MECHANISMS OF THE ANALGESIC EFFECT OF THERAPEUTIC LASERS
IN VIVO

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The analgesic effects in the course of application of therapeutic lasers to affected tissue have been described in a number of works in the literature. Although a few scientific-based reports have appeared, those on laser-induced analgesia are mainly clinical works describing the effect of the therapy which, however, do not study the mechanism of the laser action. There are several different possible responses induced by non-invasive low level laser therapy (LLLT). The purpose of the present communication is to review the arrangement and characterization of these responses. By being aware of these effects, the laser therapist can acquire a physiological and morphological scheme making possible the appropriate choice of the site of application of LLLT, choice of the irradiation technique, and selection of appropriate doses.

Key words: therapeutic laser, non-invasive laser therapy, LLLT, endorphins, analgesic effect, nerve transmission rates

Introduction

In 1966, when the late Professor Endre Mester with his co-workers first described the beneficial effects of low incident laser energy on living tissue, they surely could not have foreseen the dramatic progress of noninvasive laser therapy in the following thirty years. In these subsequent years, after some serious problems in the 1970’s occasioned by over-enthusiastic and under-controlled ‘studies’ from which laser therapy is still suffering scientifically, the beneficial effects of low level laser therapy (LLLT) have been repeatedly demonstrated. The authors have chosen to follow Ohshiro and Calderhead in their choice of ‘LLLT’ as a suitable acronym for clinical applications of laser therapy.\textsuperscript{(1)} LLLT effects concern particularly the analgesic, anti-inflammatory and other bioactivative reactions. Despite a great deal of progress, particularly in the last five years, the mechanism and pathways of laser therapy in living tissue remain unclear in many aspects.

The rapid development of laser therapy techniques combined with fervent attempts of certain physicians to offer to their clients some new approaches for their patients’ pain conditions has resulted in a state of affairs well known in medical history in the field of using ionizing radiation. In the case of the laser, we also use a certain form of the energy without being able to strictly describe or define the mechanism of its action on the living tissue. As far as laser therapy and photobioactivation is concerned, although our knowledge is currently already considerably extensive, it is however far from complete.

When speaking about (LLLT) systems, we are particularly considering dedicated laser-based instruments whose output power does not exceed 500 mW with incident power densities to the tissue of less than 3 W/cm\textsuperscript{2}. In current practice, commonly used devices in the authors’ geographical region have output power ranges between 5 mW and 40 mW and only the most expensive instruments, whose price already approaches

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that of a new domestic car, have output powers of over 150 mW. From the technical standpoint, the most frequent laser medium (source) is either a laser diode or helium-neon tube.

Having said this, it has already been pointed out by Calderhead and others that a 20 W CO₂ laser can be used in the defocused mode to produce incident power densities of under 1.0 W/cm² at spot sizes of around 10 cm in diameter.²,³ The most important factor is therefore not the system used to produce the laser energy, but the incident power density and energy density of the laser beam at the target tissue.

Effects of LLLT on Neural Transmission

The application of the therapeutic laser in clinical practice for achieving an analgesic effect is reasoned in a number of works published during the last decade, in particular the books from Ohshiro and Calderhead, and Baxter,¹,⁴,⁵ and many of the papers published in this journal. Based on these analyses it is possible to assume that the analgesic effect results from the influence of LLLT the following processes.

Pain in general is an unpleasant sensory-based perception, which is connected with actual or potential damage to the tissue although this is not so in specialized instances, such as the case of so-called phantom pain. The concept of pain is wide, and pain is induced not only by exogenous stimuli and endogenous pathophysiological processes, but also by subjective perception, which varies considerably individual by individual. The studies published up to the present have however demonstrated an analgesic stimulus response induced by the laser beam in all levels of the nervous system of living beings.

Nociceptors (from Latin nesci, 'I injure' and capio, 'I take') are specific sensors exhibiting a high degree of sensitivity to noxious stimuli, recording actual or potential physical or chemical irritation to tissue. They are essentially present in all tissues, including skin, mucosal membranes and muscles.⁶ They have a normal membrane potential. Algeassic stimuli lead to changes of the sensory membrane permeability (particularly in the opening of Na-channels) and thus also to the creation of depolarizing ion currents. The resulting depolarization is known as a sensory potential or receptor potential. It persists for the same time as the stimulus and its amplitude increases with the magnitude of the stimu-

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**Fig 1:** Schematic illustration of the pain transmission pathway from a painful stimulus on the hand. The signal is transferred through the neural cell body to the appropriate dorsal horn before being sent via the ventral horn and the second neuron to the thalamus where the pain impulse is transmitted to the postcentral gyrus, and to the frontal and lateral gyri in the cerebral cortex, where the signals are analyzed, converted to an emotional response which evokes both the sensation of pain and protective reflexes with conscious motor control.
lus, in other words it reflects the degree of algesic stimulation. We speak about the transposition, which can be positively affected in the irritated region by the laser application, by induced descetration as reported by Walker et al. In support of this assumption, Maeda et al. described a significant reduction of the density of mitochondria in bradykinin-affected trigeminal nerve axons after LLT application compared with the unirradiated controls. Sensory algereceptors in joint structures also present information about the joint motion and about extremely painful position of the joints by way of the proprioceptive α-fibres.

Information transfer from the peripheral nervous system is effected by myelinated A-fibres, of small to intermediate diameter (1 μm - 22 μm) with medium to high transmission rates (6 m/sec - 120 m/sec); and small diameter unmyelinated C-fibres (0.4 μm - 1.2 mm) with low transmission rates (0.7 m/sec - 2.3 m/sec). These afferent fibres transfer the information acquired by the nociceptors via the gray matter of the posterior horns of the spinal column to the medulla, where the nociceptive afferent pathways terminate (Figure 1).

By this ascending system of pathways, the pain information is carried into the reticular formation, thalamus and the cerebral cortex. The reticular formation imposes an 'emotional' impact on the perception of the pain due to its strong ascending and descending autonomic and endocrine functions, while the somatosensory cortex and association cortex regions participate in the production of the conscious and spatially located painful perception. We know, however, that even before this stage is reached the nociceptive information may be modulated (so-called 'gate control theory') through deceleration of the transmission rates of the afferent A- and C-fibres in the gray matter of the posterior horns and in the cells of the spinal ganglia, as well as modulation and control of the descending inhibitory systems by acceleration of the C-fibre transmission rate, and particularly of the reticulospinal tract (tractus reticulospinales).

Laser therapy also affects the release of endogenous opiates (α- and β-endorphins), which bind to opiate receptors of the nociceptive system (particularly in the substantia grisea centralis), occupying many sites and thus achieving narcotic analgesia by blocking entry of these receptors to the incoming nociceptive transmission substances. This knowledge is based, amongst others, on publications by Walker et al. and Hansen et al., who describe an increase in the elimination of 5-hydroxyindolacetic acid, (a metabolite of serotonin), in urine following the local irradiation with LLT, mainly in patients with chronic pains, so that it is to assume that the analgesic effect is induced in this case by releasing serotonin and by enhancing the level of β-endorphins. Ponnudurai et al. emphasized that the analgesia induced by LLT was not naloxon-reversible.

LLLT additionally directly affects components of the peripheral nervous system. This is supported in a publication by Walker et al., who demonstrated a direct laser effect on nerve terminals during the application of

![Fig 2: Schematic illustrating the ascending stimulation pattern resulting in and countered by the descending inhibitory pathways following laser stimulation of sensory nerve endings.](image)
therapeutic laser in spastic paraplegic patients, where the authors achieved a similar efficacy compared with transcutaneous electric stimulation (TENS). Walker additionally recorded a reduced irritability of peripheral nerves (n. radialis, n. medianus, n. saphenus), which also holds during LLLT application to the skin. From an objective consideration, it must be pointed out that some authors did not observe similar effects.

When summarizing the above mentioned data, it is possible to specify the following assumptions, which are schematically illustrated in Figure 2:

- LLLT activates the reticular formation + substantia grisea centralis.
- LLLT induces the synthesis of serotonin thereby modulating the activity of T-cells and cells of the termination zones in the gray matter of the posterior dorsal horns.
- It is also necessary to emphasize the possibility that LLLT may in some circumstances be able to potentiate the conduction of the algogenic stimulus through different fibres - this results in an increase of the perceived pain.

**LLLT and Acetylcholine**

One of the nervous system's chemical transmitters most sensitive to LLLT is acetylcholine, located on the neuromuscular plate as well as in the region of the preganglion synapses of autonomous nerves. During the production of the plate potential at the neuromuscular connection, the depolarization of presynaptic terminals caused by opening Ca++ channels occurs to produce suitable conditions for the origination of changes in the axon potential and Ca++ concentration gradient. Calcium ions stabilize the resting axon potential by increasing the threshold for the activation of rapid Na+ channels. In contrast to this, decrease in the cellular levels of Ca++ results in an increase of involuntary irritation and, in extreme cases, in tetanus. The increased cytoplasmic levels of Ca++ ions induce a synchronous release of acetylcholine from acetylcholine-filled synaptic vesicles (Figure 3). Acetylcholine molecules diffuse to the postsynaptic membrane receptors, activating them and starting the pain stimulus afferent transfer. The activation results in opening membrane channels, which become free for the passage of Na+, K+ and Ca++ ions. The current is present only for a short time (1-2 ms) and the neuromuscular plate returns to its resting potential level within 5 ms.

Anders et al. showed that LLLT application increases the activity of acetylcholine esterase and the accelerated decomposition of acetylcholine to choline and acetic acid occurs, which, after rediffusing into the presynaptic terminals, are resynthesized to acetylcholine esterase. In other words, LLLT has the potential to neutralize acetylcholine before it has a chance to cross the synaptic gap. This action of closing the synaptic gate is also assisted by the laser-modulated production of enkephalins. These actions together represent the equivalent of non-narcotic analgesia.

Data, not yet clinically applicable or proven, have been published by Zyryanova et al. who described, based on experimental works on rats, a locally enhanced activity of acetylcholine esterase after a direct local laser application onto the surface of the brain.

**LLLT Analgesia**

The analgesic effect of LLLT is also supported by the stimulation of the local metabolism, which results from the enhanced microcirculation of the blood and accelerated outflow of the lymph from the region involved. The explanation is presented by Danhof, who assumes that the therapeutic laser indirectly paralyzes precapillary muscles through the mediation of endogenous amines which include for example histamine. In the case of a higher laser power, the beam is able to induce this effect in a relatively large region. As a matter of fact, in the case of recorded therapeutic laser doses, no damage to nerve tissue occurs even after doses of 9.6 J/cm², however, concerning the analgesic effects of LLLT, studies by Czopf et al. (1987) are of interest, where a delayed response of the nerve on the stimulus is described depending on the time after the exposure to low-level laser (in minutes), and data from Snyder-Mackler et al. showed a similar result after an irritation of the n. radialis by a dose of 0.2 J/cm² in healthy individuals.

In applications of LLLT for pain attenuation, conditions have been described where patients with the chronic head and neck syndrome were treated unilaterally with LLLT, and a significant decrease in the level of the compressive pain was also achieved on the untreated side, although the increase on the treated side was, however, higher.

In LLLT applications in dentistry, the knowledge is of importance that LLLT application has been shown to reduce dentin hypersensitivity to different irritating agents by as much as 60%, and that it also had beneficial results in the treatment of trismus. The advantages of LLLT in inducing postsurgical analgesic effects include problem-free postoperative periods, frequently also free of pain, and accelerated healing of the operation wound by primary intention which also holds for inflammatory and infection-compromised wound healing conditions.
Laser acupuncture has been applied successfully for prostatitis,\(^{(38)}\) female infertility,\(^{(39)}\) scald injuries,\(^{(40)}\) torticollis,\(^{(41)}\) and diarrhoea,\(^{(42)}\) as well as many reports of veterinary applications in large animals.\(^{(43,44)}\) Thus, there is a sound body of evidence linking the efficacy of LLLT acupuncture, with or without needles (needleless laser acupuncture and needle laser acupuncture\(^{(38)}\)), and the analgesic effects induced by classic needle acupuncture techniques.\(^{(45)}\)

**Conclusions**

Although many aspects of the mechanisms by which LLLT attenuates pain remain unclear, enough has been shown scientifically to draw the firm conclusion that LLLT has a real role in pain therapy. From the scientific viewpoint, it is of course necessary to draw careful conclusions based on controlled double-blind studies with, if possible, a crossover element, in order to identify the strength of the so-called ‘placebo effect.’ There exist now some studies which have done just that: in LLLT for postherpetic neuralgia, acute soft tissue injuries and postoperative pain, all of which have appeared in this journal. These studies show that while there is a placebo effect, it is however extremely weak and very short-lived compared with the ‘real’ laser therapy treated groups. From the clinicians viewpoint, however, should we really be so worried about the placebo effect of a laser? The authors would like to hope that the main aim of laser therapists is to get rid of their patients’ pain. If the placebo effect associated with the high-tech ‘laser’ can assist in this goal, particularly when it is known that LLLT goes way beyond the placebo effect only, then that is surely one more good reason why LLLT should take its rightful place in the armamentarium of those medical professionals dealing with the treatment of pain.

It has been almost unanimously stated in the literature that LLLT is easy to apply, is pain and side effect free, and is well tolerated by patients of all types and ages. As long as we remember that LLLT is not a
magic wand, and is not capable of curing every single pain entity under the sun, in every single patient, then LLLT can be confidently used on its own or as an adjunctive therapeutic modality with an expectation of achieving an effective pain relief of around 70%-85% in about 80% of patients, if we look at the average values from the majority of large patient population case studies (> 1,000 patients per study) seen in the literature since 1988.

As a final note, we must also remember that pain is often a symptom and not the disease, so it is necessary to make sure the root cause of the painful condition is accurately identified and treated, in addition to the pain itself. The authors are confident that further scientific studies will continue to elucidate the mechanisms and pathways of LLLT pain control, and that laser therapy is poised to enter the 21st century where it will surely become even more of a leading clinical modality than it is at present.

References


