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Photobiomodulation therapy (PBMT) and low-level laser therapy (LLLT)

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ABSTRACT

Low-level laser therapy was first introduced over 50 years ago. It is a very well-researched regulation therapy in which ATP synthesis in the mitochondria is stimulated by irradiation of the skin and wounds with photons. This leads to a variety of biochemical reactions throughout the body, which trigger anti-inflammatory, immunological and analgesic effects as well as the promotion of cell proliferation. The optimal wavelength is between 633 and 690 nm, i.e. in the red range. The optimal irradiation dose is 10 J/cm². However, now that the technology has evolved we know that it does not necessarily require coherent, i.e. laser, light to stimulate biological processes in the body. LED-based devices have the same effect. The difference lies in the potential energy density that can be delivered. Science therefore considers it useful to use the term photobiomodulation which was coined by the inventor of low-level laser therapy Endre Mester. That term would better reflect the way the therapy acts on the skin and wounds and can affect the tissues.

KEYWORDS

Chronic wounds, low-level laser therapy, photobiomodulation therapy

Introduction

The efficacy of laser therapy has been repeatedly confirmed in the literature. Despite that, it is rarely used in wound treatment and continues to be imbued with a certain mystic quality. Many practitioners are unable to comprehend that red light has a relevant effect on the body's regenerative powers. They do not know which technique is applied, which laser output power is used and how long irradiation should last.

The treatment effects are not immediately discernible, thus making it difficult to assess the causal relationship with the outcome. Our knowledge as

wound treatment practitioners of the activities unfolding at cellular level is probably marginal to non-existent. The present author has for many years used laser technology in wound treatment and in this article summarizes all the available relevant, and also scientifically based, information. It is of course important that the right tools are also correctly used. That requires corresponding know how.

Historical background

We instinctively feel that natural sunlight is good for us. Red light was used in medicine already in ancient times. "Red light syndrome" was described back in the 19th century, with much experimental work taking place between 1890 and 1930. Red light therapy was among the methods intensively researched and applied by the Faroese-Danish dermatologist Niels Ryberg Finsen (Fig. 1), the father of contemporary phototherapy. He was awarded the Nobel Prize for medicine in 1903 for his successes in the treatment of smallpox, lupus erythematosus and cutaneous tuberculosis (Fig. 2) using concentrated, cooled light rich in UV radiation. Prior to that, he had already used light to treat children suffering from rickets which at that time was a widespread, but poorly understood, disease among children in large cities. Light therapy was not yet understood or accepted. For example, researchers were unable to conceive of a relationship between the effects of light and metabolism. Only after gaining insights into vitamin D metabolism was the importance of sunlight recognized [5, 10, 12].

Following the discovery of the laser (Light Amplification by Stimulated Emission of Radiation) around 1960, powerful monochromatic light sources with high light output began to be gradually used by medical researchers for experimental treatment purposes. The first scientist to achieve therapeutic effects

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was Endre Mester, the Hungarian pioneer in laser medicine and father of photobiomodulation therapy (PBMT) (Fig. 3). In the late 1960s, he published his initial findings obtained with a ruby laser (633 nm). Over the course of time he had observed that light therapy expedited healing of the most diverse wounds. He experimented with incision wounds, burns, diabetic ulcers, infected wounds and decubitus ulcers. Since then the therapeutic effects of light in the 600 nm to 1000 nm wavelength range were also observed on other types of tissues, such as muscles, nerves, tendons, gums, cartilage and bones [4, 6, 12, 13] (Tab. 1).

As thus outlined above, light therapy already has a long history of successful implementation. But why is it time and again called into question and used so little? A crucial factor is time. We expect to see results in the shortest amount of time and hardly give the wound and tissues a chance to regener-

ate and repair. Likewise, there is a widespread lack of knowledge of the activities taking place at cellular level. Photobiomodulation therapy underpins at different levels the body's repair and regeneration processes and if a powerful device is properly used, the practitioner will achieve very good results in a short time.

Definition of low-level laser therapy and photobiomodulation

This is understood to mean the irradiation of a tissue, generally the skin, with light of correspondingly low power density to effectively prevent onset of thermal or athermal damage. The irradiation process has only a stimulating effect. It is important here to point out that the warming of the tissues is a function of the power density and not of the absolute output power. The more focused the laser therapy is delivered to a tissue, the warmer it becomes. In such cases, irradiation acts like a combustion glass and can result in unintended damage. Therefore, a number of basic rules, to be explained later, should be observed [8, 10, 12, 13].

In microscopic terms, the following main effects are seen (Tab. 1):

- Anti-inflammatory effects
- Immunological effects
- Analgesic efficacy
- Regulatory/regenerative cell proliferation

Low-dose laser therapy exhibits primarily regulatory characteristics. Laser therapy acts as a trigger for endogenous regulatory loops so that they can work properly again.

Walter wrote in 1997: "In the majority of cases of impaired wound healing the



Fig. 3 Prof. Endre Mester

oxygen concentration, pH value and thus cellular metabolism in its entirety are massively disrupted. If LLLT is now delivered, cellular metabolism is triggered again because the proton gradient on the inner mitochondrial membrane needed for ATP synthesis is built up and all ATP-driven membrane pumps are started, i. e. all preconditions required for high cell proliferation are met provided that an adequate supply of nutrients is available.

But if a fresh or self-healing wound with more or less high cell proliferation is irradiated, only minimal or no improvement is achieved with LLLT. In other words, if a cell is functioning optimally, there is nothing for the laser to stimulate and hence no discernible improvement" [13].

However, the regulatory characteristics are also manifested as two other LLLT effects: Whereas for certain medical indications increased perfusion is needed (e. g. in cervical syndrome) there are also indications where the opposite, i. e. reduced perfusion, is required, e. g. in burns. Increased perfusion in burns would be very painful. Low-dose radiation regulates perfusion while taking account of these opposing requirements. Hence, the low-level laser acts more like a "perfusion regulator" than a "perfusion amplifier" [12, 13].

Biochemical principles

The Russian professor Tiina Karu demonstrated in the 1980s that the respiratory chain enzymes were the primary photoacceptors in the mitochondria (e. g. acetyl coenzyme A) (Fig. 4).

To understand where laser therapy generates its effects, one must take a



Fig. 1 Niels Ryberg Finsen

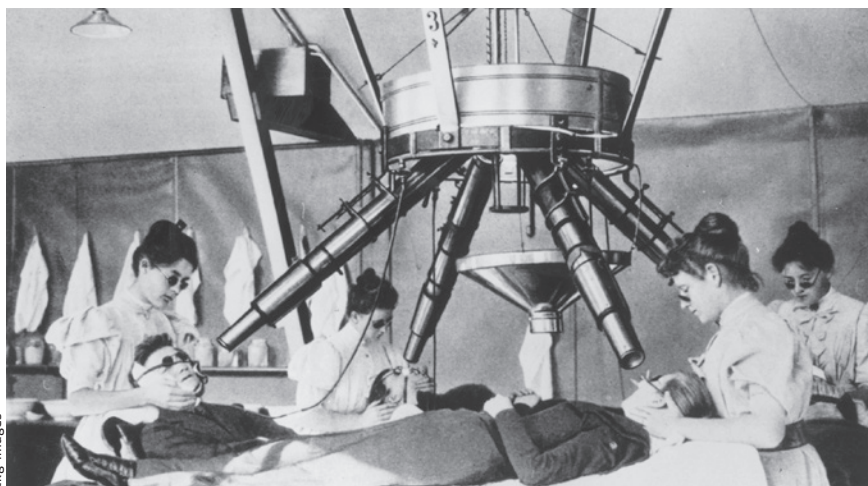


Fig. 2 Cutaneous tuberculosis therapy at Finsens Light Institute in Copenhagen

look at carbohydrate breakdown and cellular respiration (Fig. 5).

Cellular respiration comprises the following partial processes: glycolysis, the citric acid cycle (Krebs cycle) and end oxidation in the respiratory chain.

The complex components of our food are first broken down into their basic units, i.e. glucose, fatty acids, glycerol and amino acids and finally to acetyl coenzyme A. In the citric acid cycle it is this enzyme that is oxidized to CO₂.

The respiratory chain constitutes a special electron transport chain that takes place in humans on the inner membrane of the mitochondria [2, 12, 13]. This is a biological process in electron transport in which several electron carrier molecules are passed from a donor to one or several acceptors. The energy thus released drives the synthesis of energy-rich ATP (adenosine triphosphate) from ADP (adenosine diphosphate). At the end of this breakdown pathway the energy thus released enables the cell to use the energy-rich compound adenosine triphosphate (ATP), which is the body's universal energy source for many metabolic processes. Hence, ATP is a versatile transport molecule integrated in many different energy coupling systems in metabolism. In their book "Biochemistry", Reginald Garret and Charles Grisham described ATP as the "Intermediate Energy Shuttle Molecule" [2].

The authors of that book gave an example of how a person with a bodyweight of 70 kg, who consumes around 2,800 calories per day, produces 65 kg ATP per day, i.e. almost their own bodyweight. Thanks to the highly efficient recycling system for ATP/ADP utilization, our body recycles the energy consumed in intermediary metabolism to ATP, so that it can be reused again. Based on the sample calculation given, each ATP molecule in our body must be recycled around 1,300 times per day! The accomplishments of biochemistry as portrayed here in maintaining the body's wonderful activities and powers elicit our respect and fascination [2].

Photobiomodulation - principles

If a cell is now additionally irradiated with light (Figs. 6 and 7), the redox process of the aforementioned enzyme

Table 1: PBMT efficacy ranges [12, 13]

Effects	Types of cells involved	Evidence-based application fields (selection)
Anti-inflammatory	- From inflammatory mediators (e.g. platelet-derived growth factor [PDGF] through megakaryocytes to thrombocytes - From CD4+ and CD8+ T-lymphocyte surface receptors to TGF-β and TNF-β as anti-inflammatory mediators	- Mucositis e.g. following radio- or chemotherapy - Rheumatoid arthritis - Herpes simplex, herpes zoster - Otitis, rhinitis - Tendinopathy, insertion tendinopathy - Achillodynia
Analgesic	- Degranulation of mast cells with release of anti-inflammatory mediators and of lymphokines by macrophages - Lymphokines from interleukin-1 to CRH to ARH and β-endorphins confer opioid receptor-mediated analgesia	- Traumatic pain - Postoperative pain - Polyneuropathy - Fibromyalgia - Joint pain - Post-zoster neuralgia
Regenerative	- Thrombocytes (coagulation, wound closure, growth factors for inflammatory cells) - Mast cells, lymphocytes, neutrophilic granulocytes, macrophages (immune defence, phagocytosis) - Fibroblasts, vascular endothelial cells, keratinocytes (collagen synthesis, angiogenesis, epithelialization, wound defect filling with granulation tissue)	- Surgical wounds (Caesarean section, bypass, after joint replacement, jaw surgery, etc.) - Impaired diabetic wound healing - Burns - Muscle fibre tears - Tendon and ligament injuries - Nerve injuries - Abrasions - Lacerations and contusion wounds - Bone and cartilage defects - Haematomas
Immunological	- Regulation of the immune response through regulation of reactive oxygen species (ROS). According to Karu, these are formed in the NADPH oxidase system, in macrophages and neutrophilic granulocytes as well as in the mitochondrial respiratory chain - Increase in erythrocyte deformability - Leukocytes, blood plasma	- Recurrence-free periods e.g. in herpes - Improvement of immunocompetence e.g. in ICU patients - Chronic allergies and dermatosis - Exhaustion conditions - Lipid metabolic disorders - Autoimmune diseases - Diabetes mellitus

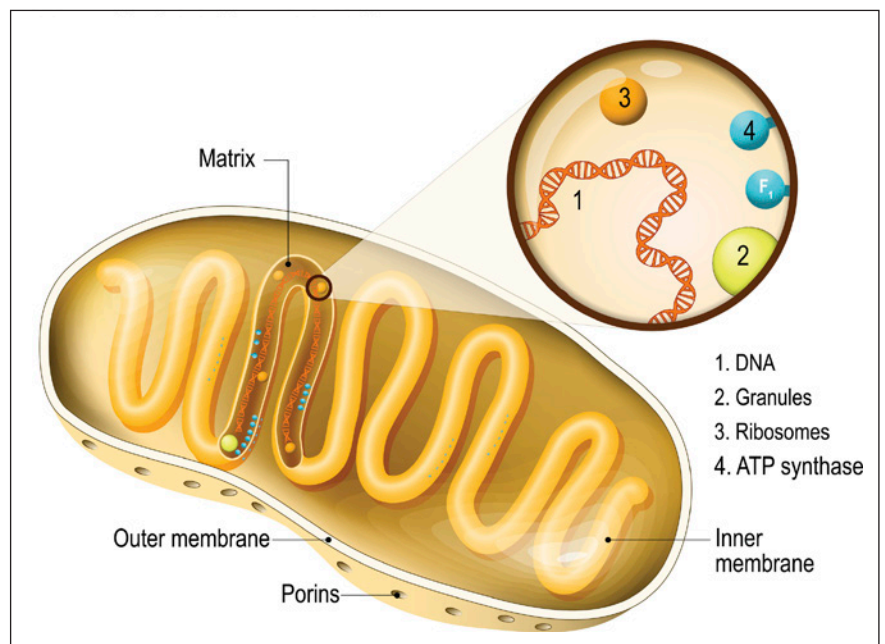


Fig. 4 Structure of a mitochondrion. Mitochondria are small greenish organelles measuring 0.5–2 μ m in length (1 μ m is equal to one thousandth of a millimetre) [7]. Cells with high energy consumption, such as myocytes, neurocytes or oocytes are especially rich in mitochondria. Mitochondria account for around 36 % of the volume percentage of cardiac muscle cells [2].

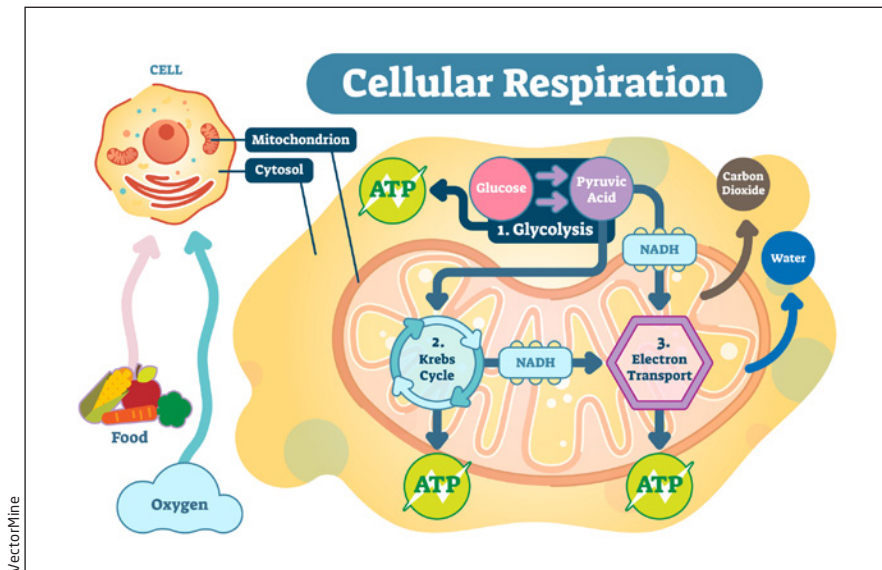


Fig. 5 In cellular respiration biochemical energy is converted to ATP.

complexes is underpinned by means of photooxidation. In their excited state electrons are less tightly bound to the respective molecule than in their unexcited state. The energy of absorbed photons is thus transferred chemically to the redox centres of the enzyme complexes of the respiratory chain where they exert a certain regulatory effect.

The precise process involved is unknown but it is thought that internal cell regulation is improved through irradiation and that repair processes are triggered.

In specific investigations showing concordance with clinical experiences, Prof. Tiina Karu demonstrated that for maximum stimulation it was not only the energy density but also the power density and thus the irradiation time which had to be within a particular range [11, 12].

The light-induced increase in ATP synthesis following irradiation in turn increases the activities of various transport systems. This stimulates DNA and RNA synthesis. Karu was the first to demonstrate in the “light signal transfer chain” that these processes led to increased cell proliferation. It should be added here that, for example, ATP-driven Ca^{2+} ion carriers control virtually all processes in the human body, such as e.g. muscle contraction, blood coagulation or nerve signal conduction.

For the past three decades it has thus been reported in the literature that irradiation with light enhances ATP synthesis and, through the associated release of neurotransmitters, has widespread effects on body processes [2, 3, 10–13].

Optimal wavelength

The same stimulation results are obtained also in the near UV and blue range as in the red and infrared range but it is best to implement irradiation in the red wavelength range. It is also important to observe the penetration depth and this depends on the wavelength. The best compromise between penetration depth and efficacy is wavelengths in the red range between 633

Effects of different wavelengths

- The shorter the wavelength, the higher is the energy content of the individual photons.
- Near infrared (750–1000 nm): Penetrates deeper but because of the lower energy content contributes less to ATP synthesis. For healing processes in deep tissues, such as muscles, tendons, bone and cartilage.
- Red light (600–750 nm): mainly for healing open skin wounds or mucosal wounds.
- Blue light (420–500 nm): When enough is delivered, bactericidal properties.
- Violet light (380–420 nm) to near ultraviolet light (200–380 nm): Enhanced bactericidal and virucidal properties



Fig. 6 Surface application of laser treatment. Distance here is 10 cm



Fig. 7 Selective irradiation using the same energy but with 1.5 cm lower distance - thus higher energy density.



Fig. 8 Case example day 1. View above: distal, View below: fingertip. The entire finger exhibits oedematous swelling and parts of the ultrasensitive fingertip are already necrotic again.



Fig. 9 Case example day 3. There is less pain and cell proliferation has been triggered.

and 690 nm [11]. The optimal dose for irradiation of human tissues is 10 J/cm² [1, 3]. The effects of the different wavelengths are illustrated in the box above.

Immune response

Impaired wound healing may also be prolonged in the absence of an immune response. Laser therapy enhances or attenuates generation of the necessary oxygen radicals. In such cases it also acts as regulatory therapy [13].

Analgesic effects

The analgesic efficacy achieved with laser therapy never fails to impress. But the mechanisms involved are very complicated. Depending on what is irradiated, and where irradiation is administered, a peripheral laser stimulus can



Fig. 10 Case example day 7. Now there is only a small wound at the fingertip. No more pain and now only dehiscence and oedematous swelling

exert a direct impact on the central nervous system via complex pathways and stimulate the immune system. Several studies have demonstrated that this leads to the release of β -endorphins and thus triggers opioid-receptor-induced analgesia and, in turn, the release of cortisol and other glucocorticoids by the adrenal glands, triggering immunosuppressive and anti-inflammatory effects. Oedema reduction is also seen in the wound area. Oedema can exert pressure on the surrounding sensory nerve endings and may thus cause severe pain. The pain is soon reduced due to the antioedematous effects of the laser.

Case example

The series of photos below depict the course of healing in a 62-year-old man who had sustained a traumatic injury to the ring finger. Wound sepsis caused by anaerobic bacteria was observed following surgery and soon afterwards he had to undergo revision surgery. Day 1 is one week after revision surgery (Fig. 8). The patient experienced



Fig. 11 Case example day 28. Everything has healed well. Still minor restricted movement but with complete restoration of load-bearing ability.

severe pain. It was very difficult to replace the dressing. The entire finger exhibits oedematous swelling and parts of the ultrasensitive fingertip are already necrotic again. After cleaning with a hypochlorous wound irrigation solution, laser therapy was administered using 400 Joules in continuous wave (cw) mode. Then the finger was covered with silicone-based PU foam. The oedema-mediated pressure pain soon resolved after irradiation. The dressing was replaced again two days later using the same procedure (Fig. 9). The dressing was left in place for four days. On day 7 the positive effects of laser irradiation are discernible (Fig. 10). These benefits included analgesic effects, massive cell proliferation, immune response and marked reduction in the bacterial burden.

Figure 11 shows the condition of the wound four weeks after initial treatment. The patient had continued self-treatment 2 × daily with a rod laser. He is able to engage in sports activities again, including paragliding and mountain biking.

Conclusions

If photobiomodulation is administered within a specific spectrum and power range, the technology is available to trigger a regulatory effect on cell metabolism, in particular on cellular respiration. There have been no reports of side effects in the literature but these cannot be ruled out. Therefore, treatment should always be initiated with a lower irradiation dose and can then be increased in line with requirements and experience.

The precise number of photons needed to stimulate, regulate and repair the cells is not known. A laser with only 1 mW and a wavelength of 670 nm emits already by itself 3×10^{15} photons per second [2, 3, 12, 13].

Therefore, practitioners need to have a certain amount of knowledge, time, experience and intuition to achieve the best results. But if one has enough patience and gives the body a chance to regenerate through photobiomodulation, one will soon see that this technology can confer important benefits on persons with impaired wound healing.

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