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Review Article

Low Level Laser Therapy Mechanisms and Applications

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Introduction

Definition of LASER

A **laser** is a device that emits light through a process of optical amplification based on the stimulated emission of electromagnetic radiation. The term "laser" originated as an acronym for "**light amplification by stimulated emission of radiation**". A laser differs from other sources of light in that it emits light coherently. Spatial coherence allows a laser to be focused to a tight spot, enabling applications such as laser cutting and lithography. Spatial coherence also allows a laser beam to stay narrow over great distances (collimation), enabling applications such as laser pointers. Lasers can also have high temporal coherence, which allows them to emit light with a very narrow spectrum, i.e., they can emit a single color of light. Temporal coherence can be used to produce pulses of light as short as a femtosecond [1].

Classification of LASER

The classification system as specified by the International electrochemical commission (IEC) 60825-1 standard **(IEC, 2007).** Classes 1,1M,2,2M,3R are considered as low level laser, while classes 3B, and 4 can be considered as high level laser [2].

Low level laser therapy(LLLT)

Low-level laser therapy (LLLT) is a form of laser medicine used in physical therapy and veterinary treatment that uses low-level (low- power) lasers or light-emitting diodes to alter cellular function. Other names for the therapy include low-power laser, soft laser, cold laser, biostimulation laser, therapeutic laser, and laser acupuncture. Whereas high-power lasers ablate tissue, low-power lasers are claimed to stimulate it and to encourage the cells to function [3].

LLLT is integrated with mainstream medicine with ongoing research to determine where there is a demonstrable effect. Areas of dispute include the ideal location of treatment (specifically whether LLLT is more appropriately used over nerves versus joints), dose, wavelength, timing, pulsing and duration. The effects of LLLT appear to be limited to a specified set of wavelengths of laser, and administering LLLT below the dose range does not appear to be effective [4].

Low level laser classification:

There are three diode types. The first is an **Indium, Gallium-Aluminum-Phosphide (InGaAlP)** laser. This is a visible red-light laser diode that operates in the 630-700 nm range. These lasers output light continuously. These lasers also might be

pulsed by an electro-mechanical method (duty cycle). A duty cycle output means the power is switched off for part of a second and then switched back on. If it was off for a ½ second and on for a ½ second, that would be referred to as a 50 percent duty cycle. This reduces the average power output by 50 percent. Red-light lasers have the least amount of penetration of the three lasers with a range of 6-10 mm. They affect the skin and superficial tissue [5].

The second semiconductor laser is a **Gallium-Aluminum Arsenide (GaAlAs)** laser. This is a near-infrared laser, which means that the light emission is invisible to the naked eye. This laser operates in the 780-890 nm range. This type of laser also has a continuous output of power and is often pulsed on a duty cycle as described above. This laser penetrates 2-3 cm in depth. These lasers often are utilized for medium to deep tissue structures such as muscles, tendons and joints [5].

The third semiconductor laser is a **Gallium-Arsenide (GaAs)** laser. This laser is unique in that it always is operated in superpulsed mode. Superpulsing means the laser produces very short pulses of high peak power. These peak power spikes usually are in the 10-100 watt range, but last for only 100-200 nanoseconds while maintaining a mean power output that is relatively low. This phenomenon is similar to what happens in a camera flash. Superpulsing allows for deep penetration into body tissues without causing the unwelcome tissue effects of continuous high-power output, such as heat production. Superpulsing allows for deeper penetration than a laser of the same wavelength that is not superpulsed, but has the same average output power. Penetration is 3-5 cm or more. Superpulsing also allows for treatment times to be the shortest possible. These lasers are extremely well-suited for medium and deep tissues, such as tendons, ligaments and joints [5].

Evidence for effectiveness of LLLT

Since 1967 over 100 phase III, randomized, double-blind, placebocontrolled, clinical trials (RCTs) have been published and supported by over 1,000 laboratory studies investigating the primary mechanisms and the cascade of secondary effects that contribute to a range of local tissue and systemic effects [6].

RCTs with positive outcomes have been published on pathologies as diverse as osteoarthritis ,tendonopathies ,wounds, back pain ,neck pain,muscle fatigue, peripheral nerve injuries and; nevertheless results have not always been positive. This failure in certain circumstances can be attributed to several factors including dosimetry (inadequate or too much energy delivered, inadequate or too much irradiance, inappropriate pulse structure, irradiation of insufficient area of the pathology),inappropriate anatomical treatment location and concurrent patient medication (such as steroidal and non-steroidal anti-inflammatories which can inhibit healing) [7].

Technique of application

There are two major types of lasers, contact and noncontact, used in medicine. Contact lasers work by sending a light through a fiber or sapphire tip. The tip absorbs energy and becomes hot. When the hot tip touches any live tissue in the body, the target cells are vaporized, which is the removal of tissue through the conversion of a solid to a gas. Noncontact lasers do not touch the tissue. They operate by transferring laser light as radiant energy in a single beam to the tissue. Heat results when the cell absorbs this energy. In both cases, the laser light is not hot. Heat is only created after the laser's radiant energy is absorbed by the targeted tissue [8].

Contact lasers can be used for cutting through bone as well as pulverizing kidney stones. A common contact laser is called the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. This laser can go deep into the tissue and even cause blood to clot. It is often used in cancer patients [9].

Some noncontact lasers are used with laser light-sensitive drugs. Such a drug is administered to a patient, and over time, the drug is absorbed into tumor cells only. By exposing the drug in the cancer cells to the laser, a chemical reaction occurs. This kills the cancer, but most healthy cells are not affected. This is called photodynamic therapy [10].

Mechanisms of action of low level light therapy

1. Cellular Chromophores and First Law of Photobiology

The first law of photobiology states that for low power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular photoacceptors, or chromophores [11]. A chromophore is a molecule (or part of a molecule) which imparts some decided color to the compound of which it is an ingredient. Chromophores almost always occur in one of two forms: conjugated pi electron systems and metal complexes [12].

Examples of such chromophores can be seen in chlorophyll (used by plants for photosynthesis), hemoglobin, cytochrome c oxidase (Cox), myoglobin, flavins, flavoproteins and porphyrins [13].

2. Action Spectrum and Tissue Optics

Irradiation Time Or Energy Delivered (*The Dose*)
Irradiation Unit of Parameter measurement

Energy (Joules) J Calculated as: Energy (J) = Power (W) x time (s)

This mixes medicine and dose into a single expression and ignores Irradiance. Using Joules as an expression of dose is potentially unreliable as it assumes reciprocity (the inverse relationship between power and time) [14].

Energy Density J/cm^2 Common expression of LLLT -dose is Energy Density(14).

This optical window runs approximately from 650 nm to 1200 nm. The absorption and scattering of light in tissue are both much higher in the blue region of the spectrum than the red, because the principle tissue chromophores (hemoglobin and melanin) have high absorption bands at shorter wavelengths,-tissue scattering of light is higher at shorter wavelengths, and furthermore water strongly absorbs infrared light at wavelengths greater than 1100-nm. Therefore the use of LLLT in animals and patients almost exclusively involves red and near-infrared light (600-1100-nm) [15].

Phototherapy is characterized by its ability to induce photobiological processes in cells. Exact action spectra are needed for determination of photoacceptors as well as for further investigations into cellular mechanisms of phototherapy. The action spectrum shows which specific wavelength of light is most effectively used in a specific chemical reaction [16].

3. Mitochondrial Respiration and ATP

Current research about the mechanism of LLLT effects inevitably involves mitochondria. Mitochondria play an important role in energy generation and metabolism. Mitochondria are sometimes described as-cellular power plants, because they convert food molecules into energy in the form of ATP via the process of oxidative phosphorylation. Several pieces of evidence suggest that mitochondria are responsible for the cellular response to red visible and near infrared (NIR) light. The effects of HeNe laser and other illumination on mitochondria isolated from rat liver, have included increased proton electrochemical potential, more ATP synthesis, increased RNA and protein synthesis and increases in oxygen consumption, membrane potential, and enhanced synthesis of NADH and ATP [17].

4. Cytochrome c oxidase and nitric oxide release

Absorption spectra obtained for cytochrome c oxidase (Cox) in different oxidation states were recorded and found to be very similar to the action spectra for biological responses to light **.**Therefore it was proposed that Cox is the primary photoacceptor for the red-NIR range in mammalian cells [18].

5. Nitric oxide signaling

In addition to NO being photodissociated from Cox as described, it may also be photo-released from other intracellular stores such as nitrosylated hemoglobin and nitrosylated myoglobin [19].

Light mediated vasodilation was first described in 1968 by **Furchgott**, in his nitric oxide research that lead to his receipt of a Nobel Prize thirty years later in 1998.

Later studies conducted by other researchers confirmed and extended **Furchgott's** early work and demonstrated the ability of light influence the localized production or release of NO and stimulate vasodilation through the effect NO on cyclic guanine [20].

6. Reactive oxygen species and gene transcription

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are involved in the signaling pathways from mitochondria to nuclei.Reactive oxygen species (ROS) are very small molecules that include oxygen ions such as superoxide, free radicals such as hydroxyl radical, and hydrogen peroxide, and organic peroxides. They are highly with biological molecules such as proteins, nucleic acids and unsaturated lipids. ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling [20], regulating nucleic acid synthesis, protein synthesis, enzyme activation and cell cycle progression [21].

LLLT was reported to produce a shift in overall cell redox potential in the direction of greater oxidation and increased ROS generation and cell redox activity have been demonstrated these cytosolic responses may in turn induce transcriptional changes. Several transcription factors are regulated by changes in cellular redox state. But the most important one is nuclear factor B (NF-B) [22-27].

7. Downstream cellular response

Although the underlying mechanism of LLLT are still not completely understood, in vitro studies, animal experiments and clinical studies have all tended to indicate that LLLT delivered at low doses may produce a better result when compared to the same light delivered at high doses. LLLT can prevent cell apoptosis and improve cell proliferation, migration and adhesion at low levels of red/NIR light illumination. LLLT at low doses has been shown to enhance cell proliferation in vitro in several types of cells: fibroblasts ,keratinocytes, endothelial cells and lymphocytes [28].

The mechanism of proliferation was proposed to involve photostimulatory effects in mitochondria processes, which enhanced growth factor release,and ultimately led to cell pro-

liferation [29].

8. Downstream tissue response

There have been a large number of both animal model and clinical studies that demonstrated highly beneficial LLLT effects on a variety of diseases, injuries, and has been widely used in both chronic and acute conditions .It may enhance neovascularisation, promote angiogenesis and increase collagen synthesis to promote healing of acute and chronic wounds [30]. It provided acceleration of cutaneous wound healing in rats with a biphasic dose response favoring lower doses [31].

It can also stimulate healing of deeper structures such as nerves [32],tendons [33], cartilage[34], bones[35] and even internal organs [36]. LLLT can reduce pain [36], inflammation [36] and swelling [37] caused by injuries, degenerative diseases or autoimmune diseases. Oron reported beneficial effect of LLLT on repair processes after injury or ischemia in skeletal and heart muscles in multiple animal models in vivo [38-41]. LLLT has been used to mitigate damage after strokes (in both animals [42] and humans) [43], after traumatic brain injury [44] and after spinal cord injury [45].

Contraindications

The North American Association for Laser Therapy (NAALT) has compiled the following list of contraindications: pregnancy (over the pregnant uterus), cancers (over the tumor site), where treatment would be over the thyroid gland, where treatment would be over pediatric joint epiphysis, transplant patients, or other immuno-suppressed patients, and photosensitive patients [46].

Caution should be used when considering the use of laser phototherapy on patients that have recently under gone steroid or Botox treatment [47].

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