Overview

The use of therapeutic low-level laser has become widespread in veterinary medicine. A number of illnesses and physical conditions are reported to respond to laser therapy (photobiomodulation.) There is support in the scientific literature for many of the physiologic effects claimed by proponents of laser therapy at the biochemical level. At the level of the organism however, there is still significant debate regarding the efficacy of laser in producing the desired clinical response.

Although a complete review of the data regarding the effect of laser light therapy on biochemical and cellular mechanisms is beyond the scope of this presentation, this overview is intended to provide a preliminary assessment of the information that is currently available. Understanding the mechanisms and effects of laser at the subcellular, cellular, systemic and organismal level will lead to informed treatment decisions and more predictable clinical outcomes. This review may also help highlight those therapeutic claims which are not currently well supported by the literature and identify areas where further investigation is warranted.

L-A-S-E-R stands for light amplification by stimulated emission. The light produced by a laser is powerful because it has three unique properties: it is monochromatic (a single wavelength), coherent (waves are in phase), and collimated (waves are parallel.)

Lasers are usually named according to the technology by which the light is created, i.e. gas, chemical, solid state, semi-conductor, etc. The technology roughly determines the wavelength or lengths that can be produced by a particular laser, although some can be adjusted to produce a wide range of wavelengths. In medicine and surgery we are most familiar with the HeNe (helium-neon) laser, which generates light by stimulating gas molecules to release energy, the diode semi-conductor laser (eg. Gallium aluminum arsenide, or GaAlAs) and the solid state YAG (yttrium aluminum garnet) laser which uses garnet (or, historically, ruby) as its excitatory medium. Therapeutic lasers are in the “near infrared” spectrum, just on the border of visible light and much shorter wavelengths and/or lower intensities than are used for surgical applications.

Lasers are classified by the FDA according to their intensity and occasionally wavelength. This classification system is intended to identify the risk of harm to the patient or user. In general, therapeutic lasers fall into the class IIIb or class IV categories. All surgical lasers are class IV. Significantly, class IV lasers are considered a risk for retinal damage from both direct and reflected exposure. Unlike class IIIb units, class IV laser light can be harmful even when reflected from a matte surface (such as paper, painted walls, or the patient’s skin.) Class IV lasers pose a risk for thermal damage to tissues and they are a combustion risk when applied to flammable materials. Because lasers in the non-visible spectrum will not trigger the blink reflex, often a visible aiming beam is built into the mechanism to avoid accidental retinal exposure.
As with any treatment modality, only a portion of the administered dose actually reaches the target tissue. When applied to tissues, laser light is subject to attenuation through absorption, reflection and scatter. Manufacturer recommendations for laser dosing attempt to take these effects into consideration. Scatter and reflection phenomenon occur at fairly consistent rates in different tissues, however absorption rates may differ widely because tissues of different molecular contents absorb different wavelengths to greater or lesser extent. Tissues composed of greater proportions of one or another type of molecule will absorb more or less light depending on the wavelength. This complicates the ability of the clinician and investigator to accurately determine the actual dose applied to the target tissue in different patients and different anatomic locations on the same patient.

The treatment dose is calculated as the amount of energy (Watts) delivered over a period of time or a specific tissue area. Doses are often listed as Watts (Joules per second) per square centimeter, or Joules (intensity of the energy in Watts multiplied by the treatment time) per square centimeter. Thus, the energy emitted per unit of time, total energy administered, the size of the area being treated and the treatment time are all important and interrelated variables in determining dose.

Laser light is emitted either in a continuous wave (CW) or pulsed form. When laser light is emitted in a pulse, the pulse frequency may impact the effectiveness of the treatment. Other variables that impact the effectiveness of a treatment include the distance from the laser source to the tissue surface and the target tissue, the speed of movement over the treatment area, and the number and frequency of treatments.

The reported physiologic effects of laser include stimulation of mitochondrial activity, increased cell turnover, recruitment and proliferation, modulation of the cellular metabolites involved in the inflammatory response, vasodilation, release of exogenous endorphins, and increased oxygen availability in the tissues. We will examine these proposed mechanisms and the supportive data for each of them more closely.

Broadly speaking, low-level laser is most often used in clinical practice for the promotion of tissue healing and pain control. Specific applications of laser are diverse, in part because each of the mechanisms listed above can be applied to a number of body systems. Examples include management of indolent or infected wounds, tissue necrosis due to envenomation, nerve injury, osteoarthritis or other chronic pain syndromes, myofascial pain, fracture healing, tendinous or ligamentous injury, and post-surgical incision care.

**Stimulation of mitochondrial activity**

The capacity of infrared light to stimulate more efficient electron transfer in the cytochrome oxidase pathway is relatively well-established. This may be the underlying mechanism of action for most of the physiologic effects attributed to low level laser therapy. Cytochrome is an enzyme in the membrane of cellular mitochondria that plays a pivotal role in the synthesis of ATP, the primary energy storage molecule for most vertebrate cells. A component of this enzyme appears to be a chromophore (light-responsive molecule) that absorbs energy from photons moving on wavelengths in the near-infrared spectrum. Excitation of this molecule with light energy accelerates the rate of electron transfer and in turn increases the capacity of mitochondria to generate ATP. Increased ATP results in increased energy available for that cell's metabolic processes. This is a non-specific effect which seems to occur in roughly the same manner in any number of cell types throughout the body.

Tissue healing: Increased cell turnover, recruitment and proliferation

There is a large and growing body of evidence supporting the ability of infrared light to stimulate increased cell turnover and proliferation in vitro. The laboratory findings appear to translate well to clinical results. These effects may be partially attributable to the stimulation of the oxidative metabolic pathways and a resulting increase in overall cell metabolism, however other factors may also be involved, such as increased intra- and inter-cell signaling, alterations in gene expression, and even intercellular adhesion effects. Although it appears that most cells will respond to wavelengths between 630-980 nm, different cell types may respond to different portions of the spectrum. Stein et al. found that 632 nm laser light at doses of 0.43 J/cm² stimulates an increase in osteoblast numbers and activity in cell culture, however Barbosa et al. found that osteoblast cultures respond better to laser light in the 790-830 nm range than the 660-690 nm range at equivalent doses. Similarly, while Bouma et al. found no effect with 904 nm light therapy, multiple groups have since published data suggesting that phototherapy in the 630-690 nm range promotes increased adhesion and proliferation of endothelial cells. It is also reasonable to suppose that the specific activity that is induced in any given cell type by laser light may depend on the wavelength applied. Both of these suppositions require further investigation.

Effective photobiomodulation does appear to be dependent on the use of an appropriate dose. It has been effectively established that when it comes to low level laser therapy, more is most certainly not “better”. Several studies (Lubart et al., Basso et al.) found that cell cultures respond best to moderate doses of infrared energy, and that the optimum dose may differ amongst cell types: around 15 J/cm² in fibroblasts and 3 J/cm² in keratinocytes (both at 780 nm.) In all cases, higher doses actually had a negative effect. A few investigators (Deise et al., Kreisler et al.) have suggested there may be a cumulative effect to successive laser treatments administered 24 hours apart – cell cultures appeared to be most responsive after the third treatment in the Deise group’s analysis. The timing of therapy may also play a role. Interestingly, one recent study (Akgul) found that delaying onset of low level laser therapy until after the acute inflammatory phase may effect a better result.

Recovery from nerve injury

Nervous system healing and recovery from injury falls under the umbrella of cell regeneration and proliferation, however this effect is highlighted here since it is of particular interest and highly relevant to the field of veterinary rehabilitation. Several published reports show promising evidence of the benefit of low-level laser therapy on nervous system recovery after injury. As with many of the proposed therapeutic benefits of low-level laser, this effect has only been demonstrated in rat studies, and with a variety of wavelengths and doses, making extrapolation to other species and derivation of clinical dosing guidelines problematic.

Angiogenesis

Also under the general category of cell proliferation, but of particular interest in healing tissues is the capacity of infrared light to promote vascular endothelial development and angiogenesis. This property of infrared light is significant both for the consideration of tissue healing and as a consideration when applying laser to highly vascularized tissues or tissues where increased vascularity is undesirable – e.g. neoplasms. Dourado et al. demonstrated increased angiogenesis at multiple wavelengths (633 and 904 nm) with increased response to 633 nm compared to 904 at lower doses while higher doses of the 633 wavelength appeared to be less effective than the 904 nm wavelength. Similarly, Cury et al. demonstrated benefit from both 660 and 780 nm but the shorter wavelength was only effective at higher doses whereas the longer wavelength was effective at both a high and low dose. Da Rosa et al. found maximum benefit in response to an 808 nm wavelength at 3.57 W/cm2.

Modulation of inflammation

Low-level laser therapy appears to not only increase the activity of macrophages and neutrophils, but to do so in a way that preferentially enhances the output of specific inflammatory mediators. This gives some indication that under certain circumstances, laser light may not be a purely non-specific stimulator of cell metabolism. This particular category of photobiomodulation effects on biologic systems has been a prime area of interest for investigators. Unfortunately, a detailed review of the diverse biochemical effects of infrared light on the cellular components of the immune system requires more attention than we
are able to devote here. In general, however, laser appears to inhibit the catabolic mediators of inflammation which suppress collagen synthesis and cell proliferation. Irradiation with low-level laser light reduces neutrophil influx into chronically inflamed tissue or fluid spaces and may stimulate production of anti-inflammatory metabolites such as COX-1 and COX-2. Laser also appears to aid in reducing edema, a significant factor in patient discomfort and retarded nutrient exchange in inflamed tissues.


**Vasodilation**

In many cases the patient’s skin can be observed to appear flushed or erythematous for a short period (minutes) following a laser treatment. It has been suggested that phototherapy may increase local circulation via smooth muscle relaxation that results in vasodilation. This may be due to an induction of NO2 in the perivascular tissue. Carrera et al. were able to demonstrate that laser therapy increases vasodilation in acute surgical wounds – an effect with questionable benefit at a time when hemostasis may be preferable to increased microvascular circulation. The study quoted earlier by Heu et al. failed to find an increase in local circulation in healthy tissues. Interestingly, an older study by Mi et al. suggests that laser may increase the deformability of the erythrocyte molecule with implications both for increasing the rate of erythrocyte flow through peripheral capillary beds and also for the availability of the hemoglobin molecule within the red blood cells.


Endogenous endorphin release

Endogenous endorphin release has been proposed as the underlying mechanism responsible for the observed and reported reduction in perceived pain after laser irradiation of painful or inflamed tissues. At least one study has reported successful elicitation of endorphins from cells in vitro. Although it is difficult to find clinical trials assessing endorphin release following administration of phototherapy, the pain relieving effects of infrared laser do appear to be increasingly supported by clinical data in both human and animal patients. As with other effects of low-level laser, it is likely that outcomes may be linked to specific wavelengths and doses.


Increased oxygen availability

It has been proposed that laser light promotes the dissociation of oxygen from the oxyhemoglobin molecule in tissue capillary beds, thus making more oxygen available for oxidative metabolism and ATP production. To date, there is little support for this claim in the published literature. The few studies that exist have produced equivocal or contradictory results. Asimova and Thanh found that oxygen levels increase in the skin of patients after infra-red irradiation with a 633 nm wavelength at a dose of 0.23 W/cm2. On the other hand, Heu et. al at the University of Erlangen-Nuremberg in Erlangen, Germany found no increase in the free oxygen levels in human skin using a 660 nm light with a dose of 5.73 J/cm2 applied over fifteen minutes. Measurements in the first study were taken simultaneously with the application of laser treatment for a period of 8 minutes, in the second study, the oxygen levels were measured 15 minutes after the treatment session.

M. Asimova and N.C. Thanh, Laser Induced Photodissociation of Oxyhemoglobin: Optical Method of Elimination of Hypoxia (Oxygen Deficiency in Biotissue), Optics and Spectroscopy Vol. 111 No. 2 2011


Tissue penetration

A persistent debate in the medical community regarding the efficacy of low-level laser therapies surrounds the question of whether light in the bioactive spectrum delivered percutaneously can penetrate to the depth of most of our target tissues. This question is absolutely elementary to any discussion of the
usefulness of low-level laser therapy in a medical context and it must be acknowledged and considered before we can attempt to prescribe this modality in the clinical setting in an ethical and informed manner. Several theoretical and experimental models have demonstrated with fair consistency that laser light administered percutaneously penetrates at therapeutic intensities anywhere between 2 to 5 cm into living tissues, depending on the precise tissue layers involved and metabolic status of the patient. There appears to be significant inter-species variability in tissue penetration. One set of investigators (Joensen et al.) made the intriguing comment that “the percentage of energy penetrating skin from the 904 nm laser increased almost linearly during the exposure period” possibly suggesting that absorption levels decrease in intervening tissue layers in a time-dependent manner (perhaps due to a ‘saturation’ effect?), allowing deeper penetration of the light energy.

In evaluating the significance of attenuation of the light beam with regard to therapeutic effect, it is important to remember that the amount of energy emitted from the laser unit is orders of magnitude greater than that required to stimulate an effect in cell cultures. As with many of our therapeutics and pharmaceuticals, only a small fraction of the dose administered may ultimately reach the target tissue. The percentage of the total dose that is delivered is less relevant than achieving a terminal dose sufficient to stimulate a biochemical response.

