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Photobiomodulation Therapy in Veterinary Medicine: A Review

Lindsay Hochman, DVM, MPH, CVA

Laser therapy, or photobiomodulation, has rapidly grown in popularity in human and veterinary medicine. With a number of proposed indications and broad, sometimes anecdotal, use in practice, research interest has expanded aimed at providing scientific support. Recent studies have shown that laser therapy alters the inflammatory and immune response as well as promotes healing for a variety of tissue types.[1–6] This review will cover the history of the modality, basic principles, proposed mechanisms of action, evidence-based clinical indications, and will guide the practitioner through its application in practice.

History

Heliotherapy, or light therapy, is far from a new concept. Evidence shows its use to treat disease in ancient Rome, Greece, China, and India.[7] Significant refinement of the modality has since occurred. Newton's initial light observations and identification of a light "spectrum" in the 17th century[8] were followed by Einstein's Theory of Relativity and its application to laser light. His theory defined the process of stimulated emission of electromagnetic radiation, a cornerstone feature of lasers, where emission is compounded in circumstances where atoms in an excited-state release stored photons when hit with another photon of the correct wavelength.[9] This principle led to the creation of the first laser in 1960—a ruby laser developed by physicist Theodore H. Maiman. Early lasers were employed primarily for their tissue destruction and coagulative abilities; however, beneficial effects were also noted in the areas of lower energy application. This led to research into the healing properties of laser, such as Endre Mester's experiments on accelerating hair regrowth on the shaved backs of mice.[10] Since that time, technologic advancements and research surrounding the modality's biochemical effects and indications have rapidly expanded.

Basic Principles

Before delving deeper into the physics, properties, and purposes of laser therapy, ambiguous terminology should be addressed. Since its development, laser therapy has been referred to by a myriad of names. These include "cold laser," "low-level laser therapy," "low-level light therapy," and "phototherapy," to name a few. In an effort to clear up the confusion of multiple terms, a nomenclature consensus meeting suggested using the term "photobiomodulation therapy" to mean "a form of light therapy that utilizes non-ionizing forms of light sources, including lasers, LEDs, and broadband light, in the visible and infrared spectrum."[11] Though the term photobiomodulation better reflects the biostimulatory effects of the modality, the term "LASER" is also not without meaning, as it is itself an acronym for "light amplification by stimulated emission of radiation." This remainder of this article will utilize photobiomodulation therapy (PBMT) and laser therapy synonymously. Additional essential terminology and accompanying definitions are listed for the reader in Table 1.

How It Works

A number of studies have shown the beneficial effects of PBMT although the exact biochemical mechanism is not precisely known. Many studies have illuminated the capacity of laser therapy to alter the inflammatory response and have isolated some of the cellular metabolites involved. Research conducted specifically investigating the modality's cellular signaling reactions have demonstrated increases in reactive oxygen species (ROS),[12-14] adenosine triphosphate (ATP),[12,15-17] and nitric oxide (NO)[18-20] as the main factors that underlie laser's therapeutic effects (Fig 1).

The fundamental step in PBMT is thought to stem from the photo-stimulation of enzyme cytochrome c oxidase in the mitochondrial respiratory chain.[21] With an absorption spectrum of approximately 500 to 1110 nm,[22] cytochrome c oxidase is an important factor when considering the possible therapeutic wavelengths. Exposure to electromagnetic radiation in the appropriate spectrum results in a higher rate of electron transfer, increased proton transport, and a subsequent increase in mitochondrial membrane potential, ATP synthase, and eventually ATP.[23] This additional energy can then be employed by the cell to perform a variety of tasks including tissue repair.

NO, frequently bound to the heme-copper active site of cytochrome c oxidase, can be photo-dissociated with the application of laser light to increase metabolic turnover.[18, 19] This process not only causes cellular respiration to resume, but also releases NO into surrounding tissues to mediate vasodilation, promote angiogenesis, and modulate the inflammatory and immune responses.[24]

Accelerated oxidative phosphorylation from PBMT invariably releases additional electrons that are accepted by oxygen to produce ROS including superoxide and peroxide.[21] With appropriate doses of laser therapy, these ROS concentrations should occur in sub-lethal levels and primarily activate the beneficial anti-oxidant enzymes (i.e., superoxide dismutase and catalase) instead of initiating the apoptotic cascade.[25, 26] Additionally, ROS at lower near-physiological levels, can have stimulatory and signaling abilities including that of cellular growth[13] and stem cell differentiation.[27]

Veterinary Clinical Use

Laser therapy has been postulated to exert 3 main effects: reduction of pain, modulation of inflammation, and acceleration of healing.[23] For these reasons, PBMT has become a popular modality in both general and specialty practices with approximately 20% of veterinary hospitals in North America using the modality.[28] Furthermore, since FDA approval of Class IIIb lasers in 2002 and class IV lasers in 2006, research interest and clinical applications have skyrocketed. Though laser therapy has been attempted for a wide variety of indications, the primary categories with the strongest support, largely via experimental studies, include its use in pain, wounds, musculoskeletal conditions, neurologic pathology, and in conjunction with complementary medicine techniques (regenerative medicine, acupuncture).[29]

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Table 1.
Fundamental PBMT Terminology.

Class	Lasers are classified for safety purposed by their potential for causing injury. Therapeutic lasers typically fall into:Class IIIb – power output of up to 500 mW, Class 4 – power ≥ 500 mW
Coherent	Emitted photons travel together in phase both in space and time.
Collimated	Ability of a laser beam to minimize light divergence over a distance.
Duty cycle	For a pulsed laser, the ratio of total emission duration to total treatment time expressed as a percentage.
Fluence (J/cm^2)	Laser energy absorbed per unit area treated.
Frequency (Hz)	The pulse repetition rate - the number of waveforms in a defined time interval.
Irradiance (W/cm^2)	The density of power incident upon a surface. Also referred to as power intensity.
Joule (J)	Energy unit used to measure dose or rate of energy delivery.
Monochromatic	Light of one specific wavelength.
Spot size	The radius of the laser beam.
Watt (W)	Unit of power measured as 1 J/s.
Wavelength (nm)	Distance between successive crests of an electromagnetic waveform measured in nanometers (nm) for PBMT.

Pain

Laser therapy can serve as a key component of a multimodal analgesic plan. With respect to the pain pathway, PBMT can act at a variety of levels to provide relief:

- Transduction: peripheral terminals of nociceptive A-delta (Aδ) and C fibers are depolarized by noxious mechanical, thermal, or chemical energy.
  - ○ Decreases bradykinins[30] and kinin receptor activity at the inflammatory source[31]
  - ○ Reduces proinflammatory interleukin-1[32]
  - ○ Decreases proinflammatory prostaglandins[33]
  - ○ Increases NO levels causing vasodilation and removal of inflammatory mediators[18]
- Transmission: afferent nerves send the electrical nociceptive signals to the spinal cord
  - ○ Blocks depolarization of C fibers[34]
  - ○ Raises nerve cell action potential[35]

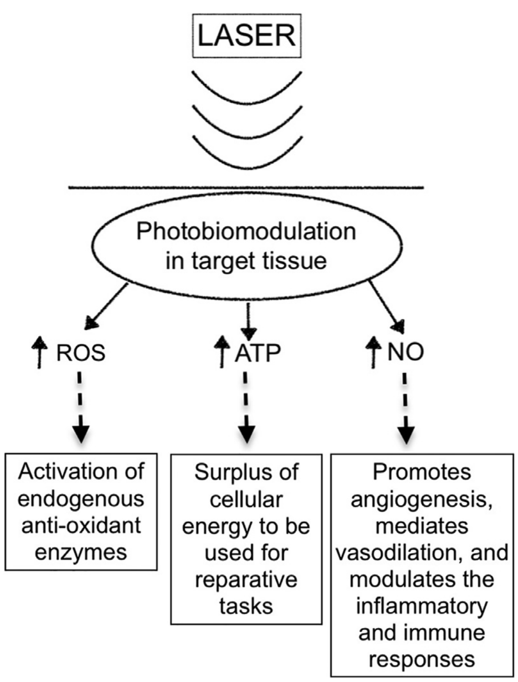

Fig 1. A number of studies have shown the beneficial effects of PBMT although the exact biochemical mechanism is not precisely known. Increases in reactive oxygen species (ROS), adenosine triphosphate (ATP), and nitric oxide (NO) are thought to be the main factors that underlie laser's therapeutic effects.

- Modulation: Excitatory or inhibitory transformation of the pain signal in the dorsal horn prior to ascent to the brain
  - ○ Produces of beta-endorphins to attenuate the pain signal[36, 37]
  - ○ Increases inhibitory neurotransmitter acetylcholine to decrease discharge of excitatory neurons[38]
- Perception: Neural processing with integration and recognition of the pain sensation
  - ○ Increases serotonin[39, 40] for mood augmentation.

Wound Healing

Wound healing is one of the most widely used and studied applications of PBMT. As demonstrated in a number of laboratory animal studies, laser therapy optimizes wound healing at multiple levels of the tissue regeneration process.[41-43] PBMT helps to restore the biologic function of injured cells via acceleration of cellular metabolism which generates additional ATP for reparative tasks as well as by locally increasing reactive oxygen species and NO.[23]

As a result, there is increased activation and production of growth factors including platelet derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and transforming growth factor (TGF).[44] These processes stimulate angiogenesis, and together with increased blood flow as a result of the vasodilatory effects of NO, increase oxygenation to the wound. This accelerates re-epithelialization and wound closure, enhances fibroblast proliferation, increases granulation tissue, and possibly deters infection.[6, 45-47] PBMT additionally improves collagen deposition and organization, increasing the tensile strength of ultimate scar tissue.[5] It may also help reduce inflammation and microbial load to improve tissue integrity during the healing process.[48] In an in vitro canine skin model, the application of laser light resulted in a dose-dependent increase in measured keratinocyte migration and proliferation.[49] Laser therapy does not cause the stressed or damaged cells to perform supra-physiological tasks. Rather it enables more normal cell function in a suboptimal, injured state in order to facilitate healing. These fundamental principles can also be applied to a number of soft tissue conditions including dermatologic and periodontal disease.

Musculoskeletal Disorders

To maximize and accelerate healing while reducing pain, a multimodal treatment strategy can be key in managing a variety of veterinary orthopedic issues. This can include surgery, weight management,[50] pharmacologic intervention, physical rehabilitation, as well as complementary and alternative therapies including PBMT. The following are some of the most commonly encountered musculoskeletal disorders in which laser therapy can serve as an adjunctive therapy: