the most recurrent injury experienced by military personnel in the Operation Enduring Freedom and Operation Iraqi Freedom (Hoge et al. 2008). Diffuse axonal injury is frequently evidenced in frontotemporal and anterior-corona-radiata regions (Niogi et al. 2008; Taber et al. 2006). Cognitive impairments result from tissue injury in the prefrontal and

frontal cortical regions and anterior cingulate gyrus within the frontal lobes. PBM has been applied in animal TBI models (Oron et al. 2007). Mice were subjected to closed head injury. Five days later, motor behavior was significantly better in the PBM-treated group. Twenty-eight days post-injury, the mean lesion size in the laser-treated group was significantly smaller than in controls. The PBM has also had positive effects in other studies (Wu et al. 2012; Moreira et al. 2009). Naeser et al. (2011) have reported in humans that chronic mTBI cases demonstrate improved cognitive function after PBM that is associated with increased ATP. In a recent study on major depression treatment, Schiffer et al. (2009) have shown that PBM increases regional cerebral blood flow in the contra-lesional frontal lobes (power density: 7.5 mW/cm^2). It also increases cellular respiration and oxygenation of hypoxic cells (Mi et al. 2004a and b).

5 Conclusions

Research into photobiomodulation is revealing the beneficial effects of light therapy for a rapidly expanding list of medical conditions and illnesses. As it becomes more widely accepted by the mainstream medicine, its mechanism of action and the biophysics appear to be poorly understood. Importantly, therapeutic benefits of photobiomodulation, using red lasers, extend far beyond superficial applications.

Acknowledgments The authors acknowledge the editorial assistance of Dr. Carl S. Hornfeldt.

Competing Interests S.S. is president of the Erchonia Corporation in Melbourne, Florida; G.L. has no fiduciary relationship with any manufacturer or marketer of therapeutic laser equipment.

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