Review

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Photobiomodulation – The Chinese approaches and advances in clinical application

Photobiomodulation – Der Chinesische Ansatz und Fortschritte in der klinischen Anwendung

Abstract: Photobiomodulation (PBM) is a biomedical treatment that uses monochromatic light or laser irradiation to stimulate or inhibit biological functions. Therapeutic applications of PBM are very common in China as the research on PBM and its therapeutic applications are very advanced. This paper reviews the literature in terms of the function-specific homeostasis, genetic redundancy and self-adaptation of the PBM phenomena and gives an overview of the clinical applications, such as laser acupuncture, intravascular low energy laser therapy, intranasal low intensity laser therapy and laser surgery, taking into consideration the approaches of functional medicine and Traditional Chinese Medicine.

Keywords: photobiomodulation; homeostasis; genetic redundancy; self-adaptation; low level laser therapy; functional medicine; Traditional Chinese Medicine (TCM).

Zusammenfassung: Die Photobiomodulation (PBM) ist eine biomedizinische Behandlung, die monochromatisches Licht oder Laserstrahlung zur Stimulierung oder Hemmung biologischer Funktionen nutzt. In China wird die PBM sehr häufig therapeutisch eingesetzt, da hier die Erforschung der PBM und ihrer therapeutischen Anwendungen sehr weit fortgeschritten ist. Der vorliegende Reviewartikel gibt – unter Berücksichtigung der Ansätze der funktionellen Medizin und Traditionellen Chinesischen Medizin – einen Überblick über die Literatur in Bezug auf die besonderen Eigenschaften der PBM (Homöostase, genetische Redundanz, Selbst-Anpassung) und über ausgewählte klinische Anwendungen wie Laser-Akupunktur, intravaskuläre und intranasale Low-Level-Laser-Therapie sowie Laser-Chirurgie.

Schlüsselwörter: Photobiomodulation; Homöostase; genetische Redundanz; Selbst-Anpassung; Low-Level-Laser-Therapie; funktionelle Medizin; Traditionelle Chinesische Medizin (TCM).

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1 Introduction

Photobiomodulation (PBM) is used to stimulate or inhibit biological functions by laser irradiation or monochromatic light. To prevent irreversible cell damage, the light used in PBM is always low intensity light (LIL) with approximately 10 mW/cm^2. Moderate intensity light (MIL) in the range of 0.1–1.0 W/cm^2 can also be used for PBM if the irradiation time is not long enough to damage the organelles or cells. However, LIL and MIL with short irradiation times are two kinds of low level light (LLL). The LLL therapy (LLLT) is being widely used in the whole world to cure a number of conditions. Recent studies on PBM in China have been advanced and many therapeutic applications of PBM have been developed by integrating the approaches of functional medicine and Traditional Chinese Medicine (TCM). Many of the Chinese therapeutic applications of PBM have been widely accepted and practiced all over the world. In this review, we will discuss those applications in detail.

2 Photobiomodulation mechanisms

2.1 A brief history of photobiomodulation

Heliotherapy (light therapy) was practiced by physicians in ancient cultures in China, Egypt, Greece, and India to

address many health-related issues. In TCM, color has been classified into two categories, the hot colors such as red, orange and yellow, and the cold colors such as green, blue and violet. Both – the hot colors and the cold colors – have been used to compliment the conditions that are either *yang* or *yin* deficiency.

In 1966, Endre Mester performed a series of experiments that identified the biostimulatory effect of visible red and infrared laser light at low intensity [1]. Since then, LLL has been widely used to relieve pain, speed up wound healing and accelerate hair growth. The first mechanistic study of laser biostimulation was performed by Kertesz et al. [2] in Hungary in 1982. In China, Ding [3] and Zhang et al. [4] were among the first to study LLLT.

2.2 Properties of photobiomodulation

2.2.1 Function-specific homeostasis

The debate as to whether PBM is effective or ineffective [5] seems endless. The numbers of positive and negative results are almost equal. Our laboratory has addressed this issue in terms of homeostasis related to the PBM mechanism [6–11].

As Tunér and Hode [1] have summarized, the light energy is thought to achieve the greatest response where it is most needed. Modiaev et al. [12] studied the beneficial effect of LLL on the natural course of disease, morphologic characteristics of gastric mucosa and key elements of systemic hemostasis in 98 patients with precancerous lesions of the stomach (gastric ulcer and chronic atrophic-hyperplastic gastritis with epithelial dysplasia). They found a correlation between clinical response and normalization of morphologic appearance and homeostasis.

Shevrygin et al. exposed the turbinate bone mucosa of 46 children, aged between 6 and 15 years, to LLL radiation for neurovegetative vasomotor rhinitis [13]. They found that abnormal microcirculation recovered after 10 s of LLL irradiation even in cases of severe alteration of using a microcirculatory bed and a long history of the disease. Zungu et al. [14] confirmed that LLL stimulated an increase in intracellular Ca^{2+} which resulted in an increase in mitochondrial membrane potential, adenosine triphosphate and 3′–5′-cyclic adenosine monophosphate, which ultimately resulted in a PBM to restore homeostasis of injured cells.

Redox homeostasis has also been discussed. As Karu [15] has pointed out, there is no effect of LIL on the cell if the redox potential is such that the cell normally functions. The lower the redox potential of a cell compared with the normal redox potential, the stronger the PBM of LIL (LPBM). Tafur and Mills [16] pointed out further that LIL may have an effect on tissues through interactions with endogenous cellular redox systems. This may partially explain why some cells in pro-oxidant states, such as those that are chronically inflamed, are more sensitive to LIL. In these sensitive cells, LIL would provide further reactive oxygen species, which may be specific to promoting proliferation, or in some cases accelerating antioxidant mechanisms. In such a scenario, these processes would provide the energy and the direction to restore redox homeostasis and improve cell functioning.

Our laboratory systematically summarized the PBM phenomena for the first time in terms of homeostasis [7]. We found that there is no PBM on a cell in homeostasis. LLL might modulate the disruption of cellular homeostasis induced by pathogenic factors such as a toxin until the homeostasis has been restored or a new homeostasis has been established, but it cannot change homeostatic processes from one to another one.

Although homeostasis maintains the internal constancy of a biosystem, oscillations are found at nearly every level of biology. From the dynamic instability of cytoskeletal elements in an individual cell to the circadian rhythms that regulate a multitude of operations at the organismal level, it is clear that periodicity is an essential characteristic of living systems. At this point, functional constancy is more basic than the internal constancy. Our homeostatic viewpoint was further developed by introducing the concept of function-specific homeostasis (FSH) [6, 8–11]. A FSH is a negative-feedback response of a biosystem to maintain the function-specific conditions inside the biosystem so that the function is perfectly fulfilled. A function far from its FSH is called a dysfunctional function, which corresponds to deficient *yang* or *yin* in TCM. A function in its FSH is recognized as a normal function, which corresponds to *yin-ping-yang-mi* in TCM. The process of improving from dysfunctional to normal is called functional normalization.

A normal function in its FSH can resist internal/external disturbance, but the FSH can be disrupted by a FSH-specific stress (FSS). A normal/dysfunctional FSS is called a successful/chronic stress.

A normal function in its FSH is maintained by FSH-essential/non-essential sub-functions (FESs/FNSs). The PBM of a LLL can be classified into two kinds of PBM, direct/indirect PBM (dPBM/iPBM). A dPBM cannot directly modulate a normal function/FSS, but may self-adaptatively modulate a dysfunctional function/FSS until it is normalized. An iPBM may self-adaptatively modulate

a dysfunctional FNS of a normal function in its FSH until it is normalized and then upgrade the FSH.

2.2.2 Genetic redundancy

There are signs that the LPBM research is maturing especially in extraocular phototransduction (EPT) although some limitations confront the researchers. In our laboratory, a quasi-hormone model of laser biostimulation from the viewpoint of EPT [17] was put forward in 1996 and then developed as the biological information model of PBM (BIMP) in 2003 [18]. The possibility of circadian EPT was suggested by Campbell and Murphy [19] in explaining their investigation that LIL exposure to the area behind the knee caused phase shifts of the human circadian rhythms. The first EPT phenomenon was observed in a LIL-induced respiratory burst of polymorphonuclear neutrophils in our laboratory in 2001 [20]. Since then, many LIL-induced EPT phenomena have been observed.

BIMP has been considered as a EPT phenomena [6, 8, 10, 11, 18]. There may be dose zone effects for LPBM so that the dose zones are named dose 1, 2, ..., and so on, starting from the lowest dose. Hot and cold colors have been extended to include infrared A (IR-A, 700–1400 nm) and ultraviolet A (UV-A, 320–400 nm), respectively. The signal transduction pathways have been classified into two groups: the Gs-protein-mediated pathways belong to pathway 1, and the other pathways mediated by Gi protein, Gq protein, non-receptor protein tyrosine kinases, phospholipase C, protein kinase C, phosphatidylinositol-3-kinase or mitogen-activated protein kinase belong to pathway 2. The corresponding relationship of LIL at different wavelengths in the n^{th} dose zone and signal transduction pathways is called BIMP (n). In the $(2n\text{-}1)^{th}$ (n=1, 2, ...) dose zone, the cold LIL and hot LIL may further activate partially activated pathways 2 and 1, respectively, according to BIMP (2n-1). In the $2n^{th}$ (n=1, 2, ...) dose zone, the cold LIL and hot LIL may further activate partially activated pathways 1 and 2, respectively, according to BIMP (2n).

The EPT has been further studied by introducing the concept of redundancy [9, 11]. Genetic redundancy means that two or more genes are performing the same function and the inactivation of one of these genes has little or no effect on the biological phenotype [21]. The two or more genes and their corresponding signal transduction pathways are called redundant genes and redundant pathways, respectively. It seems that every signal transduction pathway may mediate a LPBM. However, there is no dPBM on a normal function/FSS. In other words, a dPBM cannot modulate the set of fully activated signal transduction pathways maintaining a normal function/FSS. Therefore, a dPBM may only modulate partially activated redundant pathways. When a FSS disrupts a FSH, the redundant pathways will be activated. The redundant pathways are fully activated for a successful stress, but partially activated for a chronic stress. For a chronic stress, a dPBM may self-adaptatively promote the further activation of the partially activated redundant pathways until they are fully activated, resulting in a successful stress.

2.2.3 Self-adaptation

Since its introduction in the early 1960s, lasers have transformed phototherapy. Now in its developing years, the PBM field is still experiencing difficulties especially in the dose relationship. The dose relationship of PBM is often underestimated. A study showing excellent results has diminished value if there is no clear disclosure of the dose relationship. Our laboratory has studied the dose relationship in terms of quantum mechanics [10, 11].

The pathways mediating a cellular PBM are classified into two kinds: the specific pathway which is mediated by the resonant interaction of light with endogenous photosensitizers such as hemoglobin, flavin and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases containing the membrane-bound cytochrome b558; and the non-specific pathway which is mediated by the non-resonant interaction of light with the proteins in the membranes of cells or cellular organelles.

The primary process of a cellular PBM, the interaction of light and cellular molecules, is the key because its transition rate influences the dose relationship of a PBM [10, 11]. The Bunsen-Roscoe law of reciprocity [15] holds for the specific pathway, but does not hold for the non-specific pathway. The relationship between a PBM response and the irradiation time is a linear function for the specific pathway, but a sine function for the non-specific pathway. Studies on the dose relationship indicated that LPBM is mainly mediated by the non-specific pathway, but PBM of MIL is mainly mediated by the specific pathway.

The non-resonant transition rate is so small that it is impossible to be physically observed. However, the non-specific pathway may be nonlinearly amplified according to our identical particle model within the frame work of quantum mechanics [9–11, 18]. A cellular function is always related to a kind of membrane protein so that the protein is called function-specific protein (FSP). The number N of the FSPs mediating the non-specific pathway in a cell is about 10^{3-4}. All the FSPs of

a cellular function mediating the non-specific pathway are identical. They cooperate with one another to form coherent states when the related cellular function is dysfunctional. The coherent states can be classified into two kinds: the super radiant state in which the transition rate is a nonlinear function of the FSP numbers N so that the ultra-weak non-resonant interaction can be amplified, and the sub radiant state which has a transition rate of zero. When the FSPs mediating the non-specific pathway are in super radiant states, the cellular function is dysfunctional. The function of cells in which FSPs are in random states is optimal and normal. A PBM mediated by a non-specific pathway for FSPs to achieve random states should be a homeostatic process. The LPBM as mainly mediated by the non-specific pathway would be a homeostatic event. This is in agreement with the conclusion given in section 2.2.1 on "Function-specific homeostasis".

The LPBM is non-specific so that it may modulate any dysfunctional functions. LIL may modulate a chronic stress until it is successful so that it might be self-adaptative [9]. A LPBM is indeed self-adaptative, but it takes enough time for a chronic stress to be successful. The observation periods of many studies have been too short to observe the self-adaptative property of the LPBM, leading to contradicting views of its effectiveness.

3 Clinical photobiomodulation

As a PBM modality, sunlight has not been used directly in TCM except for chromophototherapy, but TCM takes account of its latitude and seasonal effects. Laser acupuncture, intranasal low intensity laser therapy (ILILT) and intravascular low energy laser therapy (ILELT) has been widely used in China. Their typical clinical applications as well as light wavelengths and dosimetry are listed in Table 1.

3.1 Laser acupuncture and interdigital low intensity laser therapy

Acupuncture has been used in TCM to treat a variety of illnesses for more than 2000 years. The practice of acupuncture is based on a theoretical system different from our understanding of human anatomy and physiology, and has developed through experience and observation. It involves inserting needles to stimulate selective acupoints (situated along "meridians" of the body) to restore bodily functions by promoting the flow of "vital energy", throughout the systems. Other forms of acupuncture stimulation include heat, electrical stimulation, magnetism and, more recently, laser (from 1970s onwards). The pioneers of laser acupuncture originate, unsurprisingly, from China [1].

Type of therapy	Typical indications	Wavelength (nm)	Dose
Laser acupuncture	– Cold – Bronchitis – Bronchial asthma – Hypertension – Pain – Arthritis – Cerebrovascular diseases – Acute appendicitis – Acute biliary tract disease – Gastric ulcer or enterelcosis	700–1400 (IR-A)	~10 mW/cm^2 (LIL)
Intravascular low energy laser therapy (ILELT)	– Cerebral infarction – Cerebrovascular diseases – Diabetes	632.8 or 650.0	~0.1–1.0 W/cm^2 (MIL)
Intranasal low intensity laser therapy (ILILT)	– Hyperlipidemia – Coronary heart disease – Myocardial infarction – Brain diseases (e.g., insomnia, intractable headache, Alzheimer's disease, Parkinson's disease, post-stroke depression, ache in the head or face, migraine, cerebral thrombosis, diabetic peripheral neuropathy, cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, cerebral palsy and mild cognitive impairment)	650.0	~10 mW/cm^2 (LIL)

Table 1 Popular LLL therapies in China.

Yo-Cheng Zhou has worked with laser acupuncture since 1971, mainly as an anesthesia for tooth extractions and minor operations, and published the first clinical paper overseas in 1984 [22]. Our laboratory carried out research from 2003 and continued the work until today [6, 10, 23]. Recently, interdigital LIL therapy has been devised in China. It irradiates the interdigital acupoints of pericardium meridian of hand *jueyin* (PC), heart meridian of hand *shaoyin* (HT), *sanjiao* of hand *shaoyang* (TE or SJ) and other meridians. Clinical studies are currently ongoing.

There are many pathways mediating laser acupuncture. One of the pathways is from a LPBM modulated acupuncture point cells to autonomic nervous system (ANS) which includes sympathetic nervous subfunction (SNS) and parasympathetic nervous subfunction (PNS) through the relevant meridian. LIL can be nonlinearly coupled with ANS function through the meridian. LIL used for laser acupuncture often has a hot color such as red or IR-A. As the *yin-yang* of LIL is dependent on its dosage, we have the following model for dysfunctional functions [6, 10, 23]:

- At dose 1 (10^{0-3} J/m^2), the hot color promotes deficient *yin* function such as dysfunctional PNS;
- At dose 2 (10^{3-5} J/m^2), the hot color promotes deficient *yang* function such as dysfunctional SNS;
- At dose 3 (10^{1-2} J/cm^2), the hot color promotes deficient *yin* function such as dysfunctional PNS;
- At dose 4 (10^{3-4} J/cm^2), the hot color promotes deficient *yang* function such as dysfunctional SNS.

3.2 Intravascular low energy laser therapy

ILELT as an intravascular application of MIL was put forward for cardiocirculatory diseases by Lee et al. [24] in USA in 1982. It was popular in Russia in 1980s, and then in China from 1990s onwards. Basic studies on the effect of MIL on blood have been very progressive in China. These include blood research *in vitro* [25, 26], animal blood research *in vivo* [27], human blood research *in vivo* [28] and TCM research [29].

Numerous research activities might support the efficacy of ILELT but only one study was on ILELT within the framework of evidence-based medicine. Zvereva et al. [30] made a randomized placebo-controlled study of the clinical efficacy of four different methods of ILELT with helium-neon laser on 150 patients suffering from rheumatoid arthritis.

Our laboratory conducted a meta-analysis to analyze the therapeutic effects of Chinese ILELT and drugs, compared with a "drugs only" policy on patients together with a study of the blood parameters [31]. The light wavelength used in ILELT had always been 632.8 or 650 nm. Statistical parameters were reported as odds ratio (95% confidence interval) for patient improvement and weighted mean difference (95% confidence interval) for blood parameter improvement. It was found that the symptom improvement of patients of cerebral infarction, cerebrovascular diseases and diabetes were significant ($p<0.01$). Improvements were also found in the blood parameters such as cholesterol, total cholesterol, low density lipoprotein cholesterol, triacylglycerol, high density lipoprotein, erythrocyte aggregation index, erythrocyte sedimentation rate, fibrinogen, whole blood contrast viscosity, low cut blood viscosity, high cut blood viscosity, whole blood viscosity and plasma blood contrast viscosity ($p<0.05$). In conclusion, patients of cerebral infarction, cerebrovascular diseases and diabetes might improve with ILELT, mediated by blood parameter improvement.

3.3 Intranasal low intensity laser therapy

Since 1980, many Russian groups have studied the therapeutic effects of intranasal LPBM on the local inflammation in vasomotor rhinitis, and in both acute and chronic maxillary sinusitis. In 1998, intranasal LPBM was suggested in China as a method to treat internal diseases [32]. This special treatment then became known as ILILT. Nose-mediated therapeutics in TCM is a very old system [33], but ILILT became popular from 1998 onwards [10, 34]. The light wavelength used in ILILT has always been 650 nm in China. It has been studied for the treatment of hyperlipidemia, the blood-stasis syndrome of coronary heart disease, myocardial infarction and brain diseases such as insomnia, intractable headache, Alzheimer's disease, Parkinson's disease, post-stroke depression, ache in the head or face, migraine, cerebral thrombosis, diabetic peripheral neuropathy, cerebral infarction, acute ischemic cerebrovascular disease, brain lesion, schizophrenia, cerebral palsy and mild cognitive impairment. Studies indicated that serum amyloid-β protein, malformation rate of erythrocytes, plasma cholecystokinin-octapeptide, the level of viscosity at lower shear rates, hematocrit, and serum lipid all decreased. In contrast melanin production, red cell deformability, superoxide dismutase activity and β endorphin all increased, and the blood circulation was improved and immunity was regulated.

ILILT might have a systemic effect [10, 34, 35]. There are five possible pathways mediating the ILILT: (1) olfactory nerve, (2) nasal bone, (3) blood cells, (4) meridians in TCM and (5) ANS. Recently, our laboratory designed a randomized, double-blind and placebo-controlled clinical study to assess the effects of intranasal low intensity

GaInP/AlGaInP diode 650 nm laser therapy on the blood lipid and hemorheologic behavior of patients with coronary heart disease or cerebral infarction [35]. After the treatment, blood viscosity at high shear rate (200/s) (p<0.05), plasma viscosity at low shear rate (3/s) (p<0.05), red blood cell aggregation (p<0.01), and total cholesterol (p<0.05) decreased in the treatment group, and high-density lipoprotein cholesterol increased in the treatment group (p<0.01), but no significant changes occurred in the control group. Low-density lipoprotein cholesterol, redox viscosity at low shear rate (3 s^{-1}) and high shear rate (200 s^{-1}) decreased in the treatment group (p<0.05, 0.01 and 0.05), but increased in the control group (p<0.001, 0.01 and 0.05), respectively. Blood viscosity at low shear rate (3 s^{-1}) increased in the control group (p<0.05), but no significant differences occurred in the treatment group. In conclusion, ILILT may improve blood lipid and hemorheologic behavior of patients with coronary heart disease or cerebral infarction.

3.4 Laser surgery

Laser surgery is one of the most rapidly advancing fields in laser applications. Consumer demand has generated intense interest from physicians and medical industry. This has led to the development of safer and more effective lasers with a wide range of applications. The vast number of surgical lasers available can mean that physicians are spoilt for choice. Among the many rules on the choice of laser in China, the long-term effects of laser surgery have taken priority [36]. Although the central intensity of a laser beam in laser surgery is so high that it destroys the tissue, the marginal intensity is so low that it may induce PBM. We believe that the PBM incurred by the marginal part of a laser beam is responsible for the long-term beneficial effects of laser surgery [36], supported by cellular model research [37], and animal model and clinical research [38]. Huang et al. [37] studied PBM in laser surgery by using monolayer human skin fibroblasts as models, and found evidence of PBM from the marginal irradiation of the high intensity laser beams on non-damaged monolayer human skin fibroblast cells. Yang et al. [38] studied the regeneration of new vocal cords after laser cordectomy, and the histological change in new vocal cords through animal and clinical experiment. They found that the marginal irradiation intensity of the high-intensity laser beam is so low that there is PBM on non-damage cells, modulating the regeneration of the partly damaged vocal cord. The cordectomy using a laser with different parameters resulted in different post-surgical vocal recovery profiles, although the high-intensity laser beam is so intense that it destroyed the irradiated vocal cord.

4 Discussion

PBM is a modulation of biological functions. Its basis should be functional medicine [39] such as TCM [40], of which homeostasis is a basic concept [39]. After it has developed into the FSH [8–10], a function far from its FSH corresponds to deficient *yang* or *yin*, and a function in its FSH corresponds to *yin-ping-yang-mi* in TCM. The PBM phenomena, functional medicine and TCM combine to give a reasonable explanation of the PBM mechanism for clinical outcomes.

Moreover, it provides the basis for its performance enhancement. In TCM, deficient *yang* or *yin* is modulated until it arrives at the *yin-ping-yang-mi*. iPBM may modulate a dysfunctional FNS of a normal function in its FSH until it is normalized and then upgrade the FSH. For example, low-dose UV-A radiation induced an adaptative response of dermal fibroblasts in 10% fetus calf serum and then protected the fibroblasts from damage from subsequent lethal dose of UV-A [41]; and laser acupuncture reduced body fat mass and lower body weight in a dose-dependent manner in obese persons [42]. For a normal physical function, iPBM may be used to promote health. In the same way, sunlight can promote health so that one can benefit from the latitude and season effects of sunlight. However, for tumor cells in their proliferation-specific homeostasis, iPBM may promote their normal proliferation and their resistance against anticancer drugs. Therefore, light should not be used to directly irradiate a solid tumor or circulation tumor cells [43].

5 Conclusion

As Chinese therapeutic applications of PBM are the most widely used in the world, the research of PBM and its therapeutic applications became very advanced. PBM has been found to be homeostatic and self-adaptative, and have genetic redundancy. PBM has clinical applications from a variety of modalities – laser acupuncture, ILELT, ILILT and laser surgery.

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