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Low-Level Light Irradiation Therapy and Its Action on the Mitochondrion

Bernard Cambier[1,2], Diana Barragan Ferrer[2], Iris Lebbe[1], Florence Cambier[3]

[1]Department of Plastic Surgery, Sint-Blasius Hospital, Dendermonde, Belgium
[2]Department of Cosmetology, Faculty of Medicine, Kauno Kolegija Higher Education Institution, Kaunas, Lithuania
[3]Research Department, Cerepharma SA, Ath, Belgium
Email: drcambierb@gmail.com

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Abstract

Over the last few years, laser radiation therapy has gained increasing popularity in treating difficult dermatological problems. However, the effect of radiation at the cellular level is often only briefly described. In this article, our goal is to explain the fundamental mechanisms that enable human cells to function at their best capacity. Moreover, we aim to give a clear overview of how laser radiation therapy (LRT) can influence these pathways and what crucial role the mitochondrion has in photobiomodulation.

Keywords

PBM, LLLI, Cytochrome c Oxidase, Mitochondrial ATP Production, Red/NIR Irradiation, ROS, NO Signaling, Electron Transport Chain, Cell Proliferation, Tissue Regeneration

1. Introduction

Shortly after its discovery in the 1960s, laser radiation therapy (LTR) earned its keep when scientists noticed the influence it had on different wound healing processes [1].

In 1967, Endre Mester inadvertently found that low-power LRT did not destroy the skin tumors but rather stimulated healing. These groundbreaking findings paved the way for the treatment of stubborn skin conditions [2].

Photobiomodulation (PBM) therapy describes the therapeutic application of PBM and is characterized by the interaction between light and tissue. It is generally known that extensive exposure to UV light is a risk factor for developing skin cancers, but the effect of lasers on tissue is not equally understood.

Lasers (and other light systems) are modulated to use (quasi)monochromatic

low-level light irradiation (LLLI) to trigger primarily photochemical processes in a non-invasive way [3].

All devices with a wavelength between the spectrum of visible light and infrared (IR) might have a positive effect on tissue (e.g., laser, light-emitting diodes (LEDs)) [1].

Many clinical trials have been published on this topic, but fundamental studies confirming its biological effects are still lacking. However, several aspects of this chain of reactions have already been proven. Findings from clinical trials have shown that when low-intensity lasers are used, as in LLLI therapy, they induce a cellular or tissue-level response without causing any thermal damage [4]. This article focuses on the existing studies of LLLI, its relation to mitochondria, and the enzymes involved in the achievement of PBM. Most of the experiments cited in the articles were performed *in vitro*.

2. Global and Experimental Findings

2.1. LLLI Therapy Induces Cellular Proliferation and Biosynthetic Activity

LLLI therapy is believed to lead to cell synthesis and proliferation phenomena in tissue. When cells encounter low-level light, specific intracellular photoreceptors absorb this light energy, initiating a cascade of intracellular signaling pathways. These pathways subsequently enhance the production of various chemical compounds and enzymes, including adenosine triphosphate (ATP), collagen, and DNA. As a result, cell proliferation and tissue regeneration are promoted. Numerous studies have demonstrated the value of IR and red light in tissue healing and influencing the synthesis of Vascular Endothelial Growth Factor (VEGF), known to affect angiogenesis, proliferation, migration, differentiation, and apoptosis of endothelial cells [5] [6].

In addition, infrared irradiation of the skin also increases cutaneous ferritin levels [7]. Ferritin has anti-inflammatory and antioxidant properties and is known within the anti-inflammatory immune system.

In the early 1980s, experiments on isolated mitochondria showed that low-level light irradiation (LLLI) increased mitochondrial proton electrochemical potential and ATP synthesis. Subsequent studies found that LLLI also elevated RNA levels and protein synthesis [8]. Later, it was found that light also increased RNA levels and protein synthesis [9]. Additionally, research revealed that 660 nm LLLI on rat liver mitochondria enhanced oxygen consumption, activated respiratory chain enzymes, and promoted ATP synthesis through enzymatic reactions [10].

It is important to note that DNA itself cannot be targeted by PBM, as it has no photoreceptor. However, LLLI induces mitochondrial photoreception—primarily via cytochrome-c oxidase—which increases ATP production and modulates reactive oxygen species (ROS), thereby indirectly promoting cell proliferation and stimulating DNA synthesis.

2.2. Intracellular Mechanisms Underlying Photobiomodulation

2.2.1. Mitochondria as Primary Targets of LLLI Therapy

One of the key mechanisms behind LLLI therapy is the activation of mitochondria within cells. The increased production of ATP stimulates the cells into a state of enhanced metabolism, inducing cell proliferation and tissue regeneration. To gain a better understanding, a brief summary of mitochondrial respiration is provided before further dissection of the topic of photochemical reactions.

2.2.2. Structural Organization of Mitochondria Relevant to LLLI Therapy

Mitochondria are the organelles responsible for energy metabolism in eukaryotes; they have a double-membrane structure, consisting of two membranes (outer and inner) enclosing a dense matrix [11] [12] (**Figure 1**).

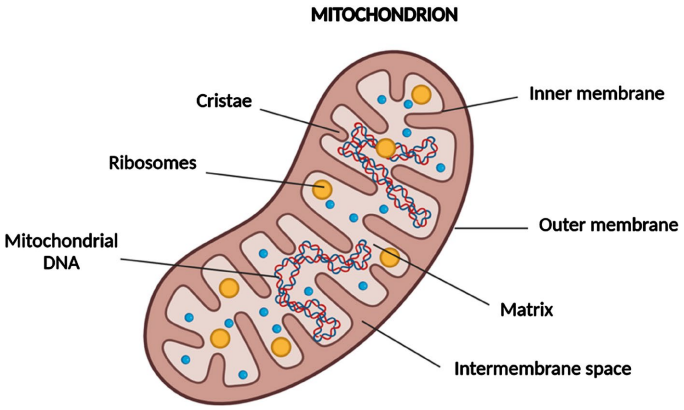

Figure 1. Schematic cross-section of a mitochondrion.

2.2.3. Mitochondrial Respiration and Bioenergetic Control

Respiration is the step-wise release of energy from carbohydrates and other molecules; this energy is used to synthesize ATP and can be divided into three major pathways: glycolysis, the Krebs cycle, and the electron transport chain (ETC). The latter two processes take place in the mitochondria [13]. This ATP can be used directly by the cell. Ultimately, this energy can be released in several forms, such as chemical, mechanical, electrical, osmotic, or thermal energy [14]. Increasing the ADP level (to be discussed later) in the mitochondrial matrix accelerates all reactions of the mitochondrial complexes. Conversely, the oxidations of all these enzymes stop in the absence of ADP in the matrix (**Figure 2**).

During glycolysis, glucose is converted into pyruvate, which is the first step in the breakdown of glucose for energy production. After glycolysis, the Krebs cycle (in the matrix) and the ETC (in the inner membrane) take place [13].

During the Krebs cycle, also known as the mitochondrial tricarboxylic acid (TCA) cycle, the six-carbon molecule citrate is generated, releasing energy that generates GTP (equivalent to an ATP molecule), electrons, and, most importantly, potential chemical energy [15]. These compounds can be further metabolized by the respiratory chain to produce 11 ATP molecules. This is done via a proton gradient and ATP synthase [16] (**Figure 3**).

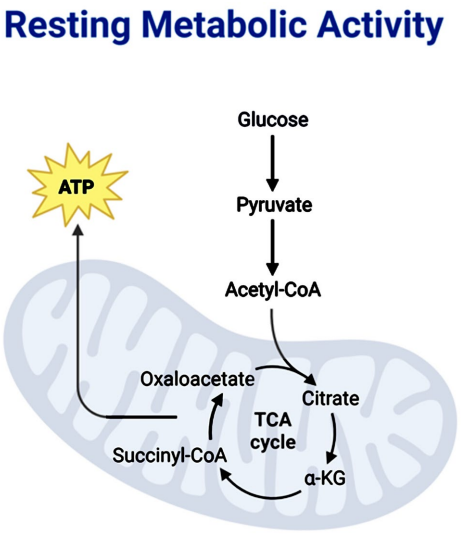

Figure 2. Schematic representation of mitochondrial resting metabolic activity.

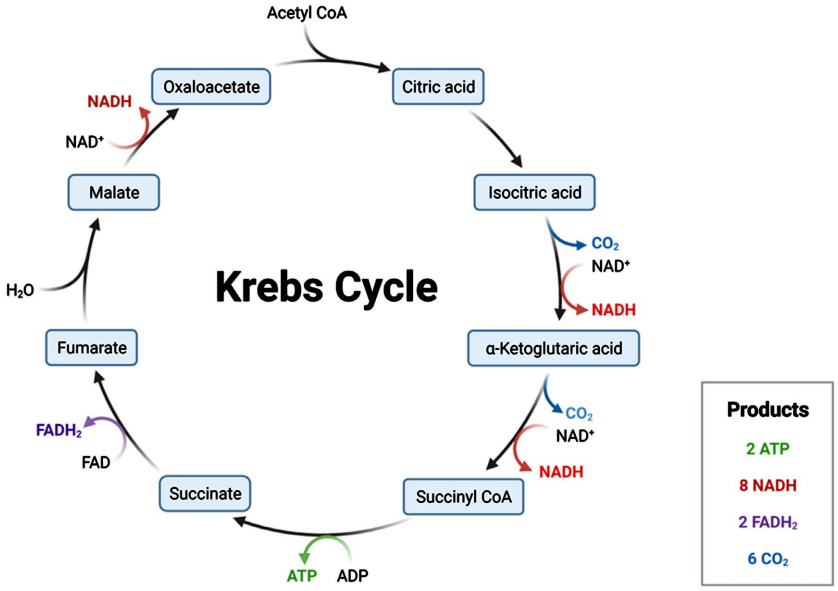

Figure 3. Schematic representation of the Krebs (tricarboxylic acid, TCA) cycle within the mitochondrial matrix, illustrating the generation of reducing equivalents and metabolic intermediates.

2.2.4. Electron Transport Chain Dynamics and the Role of Cytochrome c Oxidase

The ETC is a series of protein complexes and electron carriers located in the inner membrane of mitochondria. These complexes and carriers work together to transfer electrons, resulting in the generation of ATP through a process called oxidative phosphorylation. This chain is regulated by the relative concentrations of ATP and ADP.

Five transmembrane protein complexes (I - V) are responsible for the ETC. Each complex has a specific function in the transfer of electrons. The complexes are eventually combined to form a configured supercomplex [17]. This form of

energy, generated by mitochondrial respiratory chain oxidative phosphorylation, covers over 80% of the ATP required by the cell [18]. Explaining all the complexes would lead us too far for the scope of this article, but it is important to understand that complex IV is of utmost importance in this chain of reactions caused by LLLI [17] (**Figure 4**).

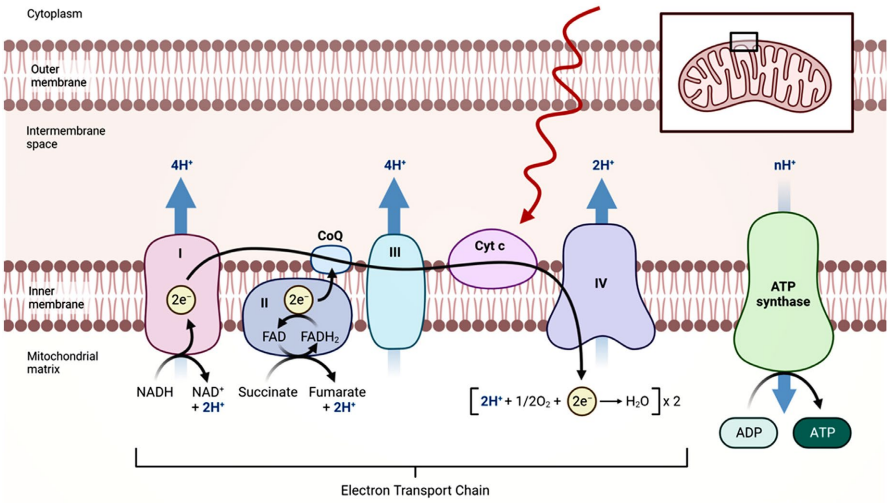

Figure 4. Organization of the mitochondrial electron transport chain (ETC) within the inner mitochondrial membrane.

This brings us to the core of where it all happens: the light-sensitive particles in the mitochondrion.

Cytochromes, **flavins**, and complex IV/the CCO belong to the ETC and can absorb light. Therefore, they are perceived as the photoreceptors of the ETC, with the CCO being the main target.

Cytochromes are coenzymes that transport electrons. Except for soluble cytochrome c, which is the substrate of complex IV, cytochromes are associated with the complexes of the ETC: cytochrome b associates with complex II, cytochrome c1 is in complex III, and cytochromes a and a3 are in complex IV.

Cytochromes absorb light in different bands of the visible light spectrum.

Flavins: Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are coenzymes that transport hydrogen. The flavin nucleus absorbs wavelengths of the visible spectrum. **Complex IV** or cytochrome c oxidase (CCO) oxidizes the cytochrome c iron ions, thereby generating H_2O by transferring electrons from cytochrome C to O_2 and pumps protons from the matrix into the intermembrane space.

We will now explain in more detail how this complex is found to be responsible for the absorption of red light and near infrared (NIR).

2.2.5. The Redox Centers of CCO

The reactive oxygen species (ROS) and nitric oxide (NO) are of major importance. The absorption of photons by the enzymes described above leads to the transient activation of the respiratory chain caused by a redox change in the CCO. This then

triggers a series of molecular reactions. This redox potential relies on two interrelated phenomena: the occurrence of reactive oxygen species (ROS) and the occurrence of nitric oxide (NO).

2.3. Redox Signaling Induced by LLLI Therapy

2.3.1. Reactive Oxygen Species as Signaling Mediators in Photobiomodulation

LLLI is responsible for promoting oxidation reactions and altering cellular redox potential by inducing ROS production in mitochondria [19] [20]. ROS are very small molecules that affect electron transfer and ATP metabolism. Moreover, ROS are important for signalling pathways from the mitochondria to the cell nucleus and can influence transient functions related to mitochondrial metabolism. Their potentially harmful effect is limited by the cell's warning systems. These systems detect ROS and activate antioxidant defenses. In cells, there are several transcription factors that are sensitive to changes in the levels of oxidants and antioxidants, called redox-sensitive transcription factors. These transcription factors control the expression of genes. Two examples of redox-sensitive transcription factors are the nuclear transcription factor NF-kB and the AP1 transcriptional complex.

LLLI causes moderate oxidative stress by stimulating the production of ROS and the induction of oxidative phosphorylation. This activates transcription factors. These transcripts lead to the synthesis or release of numerous molecules, including interleukins, growth factors, and inflammatory cytokines [21]. Among these transcription factors, the role of nuclear transcription factor kappa B (NF-κB) is essential. It regulates cAMP, the levels of cytokines, growth factors, and inflammatory mediators, and leads to an increase in anti-apoptotic proteins.

These signaling and protection systems, stimulated by LLLI, indicate that LLLI has not only restorative but also preventive effects. For example, pre-treatment with IR protects the skin from induced UVB toxicity because IR inhibits UVB-induced apoptosis. In this process, the role of the transcription factor p53 is essential as a regulatory factor that watches over the integrity of the cell [22]. It brings the cell into a resting phase, which promotes recovery, or it induces apoptosis. LLLI could therefore promote anti-apoptotic protective effects. Another study, which showed that UV-induced erythema can be preventively treated with a 660 nm LED, reinforces this conclusion [23]. Moreover, the activation of anti-apoptotic genes explains why exposure to LLLI protects the cell from the harmful effects of cyanide, tetrodotoxin, or methanol [24] [25].

Besides, PBM promotes cell proliferation and viability due to the promotion of free radical action, which affects the expression of genes involved in DNA repair. APEI and OGG1 are examples of this. Their expression, after exposure to laser irradiation, appears to be different in skin and muscle tissue and depends on the parameters and protocols [26].

ROS also regulate growth factors and enzymes involved in tissue repair. The anti-inflammatory effects of LLLI should also be highlighted. Researchers showed, in cultures of human fibroblasts, that irradiation at 635 nm can directly dissociate

ROS. This ultimately results in the inhibition of prostaglandin E2 (PGE2) release, substances that play a central role in inflammation [27].

It is suggested that LLLI therapy may be pro-oxidant in the short term by promoting oxidative phosphorylation, but antioxidant in the medium or long term through the initiation of protective pathways as illustrated above [28].

2.3.2. Absorption Spectra of Cytochrome c Oxidase in Different Redox States

CCO contains two redox centres, two hemes (heme a and heme a_3) and two copper atoms (Cu_a and Cu_{a3}) [29]. Between its fully oxidised and fully reduced forms, CCO has many intermediate forms of mixed valence with different ligation states. These different forms have different absorption spectra [30]. Researchers discovered four "active" regions of the absorption spectrum, and these seem to depend on the nature of the CCO intermediates. The first region is between 613.5 and 623.5 nm, the second is between 667.5 and 683.7 nm, the third is between 750.7 and 772.3 nm, and the last peak position is between 812.5 and 846.0 nm [31].

Thus, the absorption spectrum of CCO varies and depends on the oxidation state of CCO. The wavelengths at 710 - 790 nm are characteristic of a relatively reduced photoacceptor, while the region at 650 - 680 nm is characteristic of a relatively oxidized state of the photoacceptor [32].

2.3.3. Nitric Oxide Release and Mitochondrial Signaling Modulation

NO is a free radical and a gas that, together with other free radicals, is important in the primary defence against attacks by microorganisms, and is involved in, but not exclusive to, neurotransmission, vasodilation, wound healing, and the regulation of biochemical pathways [33].

In 2005, researchers showed that enhanced mitochondrial NO production took place after red and NIR irradiation [34]. Moreover, LLLI was found to induce both the production and release of NO, particularly from the OCC, in cultured cells. The NO thus produced in small amounts probably activates signalling pathways beneficial to the cell [35] [36].

All these biological processes demonstrate the clinical relevance and potential of LLLI. However, to achieve the most effective result, the implementation and irradiation parameters, such as dosing and frequency, need to be carefully monitored.

2.3.4. Wavelength-Dependent Effects and Dose-Response Relationships

The colour of light is determined by its wavelength, which is essential for LLLI therapy. Photons are absorbed by photoacceptors, which trigger biochemical reactions.

These biochemical effects result from complex interactions that combine activating and inhibitory effects [37]. This explains why exposure to a single wavelength can be effective in a way that is not the case when radiation is delivered in the broad visible spectrum.

Regarding the dose, it was found that the "reciprocity rule", whereby a photochemical reaction is directly proportional to the total energy dose, regardless of the time in which this dose is delivered, does not apply to PBM. Moreover, there

is a threshold dose to consider [31].

It is important to note that there is a relationship between the several parameters. As a result, fluence, power density, and duration should not be considered separately. The different parameters play an important role, which is why biphasic dose (stimulation under low-dose treatments, but inhibition under high-dose) responses exist. The Arndt-Schulz curve illustrates the complexity of this response and visualizes a possible dose "sweet spot" in the tissue. It shows that too short a duration or insufficient power density has no effect, and conversely, excessive duration and/or power density may have inhibitory effects. Therefore, the maximum beneficial effect has an optimal balance between duration and power density [36].

2.3.5. Influence of the Cellular Metabolic State on Photobiomodulation Outcomes

Furthermore, treatment results appear to be better when the cells have stopped dividing and are in a suffering state. This makes the condition of the cells at the time of irradiation essential.

The stimulatory effect of irradiation is greater on resting or slowly growing cells than on cells that are already in the growth phase. More specifically, irradiation of already growing cells even had an inhibitory effect in some experimental models [38]. Several decades later, clinical studies showed that the most damaged cells seemed to respond better to LED. After fractional laser treatment, half of the treated area was exposed to LLLI, and the difference in healing between these two areas was only visible (48 hours later) in the patients exposed to the highest fractional laser dose [39]. From this, it can be deduced that the action spectrum varies according to the proliferation phase of the cell [31] (**Figure 5**).

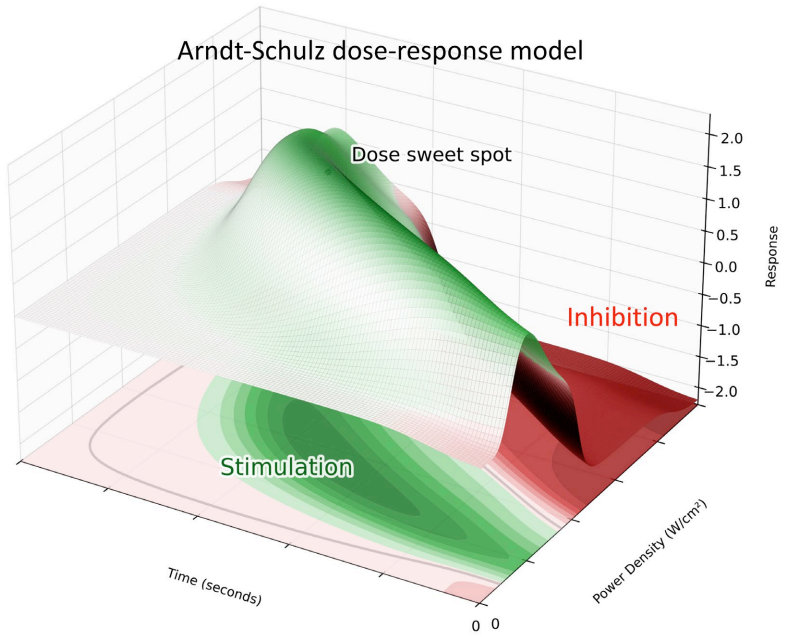

Figure 5. Three-dimensional model of the Arndt-Schulz curve illustrating how either irradiance or illumination time (fluence) can have biphasic dose response effects in LLLT.

3. Discussion and Conclusion

All these studies clearly indicate the potential biological and clinical effects of LEDs on the prevention of apoptosis, induction of cell proliferation, stimulation of fibroblasts, collagen synthesis, and angiogenesis, which are all related to tissue repair. Exposure to certain wavelengths of light could therefore increase the activity and efficiency of mitochondria, leading to improved cell function and possibly even a delay in the aging process. Overall, the effect of light on mitochondria is a complex chain of reactions in which perfect circumstances are necessary for optimal treatment and results.

Variable factors such as the initial state of the cells and the parameters of an LLLI device (e.g., wavelength, pulse system, level of deposited energy, energy density, and power density) need to be taken into account, as well as the correct positioning of the area to be treated relative to the light source, allowing enough photons to reach the target, are essential to achieve the desired result.

In this article, our aim was to demonstrate the pivotal role of mitochondria in PBM. We explained the crucial role of cytochrome c oxidase, a critical component of the mitochondrial electron transport chain (ETC), and the absorption of light by CCO. These mechanisms enable cells to respond to changes in their environment and regulate their metabolic processes. The molecular outcomes (e.g., increased ATP and VEGF) are of major importance and have an observable therapeutic benefit (e.g., accelerated wound closure).

However, many factors in this LLLI therapy remain unclear. It is suggested that LLLI therapy may act as a pro-oxidant in the short term by promoting oxidative phosphorylation, but as an antioxidant in the medium term through the initiation of protective pathways [28].

One of the problems with studies regarding LLLI is that they are hard to compare because the specifications of an LLLI device are known not to be always reliable [40]. This is one more argument for understanding that irradiations that are excessive in dose or duration can lead to a lack of impact or induce unfavourable outcomes.

Furthermore, clear guidelines regarding the appropriate dosage and duration of LLLI therapy are not yet in sight and are still being debated. The results and information collected so far may be called into question due to the fact that these experiments were performed *in vitro*.

LLLI is promising in the treatment of difficult wound healing problems, but further research is needed to gain more information about the specifications of the therapy.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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