

Mechanism of Itranasal Low Intensity Laser Irradiation Therapy

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ABSTRACT

Background and Objective: Intranasal low intensity laser therapy (ILILT) began in China in 1998. Now in China it has been widely applied to treat hyperlipidemia, the blood-stasis syndrome of coronary heart disease and brain diseases such as Alzheimer's disease, Parkinson's disease, insomnia, poststroke depression, intractable headache, ache in head or face, cerebral thrombosis, acute ischemic cerebrovascular disease, migraine, brain lesion and mild cognitive impairment. Its mechanism was discussed in this paper. **Study Design/Materials and Methods:** ILILT was an intranasal photobiomodulation (PBM), and was discussed in terms of the cellular rehabilitation of PBM from viewpoints of three pathways mediating ILILT, blood cells, Yangming channel and autonomic nervous system (ANS). **Results:** Blood cells might mediate ILILT as is intravascular low energy laser therapy. Two unhealth acupoints of Yangming channel inside nose might mediate ILILT as is laser acupuncture. Dysfunctional ANS might be modulated and then mediate ILILT. These three pathways are integrated in ILILT so that serum amyloid β protein, malformation rate of erythrocytes, CCK-8, or serum lipid might decrease, and melanin production, SOD activity or β endorphin might increase after ELILT treatment. **Conclusions:** ILILT as a safe therapy might work in view of the previous research, but it should be supported by randomized placebo-controlled trial

Keywords: photobiomodulation, low intensity laser therapy, laser acupuncture

1. Introduction

Intranasal low intensity laser therapy (ILILT) began in 1998(Li et al 1998). It has been applied to treat hyperlipidemia (Zhang et al 2003), the blood-stasis syndrome of coronary heart disease (Xiong et al 2006) and brain diseases (Jiang et al 2001) such as insomnia (Xu et al 2001&2002a), intractable headache (Li et al 1998a), Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), poststroke depression (Xu et al 2002c), ache in head or face (Li et al 1998b), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), migraine (Chen 2003), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001). The studies indicated that serum amyloid β protein(Jin et al 2000), malformation rate of erythrocytes (Li et al 1999a), CCK-8 (Li et al 1999b), the level of viscosity at lower shear rates and hematocrit (Jie et al 1999), and serum lipid (Dou et al 2003, Zhang et al 2003) decrease, respectively, and melanin production(Xu et al 2001-2003), SOD activity (Xu et al 2003) and β endorphin (Li et al 1998) increase, respectively, after ILILT. In this paper, its mechanism will be discussed.

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2. Homeostatic Regulation

Photobiomodulation (PBM) is a modulation of monochromatic light or laser irradiation (LI) on biosystems, which stimulates or inhibits biological functions but does not result in irreducible damage (Liu et al 2003&2004). The LI used in PBM is always low intensity LI (LIL), ~ 10 mW/cm². However, moderate intensity LI (MIL), $10^2\sim 10^3$ mW/cm², is of PBM if the radiation time is not so long that it damages organelles or cells. The PBM of LIL and MIL are called LPBM and MPBM, respectively, for short. There are two kinds of pathways mediating cellular PBM, the specific pathway which is mediated by the resonant interaction of LI with molecules such as photosensitizers or endogenous photosensitizers, the non-specific pathway which is mediated by the non-resonant interaction of LI with the proteins on the membrane of cells or organelles (Liu et al 2004). The concentration of endogenous photosensitizers is so low that LPBM is mainly mediated by the non-specific pathways, but MPBM is mainly mediated by the specific pathways, respectively. Therefore, MPBM is mainly mediated by reactive oxygen species (ROS) (Lubart et al 2005). ILILT is based on intranasal LPBM, but the intravascular low energy laser irradiation therapy (ILELT) (Jiang et al 2005, Liu et al 2006) is based on intravascular MPBM.

Homeostasis is a negative-feedback response of a biosystem to maintain the constant conditions inside the biosystem (Murphy et al 1983), and can be represented by the metabonomics/metabolomics of the biosystems (Dumas et al 2005). There are two kinds of homeostatic processes in the internal environment and external environment of a biosystem, the pathogenic processes which disrupt the old homeostasis, and the sanogenetic processes (Kryzhanovsky 2004) which restore the old homeostasis or establish a new homeostasis. MPBM might be a pathogenic process if the ROS level is so high that it disrupts the old homeostasis as Shefer et al (2001) have found for MPBM (177 mW/cm², 3s) on i28 myoblasts after 36h fetal calf serum deprivation that the MPBM specifically activates ROS mediated mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK) pathway. LPBM might be a sanogenetic process as Karu (1998) has pointed there is no effects of LIL on the cell which redox potential is so that the cell normally functions, and the lower the redox potential of a cell comparing with the normal redox potential, the stronger the effects of LIL. MPBM might be also a sanogenetic process if the ROS level is not so high that it disrupts the old homeostasis as Liu et al (2006) have pointed that there is no PBM on health blood for ILELT. At this point, PBM can be classified as pathogenic PBM which can disrupt a homeostasis, and sanogenetic PBM which can modulate the pathogenic factor induced disruption of a homeostasis until the homeostasis has been restored or a new homeostasis has been established, but can not change homeostatic processes from one to another one. In other words, sanogenetic PBM is just a homeostatic regulation(Liu et al 2007).

Obviously, ILILT, as an intranasal LPBM, is just a homeostatic regulation so that it only modulates dysfunctional biosystems. Tulebaev et al (1989) have found the LPBM treated patients with vasomotor rhinitis showed a significant increase of T-lymphocytes and a higher capacity of T-cells to form the migration inhibition factor. Kruchinina et al (1991) have studied therapeutic effect of He-Ne laser on microcirculation of nasal mucosa in children with acute and chronic maxillary sinusitis, and found that laser therapy produced a positive effect on microcirculation and reduced the potential of relapses. Shevrygin et al (2000) have shown that LPBM is effective in correction of microcirculatory disorders and tissue mechanisms of homeostasis in children with neurovegetative vasomotor rhinitis. Except these ILILT on the local inflammation, there are four possible pathways mediating the ILILT, olfactory nerve, blood cells, Yangming channel and autonomic nervous system. The olfactory nerves are healthy in the diseases mentioned in the introduction so that it might not play a role in ILILT. The other three pathways will be discussed in next sections.

3. Laser Hemotherapy

Laser hemotherapy was mentioned in discussing ILELT (Tsvettsikh et al 1999), and will be discussed in this section as the blood cells in the diseases mentioned in the introduction are always far from homeostasis so that there might be LPBM on their functions.

There is LPBM on erythrocytes, such as its protecting human erythrocytes from hypotonic hemolysis (Iijima et al 1991), its improving the deformability of stored human erythrocytes (Iijima et al 1993, Yokoyama et al 2003), its producing AchEase activity changes (Kujawa et al 2003) and its inducing long-term conformational transitions of erythrocytic membrane which were related to the changes in the structural states of both erythrocyte membrane proteins and lipid bilayer and which manifested themselves as changes in fluorescent parameters of erythrocyte membranes and lipid bilayer fluidity so that there was the modulation of membrane functional properties: changes in the activity of membrane ion pumps and, thus, changes in membrane ion flows (Kujawa et al 2004). Luo et al (2005) have studied the role of membrane aquaporin-1 (APQ-1) in the LPBM on erythrocytic deformability with human echinocytes and APQ-1 inhibitor, HgCl₂. Human echinocytes were irradiated by He-Ne laser irradiation at 1-5 mW and 5-30 min, respectively. They found that the He-Ne laser irradiation optimum dose promoting echinocyte deformability is $1.3 \times 10^4 \text{ J/m}^2$ at 4 mW/cm^2 , but the effect is significantly inhibited by $0.2 \mu\text{M}$ HgCl₂, which showed AQP-1 might mediate the effect of low intensity He-Ne laser irradiation on erythrocytic deformability. There were so many LPBM studies on erythrocytes, but a few of LPBM studies on platelets (Olban et al 1998), which provides the foundation for ILILT on the rheological properties of blood so that serum amyloid β protein (Jin et al 2000), malformation rate of erythrocyte (Li et al 1999a), the level of viscosity at lower shear rates and hematocrit (Jie et al 1999), and serum lipid (Dou et al 2003, Zhang et al 2003) decreased, respectively, and SOD activity increased (Xu et al 2003) after ILILT.

There is also LPBM on leukocytes, such as its stimulating lymphocytes to produce factor(s) that can modulate endothelial cell proliferation in vitro (Agaiby et al 2000), its attenuating ROS production by human polymorphonuclear neutrophils (PMNs) (Fujimaki et al 2003), its modulating nitric oxide and cytokines production by leukocytes (Klebanov et al 2002). Here is the only one signal transduction research on ILILT. Duan et al (2001) have probed signal transduction pathways of respiratory burst of bovine PMNs which were induced by He-Ne laser irradiation at a dose of 300 J/m^2 by using the protein tyrosine kinases (PTKs) inhibitor, genistein, the phospholipase C (PLC) inhibitor, U-73122, and the protein kinase C (PKC) inhibitor, calphostin C, respectively, and found the inhibitor of PTKs can completely inhibit the He-Ne laser-induced respiratory burst of PMNs, and PLC and PKC inhibitors can obviously reduce it, but not fully inhibit it. These results suggest that PTKs play a key role in the He-Ne laser-induced respiratory burst of PMNs and [PTK-PLC-PKC-NADPH oxidase] signal transduction pathways may be involved in this process. These cellular LPBM studies provide the foundation for ILILT on immunological functions so that the CD3/CD8 increased and CD4/CD8 decreased after ILILT (Zhou et al 2005)

4. Laser Acupuncture

Laser acupuncture as an alternative, noninvasive, painless and cost-effective therapy has been widely used for acute and chronic pain, nausea, circulatory functions, mood-related behavioral disorders and so forth (Jiao et al 2003). It might mediated ILILT since there are two unhealthy acupoints of Yangming channel inside human nose.

Laser acupuncture devices were cleared for marketing by FDA through the Premarket Notification/510(k) process as adjunctive devices for the temporary relief of pain (FDA 2002). The research on the effects of laser acupuncture on pain has shown that laser acupuncture can improve the expression of β endorphin (Chen KZ et al 2004), which has been also found for ILILT (Li et al

1998a&b). Zhang (2005) found therapeutic effect of acupuncture at acupoints along the Hand and Foot-Yangming Channels on trigeminal neuralgia, which has been also found for ILILT (Li et al 1998a&b). In this way, it is easily understood that there might be therapeutic effects of ILILT on intractable headache (Li Q et al 1998a), ache in head or face (Li Q et al 1998b) and migraine (Chen S 2003).

Laser acupuncture and then ILILT on cerebrovascular diseases should be in view of acupuncture at Yangming channel points (Jiang et al 2005). Zhang et al (1990) observed the effect of acupuncture at points of hand-yangming meridian was bigger than that of foot-yangming meridian on the facial temperature of the patients with facial nerve paralysis. Wu et al (1996) have adopted the principle of clearing Yangming and nourishing the kidney and heart in the treatment of 156 cases of Gilles de la Tourette's Syndrome with acupuncture, and they found the pathological waves in 54 disappeared or ameliorated after the treatment among 84 cases with abnormal EEG. Zhang et al (1999) have found one of the mechanisms governing acupuncture treatment of apoplexy acupuncture at Yangming channel points as main points was that acupuncture could produce therapeutic effects by adjusting the imbalance of important vaso-active substances, endothelin level in plasma, TXB2 and 6-Keto-PGF1 alpha levels in urine. Wang et al (2005) found the acupuncture therapy of "mother-son" reinforcing-reducing method of five Shu points of The Hand-Yangming and Foot-Yangming Channels based on differentiation of yin, yang and deficiency and excess of channels by Cunkou and Renying Vessel methods can increase clinical therapeutic effect on stroke at restoration stage. Therefore, there might be therapeutic effects of ILILT on brain diseases (Jiang et al 2001) such as Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), insomnia (Xu et al 2001&2002a), poststroke depression (Xu et al 2002c), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001).

5. Autonomic Nervous System Mediated Pathways

The autonomic nervous system inside human nose might be dysfunctional so that it might mediate ILILT. It might be also one of the pathways mediating acupuncture and laser acupuncture (Jiao et al 2003). Autonomic dysfunction is responsible for much of the morbidity associated with frequently encountered neurological disorders, such as Parkinson's disease, multiple sclerosis, cerebrovascular disease, and peripheral neuropathies, as well as with the rarer primary autonomic nervous system degenerations (Freeman et al 1993) so that there might be therapeutic effects of ILILT on brain diseases (Jiang M et al 2001) such as Alzheimer's disease (Xu et al 2002b), Parkinson's disease (Li et al 1999b, Xu et al 2003, Zhao et al 2003), insomnia (Xu et al 2001&2002a), poststroke depression (Xu et al 2002c), cerebral thrombosis (Li et al 1999a), acute ischemic cerebrovascular disease (Jie et al 1999), brain lesion (Dou et al 2003) and mild cognitive impairment (Jin et al 2000&2001). For example, melanin production can be improved in ILILT (Xu et al 2001-2003) since the activation of sympathetic subsystem can enhance melatonin production (Tang et al 2002).

6. Discussion

LPBM is a safe modality for clinical use (Wolbarsht 1994, Logan et al 1995) so that ILILT is also a safe modality for clinical use. Complete laser hatching of human embryos using the Zona infrared laser optical system does not have an adverse effect on subsequent development (Wong et al 2003). There is no cytotoxic and genotoxic potential of low intensity laser irradiation (660 nm, 12 mW, 5 kHz, 2 and 20 J/cm²) on mammalian cells (Logan et al 1995). The induction of cell-cycle delay of visible-light irradiation at 660 nm is not initiated by DNA strand breaks (Joyce et al 1999).

Following the doses of IR-A (700-2000 nm) that induced ferritin levels, there was no alteration seen for nuclear DNA type damage, oxidative stress proteins or proteases involved in the degradation of skin (Applegate et al 2002).

As a safe modality for clinical use, ILILT might be integratedly mediated by blood cells, Yangming channel and autonomic nervous system as discussed above. The mechanism can be used to extend its clinic applications. For example, ILILT might be used to promote the antimicrobial effects. There have been in vivo antimicrobial effects of LPBM (Wang et al 1998, Neimark et al 2000, Gizinger et al 2006, Dolgushin et al 2006) and ILELT (Karniushina et al 1989, Neimark et al 2000), which might be due to cellular rehabilitation of sanogenetic PBM on the induction and formation of neutrophil extracellular traps (NETs). PMNs undergo a ROS-triggered death that allows microbial killing by the formation of NETs (Fuchs et al 2007). The ILELT induced ROS level in PMNs might rehabilitate NET induction and formation but not induced PMN apoptosis or necrosis. LIL might also rehabilitate NET induction and formation since PMN number has been found to decrease in antimicrobial effects of LIL in vivo (Wang et al 1998).

ILILT might work in view of the previous research, but it should be supported by randomized placebo-controlled trial. Up to date, there has been only one clinical research according to the principle of random, single blind and parallel controlled trial (Xiong et al 2006). Xiong et al (2006) have observed the therapeutic effects of intranasal diode 650 nm laser irradiation on patients suffering from the blood-stasis syndrome of coronary heart disease, and found there was significant therapeutic effects of the ILILT on the blood-stasis syndrome of coronary heart disease, which improved some traditional Chinese medicine symptoms such as fatigue and feebleness.

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