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Review Article

Photobiomodulation Process

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Photobiomodulation (PBM) is a modulation of laser irradiation or monochromatic light (LI) on biosystems. There is little research on PBM dynamics although its phenomena and mechanism have been widely studied. The PBM was discussed from dynamic viewpoint in this paper. It was found that the primary process of cellular PBM might be the key process of cellular PBM so that the transition rate of cellular molecules can be extended to discuss the dose relationship of PBM. There may be a dose zone in which low intensity LI (LIL at different doses) has biological effects similar to each other, so that biological information model of PBM might hold. LIL may self-adaptively modulate a chronic stress until it becomes successful.

1. Introduction

Photobiomodulation (PBM) is a modulation of laser irradiation, monochromatic light, hot color light such as red, orange or yellow, or cold color light such as green, blue or violet (LI) on biosystems. Since its introduction in the early 1960s, laser has transformed phototherapy. Now in its developing years, the PBM field is still experiencing growing pains especially in dose relationship. The dose relationship of PBM is very important topic which has been often underestimated. A paper of excellent results could not been referred because there has been no clear dose relationship. Some international groups always reported negative results of PBM since their inattentive research on dose relationship, which have left other researchers or physicians confused. Many Chinese groups have done the same things so that there almost was no laser acupuncture in clinical applications, and intravascular low energy laser therapy (ILELT) was forbidden by Chinese Health Ministry. The dose relationship of PBM would be discussed from dynamic viewpoint in this paper.

2. Initial States

PBM depends on the initial state of a biosystem. Negative feedback is common in biological processes and can maintain the resistance of biosystems to internal and external perturbations [1]. The PBM was discussed from the viewpoint of negative feedback.

The negative feedback is generally used to maintain internal stability of a biosystem, which is a classical concept of homeostasis [2, 3]. However, circadians or oscillations are found at nearly every level of biology. Homeostasis is too obscure to be deeply studied so that it has been developed as function-specific homeostasis (FSH) in our laboratory. An FSH is a negative-feedback response of a biosystem to maintain the function-specific conditions inside the biosystem so that the function is perfectly performed [4, 5]. A biosystem in an FSH means the function is in its FSH. A biosystem far from an FSH means the function is far from its FSH. A function in its FSH is better performed than all the dysfunction far from the FSH so that the function in its FSH is locally the best performed one.

The negative feedback can be also used to maintain a stress. An FSH can resist internal/external disturbance, but can be disrupted by an FSH-specific stress (FSS). An FSS is also a function of a biosystem so that there is an FSS-specific homeostasis (FSSH) [6]. A FSS in its FSSH is called successful stress, but a FSS far from its FSSH is just a chronic stress.

The LI used in PBM is always low intensity LI (LIL), ~10 mW/cm^2. However, moderate intensity LI (MIL), $10^{2\sim3}$ mW/cm^2, is of PBM if the irradiation time is not so

long that it damages organelles or cells. The PBM of LIL and MIL are denoted as LPBM and MPBM, respectively. It has been found [6] that LIL or MIL with short irradiation time is a low level LI (LLL) so that it cannot directly affect a successful stress or a function in its FSH. However, an LLL can modulate a chronic stress. On the other hands, MIL with long irradiation time is a high level LI so that it can disrupt an FSH/FSSH.

3. Primary Process

The first law of photochemistry (and photophysics) states that light must be absorbed for photochemistry (or photophysics) to occur. This is a simple concept, but it is the basis for performing photobiological experiments correctly. Since photobiological and phototherapeutic effects are initiated by photochemistry (or photophysics), unless light of a particular wavelength is absorbed by a system, no photochemistry (or photophysics) will occur, and no photobiological effects will be observed, no matter how long one irradiates with that light.

The biosystem is very complicated, but it can be studied at cellular level. The primary process of cellular PBM of LI is the interaction of LI with cellular molecules. A molecule in the ground state $|n\rangle$ with energy E_n has been irradiated with LI at angular frequency ω and intensity I for irradiation time t. According to quantum mechanics, the coefficient, $\langle k \mid n\rangle$, of the ground state $|n\rangle$ in the expansion of the wavefunction of the excited state $|k\rangle$ with energy E_k at the time t is calculated by the following equation under the electric-dipole approximation [7, 8]:

$$\langle k \mid n\rangle = \frac{1}{2\hbar}\sqrt{I}D_{kn}\frac{1-\exp[i(\omega_{kn}-\omega)t]}{\omega_{kn}-\omega}, \tag{1}$$

where $\hbar$ is the reduced Plank constant, D_{kn} is the matrix element of the transition from the ground state $|n\rangle$ to the excited state $|k\rangle$, and $\omega_{kn} = (E_k - E_n)/\hbar$. $|\langle k \mid n\rangle|^2$ has been explained to be the transition probability from the ground state $|n\rangle$ to the excited state $|k\rangle$. We then have the transition rate, the transition probability per unit time, of the molecule

$$r = \frac{d}{dt}|\langle k \mid n\rangle|^2 = \frac{1}{2\hbar^2}|D_{kn}|^2 I\frac{\sin(\omega_{kn}-\omega)t}{\omega_{kn}-\omega}. \tag{2}$$

If the identical protein molecules interacting with LI are in the membrane of the cell or their organelles (Figure 1), the identical molecules might cooperate with each other to form coherent states when the related function/FSS is far from its FSH/FSSH, and the transition rate of a cell should be [7]

$$R = \frac{1}{2\hbar^2}C_k N^2|D_{kn}|^2 I\frac{\sin(\omega_{kn}-\omega)t}{\omega_{kn}-\omega}, \tag{3a}$$

where N and C_k are the number of the identical molecules and the quantum constant of the excited $|k\rangle$. For the resonant transition, $\omega_{kn} = \omega$, we have from (2)

$$r_r = \frac{1}{2\hbar^2}|D_{kn}|^2 It. \tag{4a}$$

We then have the reciprocity rule (Bunsen-Roscoe law) [9] that the photochemical response is independent of the intensity I and the irradiation time t when the dose It is kept constant.

According to whether the primary process is resonant or nonresonant, the pathways mediating cellular PBM are classified into two kinds, the specific pathway which is mediated by the resonant interaction of LI with endogenous photosensitizers such as hemoglobin, flavin and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases which consist of the membrane-bound cytochrome b558 [10], the nonspecific pathway which is mediated by the nonresonant interaction of LI with the proteins in the membrane of cells or organelles [7, 8]. Equations (3a) and (4a) hold for nonspecific pathways and specific pathways, respectively.

Obviously, the nonresonant transition rate (2) is extraordinarily small in comparison with resonant transition rate (4a) ($r \ll r_r$) so that the non-specific pathway may be impossible. However, the non-specific pathway may be nonlinearly amplified according to our identical particle model within the frame work of quantum mechanics [7]. In (3a), the number N of the membrane protein molecules (Figure 1) mediating the non-specific pathway is about $10^{3\sim4}$. All the membrane molecules mediating the non-specific pathway are identical. They cooperate with one another to form the coherent states when the related cellular function/FSS is far from its FSH/FSSH. The coherent states can be classified into two kinds, the superradiant state whose transition rate is a nonlinear function of the molecular numbers N so that the ultra-weak nonresonant interaction can be amplified according to (3a), and the subradiant state whose transition rate is zero. It has been easily shown that the function of cells whose molecules mediating the non-specific pathway are in superradiant states is not optimal and the cells are far from its FSH and the function of cells whose molecules are in subradiant states is optimal and the cells are in its FSH [8]. Therefore, the PBM mediated by non-specific pathway should be homeostatic. The PBM of LIL is mainly mediated by the non-specific pathway [8] and then might be homeostatic. This is in agreement with the conclusion in the previous section.

4. Key Process

A complicated process consists of many subprocesses each of which has its rate. The key subprocess is one of the subprocesses whose rate is the smallest one among the subprocesses. There are many processes of PBM from LI absorption to the observed biomedical effect among which one process is called the key process which is very critical for PBM, and its rate determines PBM rate. Through the dynamics of PBM we tried to find the key process, and discuss further the dose relationship of PBM. There is little research on the dynamics of PBM although its phenomena and mechanism have been widely studied, which is in the way of the deep research of PBM mechanism, especially the urgent research on the dose relationship in clinical

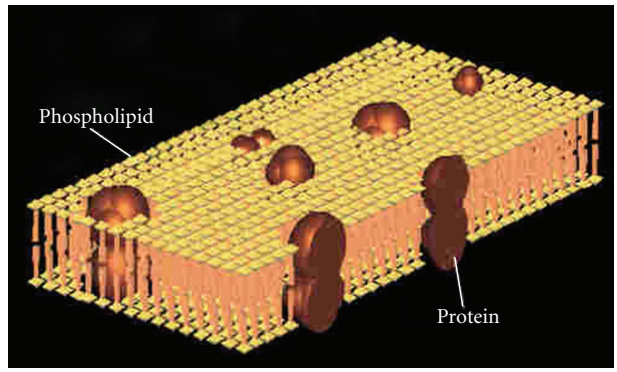

Figure 1: Cellular membrane structure illustration.

applications. The key process of cellular PBM might be studied by comparing the transition rate of its primary process with its dose relationship after reviewing cellular PBM.

The key process is the rate-limiting process. As photodegradation is a key process in governing the residence time and fate of many agrochemicals in top soils [11], the primary process of cellular PBM might be supposed to be the key process of cellular PBM so that the dose relationship of cellular PBM should be decided by transition rate of the primary process, (3a) and (4a), which was called the key process hypothesis of cellular PBM (KPHCP) for convenience. According to KPHCP, (3a) should hold for the non-specific pathway mediated response of light (NSPR):

$$\text{NSPR} \propto I \frac{\sin(\omega_{kn} - \omega)t}{\omega_{kn} - \omega}, \tag{3b}$$

and the reciprocity rule, (4a), should hold for the specific pathway mediated response of light (SPR):

$$\text{SPR} \propto It. \tag{4b}$$

Therefore, (3a), (3b) and (4a), (4b) might be the dose relationship of LPBM and MPBM because LPBM and MPBM may be mainly mediated by non-specific pathways and specific pathways [8], respectively. KPHCP was supported by its applications.

MPBM or photodynamic effects is mainly mediated by SPR so that the reciprocity rule, (4a), (4b), should hold according to KPHCP. Ben-Dov et al. [12] have studied MPBM on satellite cell proliferation in vitro and found that there was a linear relationship of PBM and irradiation time when the intensity was kept constant. Stadler et al. [13] have studied the MIL of whole blood on the lymphocyte proliferation and also found a linear relationship of the PBM and irradiation time when the intensity was kept constant. Obviously, (4a), (4b) hold for MPBM. For ILELT, the changed laser intensity is a kind of MIL, but the irradiation time, the period for blood cells to flow through the cross section of the optical fiber, is a constant. Wang et al. [14] have used ILELT to treat New Zealand rabbits with Alloxan-diabetes and observed the variations of their erythrocyte filtration index (EFI). Their data have been linearized as follows:

$$\begin{aligned} &\text{First day after treatment,} \\ &\quad y_1 = -0.00490x_1 + 0.288, \qquad R_1 = 0.9130, \\ &\text{Third day after treatment,} \\ &\quad y_3 = -0.0492x_3 + 0.386, \qquad R_3 = 0.9300, \end{aligned} \tag{5}$$

where x, y, and R are the intensity, EFI, and the correlation coefficient.

LPBM is mainly mediated by NSPR [8] so that (3a) and (3b) should hold according to KPHCP. In this case, the reciprocity rule, (4a), (4b), should not hold, and LPBM depends on intensity or irradiation time if the dose is kept constant. From the observations of different research groups and their own observations, Sommer et al. [15] concluded that the threshold parameters dose and intensity are biologically independent from each other. The analysis of intensity and irradiation time dependences for the same biological response indicated that the reciprocity rule does not hold when HeLa cells were irradiated with low intensity He-Ne laser irradiation (LHNL) [16, 17]. Although few studies have addressed the validity of the reciprocity rule in experimental and applied photobiology to date, most of these data point to the fact that the rule of reciprocity is invalid or of limited validity for many photobiological reactions, and it has been shown that at a constant total dose, the intensity of the source is a major factor that determines quality and quantity of the response for the effects of LLL [18]. Van Breugel and Bar [19] have found that LHNL at 1.24 mW/145 s can significantly promote the proliferation of human diploid skin fibroblasts in vitro, but the irradiation at 0.55 mW/330 s or 5.98 mW/30 s cannot although their doses are almost the same. Lubart et al. [20] have investigated the effect of LIL on mammalian cells. They found that the induction of fibroblast proliferation at a constant dose depends on the applied intensity in a nonlinear manner. In the research of Li et al. [21], polymorphonuclear neutrophils (PMNs) were irradiated by LHNL at doses of 800, 1,000, 1,800, and 2,000 J/m^2, respectively, and the intensity was changed at each dose. They found that the NADPH oxidase activity was different at different intensity for each dose of

LHNL. Lanzafame et al. [22] have studied the effects of red light at 670 nm from light emitting diode array (RLED 670) on pressure ulcers of C57/BL mice and found varying irradiance and exposure time to achieve a specified energy density affecting phototherapy outcomes.

When the dose of LIL is constant, the reciprocity rule might not hold so that there might be a maximum PBM according to (3a) and (3b). Let T be defined as follows:

$$T = (\omega_{kn} - \omega)t. \tag{6}$$

From (3a), we have

$$R = \frac{1}{2\hbar^2} C_k N^2 |D_{kn}|^2 It \frac{\sin T}{T}. \tag{7}$$

and then

$$\frac{dR}{dt} = \frac{1}{2\hbar^2} I C_k N^2 |D_{kn}|^2 \left(\cos T - \frac{\sin T}{T}\right). \tag{8}$$

Therefore, the transition rate of the primary process and then LPBM arrives at their maximum value, respectively, at $T = T_0$:

$$T_0 \cos T_0 = \sin T_0. \tag{9}$$

Karu [23] has measured DNA synthesis in exponentially growing HeLa cells and proliferation after constant low doses of 632.8 nm (0.01 J/cm^2) and 454 nm (0.3 J/cm^2) laser irradiation applied within different exposure times (i.e., with different intensities), respectively. Her findings pointed to the nonvalidity of the reciprocity rule as the biological response varied clearly with different intensities peaking between 1 mW/cm^2 and 20 mW/cm^2. Karu and Kolyakov [24] also observed dependence of stimulation of DNA synthesis rate on light intensity or irradiation time at a constant dose measured 1.5 h after irradiation of log-phase HeLa cells with a continuous wave dye laser pumped by an argon laser (633 nm, 8 mW/cm^2) at 100 J/m^2 and found the maximum PBM at about 10 s.

Obviously, the optimum T_0 and then the optimum radiation time t_0 are dose-independent according to (6) and (9). We also observed the maximum PBM of low intensity 810 nm GaAlAs laser irradiation at the constant dose 528 and 2130 mJ/cm^2, respectively, on NIH 3T3 fibroblasts [25]. Moreover, the optimum irradiation time 40 s at the maximum PBM has been found dose-independent [25]. This is a direct support to KPHCP.

KPHCP was also supported by the dose relationship when the intensity or the radiation time is kept constant. There are many works on the dose relationship when the intensity is kept constant [9]. In this case, the LPBM should be the SIN function of irradiation time according to KPHCP and (3a) and (3b), which is supported by Al-Watban et al., Brill et al., Karu, Yang et al., Zhang et al., and Zharov et al. [9, 26–36].

There are few works on the dose relationship when the irradiation time is kept constant. In this case, the LPBM should be the linear function of intensity according to KPHCP and (3a) and (3b), which is supported by Cheng et al., Duan et al., Karu, Liang et al., and Xu et al. [9, 37–40].

We have studied RLED 640 promotion on the recovery of differentiated PC12 (dPC12) cells from H_2O_2 cytotoxicity [41]. dPC12 cells were cultured with the medium of H_2O_2 at 150 μmol/L for 30 min and then with fresh medium for 6 h and were then irradiated with RLED 640 at 0.06 mW/cm^2 for 10, 20, 40, and 60 min and 72 mJ/cm^2 for 5, 10, 20, and 40 min, respectively. It was found among the irradiation at 0.06 mW/cm^2 or 72 mJ/cm^2, 10 and 20 min irradiation was the most effective in promoting cellular rehabilitation, respectively. Obviously, (3a) and (3b) may hold.

In a summary, KPHCP has been supported by its applications. In other words, the primary process of cellular PBM might the key process of cellular PBM.

5. Dose Zone

It has been found that there is a dose zone in which LI at different doses has biological effects similar to each other. For example, the dose zones were called dose 1, dose 2, and dose 3 from low dose on so that human skin fibroblast cell (HSF) proliferation was inhibited in dose 1 (16, 24 mJ/cm^2) and promoted in dose 2 (298, 503, 597 mJ/cm^2), and the collagen synthesis was inhibited in dose 2 (401, 526 mJ/cm^2), and promoted in dose 3 (714, 926, 1539 and 1727 mJ/cm^2) [37]. Based on these phenomena, the biological information model of PBM (BIMP) has been put forward [7, 42].

According to traditional Chinese medicine, *yin* and *yang* are antagonistic, but they transform into each other under some condition [43]. It can be extended to other systems such as cells [44]. The cellular signal transduction pathways can be classified into two kinds: pathway 1 mediated by Gs protein mediated pathway, and pathway 2 is mediated by the other pathways mediated by proteins such as G_i protein, G_q protein, or one of receptor-linked enzyme. We then have cellular *yin* and *yang* [44]:

pathway 1 belongs to *yin*, and pathway 2 belongs to *yang*. (10)

The *yin* and *yang* of LIL depend on its dose zone. The dose zones were called dose n from the lowest dose of PBM on. At dose 1 [44],

Hot color light belongs to *yin*, and cold color light belongs to *yang*. (11)

According to *yin-yang* parallel principle [44], we have

Hot color light activates pathway 1, cold color light activates pathway 2. (12)

It is called BIMP1. If the dose is at dose 2 which is larger than the threshold of dose 1, the *yin-yang* properties of LIL will transform into each other according to *yin-yang* inter-transformation [44] so that we have,

Hot color light belongs to *yang*, and cold color light belongs to *yin*. (13)

According to *yin-yang* parallel principle [44], we have from (10) and (13).

Cold color light activates pathway 1, hot color light activates pathway 2. (14)

This is called BIMP2. Generally, we have (13) according to *yin-yang* intertransformation if the dose is at dose $2n$ (n = 1, 2,3,...) which is larger than the threshold of dose $2n - 1$ if it does not damage membrane or cell compartments such as mitochondria, lysosomes, endoplasmic reticulum so that (13) is called BIMP $2n$, and we have (14) according to *yin-yang* inter-transformation if the dose is at dose $2n+1$ (n = 1, 2,3, ...) which is larger than the threshold of dose $2n$ if it does not damage membrane or cell compartments so that (14) is called BIMP $2n + 1$. BIMP n (n = 1,2,3,...) has been supported by its successful application in the cellular level, animal model level, and clinic level [7, 42].

6. Self-Adaptive Photobiomodulation

The LPBM is non-specific so that it can modulate any function far from its respective FSH according to the dosage relationship discussed above. After an FSS disrupts an existing FSH, there are many would-be FSH (wFSH) which might be established. The higher the quality of the wFSH is, the stronger it resists the disturbances of the other functions far from their respective wFSH so that only the wFSH of highest quality is established by a successful stress [6]. Therefore, LIL can modulate a chronic stress until it is successful so that it might be self-adaptive. It is indeed self-adaptive at least according to our recent following progress, but it takes time long enough for a chronic stress to be successful. The observation period of many studies has been too short to observe the self-adaptive property of the PBM.

We have found that RLED 640 self-adaptively modulate high-glucose- (hG-) induced dysfunctions of C2C12 myoblasts [45]. hG increased the ratio of nicotinamide adenine dinucleotide (NAD^+) and its reduced form NADH, NAD^+/NADH, at 4th, 24th, and 36th h, respectively, but decreased it at 72nd h, which were completely reversed by RLED 640. hG decreased the mRNA levels of sirtuin 1 and manganese superoxide dismutase (MnSOD) at 4th, 24th, 48th, and 72nd h, respectively. The hG inhibition on sirtuin 1 mRNA was reversed by RLED 640 partially at 4th and 48th h, respectively, and completely at 72nd h, but wasnot modulated at 24th h. The hG inhibition on MnSOD mRNA was completely reversed by RLED 640 at 72nd h, but were not modulated at 4th, 24th, and 48th h. hG did not modulate the activities of MnSOD at 24th and 48th h and catalase at 4th, 24th, 48th, and 72nd h, respectively, but RLED 640 increased catalase activity only at 48th h. hG decreased MnSOD activity at 4th h, but increased it at 72nd h, which wasnot modulated by RLED 640.

We also found the low intensity gallium aluminum arsenide 635 nm laser irradiation (LIGL) effects on insulin-like growth factor-1 (IGF-1) and transforming growth factor (TGF) beta1 was self-adaptive [46]. LIGL promoted IGF-1 mRNA expression on the 1st, 2nd, 3rd, and 7th d, but inhibited the one on the 14th and 21st d, respectively. LIGL increased IGF-1 level on the 2nd, 3rd, and 7th d, but decreased the one on the 14th and 21st d, respectively. LIGL decreased TGF-beta1 level on the 3rd and 28th d, but increased the one on the 7th and 14th d, respectively.

7. Discussion

The dosage, intensity, or dose discussed above should be the exact dosage at which LI exactly interacts with the target cells. The LI gets weaker and weaker the further from the surface it penetrates so that there may be a difference between the LI dosage of light source and its exact dosage absorbed by the cells especially for the clinical applications. The dosage for PBM should be location-specific in order to get the same exact dosage absorbed by the cells. This LI penetration is on tissue type, pigmentation, and dirt on the skin or membrane. LI can even penetrate bone (as well as it can penetrate muscle tissue). Fat tissue is more transparent than muscle tissue.

8. Conclusion

The primary process of cellular PBM might be the key process of cellular PBM. The specific pathways might mediate MPBM so that the reciprocity rule holds. The non-specific pathways might mediate LPBM so that the reciprocity rule does not hold, the LPBM might be the SIN function of irradiation time when the intensity is kept constant, and the LPBM might be the linear function of intensity when the irradiation time is kept constant. There may be a dose zone in which LIL at different doses has biological effects similar to each other, so that BIMP might hold. LIL may self-adaptively modulate a chronic stress until it becomes successful.

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