Low Level Laser Therapy

.Effects at the cellular level increase ATP energy and DNA synthesis and benefit acute and chronic musculoskeletal aches and pains, chronic inflammation, acute soft-tissue injuries, as well as other conditions.

I am very pleased to introduce you to Dr. Dan Murphy. He is a seasoned clinicist, having been in practice for 30 years. He is extensively published and considered an expert in cervical spine injuries as well as laser therapy. He has published many articles on the neurophysiology of therapeutic laser. In this article, Dr. Murphy elaborates on a few of the unique physiological effects of laser on cellular structures. I am excited to have Dr. Murphy sharing his extensive knowledge with us and look forward to reading more in the near future..

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By Dan Murphy DC, DABCO

In 1997, Douglas Wallace wrote an article for Scientific American titled "Mitochondrial DNA In Aging and Disease."[1] In this article, he notes that an intracellular organelle, the mitochondria, is the power plant of cells because it produces ATP energy. "Mitochondria provide about 90% of the energy that cells, and thus tissues, organs, and the body as a whole need to function." Every cell in the body contains hundreds of mitochondria that produce the energy that the body requires.

Each mitochondria contains many copies of DNA, called mitochondrial DNA, or mtDNA. Mitochondrial DNA is separate and distinct from the cell's copy of nuclear DNA. An individual's mtDNA comes from, and is identical to, the mother's mtDNA. Mitochondrial DNA (mtDNA) codes for 13 proteins (enzymes) required for the production ATP energy.

A simplified mechanism of the mitochondrial contribution to the production of ATP energy is illustrated in Figure 1 (after Audesirk[2]). Note that the primary producer of ATP energy is the "electron transport system" of the mitochondria. This is important in the understanding of laser physiology. Wallace further notes: "Anything able to compromise ATP production in mitochondria could harm or even kill cells and so cause tissues to malfunction and symptoms to develop."[1]

The inner membrane of the mitochondria contains 4 protein complexes called the respiratory chain. Electrons from food pass through these protein complexes with the help of Coenzyme Q10, interacting with oxygen and hydrogen to produce water and ATP energy. When discussing low powered laser therapy, it is important to understand that the terminal enzyme of the mitochondrial respiratory chain, the "cytochrome c oxidase" enzyme, also functions as a photoacceptor.[3,4]

"As the respiratory chain participates in energy production, toxic by-products known as oxygen free radicals are given off. These oxygen derivatives carry an unpaired electron and are highly reactive, and can attack all components of cells, including respiratory chain proteins and mitochondrial DNA. Anything that impedes the flow of electrons through the respiratory chain can increase their transfer to oxygen molecules and promote the generation of free radicals."[1] Conversely, anything that improves the flow of electrons through the respiratory chain will increases the production of ATP while reducing the generation of free radicals. This is the key to low-level laser therapy.

Wallace notes: "The mitochondrial theory of aging holds that as we live and produce ATP, our mitochondria generate oxygen free radicals that inexorably attack our mitochondria and mutate our mitochondrial DNA."[1] The accumulation of mitochondrial DNA mutations reduce ATP energy output below optimal levels. "In so doing, the mutations and mitochondrial inhibition could contribute to common signs of normal aging, such as loss of memory, hearing, vision, and stamina."[1]

In support of the writings of Wallace is the 2004 book edited by Rainer Straub and Eugenio Mocchegiani. These authors note: "One of the most accepted theories of aging is the free radical theory of aging. The overproduction of free radicals can induce cell death. Aging, as stated in free radical theory of aging, is characterized by an increased production of free radicals in several tissues or a decreased antioxidant defense leading to chronic oxidative stress."[5] The mitochondria are the major source for the production of free radicals.

As noted, the mitochondrial production of ATP is coupled with the production of Oxygen Free Radicals (Reactive Oxygen Specie,s or ROS). This is undesirable because ROS are major contributors to many diseases, including cancer. Additional support for the deleterious nature of free radical production comes from the authoritative 2006 text by Singh, titled Oxidative Stress, Disease and Cancer. The preface of this text states: "The ability of cells to reduce oxygen to produce energy is fundamental to aerobic life.

"Unfortunately, production of energy by reduction of dioxygen leads to the generation of reactive oxygen species that cause oxidative stress.

"It is now well established that oxidative stress causes extensive damage to cellular components, which can lead to a number of diseases, including cancer."[6]

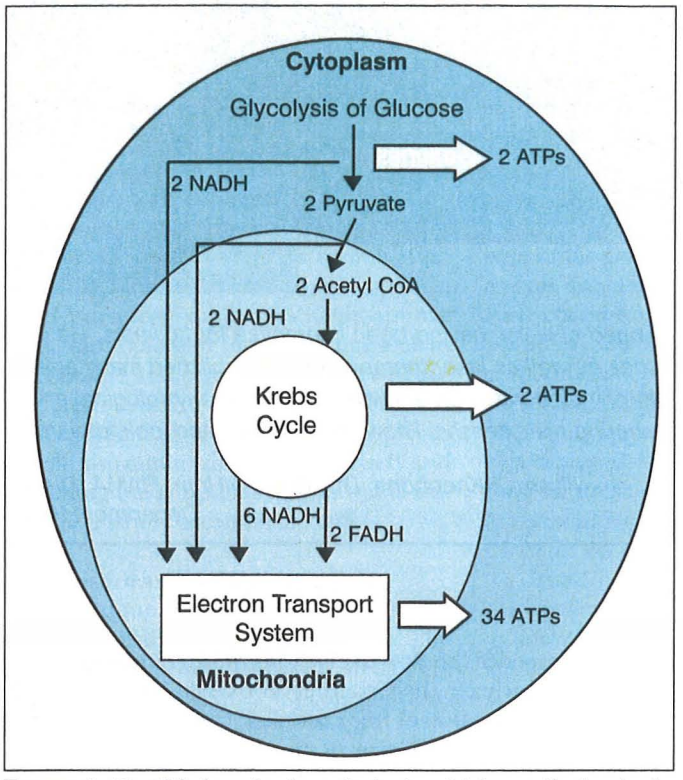

FIGURE 1. *Simplified mechanism of mitochondrial contribution in the production of ATP.*

A recent article by Pieczenik and Neustadt states: "A wide range of seemingly unrelated disorders, such as schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis, have underlying pathophysiological mechanisms in common, namely reactive oxygen species (ROS) production, the accumulation of mitochondrial DNA (mtDNA) damage, resulting in mitochondrial dysfunction."[4]

Tiina Karu wrote the chapter "Low-Power Laser Therapy" in the book Biomedical Photonics Handbook in 2003.[7] She notes that low-level laser therapy probably works because the laser light is absorbed by the mitochondria photoreceptors, which enhances cellular metabolism. She also notes that the primary reaction of laser light is in the mitochondria, which results in increased ATP energy. "The mechanism of low-power laser therapy at the cellular level is based on the increase of oxidative metabolism of mitochondria, which is caused by electronic excitation of components of the respiratory chain."[7] In her most recent book, Karu notes that the primary component of the mitochondrial respiratory chain being influenced by laser phototherapy is the terminal enzyme of the mitochondrial respiratory chain, the "cytochrome c oxidase" enzyme.[3]

Karu states: "It is known that even small changes in ATP level can significantly alter cellular metabolism."[7] The elevated levels of ATP energy increase the rate of DNA synthesis.

Consequently, the increased levels of ATP energy and DNA synthesis will benefit acute and chronic musculoskeletal aches and pains, inflamed oral tissues, help to heal skin and mucosal ulcerations; treat edema, burns, and dermatitis; relieve pain and treat chronic inflammation as well as autoimmune diseases. Laser therapy is also used in sports medicine and rehabilitation clinics (to reduce swelling and hematoma, relieve pain, improve mobility, and to treat acute soft-tissue injuries). It was shown in the 1980s that laser radiation altered the firing pattern of nerves, which is connected with pain therapy. In 1988, Rochkind et al.[8] noted that the ability of laser irradiation to affect the action potential was dependent upon the wavelength: the effect was strong at 540 nm and 632.8 nm; while laser radiation at 660, 830, 880, 904, and 950 nm had no effect.

The 2002 book by Jan Turner and Lars Hode, titled *Laser Therapy Clinical Practice and Scientific Background*, contains 1,281 references. These authors note:

1) "Today, we can safely say that therapeutic lasers have an important biological effect, and a very positive one at that."

2) "We believe that lasers have a tremendous and as yet untapped potential in the field of healthcare."

3) "Therapeutic lasers have no undesirable side effects in the hands of a reasonably qualified therapist."

4) Lasers are "sterile, painless, and often less expensive than methods already in use," and do not have the side effects as does pharmacotherapy.

5) "Laser therapy of wounds is ideal, since it promotes healing and reduces pain at the same time.

6) Laser light increases the cell's ATP energy."[9]

Therapeutic Implications

A recent representative article regarding low-level laser therapy was published October 2004 in the American Journal of Physical Medicine & Rehabilitation.[10] Researchers injured the knees of 42 rats giving them arthritis. Twenty-one of the rats were given 632 nm low-level laser, applied over the arthritic knee for 15 minutes, three times per week, for 8 weeks; the other 21 rats were not similarly exposed. The results showed a marked repair of arthritic cartilage in the lased rats, but not in the non-lased group. The authors concluded that the 632 nm low-power laser enhances protein production in arthritic joints and repairs the arthritic cartilage.

These authors also noted that lasers are "thought to cause electronic excitation of the photoacceptor molecules, which are thought to be various cytochrome enzymes that are terminal electron carriers in the respiratory chain."[10] This is thought to accelerate electron transfer. "Electron transport in the mitochondrial membrane is one of the main fueling mechanisms underpinning metabolism and proliferation of cells, including generation of adenosine triphosphate (ATP). Low-level laser mediated increase in efficiency of the electron carriers in the respiratory chain would increase generation of adenosine triphosphate, which could manifest itself as increased DNA and protein synthesis and result in cell proliferation, as shown in present study."[10] Thus, their explanation of the physiology of low-level laser therapy is consistent with Karu[7] and Turner[9] above.

Turner notes that "any wavelength will have a biological effect,"[9] while Karu notes that "the 632.8 nm and the 820 nm are the most common wavelengths used in therapeutic light sources."[7]

Turner also notes that "The first company to receive a 510(k) from the Federal Drug Administration (FDA) was Majes-Tec Innovations in the USA and its Erchonia laser."[8] Information pro-

vided by Erchonia[12] notes that the evidence Erchonia used to achieve the FDA 510(k) status involved a group of 50 patients treated for musculoskeletal neck and shoulder pain. The laser used was a 635 nm wavelength line laser using 5 mW of power, applied for 3 minutes over the area of complaint. The laser group showed a 66% improvement in pain and range of motion as compared to the placebo group following a single 3-minute exposure.

In 2001, Neira et al[13] used MRI and scanning electron microscope imaging to assess the depth of biological effects of laser irradiation. The study used an 8mW 635 nm wavelength line laser held above the skin at a distance of 6-8 inches. After 4-6 minutes of exposure, significant (80-99%) release of fat from fat cells was documented to a depth of 6 cm. It is unknown whether the biological effects documented in this study were as a consequence of primary or secondary reactions to the laser irradiation. The reproductions of the electron microscope images in the original article are stunning. Personal investigation revealed that each electron micrograph was produced at a cost of $10,000.

The book by Tuner and Hode also makes the following points: "Treatment with laser therapy is not based on heat development but on photochemical and photobiological effects in cells and tissues."[9]

Lasers "cannot penetrate the tissue more than a fraction of a millimeter, so there is no other primary responding tissue other than the outer part of the dermis." Still, such irradiation has "secondary systemic effects." Therefore, the light "leads in turn to a number of secondary effects (secondary responses) which have been studied and measured in various contexts: increased cell metabolism and collagen synthesis in fibroblasts, increased action potential of nerve cells, stimulation of the formation of DNA and RNA in the cell nucleus, local effects on the immune system, increased formation of capillaries by the release of growth factors, increased activity of leukocytes, transformation of fibroblasts to myofibroblasts, and a great number of other measured effects." Therefore, "deep light penetration is not a necessity per se in biostimulation..." "The possible reason for this is that cells in the tissues subjected to the light produce substances that then spread and circulate in blood vessels and lymphatic systems."[9]

In their literature review, Tuner and Hode also note: "There was also a group of animals on which two wounds were inflicted [bilaterally], only one of which was treated with laser. Even the untreated wound showed better results than the control group. The authors report drew the following conclusion: 'The laser irradiation can thus have released substances in the circulation apparatus so that the tensile strength increased even in the wound on the opposite, untreated side.'"[9]

'Another study notes: "...laser treatment on only the right-hand side of bilaterally inflicted skin wounds increased the healing process on both sides as compared to the control group. This also applied in the case of bilateral burn wounds."[9]

In another study of patients treated unilaterally with chronic neck and shoulder pain, "The pressure pain threshold increased significantly on both the non-treated and the treated side, although the increase was larger on the treated side."

In another animal study evaluating suppressed tuberculin reaction, "The suppression was seen not only on the irradiated side but also on the contralateral, non-irradiated side."[9]

In another study evaluating the effects of laser on the treatment of an anaphylactic reaction in the eyes of rabbits, the healing effect of the laser was obvious, and "Consensual co-reaction could be observed in the contralateral non-irradiated eyes in the experimental group."[9]

Tuner and Hode explain these results on tissues contralateral to the side of laser irradiation stating that: "The non-irradiated 'control' lesion, in fact, benefits from the treated lesion because of the systemic reaction just discussed...conventional laser therapy has both a local effect in the area treated by laser, and a systemic effect through the release of metabolites." The authors also state that "Due to transmission of neural excitation and calcium waves, photobiomodulation is a systemic effect."[9]

Wavelengths and Power Outputs

Therapeutic low powered lasers are commercially available in many different wavelengths and power outputs. In reviewing the new book by Tiina Karu[3] on Laser Phototherapy, it appears clear that there is no one wavelength that is ideal for all appropriately treated clinical syndromes. Few studies compare the outcome of different wavelengths and exposure fluences on measured outcomes. However, a recent study by Carrinho et al[14] compared the tissue repair of injured mouse tendons when treated with either a 685 nm laser or an 830 nm laser, each at fluences of both 3 J/cm^2 and 10J/cm^2. This study used 48 mice that were divided into six experimental groups and are summarized in Table 1.

Laser irradiation started 24 hours after the tenotomy of the Achilles tendon. A total of 12 laser sessions were performed on consecutive days. The rats were killed on day 13, and the injured tendons were surgically removed and analyzed with polarized light microscopy to analyze the organization and molecular order of the collagen fibers. All laser treated groups showed improved healing when compared to injured control group. The best organization and aggregation of the collagen bundles was shown by the animals

Table 1. Study results comparing tissue repair of injured mouse tendons at different wavelengths and dosage.[14]

Treatment conditions	Tissue response compared to control tendons
Group A, tenomized animals, treated with 685 nm laser, at the dosage of 3 J/cm^2	208% improved tissue response over control
Group B, tenomized animals, treated with 685-nm laser, at the dosage of 10 J/cm^2	114% improved tissue response over control
Group C, tenomized animals, treated with 830-nm laser, at dosage of 3 J/cm^2	167% improved tissue response over control
Group D, tenomized animals, treated with 830-nm laser, at dosage of 10 J/cm^2	101% improved tissue response over control
Group E, injured control (placebo treatment)	
Group F, non-injured standard control	

of group A (685 nm, 3 J/cm^2), followed by the animals of group C (830 nm, 3 J/cm^2), and B (685 nm, 10 J/cm^2), and finally, the animals of group D (830 nm, 10 J/cm^2). The authors concluded: "All wavelengths and fluences used in this study were efficient at accelerating the healing process of Achilles tendon post-tenotomy, particularly after the 685-nm laser irradiation, at 3 J/cm^2. It suggests the existence of wavelength tissue specificity and dose dependency."[14]

Interestingly, in this study, the shorter wavelength was associated with the better healing outcome. Counterintuitively, lesser exposure to laser irradiation resulted in an improved healing outcome than higher doses of exposure. These authors note: "The better tissue response was observed after the irradiation with the 685-nm laser, at the dosage of 3 J/cm^2. The animals irradiated with the 830-nm laser, at the dosage of 10 J/cm^2 presented the weaker response to laser irradiation. The best tissue response was obtained after the 685-nm laser irradiation, at the dosage of 3 J/cm^2."

Specifically, the 685-nm laser irradiation at 3 J/cm^2 showed a 16% improved tendon healing over the 830-nm laser at 3 J/cm^2; a 33% improved tendon healing over the 685-nm laser at 10 J/cm^2; and a 54% improved tendon healing over the 830-nm laser at 10 J/cm^2.

Carrinho et al concluded that "Our results suggest that laser irradiation (particularly using the 685-nm laser, at the dosage of 3 J/cm^2) produced an increase of cell proliferation through changes in mitochondrial physiology, subsequently affecting RNA synthesis, which, in turn, alters the expression of various cell regulatory proteins."[14]

Clinical Considerations

Several studies have generated caution concerning higher levels of exposure to low level lasers. Tuner and Hode note that "If a dose above the highest one suitable is administered, weaker or no biological effects will result. With an even greater dose, the bio-suppressive range is entered (inhibiting effect result)."[9]

In 2004, in an article titled "Photobiological Principles of Therapeutic Applications of Laser Radiation," the authors note that the positive action of laser biostimulation is changed "into inhibition of vital activity processes" under large doses of laser radiation, "which is a main hindrance to a successful application of laser therapy and a cause of disappointment."[15]

Possibly the most important article to be aware of regarding the effects of the energy output of lasers was published in the January 2006 issue of the journal Lasers in Surgery and Medicine. This article notes that a lower dose of laser irradiation "...has a stimulatory influence on wounded fibroblasts with an increase in cell proliferation and cell viability without adversely increasing the amount of cellular and molecular damage. Higher doses were characterized by a decrease in cell viability and cell proliferation with a significant amount of damage to the cell membrane and DNA."[16]

These authors further note that by spreading the light out over 3.3 cm, "the light is divergent and is not as harmful as a narrow parallel beam that allows the entire volume of intense laser light to be focused or concentrated on one small area."[16]The laser used in this study used only 3 mW of power.

Summary

Mitochondria present a paradox: not only are they the major producer of ATP energy, but they are also the major producer of free radicals. As the mitochondria produce the ATP energy that our bodies require to function, the mitochondria also produce the free radicals that damage and age our bodies. Lasers increase the mitochondrial production of ATP without increasing the production of free radicals. Anything that increases the production of ATP energy will speed healing and improve symptoms. Since lasers can achieve this with minimal side effects or risks, low-level laser therapy is here to stay. Reviewing the books by Karu,[3] Tuner and Hode,[9] and Baxter,[11] shows the magnitude and diversity of research that has already been completed concerning low-level laser therapy and laser photobiology. Low-level laser therapy has both local and systemic influences, and some laser wavelengths can affect the action potential of neurons. However, there is some evidence that higher amounts of laser energy delivered into the body may not improve clinical outcomes, and there are suggestions that excess exposure to laser irradiation may even be harmful. ■

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