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Photobiology of Therapeutic LASER

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Abstract

The use of Laser is worldwide. Those characteristics of Laser treatment of several injuries of the skin, blood vessels, and other parts of the body are known in all countries. The mechanisms that the Laser has its action in the human body are still uncertain in some aspects. This article is to review all the concepts in the scientific research to explain the function and action of the Laser to treat all injuries of the body.

Keywords: Therapeutic Laser, Photobiology, Injury, Inflammation, Human Body

Therapeutic Laser

Characteristics

Laser (light amplification by stimulated emission of radiation) utilizes light steamily organized to stimulate physiological alterations in the tissues. The production of laser rays is based on the availability of proper materials with atoms capable of it is maintained in the meta-stable state for adequate times [1, 2]. Analyzing the Laser terminology significance, it was said that the light amplification has high energy concentrations due to the great number of photons which it is constituted, and the phenomena of the stimulated emission that constituted of the light emission until stimulation of the matter thought of the phenomena of atoms energy [3, 4]. In 1961, at New York Presbyterian Hospital, it was realized with exit the first laser surgery: the extirpation of a retina small tumor. Starting this and other surgery experiences, it was evidenced, of empiric form, that laser radiation will stimulate the healing of accelerate manner [5-7]. In 1962, it was developed the first semiconductor laser [8]. It also was developed, two years later, the gas laser and the first carbon dioxide molecular laser [9]. Sinclair e Knoll adapted the laser to therapeutic practice [10]. In contrast with normal light, the laser rays are emitted by similar mechanisms, however with the following characteristics: all the radiations with the same energy (homogeneous and monochromatic), all the radiations in phase (coherent), and all the radiations in the same direction (directional) [11]. The characteristics of the laser rays are obtained by an emission process predicted by Einstein. In this case, after that the electron that jumps to the more external orbit can, spontaneously, return to the inferior level, the atom is stimulated by a new incident photon, of energy, hv=E2-E1. The new fact is that the incident radiation and the emitted radiation have their waves associated with the two photons in phase, that is, coherent (figure 1).

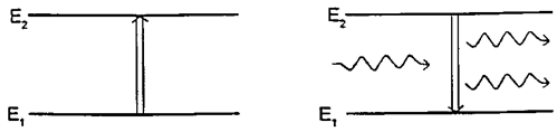

Figure 1: Scheme of stimulate emissions of electromagnetic radiations

It happened that for most of the atoms the stimulated emission is a rare relatively process. However, must record that there are physical states that it is denominated metastable in which the systems remain in the excited state by a time much bigger than the normal state. An adequate stimulus releases the energy at once [12]. The production of laser rays is based on the availability of appropriated materials with atoms capable of it sustained in the metastable state by adequate periods. The generator sets of laser rays must be an external energy producer (thermal, bright, electoral, or chemical) or bombing system, capable of exciting emission substance atoms (active medium) that can transfer electrons in the metastable state (E2). Reached the maximum electrons in the metastable state, that it is denominated population inversion, a generator photons system of thesame energy of the metastable level is actionized and stimulated the release all the electrons once, with the corresponding emission of laser rays, all with the same energy. To empower to the maximum the emission of laser rays, the generator sets are usually tubular with two devices in the extremity, one opaque and the other semitransparent. Once actionize the device the laser rays oscillate between one and other mirror, increasing more and more the number of photons until acquired enough intensities to get out through the exterior

of the semitransparent mirror. This type of device is denominated optic resonator. Once unloaded a laser rays' package, the bombing system returns to provoke the population inversion and the process is repeated. In this way, the laser rays are pulsating [13-15]. The laser ray's device not is set to generate energy, but to realize the external energy transformation in bright energy of special character; monochromatic, coherent, directional and increase bright, that is, of great photonic density, what its utility in a great number of activities in the health area.

The phototherapy with low-intensity laser (PLIL) of simply laser therapy was introduced by Mester and collaborators in 1971 [16]. It consists of tissue irradiation with laser equipment whose thermic effects in the irradiated tissue not exceed 1 ºC, that is, without cellular lesion and the caused heating not overtake the molecular level. The biological effects of laser therapy are not thermic, which differ fromthe lasers of high power that operate with the potential above 1 W, and which effects are related to the high and faster warming of the local tissue.

Classification

It can classify the types of laser generators into two groups: surgery lasers or high power and therapeutic lasers or of low and medium power [17].

In relation to the active medium of the different equipment, these can be gas lasers, solid-state, liquid state, chemic, and semiconductors [18]. The light produced can have various wavelengths. For each medical application, it uses one type of laser more appropriated, being important to consider the photonic energy, color, dimension, and intensity of the laser beam.

The variety of the lasers already employed in the health area is much big. New generations of devices, increasingly sophisticated, are being produced continuously, provoking transformations very faster of the equipment. The optical phenomena of laser radiation are the following: superficial reflection, cellular and molecular diffusion, energy absorption producing biochemical and bioelectric process, and different skin layers transmission.

Indications

The laser is indicated to stimulate healing of the lesions in different types of open wounds, to treat arthritic disturb and soft tissue lesions, and to relieve the pain.

The therapy with low power laser is used by physiotherapists (to treat a great variety of acute and chronic musculoskeletal disturbs and also the pain), by dentist (acceleration of healing of wounds, reinforced remodeling and bone repair, before lesion neural cells regeneration, the pain attenuation, endorphins stimulation and release, and in immunologic system modulation), by those work in derma to functional (inflammatory cells decrease, fibroblasts proliferation increase, granulation tissue formation, and the collagen synthesis increase), by rheumatologists (to decrease the pain and to treat chronic inflammation and autoimmune diseases) and by other specialists, as general practitioners. The laser therapy is also much utilized in veterinary medicine (especially in race horses training centre) and in sportive medicine and rehabilitation clinics (to decrease the bruise and swelling, to relieve pains, improve mobility, and to treat soft tissue acute lesions).

The therapeutic lasers, in general, it not provokes tissue destruction. Materials as the helium-neon gas (He-Ne) are energized electrically to produce an output of photonic radiation to stimulate areas, as acupuncture points and trigger-points, as well as help in the healing of superficial wounds. The produced energy by therapeutic lasers has a wavelength that is between 1 nanometer (nm) to 1 millimeter (mm). The wavelengths more used in therapy with light resources are: 632.8 nm (He-Ne Laser) and 820 nm (Gallium ArsenateLaser, As-Ga).

Dose and irradiation parameters

To the determination of the dose to be utilized it will observe the power of the device used (mW), the density of the power beam (mW/cm2), the energy (J) that it wants to apply in the treated area, and the energy density (J/cm2). The dose must be of 1 until 8 J/cm2 and the application time could leave some minutes.

Action and Laser Radiation Effects

The coherent properties of laser light not are manifested at the molecular level by light interaction with biological tissue. The laser light absorption by the biological system is of not-coherent purely nature, this is, photobiology.

In laser therapy, the irradiated energy absorption can occur through specific photons absorption by receptor atoms or molecules, called chromophores that alter their energy electronic level after light absorption or by unspecific electrons acceleration inducing an electric field on receptors molecules.

In the cells there are some chromophores that still knew that electromagnetic energy absorbs in the wavelengths between 400 until 2500 nm, as is the case of cytochrome-C-oxidase, of flavins, besides other enzymes of cellular mitochondria and endogens porphyrins [19]. These chromophores are typically metal or molecules that have metallic atoms. For example, the cytochrome-C-oxidase is a molecule whose proteic part absorbs ultraviolet light perhaps the metallic part absorbs the visible and infrared radiation [20].

The laser light absorption by chromophores being in cells would promote an initial series of chemicals reactions responsible for radiation cell response. These reactions occur in the light presence, and by this are called primary reactions, that occur in photoreceptor molecules and after excited electronic states promotion. The reaction that alters the redox state promoting the enzymatic activation, dissociation of compounds, and other chemical reactions envolve the hypothesis of the redox properties' alteration and of nitric oxide [21]. Mediated reactions by free radicals accelerate the cellular metabolism and can be toxic if in excess and involve the hypothesis of the superoxide anion and of single to oxygen. The hypothesis of transitory local heating occurs directly with the blood vessels, provoking the immediate termic relaxation [22]. The laser radiation could then act in 3 stages, the primary, the secondary, and the tertiary.

The primary action of the laser invlove the laser absorption by photoreceptor cellular molecule and metabolic alterations due to the action mechanism of the laser absorption resultant product occurred in the cell and in the tissue to which it belongs. Between the metabolic alterations suggested is the increase of the oxidative metabolism on mitochondria, which is caused by respiratory chair components electronic excitation (for example, cytochrome-C-oxidase) [23]. The laser can stimulate the tissues that are found 15 mm below of sky superficie. When the energy is absorbed by

the tissues, it is converted into termic vibration or can produce a photobiological effect.

The laser application could be activating many molecular events, among then the short duration stimulation of electron transport chair, the increase of adenosine triphosphate (ATP), and intracellular pH reduction. These actions could affect the tissue with pain, as in muscle spasm areas, restauring the normal properties of muscle tissue by the increase of the ATP formation and enzymatic activity [24].

Due to the primary action arises the secondary action with the microcirculation stimulus, cellular tropism, and tissue cicatrization [25]. The secondary reactions correspond to the various events that occur following irradiation, and that not be more light dependence. The intracellular pH alterations, related with the ATPases activation and following by intracellular levels of calcium alterations, can be one common way for signal transduction and amplification of all of the cited primary photoreactions [26]. The change of redox state for oxidation provokes an intracellular increase of calcium that stimulates the cell metabolism, once that stimulates any biological process, as RNA and DNA synthesis, cell mitosis, and protein secretion [27]. On another side, the reduction let the decrease of intracellular calcium and, cell metabolism inhibition. As the stimulation well the inhibition of the calcium intakes intro mammals' cells can be induced by monochromatic red light due to the apply dosage. More, rich energy doses can provoke photodynamic damage of photoreceptors destruction, inhibiting the cells process [28]. One example is the case of the super oxidase dismutase Cu-Zn enzyme (SOD) reactivation with medicine great importance. The enzyme inactivation will be done by the histidine residue protonation in the active center of the enzyme in acid pH and in the presence of hydrogen peroxide in cell lesion conditions. The laser radiation provokes the enzyme desprotonation in acid medium with subsequent enzyme active structure formation. The SOD function is to reduce the superoxide anion concentration that to react with other substances originated the superoxide radicals strong reactive as, for example, hidrodile radical, of cytotoxic and mutagenic action. Once that the concentration of oxygen decreases into the cells when the radical is been produced, the protected SOD action is done to catalyse the reaction of superoxide radical producing oxygen. These protective effects of SOD when recovered can avoid cerebral and cardiac damage due to oxygen deficiency that in certain points of these tissues is one of the principal deaths cause [29]. Moreover, the laser therapy has photodynamic action in membranes when hematoprofirine and/or their derivatives plus phospholipids accumulated in the cell membrane in certain diseases will be irradiated, promoting the lipidic peroxidation of membrane phospholipid layer decreasing the membrane electric stability, and damaged the calcium bombs [30]. The effects of the permeability and intracellular concentration of calcium ions increase varied due to cell type, however, result in cellular activation and/or proliferation [31].

Beyond the local effects of the irradiation, systemic effects are observed. Lipid peroxidation products and oxidated blood plasma lipoproteins after blood irradiation provoke a pre-stimulation of leucocytes that when in contact with bacterial membranes, lecithin, calcium transport antibiotics, and other substances, increase their number, fact of that the radiation in the blood provokes a nitric oxide dissociation with the hemoglobin and the liberation of the NO provoke vessel dilatation, increasing the blood flux beyond of gen activation of the vascular endothelial grow factor (VEGF)producing increase of angiogenesis before the radiation. Further, the tissue metabolism increasing, the normalization of the homeostasis, and still the increase of the cGMP (guanosine cyclic monophosphate) formed by endothelial cells taken to vasodilatation and increase of the blood flux, therefore not being resulted of thermal effect on the tissues [32].

The laser therapy also has demonstrated to be effective on dipolar molecules non-absorbing of the visible and infrared radiations, as enzymes without metallic atoms, ionic pumps, and nuclear material, and nucleotide molecules [33]. The myosin ATPase inactivated with carbonic gas was parcial activated with the helium-neon laser of 632.8 nm and of 904 nm diode, and the production of ATP was increased with the irradiation and also by a pulsed electric field [34]. The cell vials can be activated when a light-induced electric field interacts with ATP molecules, sodium-potassium-ATPase, mitochondria, enzymes, and phospholipids of the membrane that regulate the sodium signalization. In these cases, not occur the electronic absorption by atoms and molecules, but the induction of the charges of the irradiated molecules by the electric component of electromagnetic energy [35].

The adenosine molecule, presents on ATP, ADP (adenosine diphosphate) and AMP (Adenosine monophosphate) only are capable of absorbs ultraviolet light [36, 37]. Perhaps, the visible and infrared radiation caused a modification in the kinetics of chemical reactions that there are involved. In the moment in that an induced by light electric field is applied a new isoform of phosphate could be produced, leading the modifications on charges distribution in the phosphate structure that turn the molecule more unstable and easier off be cleavage by enzyme [38]. The sodium-potassium-ATPase pump is a membrane enzyme that does ATP hydrolise in the presence of sodium and potassium for their active transport. These ions gradient controls the tissular volume, permits the active transport of sugars and amino acids, controls the nerve and muscle cells electric excitation, and it is responsible for 1/3 energy consumption (ATP) in resting cells. This pump although of be estimated by helium-neon laser not have chromophores for the visible absorption, like this, a transmembrane potential generated by light-induced electric field, activates the sodium-potassium pump without the cleavage of ATP [39]. Other membranes structural phospholipid, whose phosphate could be modified by charge displacement, the phosphatidylinositol 4,5-biphosphate (PIP2), also been more unstable and it is more easily broken by phospholipase C origining IP3 (inositol triphosphate) + DAG (diacilglicerol). The IP3 acts open the calcium channels in the endoplasmatic reticulum. The free calcium provokes phosphorylation of proteins and genic expression. Besides that, calcium is important on ATP synthesis by mitochondria: decreases the membrane potential and activates the ATP synthesis [40].

Before the irradiation, the cytoplasm ATP reacts with enzymes, it is broked, which increses the quantity of ADP that by negative feedback stimulate the ATP synythesis. The light also alters the mitochondrial membrane potential stimulating the ATP synthesis, and when the cellular metabolism is in anaerobic conditions the light increase the reaction kinetic of ketokinase stimulating the ATP synthesis out of the mitochondria [41].

The therapeutic lase action becomes clear, its anti-inflammatory effect, and how consequence an analgesic effect. The stimulus of microcirculation and the production of prostaglandins are fundamentals for the antiflogistic effect of Laser. The Laser actions about the free nervous terminations with consequent liberation of beta-endorphin are essentials for located analgesie [42].

The pain reduction seems to occur as a result of muscular spasm decrease or nervous conduction velocity alteration, while

the tissue cures would occur by the collagen production increase [43]. Recent studies that investigate the low-level laser therapy effect on musculoskeletal pain and skin disturbances suggested that the laser is one of the utilized modalities for the treatment of these disturbs [7].

The photobiologic action mechanism through respiratory chair activation is a universal mechanism [44]. Firstly, photoreceptors are terminal oxidases [45] (cytochrome-C-oxidase in eukaryotic cells and cytochrome bd complex on prokaryotic cells of the Escherichia coli) as well as NADH-desidrogenase (for blue to red spectral range). These primary reactions in or with a photoreceptor molecule leads to photobiologic answer to the cellular level trough of homeostatic biochemical cascade reactions (cell signalization or photo-signal transduction and amplification chair) [46].

Crucial events of these types of cell metabolism activation occur due to a change of cellular redox potential in the direction of major oxidation. Activation of cellular metabolism through respiratory chair occurs in all susceptive cells to irradiation by light [47]. Susceptibility to irradiation and capability to activation due of physiologic stade of the irradiated cells; cells in which the redox potential there is altered to a stade more reduced (example, certain pathologic conditions) are more sensitive to the irradiation [48].

The specificity of the photobiologic final answer is determined not to the level of respiratory chair primary reactions, but the level of transcription during cell signalization events [49]. In some cases, only the partial activation of the cellular metabolism happens (example, lymphocyte activating).

Other oxide reduction events in the cells could also be activated by irradiation. In phagocytic cells irradiation begins a respiratory, not mitochondrial begin (production of oxygen active species, especially superoxide anion) through the activation of NADPH-oxidase located in the plasma membrane of these cells [50]. The irradiation effect in phagocyting cells depend on the physiologic state of the hosper organism as well as on the radiation parameters [51].

Direct activations of cells could take along the indirect other cells' activation. This occurs via secondary messengers liberated by directly activated cells: oxygen reactive species produced by phagocytes, lymphokines, and cytokines produced by various lymphocytes subpopulations, or not produced by macrophages or as a result of none photolysis of the hemoglobin of red blood cells [52]. Coherent properties of laser light not are presented to the molecular level by interaction of the light with the biologic tissue.

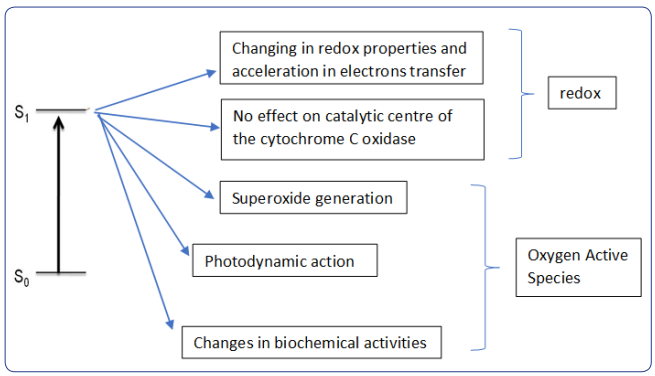

Figure 2: Açtion of the photoreceptor molecule after interaction with the laser radiation; S0 (fundamental state); S1 (activated state).

The absorption of low-intensity laser light by biologic systems is of nature purely not coherent (it is photobiologic) [53, 54]. To the cellular level, all the biological answers are determined by light absorption with photoreceptors molecules (Figure2). This form the increase in cellular metabolism, proliferation, protein synthesis, increase in nerve cells action potential, the stimulus of DNA and RNA formulation in the cellular nucleus, effects on the immunologic system by lymphocyte activation, formation of capilar stimulated by grow factors release and increase on leucocytes activity, and laser irradiation anti-inflammatory action, are other secondary effects of phototherapy with low-intensity laser [55-63].

Acute Inflammation

The inflammatory answer is due to a holl of morphologic and biochemical alterations of conjunctive tissue associated with the vascular and cellular events and have as an objective to produce the homeostasis of injured tissue. The varied agents sensibilizing, evade or destroy the primary barriers (epithelial or endothelial cells and theirs specialized structures) beginning the defense process, initially denominated acute inflammation [64].

The several inflammatory agents could be the more variable as bacteria, virus, parasites, irritant endogenous substances (carragenine), no-irritant endogenous (urate cristals, immune complexes), mechanical stimulus, physical stimulus (burning, ionizing radiation) and chemical stimulus (caustic substances) [65-72].

Different from the nature of the used stimulus, the injured cells activate the mononuclear phagocytic system (circulating monocytes and tissue macrophages) initiating a series of events by cytokines secretions of the IL-1 and TNF (Tumoral Necrosis Factor) [73]. These molecules have pleiotropic action, act on multiple targets, and with multiple actions [74]. They act both locally and systematic levels. In local level, act on matrix cells or tissue estroma, mainly fibroblasts and endothelial cells, causing the liberation of a second cytokines that includes, besides IL-1 and TNF, the IL-6 and IL-8 and inflammatory proteins (MIP-1) and chemotactic (MCP) of macrophages [75]. The group MCP + IL-1 + IL-8 + TGF-βattracts to the inflammatory focus monocytes and neutrophils, each one secretes a third cytokines group, including TNF and other chemotactic factors that feedback the inflammatory process [76].

The vascular endothelium executes a central function on communication between the inflammatory site and the circulant leukocytes, as much by adhesion molecules expression, that facilitates the tissue migration of defense cells, as by vascular tonus modification mediate by araquidonic acid metabolites (prostaglandins, tromboxanes and leucotrienes), by nitric oxide and by kinines, causing vasodilatation (eritema), increasing of vascular permeability by histamine (edema) and arterial hypotension [77]. The other inflammation classic manifestation, the pain, is mediated by prostaglandins and by bradicinina, a nano peptide that participates in coagulation cascade activation beside the most recently describes neurokinin [78].

The prostaglandins are important mediators of a great variety of physiological processes. They are produced starting of araquidonic acid by ciclo-oxigenase enzyme (COX) that has various isoforms, between then the COX-1 and the COX-2 [79, 80]. The COX-1 is express in the majority of cellular types regulating normal

physiologic functions as the gastrointestinal contraction, mucous protection, palets aggregation and renal function maintenance [81]. The COX-2 is considered the physiological expression in some tissues (renal, cerebral. and pulmonary), but it is predominantly inflammatory. His induction results in the prostaglandins production that contribute for the pain, edema and tissue destruction associated with the inflammation acute episodes [82]. More recently was demonstrated that the COX-2 activation could take the production of other inflammatory mediators as the lipoxins and resolvins, which are important for the inflammation resolution contributing for gastric ulcers repair [83].

The inflammatory process that occurs after the tissue injury is mediated partly by phospholipase A2 broken, a constituent of lesionated cell membrane, in their acid lipidic components. One of these components, the araquidonic acid is then converted in prostaglandins, prostaciclins and tromboxanes by one of their various COXs enzymes [84]. Between these mediators, the prostaglandins are the more important responsables by hirealgesy and inflammation sensibilizing the nervous terminations to the actions of the bradicinins and histamins increasing the pain and the inflammation severity. Even more, high tissue concentrations of prostaglandins are responsible to initiate the vasodilatation leading clinically to the eritema and edema. On other side, while the thromboxane liberated by thrombocytes characterizes to determine the platelets aggregation as the vasodilatation, the prostaglandins inhibit the platelet aggregation and determine the vascular relaxation, by having his origin in the arterial walls [85].

The progression of inflammatory reaction occurs with the immunologic system help that walks together in the direction of the resolution of the destructive process. The lymph nodes and other secondary lymphatic organs as the spleen, are the locals more important where the immunologic cells change information, stay, development, and begin the adaptative immunologic response [86]. Begin with the interstitial liquid drainage and conduction of potentials antigens to the lymphatic gangles, the system turns on the immunologic response permiting the search of lymphocyte specific-antigens yet in the linfatic gangles without the necessity of being present in the peripheric tissues [87].

The lymphatic system fulfills the venous way of circulation draining the excess fluids and solutes of interstitial space and returning them to the blood. During the inflammation, the drainage of the tissue liquid can be increased by ten times or more, which increase the delivery tax of the antigen of periferia to the lymph nodes as to the circulating dendriticcells or antigen presenting cells (APC) that are physically positioned to take the peripheries tissue antigen to the lymphatic nodes [88].

Besides this, the cytokines that are produced on affected local are taken to the lymph nodes of drainage, where can provoke alterations that permit increase the traffic of immunologic cells, including the arteriola expansion that increase the blood flux and the lymphocyte traffic to the affected lymph nodes [89]. The inflammation also can induce the expansion of the lymphatic web on lymph nodes that can help to recruit more dendritic cells of periferia to the lymph nodes or increase the T-Cells traffic out the lymph nodes [90]. One series of mechanisms of exist positive feedback do with that the inflammation induces a high exposition of peripheric antigens to the lymph nodes.

The inflammation treatment is actually realized with the traditionalsteroidsanti-inflammatory drugs (EAIs) as the dexamethasone and the prednisolone and not-steroids (NEAIs) as the ibuprofen, diclofenac and naproxen besides the specific inhibitors of the COX-2 (celecoxib and rofecoxib) [91, 92]. These last ones have been utilized as EAIs substitutes by not provoke the usual collaterals effects (gastric ulcers, bleeding, and hepatic toxicity) caused by inhibition of the isoforms Cox-1. Although, their cardiovascular deleterious effects have been much questioned beyond news researches showed that the COX-2 has great importance on inflammatory process resolution [92].

Beyond these drugs, other alternative techniques as electric stimulation, shortwaves, infrared, ultrasound and laser therapy have been utilized with satisfactory results on inflammatory diseases treatment [93].

Laser Therapy in the Inflammation and Edema

The therapeutic advantages of the laser therapy in inflammation have been suggested in various scientific researches [94-103]. The principal mechanisms responsible by modulation of the inflammation triggered by laser radiation involve the increase of the local microcirculation, promotion of angiogenesis, inhibition of inflammatory mediators as the prostaglandin, activation of defense cells, antioxidant effects and acceleration of cellular cicatrisation. All these effects can occur simultaneously resulting in inflammatory response laser modulator effect that wraps pro and anti-inflammatory actions.

The analgesic action of laser therapy can be explained starting with some hypothesis: modulation of inflammatory process or alteration of nervous excitation and conduction of the peripheric neurons or by endogenous endorphins release stimulated by irradiation [104].

The action of neuron inhibition by laser occurs starting of mitochondrial membrane potential reduction promoted by radiation, with the decrease of available ATP, fundamental to the transmission of nervous stimulus by axone [105]. The 830nm laser induced the formation of varicosities, reducing the mitochondrial membrane potential and blocking the axonal transmission in dorsal ganglionar roof neurons of small and medium diameter [106]. The continuous application of laser therapy in clinical studies showed modulation of nociception and pain reduction could be an alternative not pharmacologic in the chronic pain treatment [107].

The laser anti-inflammatory effects as the edema reduction can be related to the increase of blood circulation [108]. The laser therapy stimulates the microcirculation, vasodilatation and angiogenesis, being that the improvement of tissue microcirculation is one of the aspects more important of laser therapy. The capability of auto-regeneration and tissue defense will be increase considerably if the local circulation is increased as the absorption of the pharmacologic agents also will be benefited [109].

Besides that, the effects of laser on the modulation of inflammatory mediators are widely related. Between the involved inflammatory mediators, the more cited is the prostaglandin E2 (PGE2). The PGE2 is a potent mediator involved in the inflammatory and allergic process, been the key mediator of arthritis [110, 111]. It causes hyperalgesia and vasodilation and, in combination with other agents, the releasing of liquids to the adjacent tissues, that provoke the edema formation [112].

The laser inhibits the PGE2 synthesis in the inflammatory processes induced in rats and also in knee arthritis patients. In

zymosan induced arthritis, the infrared radiation showed to reduce the articular edema of correlated form with the reduction of PGE2 inflammatory marker [113].

Beyond PGE2 level reduction, the laser therapy also inhibits the expression of cyclooxygenase-2 [114]. Through a model of hyperplasia induced by carragenin was demonstrated that the analgesic effect caused by laser no involve only one peripheral opioid receptor, but the after events of the liberation of PGE2 during the acute inflammation [115].

The laser therapy modulates the inflammatory pain reducing the levels of biochemistry markers (PGE2, mRNA, COX-2, IL-1, and TNF), the neutrophils influx, oxidative stress, and edema and hemorrhage formation [116]. The laser also showed to be effective in chronic articular disorders as osteoarthritis [117]. The laser has still shown effective in the bronchial asthma treatment, increasing lung compliance and ventilation, and in inflammatory diseases as bursitis, tendonitis and peritonitis [118-120].

Even more, the laser therapy changed the mRNA expression of canine receptors in carrageenan induced edema model [121]. Both the B1 and B2 receptors had their expression decrease after the irradiation. These receptors are fundamentals to the pain and inflammation etiology, been the constitutive B2 and commonly associated with the acute phase of inflammation and nociception, while that the B1 is inducible and bond to chronic inflammation phase.

On laser therapy, many factors can interfere with clinical treatment as the patient characteristics, the type and phase of the injury, the tissues that will be irradiated, the physical parameters associated with the irradiation (energy, fluency, potency, intensity, laser bundle area, lesion area, wavelength, exposition time and application mode), the frequency, local and the number of irradiations, and still the right moment of to do the irradiation according to the type and phase of the disease to be treated [122, 123].

This great variety of factors that interfere withclinical results become critical individualized elaboration of protocols, entailing sometimes in unsuccessful treatments.

In relation to the choice of the wavelength to be utilized on laser therapy is reported the utilization of red emission laser in superficial injuries as on tissue cicatrizations, while that the infrared emission laser is more used in deep tissues and inflammation modulation. The great red wavelength absorption by blood justified its lowest penetration on tissues in relation to infrared irradiation. However, many are the factors that influence in the laser-tissue interaction as the tissue attenuation characteristics, the emitted photons number between other, therefore, both the wavelength can be effective [124]. The laser and the light emitter diode (LED) effects about edema, increase of the vascular permeability and articular hyperalgesia were studied in an experimental model of zymosan induced arthritis. In this study, the laser therapy anti-inflammatory effect showed to be efficient independent of the wavelength used, red (685nm) or infrared (830nm). The LED (628nm) was utilized in the same dosimetric conditions that the laser not presented no-effect in this experimental model [125]. In other study, the infrared radiation was that presented better results in relation to the control group and the other irradiations to wound healing [20]. This demonstrates that other factors more important than the wave length can be influencing in laser therapy effectivity.

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