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REVIEW ARTICLE

Cardio-light: nitric oxide uncaged

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Abstract
Photobiomodulation (PB) is a utilization of low-level laser therapy (LLLT) in the far red (R) to near infrared (NIR) spectrum (600–1000 nm) to wield its therapeutic effects. To explore the therapeutic potential of biomodulation of different tissues, LLLT has been extensively researched, especially in the light of its very low side effect profile. We believe there is an opportunity to unearth its dynamic effects on the coronaries which can be promising for the patients with chronic stable angina. NIR treatment of the heart may be protective on patients after acute myocardial infarction or on ischemic heart conditions that are not accessible to current revascularization procedures.

Keywords Nitric oxide · Laser · NO · Photobiomodulation · LLLT · Low-level laser therapy · NIR · Near infrared · Coronary · Cardiology laser · Interventional cardiology · Cardioprotection · Vasodilation · Cardio-light

Introduction

Photobiomodulation (PB) is a utilization of low-level laser therapy (LLLT) in the far red (R) to near infrared (NIR) spectrum (600–1000 nm) to wield its therapeutic effects. Hungarian Surgeon and Physicist Endre Mester, in 1967, discovered the biological effects of the laser after he accidently induced hair growth while examining the effects of laser on tumors in mice. To explore the therapeutic potential of biomodulation of different tissues, LLLT has been extensively researched, especially in the light of its very low side effect profile. We believe there is an opportunity to unearth its dynamic effects on the coronaries which can be promising for the patients with chronic stable angina.

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Therapeutic potentials

The most extensively studied spectrum for PB includes light in the spectrum of 630–830 nm. The light in this spectrum penetrates the tissue well enough with minimal heat production owing to decreased absorption by melanin and water [1–3]. The non-ionizing nature of this spectrum reduces its potential for tissue damage. PB has been found useful in stimulation of angiogenesis, skeletal muscle regeneration, and wound healing [4–11]. It improves granulation and healing of diabetic ulcers refractory to other treatments [12]. It facilitates bone repair, prevents chemotherapy-induced mucositis, and slows the rate of nerve degeneration after crush injury [13–15]. Other effects include but are not limited to enhancement of neuroprotection in methanol toxicity and improved clinical rating scores after embolic strokes [16, 17]. It also helped in reduction in frequency and severity of attacks in patients with Raynaud's phenomenon, decreased pain and improved function in patients suffering from rheumatoid arthritis, decreased symptoms from tendinopathies and temporomandibular disorders, and improved nocturnal pain and paresthesia in idiopathic carpal tunnel syndrome [18–23]. LLLT of scalp at 665 nm significantly improved hair counts in males and females with androgenic alopecia at comparable rates [24, 25]. On the cardiovascular front, through its anti-oxidative properties, it aided in reduction of the infarct size after myocardial infarction by inhibition of cardiomyocyte degeneration and was also found to help recover myocardial contractility at

much faster rates owing to decreased products of lipid peroxidation and rising superoxide dismutase activity [26, 27].

The effects of PB vary with the properties of light used. Frequently studied parameters include coherence and chromaticity. Both laser and LED were found capable of stimulating angiogenesis in vivo on cutaneous wounds [28]. Comparable rates of photo relaxation were achieved in porcine coronaries irrespective of coherence [29, 30]. But increasing energy density led to an increase in vasodilation representing a dose-dependent photo relaxatory effect. After a particular limit, further increase in energy density caused diminished effect. Therefore, energy is more important than the type of light used [30, 31]. Deeper tissues may need a coherent light source. Tissue-specific wavelength and power is needed for maximal effect.

Nitric oxide

Source of nitric oxide

Alterations in mitochondrial physiology have been the basis for the photochemical and photobiological effects of LLLT. Cytochrome c in the electron transport chain is the target for PB. When complexed with mitochondrial cardiolipin, it binds nitric oxide (NO) which is released with photostimulation. It has been found that most of the effects of LLLT are mediated by light-induced vasodilation, in which increase in the levels of NO has been postulated. It is typically generated through oxygen-dependent or oxygen-independent mechanisms. Oxygen-dependent pathway involves production of NO through nitric oxide synthase (NOS) during conversion of l-arginine to l-citrulline. NOS activity is limited by hypoxic and anoxic conditions [32–34]. Under these conditions of oxygen paucity, various pools of NO known as caged NO, which are present throughout the body, lead to increase in its bioavailability. Bulk of NO made in hypoxic conditions is from nitrite reductase activities of multiple biochemical present in the body. These include heme containing proteins such as hemoglobin (Hb) and myoglobin (Mb), which exhibit nitrite reductase activity resulting in increase in NO bound to heme iron of Hb and Mb [35, 36]. As these complexes are stable, there is a slow off rate of NO from them [36–40]. R/NIR at 670 nm facilitates the decay of nitrosyl hemes to release the bound NO and thus increases the rate of release of NO [41]. The caged NO can be released with exogenous stimulation in a site-specific manner which has various physiological and therapeutic implications [42]. Light sensitive proteins are activated by NIR which leads to modification of biological systems. These include photochemicals like cytochrome c, which on interaction with NIR releases bound NO that can be used for biological applications like vasodilation [43–46]. Ischemia leads to low oxygen tension and high concentration of reduced cytochrome c which favor the formation of photosensitive nitrosyl species. Other potential photosensitive sources of NO include guanylate cyclase, cytoglobin, and S-nitrosothiols. Guanylate cyclase is the chemoreceptor for NO-mediated vascular relaxation, which is activated when NO binds its heme site [47]. Cytoglobin can reduce nitrite to NO in anaerobic conditions through its nitrite reductase property [48]. In the presence of photosensitizers like hematoporphyrins, there is increased release of NO from S-nitrosothiols and other donor compounds [49, 50]. Light-induced vasodilation of S-nitrosothiols can be abolished with the depletion of former [51].

The enhanced release of local NO is only partly attributable to the activation of NOS, suggesting an important role of NOS-independent sources. The protective effect of NIR is completely reversed by the NO scavengers but only partially blocked by the NOS inhibitor [30, 52, 53]. Induction of femoral artery collateralization with NIR was found to abolished with carboxypheynl tetramethylimidazoline oxide (c-PTIO), a direct NO scavenger but could not be attenuated with nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor. Thus, NO levels were found to be elevated independent of the NOS activity. Similarly, NIR-induced vasodilation of porcine coronaries and mouse facial arteries could be inhibited by administration of NO scavenger and but not with NOS inhibitor [30, 54]. This strongly points to the conclusion that light exposure results in vasodilation from a NO store that is not affected by the inhibition of NOS activity.

Role of nitric oxide

NO has been found to be a vital transmitter between the light and human cell enzyme systems. Storage pools of NO in body called caged NO can be manipulated for therapeutic purposes in a site-specific manner. It is an important messenger in key biological processes like angiogenesis and hypoxic vasodilation. NIR-induced femoral artery collateralization in the ischemic hind limb of mouse was found to be mediated through NO [53, 55]. Vasodilatory effects observed on porcine coronaries and mouse facial arteries were also found to be mediated through NO released from NIR exposure [30, 54]. It limits the effects of hypoxic-reperfusion injury on the myocardial tissue thus establishing its role in cardioprotection [41, 56]. Transitory exposure to NIR immediately before and during early perfusion protects myocardium against infarction or at least reduces the extent of it if done at the time of reoxygenation [56]. It leads to the reduction of infarct size and was also found to dilate the coronaries during the NIR exposure provided during arterial anastomosis at the time of CABG [57].

Cardiovascular disease

Coronary artery disease, also known as ischemic heart disease, is a leader in all-cause mortality and morbidity nearly effecting

110 million people. It accounts for 15.9% of all deaths globally. Its incidence is increasing every year. It includes spectrum of diseases from stable angina to acute coronary syndrome with latter including unstable angina, non-ST-elevated myocardial infarction, and ST-elevated myocardial infarction. Stable angina is the chest discomfort or pressure like sensation often occurring on exertion and resolving with rest or nitroglycerine. Nitroglycerine has been the cornerstone of therapy for chronic stable angina. It has been administered through different drug delivery systems like sublingual, intravenous pushes and controlled drips, oral powders, and transdermal patches with all leading to one final metabolite, i.e., nitrous oxide (NO). Angina refractory to medical therapy has been treated with transmyocardial revascularization (TMR) [58]. TMR involves creation of laser channels in the myocardium of patients with diffuse coronary artery disease not amenable to percutaneous or surgical interventions. US Food and Drug Administration (FDA) has approved two types of lasers for the same, CO2 and holmium:yttrium–aluminum–garnet (Ho:YAG). Both lasers have different efficacies owing to the different properties of each. Access to the myocardium is gained from thoracotomy. Improvement in angina, increased exercise tolerance, and better quality of life has been achieved with TMR. Its most of the effects can be explained by increased myocardial perfusion attained with angiogenesis directed by the laser. This beneficial yet invasive technique formed the basis for percutaneous myocardial revascularization (PMR). But PMR was not able to get the approval from FDA owing to suboptimal results from the technique.

LLLT is a noninvasive, inexpensive, painless, and easy to administer form of treatment with low rate of adverse effects and serious events [59, 60]. It has an important role to play in cardioprotection. The patients with coronary artery disease in Russia underwent LLLT with repeated exposure of NIR to the precordium. It was found that lipid peroxidation improved significantly but not much results came out in terms of cardioprotection. Later in 2001, improved mortality rates and reduction in infarct sizes were found in the animals exposed with NIR [26]. It weakens the tone of pial arteries leading to augmentation of constrictor action of norepinephrine [61]. Improved collateralization in mouse with scleroderma was observed in the mouse exposed to NIR [55]. The effect was also found to be in the contralateral nonirradiated area [62], suggesting a systemic rather than a localized effect through biochemical.

Unlocking tissue NO for cardiovascular benefits

The prospect of smearing biological effects on remote organ systems in a noninvasive manner through excitation of NO stores in the blood or muscle is feasible and can be targeted towards ischemic regions. One treatment would be to stimulate the ischemic regions in the heart leading to localized vasodilation and resolution of ischemia, thus, leading to relief from angina. Due to the reasonably high tissue penetration paralleled by limited potential of tissue damage, NIR is attractive for the use in ischemic heart disease. We hypothesize a portable source of NIR which can be placed on the precordium. Whenever user experiences anginal symptoms, this source of light can be activated with a simple push of a button. While the required light power needs to be verified for human cardiac use, by comparing animal studies through various species and investigational settings, an irradiance of 10–100 mW/cm^2 for 2–10 min seems a reasonable starting point to achieve beneficial effects of NIR to unlock tissue NO. A higher irradiance may be required for acute prevention of ischemia and reperfusion injury at the time of reperfusion. The highest release of NO has been recorded at 670 nm when protection against ischemia and reperfusion is present.

Summary

The clinical promise for the combined use of R/NIR light and NO is of considerable interest. NIR treatment of the heart may be protective on patients after acute myocardial infarction or on ischemic heart conditions that are not accessible to current revascularization procedures. The combination of LLLT and NO has the advantage over other NO donors as the former will sway against the tolerance that we usually see from the latter. While there is substantial clinical promise for the use of NIR in heart disease, several hurdles need to be considered and overcome.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a review article and non-human research study so ethics approval was not required.

Informed consent This is a review article and non-human research study so informed consent was not applicable.

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